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Original article

Synthesis and biological evaluation of new 3-(6-hydroxyindol-2-yl)-5-(Phenyl) pyridine or pyrazine V-Shaped molecules as kinase inhibitors and cytotoxic agents

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ABSTRACT

We here report the synthesis and biological evaluation of new 3-[(2-indolyl)]-5-phenyl-3,5-pyridine, 3-[(2-indolyl)]-5-phenyl-2,4-pyridine and 3-[(2-indolyl)]-5-phenyl-2,6-pyrazine derivatives designed as potential CDK inhibitors. Indoles and phenyls were used to generate several substitutions of the pyridine and pyrazine rings. The synthesis included Stille or Suzuki type reactions, which were carried out on the 3,5-dibromopyridine, 2,4-dichloropyridine and 2,6-dichloro-1-4-pyrazine moieties. Cell effects of the V-shaped family were in the micromolar range. Kinase assays were conducted and showed that compound **11** inhibited CDK5 with an inhibitory concentration of 160 nM with a moderate selectivity over GSK3 compared to the reference **C** which exhibited a slightly lower activity on CDK5 (1.5 μM). Compound **11** was also found to be the most potent compound in the series and was identified as a new lead for DYRK1A inhibitor discovery (IC_{50} = 60 nM). Docking studies were carried out in order to investigate the inhibition of DYRK1A.

1. Introduction

More than 500 protein kinases control the phosphorylation of proteins in cellular life [1,2]. Alterations of this process are found in numerous human pathologies, hence the interest in the search for kinase inhibitors [3,4]. This interest was boosted following the approval of the first marketed inhibitor Gleevec™, used in myeloid leukaemia [5]. Among all the kinases, cyclin-dependent kinases (CDKs), which regulate the cell cycle and apoptosis, have been well studied [6–10]. CDKs are also involved in neurodegenerative disorders [11] such as Alzheimer's disease. Other related kinases such as glycogen synthase kinase GSK3 [12] induce neurodegeneration and deficits in memory formation related to Alzheimer's disease; the implication of GSK3 in cancer development has been additionally proven [13,14]. Several drugs are able to efficiently inhibit these enzymes and some of them are currently in clinical assays, many of them containing an indole structure [15,16].

The indole scaffold is a popular privileged structure encountered in medicinal chemistry [17,18]. The discovery of plant indole alkaloids or marine indolic drugs, which exhibit a wide range of biological properties, greatly supports this privileged structure. The design of new drugs is often based on core scaffolds with an indole structure. In the indolocarbazole series, for example, our group developed naphtho [19] and azaindolocarbazole [20] derivatives as cytotoxic agents and/or check point kinase 1 inhibitors.

We have now started another program aimed at developing CDK inhibitors on V-shaped structures. We recently developed the synthesis of tris-aromatic compounds of the **A**-**C** type, i.e. a pyridine (or a pyrimidine) core substituted respectively in positions *C*-3,5 or *C*-2,5 by a phenyl or an indole motif [21–23]. These three **A**–**C** structures were synthesized in order to partially mimic some

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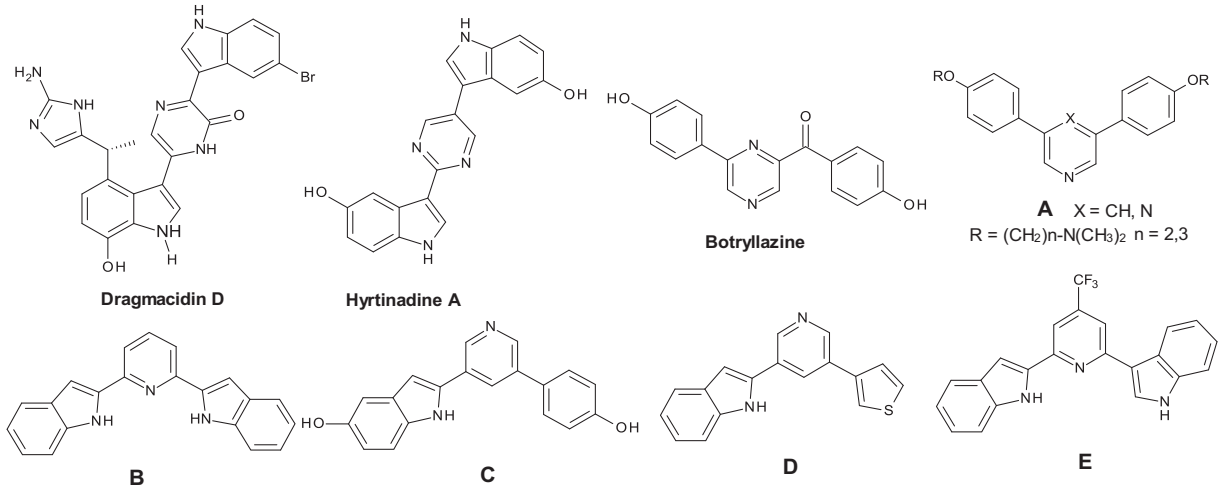


Fig. 1. Related synthetic or natural products and envisioned derivatives.

natural bis indole alkaloids such as Dragmacidin D [24], Hyrtinadine A [25], Botryllazine [26] or the synthetic bis indole derivatives **D** [27] and **E** [28] (Fig. 1).

The promising preliminary biological evaluations (i.e. CDK inhibition and cytotoxic properties) of our analogs prompted us to mix structures of type **A** and **B** and investigate compounds of type **C** with various substituents on the indole and phenyl rings with a view to enhancing biological activity and in particular kinase inhibition. The substituents would be chosen for their ability to accept or donate H-bonds with the residues of the active ATP site of kinases [23]. CDK, GSK and DYRK1A are privileged targets for their implication in cancer or neurodegenerative diseases.

In this paper, we present the synthesis of a new library corresponding to the general indole structure **I** (Fig. 2) from **II**–**IV** by using palladium catalyzed cross-coupling reactions (Stille, Suzuki and Buchwald) mostly carried out under microwave irradiation. The biological activity of the final compounds as kinase inhibitors and cytotoxic agents are given and SAR are explored.

2. Chemistry

2.1. Synthesis of (2-indoyl)-(pyridine or pyrazine)-phenyl V-shaped molecules

The 1-phenylsulfonyl-6-methoxyindole [29] **2** was obtained from 3-methoxyaniline **1** via a modified Bischler reaction which offered the advantage of yielding **2** ready to be regioselectively functionalized in position *C*-2 by lithiation (LDA 1.5 eq.) followed by condensation with tributylstannyl chloride at −78 °C (Scheme 1). The resulting stannylated indole **3** was involved in a mono Stille reaction with 3,5-dibromopyridine (1.0 eq.) in THF in presence of CuI, $Pd(PPh_3)_4$ (5%) under microwave irradiation at 100 °C for 20 min [23,30]. The bromopyridine **4** was obtained in a near quantitative yield.

The second aromatic moiety was next introduced under a Suzuki-Miyaura type reaction using (4-methoxyphenyl, 4-cyanophenyl or 4-methanesulfonylphenyl) boronic acids. The reaction was carried out with a small excess of the required boron derivative (1.2 eq.) in a mixture of toluene/ethanol (1.6/1) and saturated aqueous solution of $NaHCO_3$ in presence of $Pd(PPh_3)_4$ (10%). The reactions were run in a sealed tube under microwave irradiation at 150 °C for 15 min [30]. Compounds **5** ($R = OCH_3$), **6** ($R = CN$) and **7** ($R = SO_2CH_3$) were respectively obtained in 78%, 70% and 72% yields.

Deprotection of the indolic nitrogen atom was accomplished with TBAF in refluxing THF and led to **8**–**10** respectively in excellent yields. Methyl ether deprotections were performed at r.t. with BBr_3 in dichloromethane. The amounts of Lewis acid and the reaction times were adapted in each case and the final derivatives **11**–**13** were obtained in satisfactory yields. All the NMR, IR and HMRS spectral data are in agreement with the structure of the synthesized indole derivatives **8**–**10**.

The pyrazine analogs of **11**–**13** were obtained from the chloropyrazine **14**, which was obtained from 2-stannylindole **3** and 2,6-dichloropyrazine *via* our previously reported Stille type reaction in 98% yield (Scheme 2). Next, a Suzuki reaction of **14** with the 4-

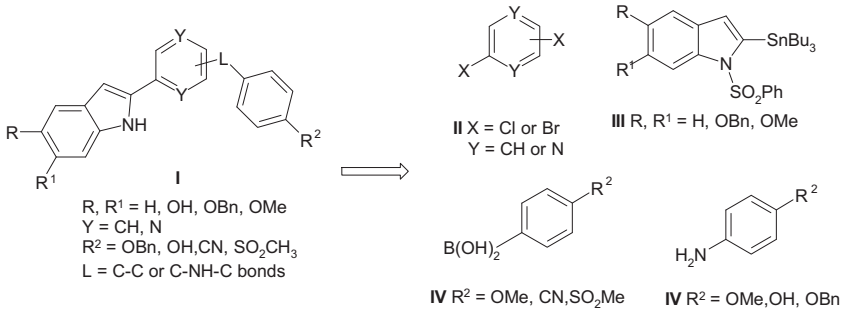
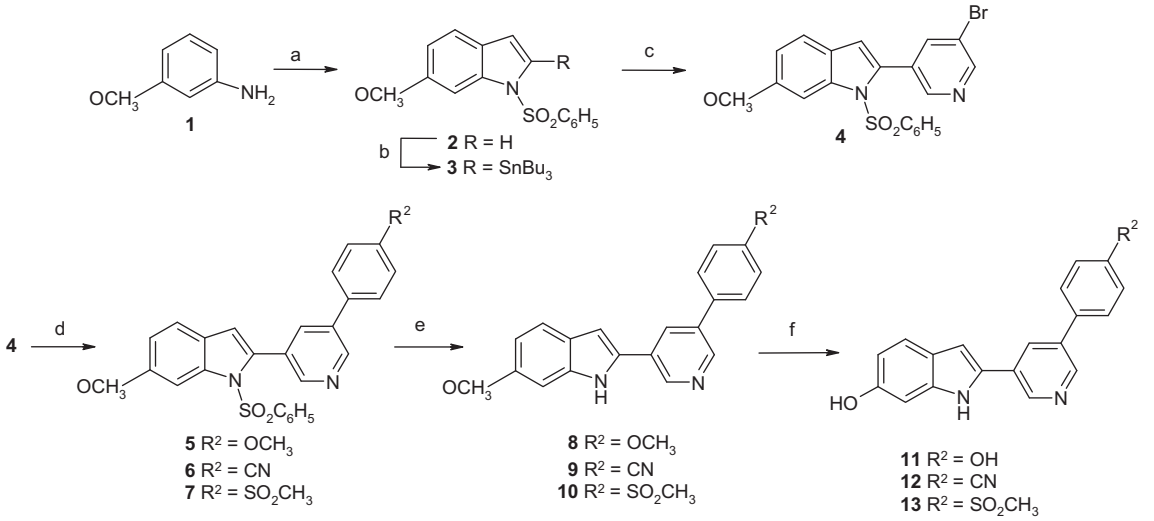


Fig. 2. Indole V-Shaped library.



Scheme 1. *Reagents and conditions* : a) Bischler procedure *i)* $C_6H_5SO_2Cl$, pyridine, CH_2Cl_2, 98%, *ii)* $NaHCO_3$, DMF, $BrCH_2CH(OC_2H_5)_2$, 100 °C, 86%, *iii)* $BF_3.Et_2O$, CH_2Cl_2, 0 °C, 10 min, 97%; b) *C*-2 functionalization procedure *i)* LDA, THF, −20 °C 30 min, *ii)* Bu_3SnCl, −78 °C to r.t, 2 h 75%; c) CuI (10%), $Pd(PPh_3)_4$ (5%), THF, 3,5-dibromopyridine (1.1 eq.), μWave, 100 °C, 20 min, 99%; d) 4-substituted phenylboronic acid (1.3 eq.), aq. $NaHCO_3$, toluene/EtOH, $Pd(PPh_3)_4$ (10%), μWave, 150 °C, 15 min, **5** 78%, **6** 70%, **7** 72%; e) Bu_4NF (1.5 eq.), THF, reflux, *from* ***5*** : 6 h, **8** 97%, *from* ***6*** : 6 h, **9** 86%, *from* ***7*** : 15 h, **10** 99%. f) CH_2Cl_2, 0 °C to r.t., *from* ***8*** : BBr_3 (3.0 eq.), 6 h, **11** 72%, *from* ***9***: BBr_3 (1.5 eq.),12 h, **12** 58%, *from* ***10*** : BBr_3 (2.0 eq.), 3 h, **13** 53%.

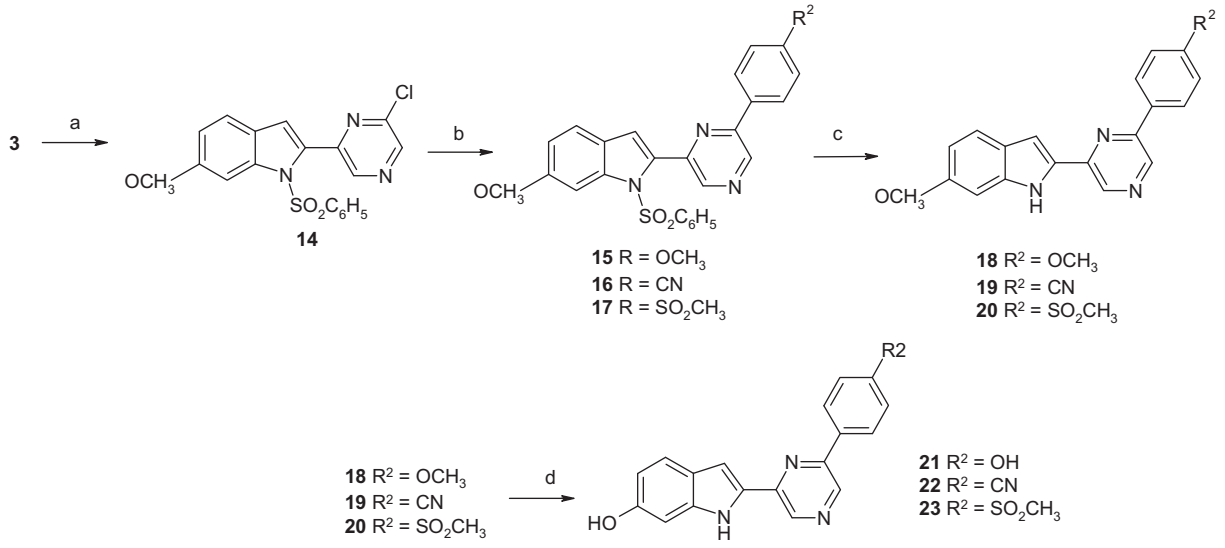
substituted (OMe, CN, SO_2CH_3) phenylboronic acids led to compounds **15**–**17** respectively in 72%, 73% and 65% yields. Removal of the benzenesulfonyl indolic protections followed by methyl ether cleavages led to compounds **21**–**23** in satisfactory yields.

In a previous paper, we reported the preparation of the stannyl derivative **24** and under classical thermal activation the derivative **25** [23]. Here we report as a new result that the reaction of **24** with the 2,6-dichloropyrazine led under microwave irradiation to the targeted compound **26**. The two derivatives **25** and **26** were used to build a new library of final V-shaped compounds **27**–**31** by Suzuki cross coupling reactions in good yields; the two deprotection steps led successively to **32**–**36** and next to the original final compounds **37**–**41** (Scheme 3 and Tables 1 and 2).

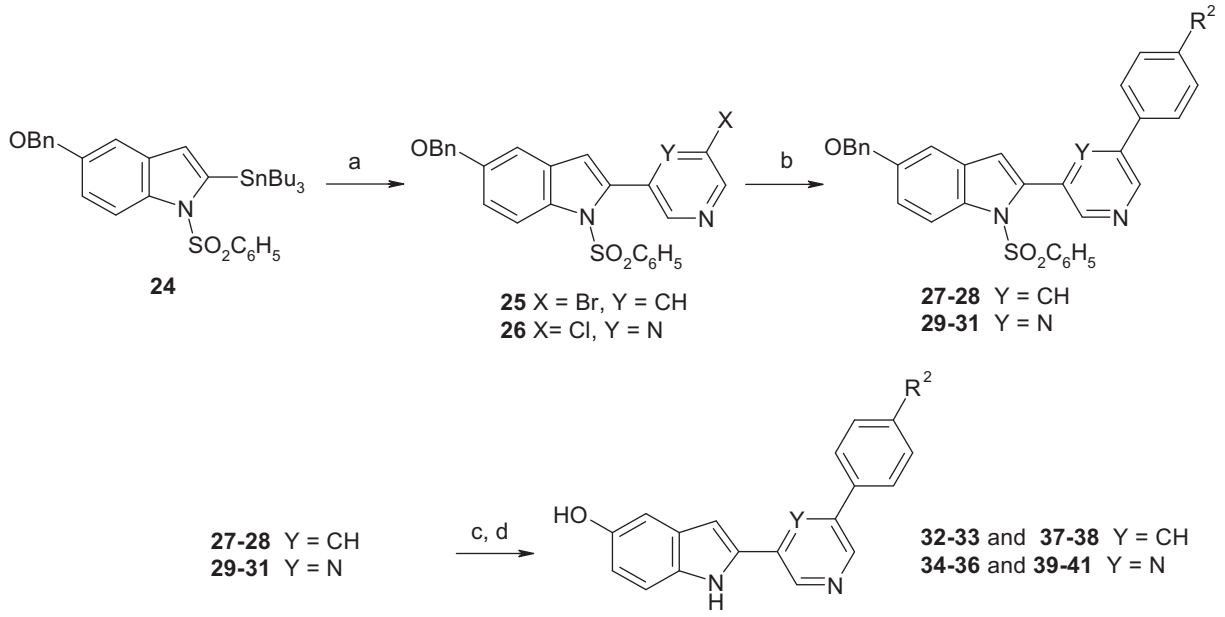
To obtain information about the interactions of heteroatoms with the kinase ATP active site, we used 2,4-dichloropyridine instead of 3,5-dibromopyridine. The reaction was carried out with stannyl derivatives **3** and **24** to afford compounds **42** and **43** in good yields. As expected, we observed exclusively a mono reaction at the *C*-2 position of the pyridine ring. Suzuki reaction of **42** and **43** with 4-methoxyphenylboronic acid led respectively to **44** (77% yield) and **45** (79% yield). The further deprotection of the indolic nitrogen atoms afforded compounds **46** and **47** in 80% yield while the cleavage of ethers completed the synthesis, affording the final derivatives **48** and **49** in nearly quantitative yields.

2.2. Synthesis of (2-indoyl)-(pyridine or pyrazine)-(aminophenyl)-V-shaped molecules

In order to give more flexibility to the tri-aromatic V-shaped structure, we then sought to introduce on the pyridine or pyrazine



Scheme 2. *Reagents and conditions* : a) CuI (10%), $Pd(PPh_3)_4$ (5%), THF, 2,6-dichloropyrazine (1.0 eq.), μWave, 100 °C, 20 min, 98%; b) 4-substituted phenylboronic acid (1.3 eq.), aq. $NaHCO_3$, toluene/EtOH, $Pd(PPh_3)_4$ (10%), μWave, 150 °C, 15 min, **15** 72%, **16** 73%, **17** 65%; c) Bu_4NF (1.5 eq.), THF, reflux, 15 h, **18** 88%, **19** 88%, **20** 99%. d) CH_2Cl_2, 0 °C to r.t., *from* ***18*** : BBr_3 (3.0 eq.), 10 h, **21** 73%, *from* ***19*** : BBr_3 (5.0 eq.), 5 h, **22** 63%, *from* ***20*** : BBr_3 (5.0 eq.), 5 h, **23** 42%.



Scheme 3. *Reagents and conditions* : a) 3,5-dibromopyridine or 2,6-dichloropyrazine (1.05 eq.), CuI (10%), $Pd(PPh_3)_4$ (5%), THF, μWave, 100 °C, 20 min, **25**, 89% **26,** 83%; b) 4-substituted phenylboronic acid (1.3 eq.), aq. $NaHCO_3$, toluene/EtOH, $Pd(PPh_3)_4$ (10%), see Table 1; c) THF, reflux, see Table 2; d) CH_2Cl_2, 0 °C to r.t., see Table 2.

Table 1
Cross-coupling reactions of compounds **25** or **26** leading to **27**–**31**.

Entry	*Y*	R^2	Time	Δ or M.W	Product	Yield (%)
1	CH	CN	4 h	reflux	**27**	76
2	CH	SO_2CH_3	8 h	reflux	**28**	96
3	N	OCH_3	30 min	M.W, 150 °C	**29**	78
4	N	CN	30 min	M.W, 150 °C	**30**	90
5	N	SO_2CH_3	30 min	M.W, 150 °C	**31**	82

ring a "kneecap" through a 4-hydroxyaniline moiety. To achieve this, the Buchwald–Hartwig reaction was used [31]. It was first performed on the bromo derivative **25** with 4-methoxyaniline using potassium carbonate, $Pd(OAc)_2$, Xantphos in dioxane under microwave irradiation for 1 h at 140 °C [32]. Under these classical conditions, compound **50** was obtained in 87% yield. Similarly, **51** and **52** were obtained from the chloro derivatives **26** and **14** in 83% and 86% yields respectively. Deprotection with Bu_4NF (10.0 eq.) was achieved in refluxing THF (12–15 h) to afford the pyrazine derivatives **54** and **55** respectively in 99% and 86% yield; curiously the pyridine derivative **50** did not react at all in these conditions and required the use of 1.5 eq of NaOH (2 M) in refluxing methanol to afford the deprotected derivative **53** in 70% yield. Unfortunately, whatever the method used (BBr_3, HBr/acetic acid or NaI/TMSCl), we were unable to cleave the benzyl or the methyl ether bonds of compounds **53**–**55**.

As we were interested in hydroxyl substituents on indole and aniline due to previous results on CDK inhibition [23], we envisaged catalytic hydrogenolysis as a deprotective method. The 6-benzyloxy-1-phenylsulfonyl indole was therefore prepared and stannylated in the same way as described for compound **3,** to give **56**. A Stille reaction with 2,6-dichloropyrazine led to the chloropyrazine **57**. A Buchwald reaction was then carried out using bromo derivative **25** and 4-hydroxyaniline or **57** and 4-benzyloxyaniline to yield respectively **58** and **59** in 80% and 87% yield. Deprotection of the nitrogen indole atom was achieved in both cases with Bu_4NF and led to **61** in 75% yield but sensitivity of the 4-aminophenol residue on **58** in basic media led to **60** in only 37% yield. Unfortunately in all cases the envisioned hydrogenolysis reaction failed (no reaction or degradation).

3. Kinase inhibitions

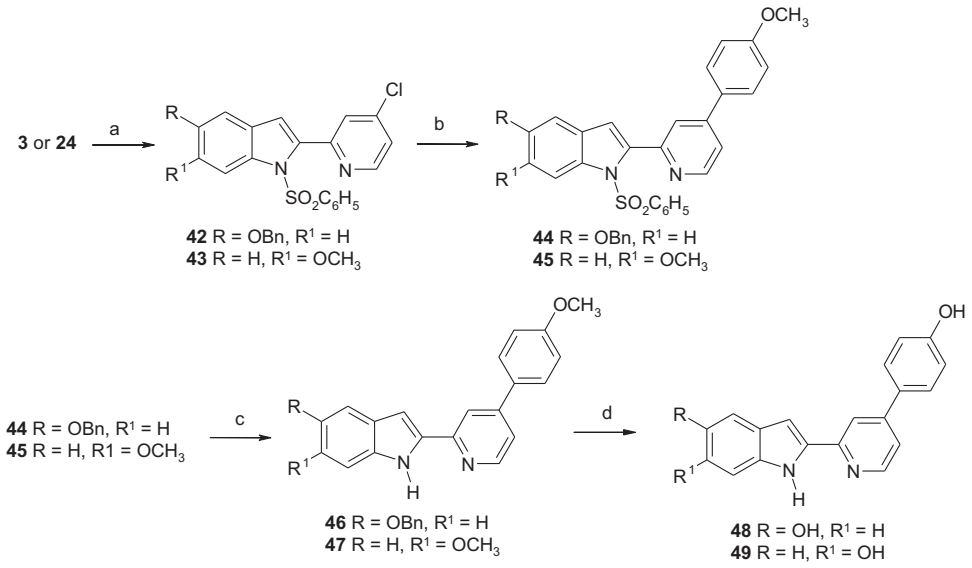
We evaluated 13 final compounds on 3 types of kinases CDK5, GSK3 and DYRK1A (Table 3). In a previous paper [23] we reported the activity of our reference compound **C** which inhibited 50% of CDK5 activity at a 1.5 μM and appeared to be 26 times more active against this kinase versus GSK3 (Table 3, entry 0).

The 4-hydroxy substituent (donor and acceptor of H-bond) in the phenyl ring seems to be the best to interact with the ATP binding site of CDK5, while the presence of a substituent able to

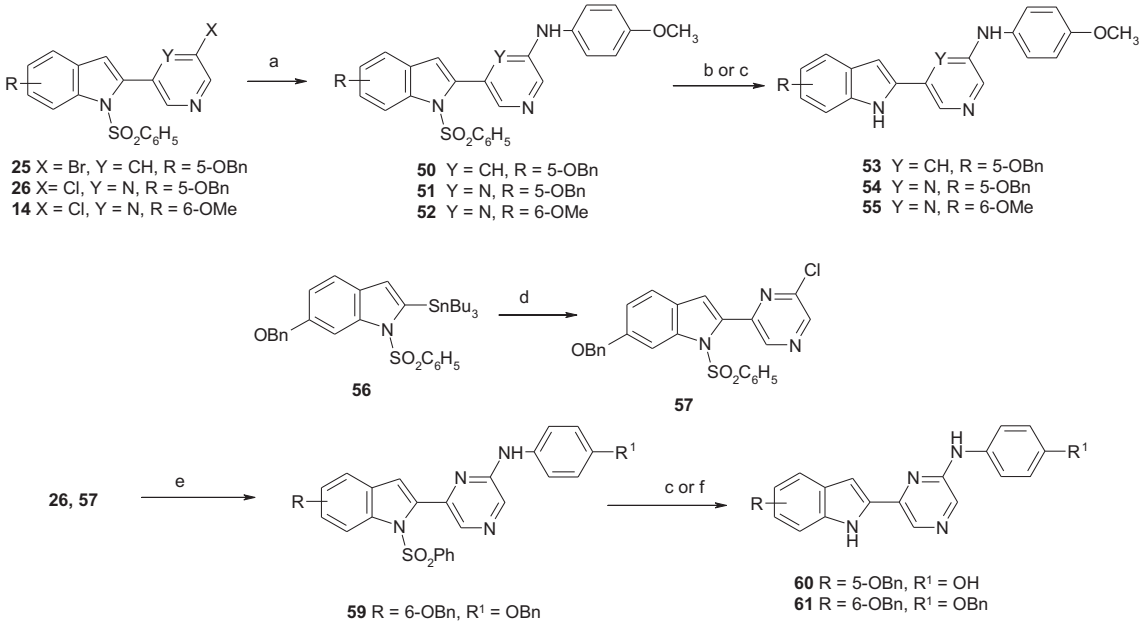
Table 2
Deprotection steps leading to **32**–**36**.

Entry	*Y*	R^2	Starting Material for step c	Bu_4NF (eq.)	Time	Product, yield	BBr_3 (eq.)	Time	Product after step d, yield
1	CH	CN	**27**	1.5	4 h	**32**, 73%	1.1	4 h	**37**, 71%
2	CH	SO_2CH_3	**28**	1.5	4 h	**33**, quant	1.5	6 h	**38**, 58%
3	N	OCH_3	**29**	3.0	6 h	**34**, 96%	11.8	15 h	**39**[a], 99%
4	N	CN	**30**	3.0	12 h	**35**, 76%	10.0	12 h	**40**, 99%
5	N	SO_2CH_3	**31**	3.0	10 h	**36**, 94%	6.0	7 h	**41**, 41%

[a] R^2 = OH.



Scheme 4. *Reagents and conditions* : a) **3** or **24** and 2,4-dichloropyridine (1.5 eq.), CuI (10%), $Pd(PPh_3)_4$ (5%), THF, μWave, 100 °C, 30 min, **42**, 72% or **43**, 70%; b) 4-methoxyphenylboronic acid (1.5 eq.), aq. satd $NaHCO_3$, toluene/EtOH, $Pd(PPh_3)_4$ (10%), μWave, 150 °C, *from* ***42*** : 30 min, **44**, 77%, *from* ***43*** : 40 min, **45**, 79%; c) Bu_4NF (3.0 eq.), THF, reflux, *from* ***44***: 12 h, **46**, 80%, *from* ***45*** : 4 h, **47**, 80%; d) CH_2Cl_2, 0 °C to r.t., *from* ***46***: BBr_3 (8.0 eq.), 12 h, **48**, 99%, *from* ***47***: BBr_3 (5.0 eq.), 5 h, **49**, 97%.

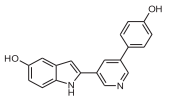
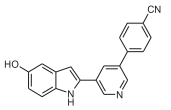
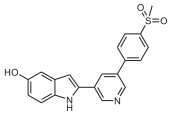
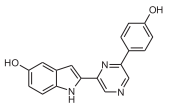
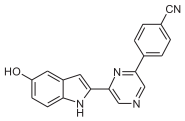
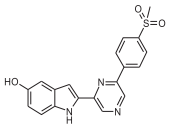
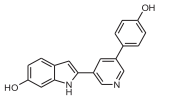
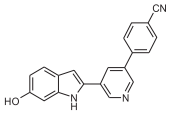
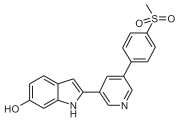
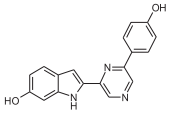
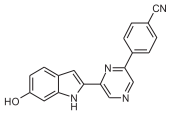
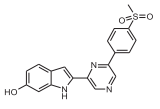
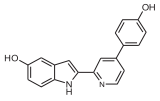
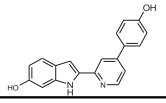


Scheme 5. *Reagents and conditions*: a) *p*-anisidine (1.5 eq.), K2CO3 (2.0 eq.), Pd(OAc)2 (10% mol), Xantphos (20% mol), dioxane, μWave, 140 °C, 1 h, **50** 87%, **51** 83%, **52** 86%; b) NaOH (1.5 eq.), $MeOH/H_2O$, rflx, 12 h, from **50**: **53**, 70%; c) Bu_4NF (10.0 eq.), THF, 12 h, reflux, **54** 99%, **55** 86%, *from* ***59***: 10 h, **61** 75%; d) 2,6-dichloropyrazine (1.2 eq.), CuI (10%), $Pd(PPh_3)_4$ (5%), THF, μWave, 100 °C, 30 min, **57**, 91%; e) Pd(OAc)2 (10% mol), Xantphos (20% mol), dioxane, μWave, 140 °C, 1 h, *from* ***26*** : 4-hydroxyaniline (1.5 eq.), K_2CO_3 (2.0 eq.), **58** 87%, *from* ***57*** : 4-benzyloxyaniline (1.5 eq.), K_2CO_3 (3.0 eq.), **59** 80%. f) Bu_4NF (4.0 eq.), THF, rflx, 8 h, **60** 37%.

accept only H-bonds of the SO_2CH_3 and CN type (entries 1, 2) reduces drug/enzyme interactions. The same result was observed by changing the central pyridine ring by the less basic pyrazine despite its ability to give an additional hydrogen bond with the kinase active site (entries 3–5). Fortunately, varying the position of the hydroxyl group on the indole core increases the activity on CDK5; the 6-hydroxy indole series gave better inhibition (in the sub micromolar range) for the same substituents (OH, SO_2CH_3, CN). Compound **11** ($IC_{50} = 160$ nM) is 10 fold more active than derivative **C,** leading to a new V-shaped kinase inhibitor lead.

The pyridine derivatives **32**, **38** and **11**–**13** appeared to be more efficient than their pyrazine analogs **40**, **41** and **21**–**23**. This analysis showed an increase in activity by a factor of 5–10 except for the compounds reference **C** and **39** which affected CDK5 in a similar

Table 3
DYRK1A, CDK5 and GSK3 inhibitions.

Entry	Compounds		IC_{50} (μM)		
			DYRK1A	CDK5	GSK3β
0		**C**	ND	**1.5**	40
1		**32**	3.3	5.3	> 100
2		**38**	2.3	1.8	7.3
3		**39**	0.34	1.5	4.7
4		**40**	1	4.4	26
5		**41**	3.1	6.3	26
6		**11**	0.06	0.16	1.1
7		**12**	1.6	0.9	4
8		**13**	0.35	0.38	1.1
9		**21**	0.54	1.5	5.3
10		**22**	5	5.4	5.7
11		**23**	2.7	2.6	2.3
12		**48**	0.23	0.36	ND
13		**49**	0.3	0.83	ND

manner. In addition, with 2,4-disubstituted pyridine compounds **48** and **49** (IC_{50} = 360 and 830 nM respectively, entries 12, 13), inhibition of the enzyme was always better than in the pyrazine series but lower than in the 3,5-disubstituted pyridine series. A higher basicity of the pyridine compared to the pyrazine ring and the optimal position of the nitrogen atom may explain these differences and this weaker ability of forming H-bonds with the active site.

Selectivity in kinase inhibition was next measured on the GSK3β and DYRK1A [33], two kinases involved mainly in neurodegenerative disorders such as Alzheimer's disease and mental retardation. In all cases our derivatives are selective for CDK versus GSK3β(except **22** and **23**). Nevertheless, interesting results were obtained by performing tests on DYRK1A. Our lead derivative **11** is very active and a noteworthy IC_{50} = 60 nM was measured. This new inhibition is sensitive to the same structure modifications depicted by the CDK SAR studies.

4. Molecular modeling

In order to explain the inhibition results obtained with our synthesized compounds, and more specifically with our lead derivative **11**, we focused molecular modeling studies on DYRK1A and docking studies were carried out. The crystal structure of DYRK1A in complex with 7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*] indole currently named HRM (PDB code 3ANR) was chosen to study the binding mode of our active compounds [34,35]. First of all, HRM was docked again to reproduce the co-crystal complex. Superimposition of the best docked pose, i.e. the top score conformer, on the crystal structure fits well between the two structures: this initial step of rigid docking gave an RMSD deviation, based on heavy atoms, of 0.12 Å.

Next all the ligands (14 compounds, Table 3) were docked using the previously validated protocol. All the compounds adopted conformations within the binding site positioning the pyridine ring (or pyrazine ring) near the hinge region (Leu241, Met240, Glu239), allowing H-bond interactions with the protein through a nitrogen atom. The ligands interacted by means of H-bonds with two other regions of the protein. The first one corresponds to solvent access (H-bond with Asp247) and the second one is named pocket 1 (H-bond with Lys188 and Glu203). Thus, regarding the other parts of our compounds, two modes of binding were observed, excepted for compounds **38**, **41**, **13** and **23** which preferred only binding mode 1 (Fig. 3).

These two binding modes are illustrated with the most active compound **11** (Fig. 3) which inhibited DYRK1A in the nanomolar range. Binding mode 1 (left pose) described mainly H-bond interactions between the 6- or 5-hydroxy substituent on the indole moiety in pocket 1 whereas the 4-phenol ring pointed in the direction of the solvent toward Asp247.

Left: binding mode 1 where the substituted phenyl ring points to the solvent. *Right:* binding mode 2 where hydroxyindole points to the solvent. Only polar hydrogen atoms are represented for clarity. H-bonds are shown in dashed yellow lines.

In binding mode 2 (right pose), the indole group of **11** pointed to the solvent whereas the substituted phenyl ring found an optimal interaction in pocket 1. Similar crucial H-Bond interactions, as for binding mode 1, were found between the drug and the enzymatic active site. Steric hindrance on the phenyl ring could impose the orientation of the synthesized compounds to the solvent. This could be the case with methylsulfonyl containing derivatives **38**, **41**, **13** and **23.** It should also be mentioned that varying substituents on the phenyl ring decreases activity but does not result in a total lack of activity. This could be in favor of binding mode 1 where

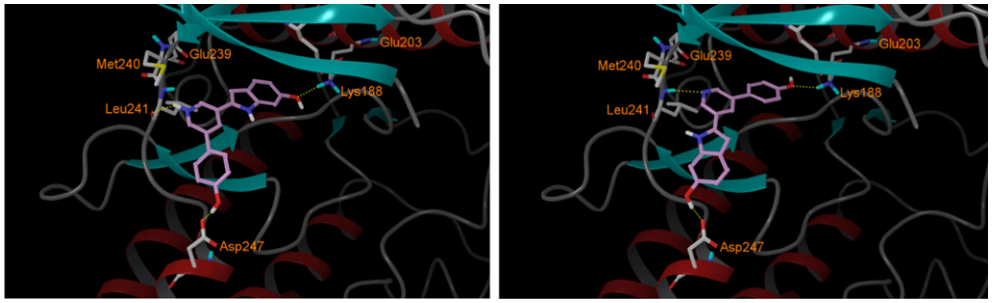


Fig. 3. The two binding modes of compound **11** observed in the active site of DYRK1A.

substituents point to the solvent, limiting modifications in the protein–ligand interactions.

5. Cell effects

As the optimization of our V-shaped scaffold led to more efficient kinase inhibitors than reference **C**, we studied their effects on cells. In a previous paper we showed that compound **C** inhibits cell survival in a micromolar range (CEM Cells IC_{50} = 4.6 μM) [23]. To evaluate the potency of the 13 new V-shaped compounds we now used 6 representative tumoral cell lines of liver (Huh7), colon (Caco, HCT116), breast (MDA-MB 231), prostate (PC3), lung (NCI) and one normal cell line (fibroblasts) and measured survival. Results are reported in Table 4.

Observation of the biological material in presence of our V-shaped indole molecules showed a clear cytostatic effect but the cells could not be induced to enter in apoptosis. This effect is currently associated with a kinase functioning disorder. Our derivatives possess good cell penetration parameters but their efficiency on the signaling pathway was not sufficient to induce strong cell death. Our newly identified CDK5 inhibitors (i.e. **11**–**13**, **48, 49**) were globally more efficient than Roscovitin and exhibited a similar cell profile to **C**.

The most active compounds were clearly the pyridine derivatives **12**, **13** and **48** (entries 7, 8, 12) with 50% of survival at only 1.5–2 μM range and selectivity for particular cell lines. Compound **12** was the most interesting molecule, even if its effect on CDK5 was limited. In this case, a higher preference for liver Huh7 cells without any effect on normal cells was observed. Since the effect on the diploid cell line is much weaker than on abnormal cells, our new library possesses the criteria for further developments as non toxic agents.

6. Conclusion

We have reported here the synthesis and biological evaluation of a new V-shaped library including 3-[(2-indolyl)]-5-phenyl-3,5-pyridine, 3-[(2-indolyl)]-5-phenyl-2,4-pyridine and 3-[(2-indolyl)]-5-phenyl-2,6-pyrazine derivatives, and have identified their biological effects. We successfully used Stille or Suzuki type reactions to create C–C bonds. Kinase and cell effects were measured on 13 new derivatives and compared with our reference **I**. Cancer cell lines are always targeted by the V-shaped derivatives in the μM range in adequacy with the strength of kinase inhibition. Results in kinase assays show that compound **11** inhibited CDK5 at IC_{50} = 160 nM range (versus 1.5 μM for **I**). A good selectivity over GSK3 is maintained. Additionally compound **11** was also identified as a new lead for DYRK1A inhibitor discovery (IC_{50} = 60 nM).

7. Experimental section

7.1. Chemistry

^{1}H-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. HMRS were performed by the Centre Commun de Spectrométrie de Masse (Clermont-Ferrand, France). Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F254). Spots were visualized by UV light at 254 nm and 356 nm. Columns chromatography were performed using silica gel 60 (0.063–0.200 mm, Merck). Microwave experiments were performed on a Biotage Initiator apparatus.

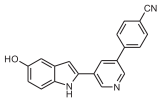
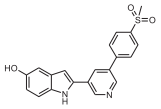
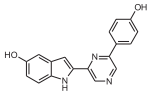
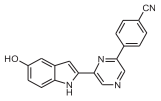
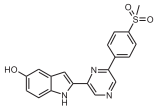
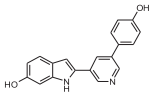
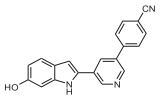
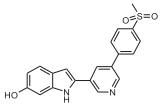
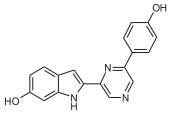
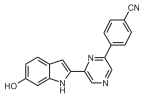
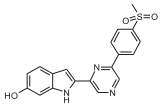
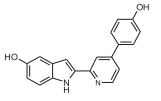
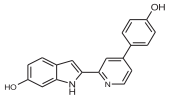
7.1.1. General procedure A for Stille cross coupling reaction

A solution of the stannylated indole derivative, the corresponding halogenated derivative (1.2 eq) and CuI (0.1 eq) in THF was degassed under vigorous stirring by argon bubbling for 20 min. Pd(PPh3)4 (5 or 10% mol/stannylated indole) was added. The reaction mixture was irradiated in a microwave oven for the indicated time. After cooling, water was added and the crude product was extracted with EtOAc. The combined organic layers were successively washed with brine, dried with MgSO4 and filtered off. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography.

7.1.2. General procedure B for Suzuki cross coupling reaction

The phenylboronic acid derivative (1.3 eq.) was added to a solution of the halogenated pyridine (pyrazine) derivative in a mixture of toluene, ethanol, and aqueous saturated NaHCO3 solution. The reaction mixture was then degassed under vigorous stirring by argon bubbling for 20 min. Pd(PPh3)4 (10% mol/halogenated derivatives) was added and the mixture immediately transferred in a pre-heated oil bath and refluxed for the indicated time or irradiated in a microwave oven. After cooling, water was added and the crude product was extracted with EtOAc. The combined organic layers were washed with brine, dried with MgSO4 and filtered off. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography. In the NMR assignments the exponent ‘ refers to pyridine or pyrazine hydrogens (central ring B) and exponent “ refers to phenyl hydrogens (C ring).

Table 4
Cell effects.

Entry	Compounds		Cell lines IC_{50} (μM)						
			Huh7	Caco	MDA-MB 231	HCT 116	PC3	NCI	Fibroblasts
1		**32**	7	10	12	9	5	20	>25
2		**38**	15	12	15	8	6	25	>25
3		**39**	8	3	3	6	3	7	15
4		**40**	8	9	6	3	5	5	5
5		**41**	4	**3**	4	2.5	10	15	25
6		**11**	3	6	20	3	6	20	>25
7		**12**	**1.5**	10	12	6	7	25	25
8		**13**	3	3	5	**2**	4	7	3
9		**21**	5	7	10	3	5	4	20
10		**22**	7	15	6	13	8	9	25
11		**23**	7	13	9	12	10	20	25
12		**48**	3	4	6	**1.5**	5	10	2
13		**49**	5	3	12	8	15	20	12
14	Roscovitin		10	10	15	8	8	20	>25
15	DMSO		>25	>25	>25	>25	>25	>25	>25

7.1.3. General procedure C for deprotection of methoxy or benzyloxy ethers

A solution of BBr3 (1 M in CH2Cl2, for the number of equivalents, see below) was added dropwise to a solution of methoxylated or benzyloxy compound in CH2Cl2 at 0 °C. The stirring was continued for the indicated time at room temperature. The reaction mixture was then poured over ice and extracted with EtOAc. The organic layer was dried with MgSO4, and filtered off. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography.

7.1.4. General procedure D for deprotection of indolic N-phenylsulfonyl group

A 1 M solution of Bu4NF in THF (for the number of equivalents, see below) was dropwise added to a solution of protected indole compound in dry THF. The reaction was refluxed for the indicated time. After cooling, the mixture was concentrated under reduced pressure. After hydrolysis with water, the mixture was extracted with EtOAc, the organic layer washed with brine then dried with MgSO4, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography.

7.1.5. General procedure E for Buchwald–Hartwig cross coupling reaction

A solution of the halogenated derivative, the corresponding amine (1.5 eq.) and K2CO3 (2.0 eq.) in 1,4-dioxane was degassed under vigorous stirring by argon bubbling for 20 min. $Pd(OAc)_2$ (10% mol./halogenated derivative) and Xantphos (20% mol./halogenated derivative) were then added and the mixture was charged in a microwave vial equipped with a stirring bar. It was subjected to irradiation for 1 h at 140 °C. After cooling, water was added and the aqueous layers were extracted with EtOAc. The combined organic layers were successively washed with brine (10 mL), dried with MgSO4 and filtered off. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography.

7.1.6. N-Phenylsulfonyl-6-methoxy-1H-indole (2) [29]

To a solution of *N*-(2,2-diethoxyethyl)-*N*-(3-methoxyphenyl)-benzene-sulfonamide (188 mg, 0.49 mmol) in CH2Cl2 (7 mL), BF3.Et2O (93.5 μL, 0.74 mmol) was added dropwise at 0 °C under argon. After 15 min, an aqueous saturated solution of NaHCO3 (10 mL) was added and the crude product was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were successively washed with brine (5 mL), dried with $MgSO_4$ and filtered off. The solvents were removed under reduced pressure and the crude material was purified by recrystallization from dichloromethane/MeOH 90/10 to afford compound **2** as a colorless solid (686 mg, 97%). Rf: 0.6 (petroleum ether/EtOAc 60/40); mp 133 °C; ^{1}H NMR (CDCl3, 250 MHz) δ 3.87 (s, 3H, OCH3), 6.58 (d, 1H, J = 5.0 Hz, H3), 6.87 (dd, 1H, J = 8.8 Hz, J' = 2.5 Hz, H5), 7.38 (d, 1H, J = 8.8 Hz, H4), 7.42–7.47 (m, 3H, Harom), 7.51–7.54 (m, 2H, H2 + H7), 7.84–7.88 (m, 2H, Harom).

*7.1.7. 1-Benzenesulfonyl-6-methoxy-2-tributylstannyl-1H-indole (**3**)*

To a solution of 1-benzenesulfonyl-6-methoxy-1*H*-indole **2** (1.0 g, 3.48 mmol) in dry THF (20 mL) under argon at −20 °C was added dropwise a solution of LDA in hexane (2 M, 2.78 mL, 5.56 mmol). After 30 min stirring at −20 °C, the resulting red solution was cooled to −78 °C and treated with Bu3SnCl (1.60 mL, 5.91 mmol). The mixture was warmed to room temperature within 2 h under stirring and then hydrolyzed with water (50 mL). The mixture was extracted with EtOAc (3 × 50 mL), the combined organic layers were successively washed with a saturated solution of KF (50 mL), water (50 mL) then dried with $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude materiel was purified by flash chromatography (petroleum ether), compound **3** was obtained as colorless oil (1.50 mg, 75%). Rf: 0.62 (petroleum ether/EtOAc 80/20); IR (ATR Diamond, KBr, cm^{-1}) ν 2957, 2931, 2853, 1612, 1486, 1360, 1277, 1202, 1169, 1158, 1122, 824, 722; ^{1}H NMR (CDCl3, 250 MHz) δ 0.89 (t, 9H, J = 7.5 Hz, 3 × CH3), 1.13–1.19 (m, 6H, 3 × CH2), 1.26–1.41 (m, 6H, 3 × CH2), 1.49–1.63 (m, 6H, 3 × CH2), 3.79 (s, 3H, OCH3), 6.74 (s, 1H, H3), 6.82(dd, 1H, J = 8.8 Hz, J' = 2.5 Hz, H5), 7.34–7.41 (m, 4H, Harom + H4 + H7), 7.47–7.52 (m, 1H, Harom), 7.60–7.63 (m, 2H, Harom); ^{13}C NMR (CDCl3, 100.6 MHz) δ 11.7 (3 × CH2), 13.6 (3 × CH3), 27.3 (3 × CH2), 28.9 (3 × CH2), 55.6 (CH3), 98.1 (CH), 112.2 (CH), 120.5 (CH), 120.6 (CH), 125.9 (Cq), 126.2 (2 × CH), 129.0 (2 × CH), 133.2 (CH), 139.3 (Cq), 139.4 (Cq), 141.8 (Cq), 157.4 (Cq); MS (ion spray): m/z 577 $[M + H]^+$.

*7.1.8. 1-Benzenesulfonyl-2-(5-bromo-pyridin-3-yl)-6-methoxy-1H-indole (**4**)*

Compound **4** was obtained following the general procedure **A**. A solution of 1-benzenesulfonyl-6-methoxy-2-tributyl stannyl-1*H*-indole **3** (1.0 g, 1.53 mmol), 3,5-dibromopyridine (380 mg, 1.69 mmol) and CuI (29.13 mg, 0.153 mmol) in THF (25 mL) were used. The reaction mixture was irradiated in a μWave oven for 20 min at 100 °C. After flash chromatography (petroleum ether/EtOAc 80/20), compound **4** was obtained as a yellow solid (680 mg, 99%). Rf: 0.28 (petroleum ether/EtOAc 70/30); mp 155–159 °C; IR (ATR Diamond,KBr, cm^{-1}) ν 2956, 2923, 2866, 2854, 1606, 1488, 1439, 1371, 1272, 1170, 1105, 836, 726, 684; ^{1}H NMR (CDCl3, 250 MHz) δ 3.94 (s, 3H, OCH3), 6.58 (s, 1H, H3), 6.93 (dd, 1H, J = 2.3 Hz, J' = 8.8 Hz, H5), 7.28–7.39 (m, 5H, Harom), 7.45–7.51 (m, 1H, H4), 7.85 (d, 1H, J = 2.0 Hz, H7), 7.99 (s, 1H, H4′), 8.55 (br s, 1H, H2′), 8.70 (br s, 1H, H6′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.8 (CH3), 100.7 (2 × CH), 114.0 (CH), 115.5 (CH), 121.7 (CH), 123.8 (Cq), 126.5 (2 × CH), 128.9 (2 × CH), 133.9 (2 × CH), 137.1 (Cq), 139.7 (Cq), 140.0 (CH), 143.0 (Cq), 150.3 (Cq), 158.7 (2 × Cq); HRMS (EI-MS): calculated for C20H16 N2O3S79Br 312.1137 found 312.1148.

*7.1.9. 1-Benzensulfonyl-6-methoxy-2-[5-(4-methoxy-phenyl)-pyridin-3-yl]-1H-indole (**5**)*

Compound **5** was obtained following the general procedure **B**. Compound **4** (500 mg, 1.12 mmol) and 4-methoxyphenylboronic acid (221.25 mg, 1.45 mmol), in a mixture of toluene (51.5 mL), ethanol (26.5 mL) and aqueous saturated $NaHCO_3$ solution (17 mL) were used. The reaction was realized in a μWave oven for 15 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 60/40) afforded compound **5** as a yellow solid (411 mg, 78%). Rf: 0.13 (petroleum ether/EtOAc 60/40); Mp 156 °C; IR (ATR Diamond,KBr, cm^{-1}) ν 3856, 3653, 2963, 2370, 1608, 1512, 1432, 1372, 1245, 1181, 1027, 834, 751, 726, 689; ^{1}H NMR (CDCl3, 250 MHz) δ 3.88 (s, 3H, OCH3), 3.95 (s, 3H, OCH3), 6.60 (s, 1H, H3); 7.68 (dd, 1H, J = 8.8 Hz, J' = 2.3 Hz, H5), 7.04 (d, 2H, J = 10.0 Hz, 2 × H3″), 7.25–7.39 (m, 5H, Harom), 7.47 (d, 1H, J = 7.5 Hz, H4), 7.61 (d, 2H, J = 10.0 Hz, 2 × H2″), 7.90 (d, 1H, J = 2.0 Hz, H7), 8.05 (s, 1H, H4′), 8.49 (s, 1H, H2′), 8.83 (s, 1H, H6′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 55.8 (CH3), 100.8 (CH), 112.5 (Cq), 113.8(CH), 114.7 (3 × CH), 121.5 (2 × CH), 124.0 (2 × Cq), 126.5 (2 × CH), 128.4 (3 × CH), 128.8 (2 × CH), 129.7 (Cq), 133.8 (2 × CH), 137.3 (Cq), 139.8 (Cq), 158.4 (Cq), 159.9 (2 × Cq); HRMS (EI-MS): m/z calculated for C27H22 N2O4S 471.1379 found 471.1368.

*7.1.10. 4-[5-(1-Benzenesulfonyl-6-methoxy-1H-indol-2-yl)-pyridin-3-yl]-benzonitrile (**6**)*

Compound **6** was obtained following the general procedure **B**. Compound **4** (400 mg, 0.9 mmol) and 4-cyanophenylboronic acid (171.9 mg, 1.17 mmol) in a mixture of toluene (42 mL), ethanol (21.3 mL) and aqueous saturated NaHCO3 solution (13.6 mL) were

used. The reaction mixture was realized in a μWave oven 15 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 70/30) afforded compound **6** as a yellow solid (298 mg, 70%). Rf: 0.57 (petroleum ether/EtOAc 60/40); mp 106 °C; IR (IR (ATR Diamond, cm^{-1}) ν 2226, 1610, 1117; ^{1}H NMR (CDCl3, 250 MHz) δ 3.96 (s, 3H, OCH3), 6.64 (s, 1H, H3), 6.95 (dd, 1H, J = 8.5 Hz, J' = 2.3 Hz, H5), 7.30–7.38 (m, 5H, Harom), 7.49 (d, 1H, J = 7.0 Hz, H4), 7.80 (br s, 4H, 2 × H3″ + 2 × H2″), 7.89 (d, 1H, J = 2.0 Hz, H7), 8.16 (t, 1H, J = 2.0 Hz, H4′), 8.62 (s, 1H, H2′), 8.87 (s, 1H, H6′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.8 (CH3), 100.9 (CH), 112.1 (Cq), 113.9 (CH), 115.2 (CH), 118.5 (Cq), 121.6 (CH), 123.9 (Cq), 126.4 (2 × CH), 127.9 (2 × CH), 128.8 (2 × CH),132.8 (2 × CH), 133.9 (2 × CH), 136.1 (Cq), 137.0 (Cq), 137.1 (Cq), 139.8 (Cq), 141.9 (Cq), 147.6 (CH), 148.6 (CH), 158.6 (2 × Cq); HRMS (EI-MS): m/z calculated for C27H20 N3O3S 466.1225 found 466.1224.

7.1.11. 1-Benzenesulfonyl-2-[5-(4-methanesulfonyl-phenyl)-pyridin-3-yl]-6-methoxy-1H-indole (**7**)

Compound **7** was obtained following the general procedure **B.** Compound **4** (400 mg, 0.9 mmol) and 4-methanesulfonyl-phenylboronic acid (216 mg, 1.08 mmol) in a mixture of toluene (42 mL), ethanol (21.3 mL) and aqueous saturated $NaHCO_3$ solution (13.6 mL) were used. The reaction mixture was realized in a μWave oven for 15 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 40/60) afforded compound **7** as a yellow solid (333 mg, 72%). Rf: 0.25 (petroleum ether/EtOAc 40/60); mp 150 °C; IR (IR (ATR Diamond, cm^{-1}) ν 2369, 1366, 1301, 1186, 1149, 1117, 840, 732, 688; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.30 (s, 3H, SO2CH3), 3.88 (s, 3H, OCH3), 6.97 (dd, 1H, J = 8.5 Hz, J' = 2.3 Hz, H5), 7.06 (s, 1H, H3), 7.47 (m, 7H, Harom), 8.08 (d, 2H, J = 8.8 Hz, 2 × H3″), 8.13 (d, 2H, J = 9.0 Hz, 2 × H2″), 8.32 (s, 1H, H4′), 8.78 (d, 1H, J = 1.8 Hz, H2′), 9.03 (d, 1H, J = 2 Hz, H6′); ^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 43.4 (CH3), 55.5 (CH3), 100.3 (CH), 113.5 (CH), 115.7 (CH), 126.2 (CH), 127.7 (CH), 127.9 (CH), 128.4 (Cq), 128.6 (2 × CH), 129.5 (CH), 131.4 (2 × CH), 131.9 (CH), 132.1 (Cq), 132.8 (Cq), 133.1 (Cq), 134.5 (Cq), 135.5 (Cq), 136.3(CH), 138.9 (CH), 140.4 (Cq), 141.6 (Cq), 147.4 (CH), 149.2 (CH), 157.9 (Cq). HRMS (EI-MS): m/z calculated for C27H23 N2O5S2 519.1048 found 519.1056.

7.1.12. 6-Methoxy-2-[5-(4-methoxy-phenyl)-pyridin-3-yl]-1H-indole (**8**)

Compound **8** was obtained following the general procedure **D**. Compound **5** (350 mg, 0.743 mmol) in THF (10 mL) and Bu4NF (1.5 eq, 1.11 mL, 1.0 M in THF, 1.11 mmol) were used. The reaction was refluxed for 6 h. Flash chromatography (petroleum ether/EtOAc 60/40) afforded compound **8** as a white solid (238 mg, 97%). Rf: 0.12 (petroleum ether/EtOAc 50/50); mp 218 °C; IR (ATR Diamond, cm^{-1}) ν 2924, 1624, 1503, 1456, 1290, 1247, 1164, 1111, 1023, 834; ^{1}H NMR (CDCl3, 250 MHz) δ 3.88 (s, 6H, 2 × OCH3), 6.82 (dd, 1H, J = 8.3 Hz, J' = 2.3 Hz, H5), 6.88 (s, 1H, H3), 6.92 (s, 1H, H7), 7.03 (d, 2H, J = 10.0 Hz, 2 × H3″), 7.52 (d, 1H, J = 7.5 Hz, H4), 7.52 (d, 2H, J = 10.0 Hz, 2 × H2″), 8.01 (t, 1H, J = 2.0 Hz, H4′), 8.42 (br s, 1H, NH), 8.70 (d, 1H, J = 2.0 Hz, H2′), 8.83 (d, 1H, J = 2.0 Hz, H6′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 55.6 (CH3), 94.5 (CH), 101.4 (CH), 110.7(CH), 114.6 (2 × CH), 121.5 (2 × Cq), 128.3 (3 × CH), 128.4 (Cq), 129.7 (Cq), 129.7 (CH), 133.4 (Cq), 134.1 (Cq), 136.5 (2 × Cq), 144.0 (CH), 146.3 (CH); HRMS (EI-MS): m/z calculated for C21H19 N2O2 331.1447 found 331.1451.

7.1.13. 4-[5-(6-Methoxy-1H-indol-2-yl)-pyridin-3-yl]-benzonitrile (**9**)

Compound **9** was obtained following the general procedure **D**. A solution of compound **6** (200 mg, 0.43 mmol) in THF (5 mL) and Bu4NF (1.5 eq, 0.65 mL, 1 M in THF, 0.65 mmol) were used. The reaction was refluxed for 6 h. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **9** as a yellow solid (120 mg, 86%). Rf: 0.30 (petroleum ether/EtOAc 50/50); mp 210 °C; IR (ATR Diamond, cm^{-1}) ν 3706, 2222, 1597, 1646, 1291, 1260, 1200, 1159, 1036, 829; ^{1}H NMR (CDCl3, 250 MHz) δ 3.87 (s, 3H, OCH3), 6.84 (dd, 1H, J = 8.5 Hz, J' = 1.8 Hz, H5), 6.91 (s, 2H, H3 + H7), 7.53 (d, 1H, J = 8.8 Hz, H4), 7.73 (d, 2H, J = 8.5 Hz, 2 × H3″), 7.79 (d, 2H, J = 8.0 Hz, 2 × H2″), 7.89 (d, 1H, J = 1.7 Hz, H4′), 8.58 (s, 1H, NH), 8.71 (s, 1H, H2′), 8.94 (s, 1H, H6′);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.6 (CH3), 99.4 (CH), 101.9 (CH), 110.9 (CH), 112.1(Cq), 118.5 (Cq), 121.7 (CH), 123.2 (Cq), 127.9 (2 × CH), 128.9 (Cq), 130.1 (CH), 132.5(Cq), 132.9 (2 × CH), 135.0 (Cq), 138.3 (Cq), 142.1 (Cq), 145.7 (CH), 146.2 (CH), 157.4 (Cq); HRMS (EI-MS): m/z calculated for C21H16 N3O 326.1293 found 326.1292.

7.1.14. 2-[5-(4-Methanesulfonyl-phenyl)-pyridin-3-yl]-6-methoxy-1H-indole (**10**)

Compound **10** was obtained following the general procedure **B**. Compound **7** (250 mg, 0.48 mmol) in THF (5 mL) and Bu4NF (1.5 eq, 0.75 mL, 1 M in THF, 0.75 mmol) were used. The reaction was refluxed for 15 h. Flash chromatography (dichloromethane/MeOH 98/02) afforded compound **10** as a yellow solid (190 mg, 99%). Rf: 0.32 (dichloromethane/MeOH 90/10); mp 86 °C; IR (ATR Diamond,cm^{-1}) ν 3730, 2226, 1597, 1292, 1260, 1200, 1154, 1116, 827, 724;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.30 (s, 3H, SO2CH3), 3.80 (s, 3H, OCH3), 6.71 (dd, 1H, J = 8.5 Hz, J' = 2.2 Hz, H5), 6.91 (s, 1H, H3), 7.12 (s,1H, H7), 7.47 (d, 1H, J = 8.8 Hz, H4), 8.09 (d, 2H, J = 8.7 Hz, 2 × H3″), 8.14 (d, 2H, J = 8.2 Hz, 2 × H2″), 8.53 (s, 1H, H4′), 8.85 (d, 1H, J = 1.0 Hz, H2′), 9.11 (d, 1H, J = 1.0 Hz, H6′), 11.6 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 43.4 (CH3), 55.1 (CH3), 100.5 (CH), 110.0 (Cq), 121.1(CH), 122.6 (Cq), 127.6 (CH), 127.8 (CH), 128.6 (2 × CH), 131.3 (2 × CH), 131.9 (CH), 133.1(Cq), 133.9 (Cq), 138.2 (Cq), 140.3 (Cq), 141.0 (Cq), 141.8 (CH), 145.7 (CH), 156.3 (Cq); HRMS (EI-MS): m/z calculated for C21H19 N2O3S 379.1116 found 379.1134.

7.1.15. 2-[5-(4-Hydroxy-phenyl)-pyridin-3-yl]-1H-indol-6-ol (**11**)

Compound **11** was obtained following the general procedure **C**. A solution of compound **8** (200 mg, 0.6 mmol) in CH2Cl2 (15 mL) and BBr3 (3.0 eq., 1.8 mL, 1.8 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 6 h. After flash chromatography (CH_2Cl_2), compound **11** was obtained as a brown solid (115 mg, 72%). Rf: 0.12 (petroleum ether/EtOAc 40/60); mp >250 °C; IR (ATR Diamond, cm^{-1}) ν 3329, 1702, 1592, 1514, 1439, 1246, 1175, 1117, 1043, 813, 691; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 6.56 (d, J = 7.5 Hz, 1H, H4), 6.79 (s, 1H, H3), 6.92 (d, 2H, J = 7.5 Hz, 2 × H3″), 6.99 (s, 1H, H7), 7.34 (d, 1H, J = 10.0 Hz, H5), 7.66 (d, 2H, J = 7.5 Hz, 2 × H2″), 8.32 (s, 1H, H4′), 8.66 (s, 1H, H2′), 8.92 (s, 1H, H6′), 9.10 (s, 1H, OH), 9.72 (s,1H, OH), 11.33 (s, 1H, NH); ^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 96.2 (CH), 100.0 (CH), 110.4 (CH), 115.9 (2 × CH),120.8 (CH), 121.8 (Cq), 127.5 (Cq), 128.1 (CH), 128.1 (2 × CH), 128.3 (Cq), 132.5 (Cq),135.4 (Cq), 138.5 (Cq), 144.1 (CH), 145.1 (CH), 153.8 (Cq), 157.8 (Cq); HRMS (EI-MS): m/z calculated for C19H15 N2O2 303.1134 found 303.1138.

7.1.16. 4-[5-(6-Hydroxy-1H-indol-2-yl)-pyridin-3-yl]-benzonitrile (**12**)

Compound **12** was obtained following the general procedure **C**. A solution of compound **9** (80 mg, 0.246 mmol) in CH2Cl2 (10 mL) and BBr3 (1.5 eq., 0.51 mL, 0.37 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 12 h. After flash chromatography (CH2Cl2/MeOH 95/05), compound **12** was obtained as a yellow solid (45 mg, 58%). Rf: 0.4 (CH2Cl2/MeOH 90/10); mp 220 °C; IR (ATR Diamond, cm^{-1}) ν 3433, 3335, 2234, 1627, 1594, 1443, 1244, 1219, 1142, 821;^{1}H NMR (CDCl3, 250 MHz) δ 6.57 (d, 1H, J = 8.3 Hz, H5), 6.80 (s, 1H, H3), 7.06 (s, 1H, H7), 7.36 (d, 1H, J = 8.5 Hz, H4), 8.03 (d, 2H, J = 7.5 Hz, 2 × H3″), 8.08 (d, 2H,

J = 7.5 Hz, 2 × H2″), 8.50 (s, 1H, H4′), 8.82 (s, 1H, OH), 9.11 (s, 1H, H2′), 9.10 (s, 1H, H6′), 11.37 (s, 1H, NH);^{13}C NMR (CDCl3, 100.6 MHz) δ 96.1 (CH), 99.5 (CH), 110.5 (Cq), 110.8 (Cq), 118.7 (Cq), 120.9 (CH), 121.8 (CH), 127.8 (2 × CH), 128.6 (Cq), 129.2 (CH), 132.0 (Cq), 132.9 (2 × CH), 133.7 (Cq), 138.6 (CH), 141.5 (CH), 145.3 (Cq), 145.6 (CH), 154.0 (Cq); HRMS (EI-MS): m/z calculated for C20H14 N3O 312.1137 found 312.1135.

7.1.17. 2-[5-(4-Methanesulfonyl-phenyl)-pyridin-3-yl]-1H-indol-6-ol (**13**)

Compound **13** was obtained following the general procedure **C**. A solution of compound **10** (70 mg, 0.185) in CH2Cl2 (10 mL) and BBr3 (2.0 eq., 0.37 mL, 0.37 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 3 h. After flash chromatography (dichloromethane/MeOH 90/10), compound **13** was obtained as a yellow solid (35 mg, 53%). Rf: 0.2 (dichloromethane/MeOH 90/10), mp 250 °C; IR (ATR Diamond, cm^{-1}) ν 3698, 3356, 2919, 1627, 1599, 1439, 1294, 1222, 1144, 954, 830, 789, 775;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.30 (s, 3H, SO2CH3), 6.57 (dd, 1H, J = 8.5 Hz, J' = 2.3 Hz, H5), 6.80 (s, 1H, H3), 7.07 (s, 1H, H7), 7.36 (d, 1H, J = 8.3 Hz, H4), 8.11 (dd, 4H, J = 12.8 Hz, J' = 8.8 Hz, 2 × H3″ + 2 × H2″), 8.53 (dd, 1H, J = J' = 2.3 Hz, H4′), 8.83 (d, 1H, J = 2.0 Hz, H2′), 9.09 (d, 1H, J = 2.0 Hz, H6′), 9.14 (s, 1H, OH), 11.40 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 43.4 (CH3), 96.8 (CH), 99.4 (CH), 120.8 (Cq), 124.1 (Cq), 126.9 (2 × CH), 127.6 (2 × CH), 127.8 (2 × CH), 131.9 (CH), 133.1 (Cq), 133.9 (Cq), 138.2 (Cq), 140.1 (Cq), 140.3 (Cq), 140.5 (CH), 141.9 (CH), 154.0 (Cq); HRMS (EI-MS): m/z calculated for C20H17 N2O3S 365.0960 found 365.0977.

7.1.18. 1-Benzensulfonyl-2-(6-chloro-pyrazin-2-yl)-6-methoxy-1H-indole (**14**)

Compound **6** was obtained following the general procedure **A**. A solution of compound **3** (300 mg, 0.53 mmol), 2,6-dicholoropyrazine (83 mg, 0.55 mmol) and CuI (10 mg, 0.053 mmol) in THF (10 mL) were used. The reaction was carried out under μWave irradiation for 20 min at 100 °C. After flash chromatography (petroleum ether/EtOAc 90/10), compound **14** was obtained as yellow oil (211 mg, 98%). Rf: 0.25 (petroleum ether/EtOAc 90/10); IR (ATR Diamond, cm^{-1}) ν 1616, 1509, 1407, 1366, 1279, 1190, 1166, 1089, 1008, 726; ^{1}H NMR (CDCl3, 250 MHz) δ 3.92 (s, 3H, OCH3), 6.91 (dd, 1H, J = 8.8 Hz, J' = 2.2 Hz, H5), 6.96 (s, 1H, H3), 7.36 (m, 3H, Harom), 7.48 (d, 1H, J = 7.7 Hz, H4), 7.66 (d, 2H, J = 7.5 Hz, Harom), 7.73 (d, 1H, J = 1.7 Hz, H7), 8.58 (s, 1H, H3′), 8.87 (s, 1H, H5′);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.9 (CH3), 100.4 (CH), 114.1 (CH), 114.6 (CH), 118.1(CH), 122.4 (CH), 123.8 (Cq), 127.0 (CH), 128.3 (CH), 128.9 (CH), 134.0 (CH), 134.9 (Cq), 136.7 (Cq), 140.1 (Cq), 142.6 (CH), 143.8 (CH), 146.9 (Cq), 147.8 (Cq), 159.2 (Cq); HRMS (EI-MS): m/z calculated for C19H15 N3O3SCl 400.0523 found 400.0520.

7.1.19. 1-Benzenesulfonyl-6-methoxy-2-[6-(4-methoxyphenyl)-pyrazin-2-yl]-1H-indole (**15**)

Compound **15** was obtained following the general procedure **B**. A solution of compound **14** (500 mg, 1.25 mmol) and 4-methoxyphenylboronic acid (285 mg, 1.87 mmol) in a mixture of toluene (7 mL), ethanol (5 mL) and aqueous saturated NaHCO3 solution (4 mL) was added. The reaction was carried out under μWave irradiation for 15 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 60/40) yielded compound **15** as an orange solid (424 mg, 72%). Rf: 0.25 (petroleum ether/EtOAc 60/40); mp 138 °C; IR (ATR Diamond, cm^{-1}) ν 2361, 1607, 1513, 1361, 1280, 1249, 1169, 1029, 830, 808, 725; ^{1}H NMR (CDCl3, 250 MHz) δ 3.89 (s, 3H, OCH3), 3.92 (s, 3H, OCH3), 6.90 (s, 1H, H3), 6.93 (d, 1H, J = 8.8 Hz, H4), 7.03 (d, 2H, J = 9.0 Hz, 2 × H3″), 7.32–7.38 (m, 3H, Harom), 7.47 (d, 1H, J = 4.7 Hz, H5), 7.67 (d, 2H, J = 7.2 Hz, Harom), 7.76 (s, 1H, H7), 7.98 (d, 2H, J = 9.0 Hz, 2 × H2″), 8.75 (s, 1H, H3′), 8.95 (s, 1H, H5′);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 55.8 (CH3), 100.4 (CH), 112.9 (Cq), 113.8 (CH), 114.4 (2 × CH), 116.2 (CH), 116.9 (Cq), 122.1 (CH), 123.9 (Cq), 127.0 (2 × CH), 128.4 (Cq), 128.5 (2 × CH), 128.8 (2 × CH), 129.5 (Cq), 133.6 (CH), 136.8 (Cq), 137.4 (Cq), 139.6 (Cq), 139.8 (CH), 143.2 (CH), 158.8 (Cq); HRMS (EI-MS): m/z calculated for C26H22 N3O4S 472.1331 found 472.1348.

7.1.20. 4-[6-(1-Benzenesulfonyl-6-methoxy-1H-indol-2-yl)-pyrazin-2-yl]-benzonitrile (**16**)

Compound **16** was obtained following the general procedure **B**. A solution of 1-benzensulfonyl-2-(6-chloro-pyrazin-2-yl)-6-methoxy-1*H*-indole **14** (500 mg, 1.25 mmol) and 4-cyanophenylboronic acid (239 mg, 1.62 mmol) in a mixture of toluene (7 mL), ethanol (5 mL) and aqueous saturated $NaHCO_3$ solution (4 mL) was added. The reaction was carried out under μWave irradiation for 15 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 70/30) yielded compound **16** as an orange solid (424 mg, 73%). Rf: 0.2 (petroleum ether/EtOAc70/30); mp 142 °C; IR (ATR Diamond, cm^{-1}) ν 2930, 2226, 1610, 1518, 1368, 1253, 1117, 1145, 1111, 848, 758, 726; ^{1}H NMR (CDCl3, 250 MHz) δ 3.91 (s, 3H, OCH3), 6.93 (dd, 1H, J = 7.5 Hz, J' = 2.5 Hz, H5), 6.97 (s, 1H, H3), 7.27–7.48 (m, 3H, Harom), 7.46 (d, 1H, J = 7.5 Hz, H4), 7.58 (d, 2H, J = 7.5 Hz, Harom), 7.72 (s, 1H, H7), 7.78 (d, 2H, J = 7.5 Hz, 2 × H3″), 8.13 (d, 2H, J = 7.5 Hz, 2 × H2″), 8.90 (s, 1H, H3′), 9.00 (s, 1H, H5′);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.8 (CH3), 100,4 (CH), 114,1 (CH), 116.0 (Cq), 117.2 (CH), 122.2 (CH), 116.2 (CH), 116.9 (Cq), 122.1 (CH), 123.8 (Cq), 126.7 (2 × CH), 127.5 (2 × Cq), 127.6 (2 × CH), 128.8 (2 × CH), 132.7 (2 × CH), 133.8 (CH), 136.2 (Cq), 137.2 (Cq), 139.9 (Cq), 140.3 (Cq), 145.2 (Cq); HRMS (EI-MS): m/z calculated for C26H19 N4O3S 467.1178 found 467.1186.

7.1.21. 1-Benzenesulfonyl-2-[6-(4-methanesulfonyl-phenyl)-pyrazin-2-yl]-6-methoxy-1H-indole (**17**)

Compound **17** was obtained following the general procedure **B.** A solution of compound **14** (450 mg, 1.12 mmol) and 4-methanesulfonylphenylboronic acid (270 mg, 1.35 mmol) in a mixture of toluene (7 mL), ethanol (5 mL) and aqueous saturated NaHCO3 solution (4 mL) was added. The reaction was carried out under μWave irradiation for 15 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **17** as an orange solid (264 mg, 65%). Rf: 0.25 (petroleum ether/EtOAc 50/50), mp 163 °C; IR (ATR Diamond, cm^{-1}) ν 2924, 1623, 1368, 1308, 1172, 1150, 1091, 839, 776, 763, 726;^{1}H NMR (CDCl3, 250 MHz) δ 3.31 (s, 3H, SO2CH3), 3.88 (s, 3H, OCH3), 6.99 (dd, 1H, J = 8.5 Hz, J' = 2.0 Hz, H5), 7.26 (s, 1H, H3), 7.51–7.57 (m, 4H, Harom), 7.65–7.69 (m, 3H, H4 + H7 + Harom), 8.11 (d, 2H, J = 8.5 Hz, 2 × H3″), 8.39(d, 2H, J = 8.5 Hz, 2 × H2″), 9.02 (s, 1H, H3′), 9.39 (s, 1H, H5′);^{13}C NMR (CDCl3, 100.6 MHz) δ 43.38 (CH3), 55.6 (CH3), 99.7 (CH), 113.6 (CH), 116.8 (CH), 122.7 (CH), 123.3 (Cq), 126.4 (2 × CH), 127.6 (2 × CH), 127.8 (2 × CH), 129.5 (2 × CH),134.5 (CH), 135.7 (Cq), 136.1 (Cq), 138.8 (Cq), 140.3 (CH), 141.2 (Cq), 1341.7 (Cq), 144.6 (CH), 146.3 (Cq), 148.4 (Cq), 158.3 (Cq); HRMS (EI-MS): m/z calculated for C26H22 N3O5S2 520.1001 found 520.1002.

7.1.22. 6-Methoxy-2-[6-(4-methoxy-phenyl)-pyrazin-2-yl]-1H-indole (**18**)

Compound **18** was obtained following the general procedure **D**. A solution of compound **15** (300 mg, 0.636 mmol) in THF (7 mL) and Bu4NF (1.5 eq., 0.95 mL, 1 M in THF, 0.95 mmol) were used. The reaction was refluxed for 15 h. Flash chromatography (CH2Cl2/MeOH 90/10) afforded compound **18** as a yellow solid (187 mg, 88%). Rf: 0.25 (petroleum ether/EtOAc 60/40); mp 140 °C; IR (ATR Diamond, cm^{-1}) ν 3245; 2332; 1606; 1542; 1510; 1438; 1306; 1251; 1170; 1023; 833. ^{1}H NMR (CDCl3, 250 MHz) δ 3.89 (s, 3H, OCH3), 3.91 (s, 3H, OCH3), 6.83 (dd, 1H, J = 8.8 Hz, J' = 2.3 Hz, H5), 6.95 (s,

1H, H3), 7.06 (d, 2H, $J = 8.8$ Hz, 2 × H3″), 7.05 (s,1H, H7), 7.56 (d, 1H, $J = 8.8$ Hz, H4), 8.85 (d, 2H, $J = 8.8$ Hz, 2 × H2″), 8.75 (s, 1H, H3′), 8.89 (s, 1H, H5′), 9.36 (s, 1H, NH). ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 55.6 (CH3), 94.2 (CH), 102.2 (CH), 111.2(CH), 114.4 (2 × CH), 122.3 (CH), 123.4 (Cq), 128.3 (2 × CH), 128.9 (Cq), 132.9 (Cq), 137.7 (Cq), 138.2 (CH), 138.7 (CH), 145.2 (Cq), 150.9 (Cq), 157.8 (Cq), 161.2 (Cq). HRMS (EI-MS): *m*/*z* calculated for C20H18 N3O2 332.1399 found 332.1404.

7.1.23. 4-[6-(6-Methoxy-1H-indol-2-yl)-pyrazin-2-yl]-benzonitrile (**19**)

Compound **19** was obtained following the general procedure **D**. A solution of compound **16** (400 mg, 0.85 mmol) in THF (7 mL) and Bu4NF (1.5 eq., 1.27 mL, 1 M in THF, 1.27 mmol) were used. The reaction was refluxed for 15 h. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **19** as a yellow solid (244 mg, 88%). Rf: 0.18 (petroleum ether/EtOAc 60/40); mp 200 °C; IR (ATR Diamond, cm^{-1}) ν 3408, 2924, 2230, 1628, 1524, 1511, 1448, 1254, 1192, 1163, 1112, 1013, 819; ^{1}H NMR (CDCl3, 250 MHz) δ 3.89 (s, 3H, OCH3), 6.84 (dd, 1H, $J = 8.8$ Hz, $J' = 2.0$ Hz, H5), 6.95 (s, 1H, H3), 7.17 (d, 1H, $J = 1.2$ Hz, H7), 7.57 (d, 1H, $J = 8.8$ Hz, H4), 7.85 (d, 2H, $J = 8.5$ Hz, 2 × H3″), 8.22 (d, 2H, $J = 8.5$ Hz, 2 × H2″), 8.82 (s, 1H, H3′), 9.03 (s, 1H, H5′), 9.30 (s, 1H, NH); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.8 (CH3), 94.1 (CH), 103.3 (CH), 111.6 (CH), 118.9 (Cq), 120.5 (Cq), 122.5 (CH), 127.5 (2 × CH), 132.7 (2 × CH), 138.0 (Cq), 138.5 (Cq), 138.8(Cq), 139.3 (CH), 140.6 (Cq), 140.9 (CH), 142.8 (Cq), 150.2 (Cq), 154.4 (Cq); HRMS (EI-MS): *m*/*z* calculated for C20H15 N4O 327.1246 found 327.1239.

7.1.24. 2-[6-(4-Methanesulfonyl-phenyl)-pyrazin-2-yl]-6-methoxy-1H-indole (**20**)

Compound **20** was obtained following the general procedure **D**. A solution of compound **17** (460 mg, 0.88 mmol) in THF (15 mL) and Bu4NF (1.5 eq., 1.32 mL, 1 M in THF, 1.32 mmol) were used. The reaction was refluxed for 15 h. Flash chromatography (CH2Cl2/MeOH 90/10) afforded compound **20** as a yellow solid (330 mg, 99%), Rf: 0.2 (petroleum ether/EtOAc 50/50); mp 246 °C; IR (ATR Diamond, cm^{-1}) ν 3587, 3005, 1586, 1512, 1305, 1249, 1173, 1148, 839, 826, 813, 711; ^{1}H NMR (CDCl3, 250 MHz) δ 3.28 (s, 3H, SO2CH3), 3.82 (s, 3H, OCH3), 6.74 (dd, 1H, $J = 8.8$ Hz, $J' = 2.3$ Hz, H5), 7.02 (s, 1H, H3), 7.37 (s, 1H, H7), 7.52 (d, 1H, $J = 10$ Hz, H4), 8.12 (d, 2H, $J = 8.5$ Hz, 2 × H3″), 8.67 (d, 2H, $J = 8.5$ Hz, 2 × H2″), 9.18 (s, 1H, H3′), 9.25 (s, 1H, H5′), 11.69 (s, 1H, NH); ^{13}C NMR (CDCl3, 100.6 MHz) δ 43.4 (CH3), 55.1 (CH3), 94.4 (CH), 103.1 (CH), 110.8 (Cq), 121.9 (CH), 122.6 (Cq), 127.4 (2 × CH), 127.8 (2 × CH), 132.8 (Cq), 138.7 (Cq), 138.9(CH), 140.5 (Cq), 141.0 (CH), 141.7 (Cq), 145.7 (Cq), 148.2 (Cq), 157.0 (Cq).

7.1.25. 2-[6-(4-Hydroxy-phenyl)-pyrazin-2-yl]-1H-indol-6-ol (**21**)

Compound **21** was obtained following the general procedure **C**. A solution of compound **18** (150 mg, 0.452 mmol) in CH2Cl2 (7 mL) and BBr3 (3.0 eq, 1.35 mL, 1.35 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 10 h. Flash chromatography (CH2Cl2) afforded compound **21** as a brown solid (101 mg, 73%). Rf: 0.4 (CH2Cl2/MeOH 96/04); mp >250 °C; IR (ATR Diamond, cm^{-1}) ν 3637, 3576, 3394, 2956, 1593, 1511, 1417, 1400, 1266, 1204, 1175, 1116, 807; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 6.59 (dd, 1H, $J = 8.5$ Hz, $J' = 2.2$ Hz, H5), 6.89–6.95 (m, 3H, H3, 2 × H3″), 7.22 (s,1H, H7), 7.39 (d, 1H, $J = 8.5$ Hz, H4), 8.25 (d, 2H, $J = 8.8$ Hz, 2 × H2″), 8.91 (s, 1H, H3′), 8.99 (s, 1H, H5′), 9.22 (s, 1H, OH), 9.91 (s, 1H, OH), 11.35 (s, 1H, NH); ^{13}C NMR (CDCl3, 100.6 MHz) δ 96.5 (CH), 99.8 (CH), 110.9 (CH) 115.5 (2 × CH), 121.4 (Cq), 126.9 (CH), 127.2 (Cq), 128.4 (2 × CH), 137.4 (Cq), 138.2 (Cq), 138.8 (Cq), 145.2 (Cq), 154.4 (2 × CH), 154.5 (Cq), 159.3 (Cq). HRMS (EI-MS): *m*/*z* calculated for C18H14 N3O2 304.1086 found 304.1082.

7.1.26. 4-[5-(6-Hydroxy-1H-indol-2-yl)-pyrazin-2-yl]-benzonitrile (**22**)

Compound **22** was obtained following the general procedure **B** C. A solution of compound **19** (200 mg, 0.612 mmol) in CH2Cl2 (10 mL) and BBr3 (5.0 eq., 3.06 mL, 3.06 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 5 h. After flash chromatography (petroleum ether/EtOAc 50/50), compound **22** was obtained as a green solid (120 mg, 63%). Rf: 0.2 (petroleum ether/EtOAc 50/50); mp 241 °C; IR (ATR Diamond, cm^{-1}) ν 3718, 3368, 2230, 1626, 1543, 1517, 1442, 1246, 1217, 1186, 1146, 1112, 817, 739, 693, 678; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 6.61 (dd, 1H, $J = 7.2$ Hz, $J' = 1.7$ Hz, H5), 6.91 (s, 1H, H3), 7.31 (s,1H, H7), 7.40 (d, 1H, $J = 4.2$ Hz, H4), 8.06 (d, 2H, $J = 7.0$ Hz, 2 × H3″), 8.62 (d, 2H, $J = 7.0$ Hz, 2 × H2″), 9.91 (s, 1H, H3′), 9.20 (s, 1H, H5′), 9.23 (s, 1H, OH), 11.51 (s, 1H, NH); ^{13}C NMR (DMSO-d6, 100.6 MHz) δ 96.5 (CH), 103.2 (CH), 111.2 (CH) 112.2 (Cq), 118.7 (Cq), 121.7 (CH), 121.8 (Cq), 127.5 (2 × CH), 132.1 (Cq), 132.7 (2 × CH), 138.6 (CH), 139.1 (Cq), 140.1 (Cq), 140.9 (CH), 145.8 (Cq), 147.8 (Cq), 154.9 (Cq). HRMS (EI-MS): *m*/*z* calculated for C19H13 N4O 313.1089 found 313.1102.

7.1.27. 2-[6-(4-Methanesulfonyl-phenyl)-pyrazin-2-yl]-1H-indol-6-ol (**23**)

Compound **23** was obtained following the general procedure **C**. A solution of compound **20** (150 mg, 0.41 mmol) in CH2Cl2 (10 mL) and BBr3 (5.0 eq., 2.05 mL, 2.05 mmol 1 M in CH2Cl2) were used. The reaction mixture was stirred for 5 h. After flash chromatography (CH2Cl2/MeOH 90/10), compound **23** was obtained as a red solid (62 mg, 42%). Rf: 0.12 (CH2Cl2/MeOH 90/10); mp >250 °C; IR (ATR Diamond, cm^{-1}) ν 3947, 3743, 3559, 2911, 1146, 1062, 829, 700; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.29 (s, 3H, SO2CH3), 6.61 (dd, 1H, $J = 5.5$ Hz, $J' = 1.3$ Hz, H5), 6.91 (s, 1H, H3), 7.32 (s, 1H, H7), 7.42 (d, 1H, $J = 5.2$ Hz, H4), 8.11 (d, 2H, $J = 5.2$ Hz, 2 × H3″), 8.66 (d, 2H, $J = 5.2$ Hz, 2 × H2″), 9.15 (s, 1H, H3′), 9.21 (s, 1H, H5′), 9.23 (s, 1H, OH), 11.50 (s, 1H, NH); ^{13}C NMR (CDCl3, 100.6 MHz) δ 43.4 (CH3), 96.5 (CH), 103.3 (CH), 111.2 (CH) 121.7 (CH), 121.8 (Cq), 127.4 (2 × CH), 127.7 (2 × CH), 132.1 (Cq), 138.6 (CH), 139.1 (Cq), 140.5 (Cq), 140.8 (CH), 141.6 (Cq), 145.8 (Cq), 148.1 (Cq), 154.9 (Cq); HRMS (EI-MS): *m*/*z* calculated for C19H16 N3O3S 366.0912 found 366.0926.

7.1.28. 1-Benzenesulfonyl-5-benzyloxy-2-(5-chloro-pyrazin-3-yl)-1H-indole (**26**)

Compound **26** was obtained following the general procedure **A**. A solution of compound **24** (500 g, 0.76 mmol), 2,6-dichloropyrazine (125.5 mg, 0.84 mmol) and CuI (14.6 mg, 0.076 mmol) in THF (15 mL) were used. The reaction was realized under μWave irradiation for 20 min at 100 °C. After flash chromatography (petroleum ether/EtOAc 80/20), compound **26** was obtained as yellow oil (3.02 g, 83%). Rf: 0.25 (petroleum ether/EtOAc 80/20); IR (ATR Diamond, cm^{-1}) ν 3616, 2923, 2348, 1578, 1513, 1449, 1372, 1221, 1177, 1153, 1089, 1007, 881, 754, 726, 684; ^{1}H NMR (CDCl3, 250 MHz) δ 5.10 (s, 2H, OCH2), 6.95 (s, 1H, H3), 7.01 (d, 1H, $J = 2.5$ Hz, H4), 7.12 (dd, 1H, $J = 9.0$ Hz, $J' = 2.5$ Hz, H6), 7.33–7.50 (m, 8H, Harom), 7.60–7.64 (m, 2H, Harom), 8.11 (d, 1H, $J = 9.0$ Hz, H7), 8.60 (s, 1H, H3′), 8.88 (s, 1H, H5′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 70.5 (CH2), 105.1 (CH), 116.2 (CH), 117.3 (CH), 118.0 (CH), 127.0 (2 × CH), 127.5 (2 × CH), 128.0 (Cq), 128.6 (2 × CH), 128.8 (2 × CH), 131.0 (Cq),133.2 (Cq), 133.8 (CH), 136.5 (Cq), 136.6 (Cq), 136.8 (Cq), 143.0 (CH), 143.9 (CH), 146.6 (Cq), 147.9 (Cq), 156.4 (Cq); HRMS (EI-MS) *m*/*z* calculated for C25H18ClN3O3S 476.0836 found 476.0854.

7.1.29. 4-[5-(1-Benzenesulfonyl-5-benzyloxy-1H-indol-2-yl)-pyridin-3-yl]-benzonitrile (**27**)

Compound **27** was obtained following the general procedure **B**. Compound **25** (250 mg, 0.48 mmol) and 4-cyanophenylboronic

acid (85 mg, 0.58 mmol) in a mixture of toluene (22 mL), ethanol (11 mL) and aqueous saturated NaHCO3 solution (7 mL) were used. The reaction was refluxed for 4 h. Flash chromatography (petroleum ether/EtOAc 70/30) afforded compound **27** as a yellow solid (198 mg, 76%). Rf: 0.1 (petroleum ether/EtOAc 60/40); mp 195 °C; IR (ATR Diamond, cm^{-1}) ν 2230, 1608, 1474, 1447, 1369, 1203, 1170, 1145, 1089, 840, 743, 724, 685; ^{1}H NMR (CDCl3, 250 MHz) δ 5.09 (s, 2H,OCH2), 6.64 (s, 1H, H3), 7.00 (d, 1H, $J = 2.5$ Hz, H4), 7.11 (dd, 1H, $J = 9.0$ Hz, $J' = 2.5$ Hz, H6), 7.25–7.43 (m, 10H, Harom), 7.81 (br s, 4H, 2 × H2″ + 2 × H3″), 8.18 (t, 1H, $J = 2.5$ Hz, H4′), 8.23 (d, 1H, $J = 10.0$ Hz, H7), 8.63 (d, 1H, $J = 2.5$ Hz, H2′), 8.89 (d, 1H, $J = 2.5$ Hz, H6′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 70.5 (CH2), 104.7 (CH), 115.3 (2 × CH), 117.7 (CH), 118.6 (Cq), 126.5 (2 × CH), 127.5 (3 × CH), 128.0 (2 × CH), 128.6 (2 × CH), 128.9 (2 × CH), 130.8 (Cq), 131.3 (Cq), 132.9 (2 × CH), 133.0 (Cq), 133.5 (Cq), 133.9 (CH), 136.8 (Cq), 136.9 (Cq), 137.2 (CH), 138.4 (Cq), 141.9 (Cq), 147.9 (Cq), 148.0 (CH), 148.7 (CH), 156.6 (Cq); HRMS (EI-MS): *m/z* calculated for C33H24 N3O3S 542.1538 found 542.1556.

7.1.30. 1-Benzenesulfonyl-5-benzyloxy-2-[5-(4-methanesulfonyl-phenyl)-pyridin-3-yl]-1H-indole (*28*)

Compound **28** was obtained following the general procedure **B**. Compound **25** (500 mg, 0.96 mmol) and 4-methylsulfonylphenylboronic acid (231 mg, 1.15 mmol) in a mixture of toluene (44 mL), ethanol (22 mL) and aqueous saturated NaHCO3 solution (14 mL) were used. The reaction was refluxed for 8 h. Flash chromatography (petroleum ether/EtOAc 40/60) afforded compound **28** as a yellow solid (198 mg, 96%). Rf: 0.25 (petroleum ether/EtOAc 40/60); mp 147 °C; IR (ATR Diamond, cm^{-1}) ν 3050, 1431, 1371, 1145, 799, 743; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.29 (s, 3H, SO2CH3), 5.11 (s, 2H,OCH2), 7.07 (s, 1H, H3), 7.12 (dd, 1H, $J = 9.0$ Hz, $J' = 2.5$ Hz, H6), 7.18 (d, 1H, $J = 10.0$ Hz, H7), 7.33–7.49 (m, 10H, Harom), 8.04 (s, 1H, H4), 8.09 (d, 2H, $J = 8.5$ Hz, 2 × H3″), 8.12 (d, 2H, $J = 8.5$ Hz, 2 × H2″), 8.35 (t, 1H, $J = 2.5$ Hz, H4′), 8.79 (d, 1H, $J = 2.5$ Hz, H2′), 9.05 (d, 1H, $J = 2.5$ Hz, H6′); ^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 59.3 (CH3), 83.3 (CH2), 126.1 (2 × CH), 127.6 (4 × CH), 127.7 (2 × CH), 128.0 (Cq), 128.1 (Cq), 128.2 (Cq), 128.4 (4 × CH), 128.5 (Cq), 128.6 (3 × CH), 128.7 (3 × CH), 128.8 (Cq), 129.3 (CH), 131.3 (CH), 131.4 (CH), 131.9 (Cq), 132.6 (Cq), 132.8 (Cq), 155.9 (2 × Cq); HRMS (EI-MS): *m/z* calculated for C33H27 N2O5S2 595.1361 found 595.1342.

7.1.31. 1-Benzenesulfonyl-5-benzyloxy-2-[6-(4-methoxy-phenyl)-pyrazin-2-yl]-1H-indole (*29*)

Compound **29** was obtained following the general procedure **B**. A solution of compound **26** (500 mg, 1.05 mmol) and 4-methoxyphenylboronic acid (192 mg, 1.26 mmol) in a mixture of toluene (3.3 mL), ethanol (2.1 mL) and aqueous saturated NaHCO3 solution (1.8 mL) was used The reaction was carried out under μWave irradiation for 30 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 70/30) yielded compound **29** as a yellow solid (447 mg, 78%). Rf: 0.45 (petroleum ether/EtOAc 60/40); mp 136 °C; IR (ATR Diamond, cm^{-1}) ν 3068, 1031, 1608, 1513, 1449, 1418, 1369, 1303, 1253, 1219, 1185, 1167, 1149, 1122, 1087, 1070, 1014, 845, 813, 753, 722, 700; ^{1}H NMR (CDCl3, 250 MHz) δ 3.90 (s, 3H, OCH3), 5.08 (s, 2H, OCH2), 6.90 (s, 1H, H3), 7.07 (m, 2H, Harom), 7.50 (s, 1H, H4), 7.10 (dd, 1H, $J = 5.8$ Hz, $J' = 1.8$ Hz, H6), 7.27–7.47 (m, 8H, Harom), 7.64 (d, 2H, $J = 8.8$ Hz, 2 × H3″), 8.0 (d, 2H, $J = 8.8$ Hz, 2 × H2″), 8.12 (d, 1H, $J = 9.0$ Hz, H7), 8.77 (s, 1H, H3′), 8.98 (s, 1H, H5′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 70.5 (CH2), 105.1 (CH), 114.4 (2 × CH), 115.5 (CH), 116.3 (CH), 117.2 (CH), 127.0 (2 × CH), 127.5 (2 × CH), 128.0 (CH), 128.5 (2 × CH), 128.6 (2 × CH); 128.8 (2 × CH), 131.2 (Cq), 133.0 (Cq), 133.6 (CH), 136.8 (2 × Cq), 137.2 (Cq), 138.8 (Cq), 140.1 (CH), 143.3 (CH), 146.3 (Cq), 150.9 (Cq), 156.3 (CH), 161.2 (Cq); HRMS (EI-MS) *m/z* calculated for C32H26 N3O4S 548.1644 found 548.1642.

7.1.32. 4-[6-(1-Benzenesulfonyl-5-benzyloxy-1H-indol-2-yl)-pyrazin-2-yl]-benzonitrile (*30*)

Compound **30** was obtained following the general procedure **B**. A solution of compound **26** (500 mg, 1.05 mmol) and 4-cyanophenylboronic acid (231 mg, 1.57 mmol) in a mixture of toluene (3.3 mL), ethanol (2.1 mL) and aqueous saturated NaHCO3 solution (1.8 mL) was used. The reaction mixture was carried out under μWave irradiation for 30 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 70/30) yielded compound **30** as a yellow solid (512 mg, 90%). Rf: 0.25 (petroleum ether/EtOAc 70/30); mp 217 °C; IR (ATR Diamond, cm^{-1}) ν 2226, 1605, 1523, 1451, 1364, 1219, 1153, 1088, 1064, 1012, 863, 814, 811, 747, 725, 702; ^{1}H NMR (CDCl3, 250 MHz) δ 5.11 (s, 2H, OCH2), 6.98 (s, 1H, H3), 7.06 (d, 1H, $J = 2.5$ Hz, H4), 7.15 (dd, 1H, $J = 9.0$ Hz, $J' = 2.5$ Hz, H6), 7.30–7.61 (m, 10 H, Harom), 7.85 (d, 2H, $J = 8.5$ Hz, 2 × H3″), 8.15 (d, 1H, $J = 9.0$ Hz, H7), 8.20 (d, 2H, $J = 8.5$ Hz, 2 × H2″), 8.97 (s, 1H, H3′), 9.05 (s, 1H, H5′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 70.5 (CH2), 105.2 (CH), 113.5 (Cq), 116.0 (CH), 117.2 (CH), 117.3 (CH), 118.0 (Cq), 118.5 (Cq), 126.8 (2 × CH), 127.5 (2 × CH), 127.6 (2 × CH); 128.1 (CH), 128.6 (2 × CH), 128.8 (2 × CH), 131.1 (Cq), 132.8 (CH), 133.2 (Cq), 133.8 (2 × CH), 136.7 (Cq), 137.0 (Cq), 138.2 (Cq), 140.4 (Cq), 140.7 (CH), 145.4 (CH), 146.9 (Cq), 149.0 (Cq); HRMS (EI-MS): *m/z* calculated for C32H23 N4O3S 543.2643 found 543.2645.

7.1.33. 1-Benzenesulfonyl-5-benzyloxy-2-[6-(4-methanesulfonyl-phenyl)-pyrazin-2-yl]-1H-indole (*31*)

Compound **31** was obtained following the general procedure **B**. A solution of compound **26** (620 mg, 1.30 mmol) and 4-methylsulfonylphenylboronic acid (390 mg, 1.95 mmol) in a mixture of toluene (3.3 mL), ethanol (2.1 mL) and aqueous saturated NaHCO3 solution (1.8 mL) was used. The reaction was carried out under μWave irradiation for 30 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 50/50) yielded compound **31** as a yellow solid (635 mg, 82%). Rf: 0.25 (petroleum ether/EtOAc 50/50); mp 186 °C; IR (ATR Diamond, cm^{-1}) ν 1601, 1507, 1446, 1369, 1253, 1218, 1185, 1167, 1149, 1088, 1012, 844, 811, 753, 722, 699, 682; ^{1}H NMR (CDCl3, 250 MHz) δ 3.12 (s, 3H, SO2CH3), 5.07 (s, 2H, OCH2), 6.96 (s, 1H, H3), 7.07 (d, 1H, $J = 2.2$ Hz, H4), 7.11 (dd, 1H, $J = 9.0$ Hz, $J' = 2.5$ Hz, H6), 7.30–7.70 (m, 10H, Harom), 8.07–8.13 (m, 3H, 2 × H3″ + H7), 8.25 (d, 2H, $J = 8.8$ Hz, 2 × H2″), 8.26 (s, 1H, H3′), 9.02 (s, 1H, H5′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 44.5 (CH3), 70.5 (CH2), 105.1 (CH), 112.3 (Cq), 115.9 (CH), 117.2 (CH), 117.3 (CH), 126.8 (2 × CH), 127.4 (2 × CH), 127.5 (CH), 127.9 (CH), 128.0 (2 × CH), 128.5 (CH), 128.6 (2 × CH), 128.8 (2 × CH), 131.1 (Cq), 133.1 (Cq), 133.8. (CH), 136.7 (2 × Cq), 136.9 (Cq), 138.1 (Cq), 140.7 (CH), 141.3 (Cq), 141.5 (Cq), 145.5 (CH), 156.4 (Cq); HRMS (EI-MS): *m/z* calculated for C32H26 N3O5S2 596.1314 found 596.1306.

7.1.34. 4-[5-(5-Benzyloxy-1H-indol-2-yl)-pyridin-3-yl]-benzonitrile (*32*)

Compound **32** was obtained following the general procedure **D**. A solution of compound **27** (130 mg, 0.24 mmol) in THF (4 mL) and 1.5 eq of Bu4NF (0.36 mL, 1 M in THF, 0.36 mmol) were used. The reaction was refluxed for 4 h. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **32** as a yellow solid (70 mg, 73%). Rf: 0.34 (petroleum ether/EtOAc 40/60); mp 93 °C; IR (ATR Diamond, cm^{-1}) ν 2226, 1587, 1456, 1386, 1295, 1212, 1160, 1023, 835, 790; ^{1}H NMR (CDCl3, 250 MHz) δ 5.30 (s, 2H, OCH2), 6.89 (s, 1H, H3), 7.00 (dd, 1H, $J = 9.0$ Hz, $J = 2.5$ Hz, H6), 7.18 (d, 1H, $J = 2.0$ Hz, H4), 7.33–7.50 (m, 5H, Harom), 7.75 (d, 2H, $J = 8.5$ Hz, 2 × H3″), 7.82 (d, 2H, $J = 8.5$ Hz, 2 × H2″), 8.07 (dd, 1H, $J = J' = 2.0$ Hz, H4′), 8.43 (d, 1H, $J = 10$ Hz, H7), 8.75 (s, 1H, H2′), 8.83 (s, 1H, H6′), 11.2 (s, 1H,

NH);^{13}C NMR (CDCl3, 100.6 MHz) δ 70.9 (CH2), 101.9 (CH), 103.9 (CH), 106.2 (Cq), 111.9(CH), 114.6 (CH), 118.5 (Cq), 127.5 (3 × CH), 127.8 (2 × CH), 128.0 (2 × CH), 128.5 (2 × CH),129.4 (Cq), 130.6 (Cq), 132.6 (Cq), 132.7 (Cq), 133.0 (2 × CH), 137.5 (2 × Cq), 154.0 (2 × Cq), 155.0 (Cq); HRMS (EI-MS): *m*/*z* calculated for C27H20 N3O 402.1626 found 402.1606.

7.1.35. 5-Benzyloxy-2-[5-(4-methanesulfonyl-phenyl)-pyridin-3-yl]-1H-indole (**33**)

Compound **33** was obtained following the general procedure **D** D. A solution of compound **28** (300 mg, 0.50 mmol) in THF (10 mL) and 1.5 eq of Bu4NF (0.75 mL, 1 M in THF, 0.75 mmol) were used. The reaction mixture was refluxed for 4 h. Flash chromatography (petroleum ether/EtOAc 40/60) afforded compound **33** as a white solid (229 mg, quant). Rf: 0.2 (petroleum ether/EtOAc 40/60); mp 211 °C; IR (ATR Diamond, cm^{-1}) ν 3349, 1734, 1589, 1460, 1303, 1211, 1145, 1089, 956, 759;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.30 (s, 3H, SO2CH3), 5.12 (s, 2H, OCH2), 6.89 (dd, 1H, J = 9.0 Hz, J' = 2.5 Hz, H6), 7.10 (s, 1H, H3), 7.15 (d, 1H, J = 2.5 Hz, H4), 7.32–7.65 (m, 6H, Harom + H7), 8.09 (d, 2H, J = 8.8 Hz, 2 × H3″), 8.14 (d, 2H, J = 8.5 Hz, 2 × H2″), 8.57 (dd, 1H, J = J' = 2.0 Hz, H4′), 8.88 (d, 1H, J = 1.75 Hz, H2′), 9.14 (d, 1H, J = 1.75 Hz, H6′), 11.63 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 43.4 (CH3), 69.6 (CH2), 100.2 (CH), 103.2 (CH), 112.0 (CH), 113.3 (CH), 127.5 (2 × CH), 127.6 (CH), 127.8 (2 × CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 129.9 (CH), 131.3 (CH), 131.4 (Cq), 131.9 (Cq), 132.6 (Cq), 133.9 (Cq), 134.5 (Cq) 137.6 (Cq), 140.4 (Cq), 141.8 (Cq), 146.0 (CH), 146.1 (CH), 152.7 (Cq); HRMS (EI-MS): *m*/*z* calculated for C27H23 N2O3S 455.1429 found 455.1428.

7.1.36. 5-Benzyloxy-2-[6-(4-methoxy-phenyl)-pyrazin-2-yl]-1H-indole (**34**)

Compound **34** was obtained following the general procedure **D**. A solution of compound **29** (350 mg, 0.64 mmol) in THF (10 mL) and 3.0 eq. of Bu_4NF (1.92 mL, 1 M in THF, 1.92 mmol) were used. The reaction was refluxed for 6 h. Flash chromatography (petroleum ether/EtOAc 60/40) afforded compound **34** as a yellow solid (250 mg, 96%). Rf: 0.25 (petroleum ether/EtOAc 60/40); mp 176 °C; IR (ATR Diamond, cm^{-1}) ν 3243, 2230, 1654, 1605, 1450, 1364, 1218, 1153, 1088, 1012, 840, 810, 746, 724, 681;^{1}H NMR (CDCl3, 250 MHz) δ 3.90 (s, 3H, OCH3), 5.13 (s, 2H, OCH2), 7.03 (dd, 1H, J = 9.0 Hz, J = 2.3 Hz, H6), 7.06 (s, 1H, H3), 7.09 (d, 2H, J = 8.8 Hz, 2 × H3″), 7.20 (d, 1H, J = 2.3 Hz, H4), 7.33–7.44 (m, 4H, Harom), 7.50 (d, 2H, J = 6.8 Hz, Harom + H7), 8.07 (d, 2H, J = 8.8 Hz, 2 × H2″), 8.79 (s, 1H, H3′), 8.91 (s, 1H, H5′), 9.37 (s, 1H, NH);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 70.8 (CH2), 101.8 (CH), 104.1 (CH), 112.2 (CH), 114.4 (2 × CH), 115.4 (CH), 127.5 (2 × CH), 127.8 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 128.8 (Cq), 129.4 (Cq), 132.3 (Cq), 134.5 (2 × Cq), 137.5 (Cq), 138.8 (CH), 139.0 (CH), 151.1 (Cq), 153.8 (Cq), 161.3 (Cq); HRMS (EI-MS) *m*/*z* calculated for C26H22 N3O2 408.1712 found 408.1728.

7.1.37. 4-[6-(5-Benzyloxy-1H-indol-2-yl)-pyrazin-2-yl]-benzonitrile (**35**)

Compound **35** was obtained following the general procedure **D**. A solution of compound **30** (286 mg, 0.52 mmol) in THF (10 mL) and 3 eq. of Bu4NF (4.74 mL, 1 M in THF, 4.74 mmol) were used. The reaction was refluxed for 12 h. Flash chromatography (petroleum ether/EtOAc 70/30) afforded compound **35** as a yellow solid (161 mg, 76%). Rf: 0.25 (petroleum ether/EtOAc 70/30); mp 211 °C; IR (ATR Diamond, cm^{-1}) ν 3403, 2234, 1542, 1451, 1307, 1239, 1222, 1148, 1107, 1039, 1011, 830, 776, 734;^{1}H NMR (CDCl3, 400 MHz) δ 5.13 (s, 2H, OCH2), 7.05 (dd, 1H, J = 5.5 Hz, J' = 1.5 Hz, H6), 7.15 (d, 1H, J = 1.0 Hz, H3), 7.20 (d, 1H, J = 1.5 Hz, H4), 7.33–7.50 (m, 6H, H7 + Harom), 7.85 (d, 2H, J = 5.0 Hz, 2 × H3″), 8.22 (d, 2H, J = 5.0 Hz, 2 × H2″), 8.86 (s, 1H, H3′), 9.05 (s, 1H, H5′), 9.29 (s, 1H, NH);^{13}C NMR (CDCl3, 100.6 MHz) δ 70.8 (CH2), 102.8 (CH), 104.1 (CH), 112.3 (CH), 116.1 (CH), 127.5 (2 × CH), 127.6 (2 × CH), 127.9 (2 × CH), 128.1 (Cq), 128.6 (2 × CH), 129.1 (Cq), 129.4 (Cq), 132.5 (Cq), 132.8 (2 × CH), 133.7 (Cq), 137.4 (Cq), 139.3 (Cq), 140.5 (Cq), 141.2 (CH), 142.1 (Cq), 154.0 (Cq); HRMS (EI-MS): *m*/*z* calculated for C26H19 N4O 403.1559 found 403.1545.

7.1.38. 5-Benzyloxy-2-[6-(4-methansulfonyl-phenyl)-pyrazin-2-yl]-1H-indole (**36**)

Compound **36** was obtained following the general procedure **D**. A solution of compound **31** (480 mg, 0.80 mmol) in THF (15 mL) and 3.0 eq. of Bu4NF (2.4 mL, 1 M in THF, 2.4 mmol) were used. The reaction was refluxed for 10 h. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **36** as a yellow solid (340 mg, 94%). Rf: 0.25 (petroleum ether/EtOAc 50/50); mp 245 °C; IR (ATR Diamond, cm^{-1}) ν 3358, 1540, 1446, 1294, 1231, 1217, 1187, 1167, 1145, 1122, 1105, 1089, 1009, 962, 834, 777, 764, 744, 731, 694;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.32 (s, 3H, SO2CH3), 5.13 (s, 2H, OCH2), 6.96 (dd, 1H, J = 10.0 Hz, J' = 2.5 Hz, H6), 7.21 (d, 1H, J = 2.5 Hz, H4), 7.32–7.44 (m, 6H, Harom + H3), 7.50 (d, 1H, J = 7.5 Hz, H7), 8.12 (d, 2H, J = 7.5 Hz, 2 × H3″), 8.67 (d, 2H, J = 7.5 Hz, 2 × H2″), 9.22 (s, 1H, H3′), 9.28 (s, 1H, H5′), 11.76 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 43.4 (CH3), 69.6 (CH2), 102.5 (CH), 103.4 (CH), 112.9 (CH), 114.8 (CH), 127.4 (CH), 127.6 (3 × CH), 127.8 (2 × CH), 128.3 (3 × CH), 128.6 (Cq), 133.1 (Cq), 134.3 (Cq), 137.6 (Cq), 139.5 (CH), 140.4 (Cq), 141.2 (CH), 141.7 (Cq), 145.5 (Cq) 148.3 (Cq), 152.9 (Cq); HRMS (EI-MS): *m*/*z* calculated for C26H22 N3O3S 456.1382 found 456.1396.

7.1.39. 4-[5-(5-Hydroxy-1H-indol-2-yl)-pyridin-3-yl]-benzonitrile (**37**)

Compound **37** was obtained following the general procedure **C**. A solution of compound **32** (50 mg, 0.12 mmol) in CH2Cl2 (5 mL) and 1.1 eq. of BBr3 (0.13 mL, 0.13 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 4 h. After flash chromatography (petroleum ether/EtOAc 50/50), compound **37** was obtained as a yellow solid (27 mg, 71%). Rf: 0.12 (petroleum ether/EtOAc 60/40); mp 251 °C; IR (ATR Diamond, cm^{-1}) ν 3268, 2915, 2226, 1585, 1432, 1214, 1161, 1134, 1046, 840, 791;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 6.68 (dd, 1H, J = 9.0 Hz, J' = 2.5 Hz, H6), 6.87 (d, 1H, J = 2.5 Hz, H4), 7.01 (s, 1H, H3), 7.24 (d, 1H, J = 10.0 Hz, H7), 8.04 (d, 2H, J = 7.5 Hz, 2 × H3″), 8.09 (d, 2H, J = 7.5 Hz, 2 × H2″), 8.55 (d, 1H, J = 2.5 Hz, H4′), 8.78 (s, 1H, OH), 8.86 (d, 1H, J = 2.5 Hz, H2′), 9.11 (d, 1H, J = 2.5 Hz, H6′), 11.47 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 88.3 (CH), 92.32 (CH), 98.3 (CH), 99.4 (Cq), 109.7 (CH), 110.8 (Cq), 115.1 (Cq), 126.9 (Cq), 127.8 (2 × CH), 130.0 (CH), 131.4 (Cq), 132.9 (2 × CH), 140.2 (Cq), 144.0 (Cq), 145.4 (2 × CH), 150.5 (Cq), 154.4 (Cq); HRMS (EI-MS): *m*/*z* calculated for C20H13 N3O 312.1137 found 312.1148.

7.1.40. 2-[5-(4-Methanesulfonyl-phenyl)-pyridin-3-yl]-1H-indol-5-ol (**38**)

Compound **6** was obtained following the general procedure **C** C. A solution of compound **33** (200 mg, 0.44 mmol) in CH2Cl2 (15 mL) and 1.5 eq. of BBr3 (0.66 mL, 0.66 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 6 h. After flash chromatography (dichloromethane), compound **38** was obtained as a pale brown solid (93 mg, 58%). Rf: 0.17 (CH2Cl2); mp 195 °C; IR (ATR Diamond, cm^{-1}) ν 2950, 1716, 1593, 1493; 1396, 1301, 1226, 1149, 1046, 834, 774;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.32 (s, 3H, SO2CH3), 6.70 (dd, 1H, J = 10 Hz, J' = 2.5 Hz, H6), 6.88 (s, 1H, H3), 7.02 (s, 1H, H4), 7.25 (d, 1H, J = 10.0 Hz, H7), 8.09 (d, 2H, J = 7.5 Hz, 2 × H3″), 8.14 (d, 2H, J = 7.5 Hz, 2 × H2″), 8.56 (d, 1H, J = 2.0 Hz, H4′), 8.77 (s, 1H, H2′), 8.87 (s, 1H, H6′), 9.12 (s, 1H, OH), 11.47 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 43.4 (CH3), 99.7 (CH), 103.8 (CH), 111.8 (CH), 112.9 (CH), 127.6 (2 × CH), 127.9 (2 × CH), 129.1

(2 × Cq), 129.9 (CH), 132.0 (Cq), 134.2 (Cq), 140.4 (2 × Cq), 141.8 (Cq), 145.9 (2 × CH), 151.1 (Cq); HRMS (EI-MS): *m*/*z* calculated for C20H17 N2O3S 365.0960 found 365.0966.

*7.1.41. 2-[6-(4-hydroxy-phenyl)-pyrazin-2-yl]-1H-indol-5-ol (**39**)*

Compound **39** was obtained following the general procedure **C**. A solution of compound **34** (200 mg, 0.49 mmol) in CH2Cl2 (10 mL) and 11.8 eq. of BBr3 (5.8 mL, 5.8 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 15 h. After flash chromatography (CH2Cl2), compound **39** was obtained as a brown solid (148 mg, 99%). Rf: 0.25 (CH2Cl2); Mp 195 °C; IR (ATR Diamond, cm^{-1}) ν 3391, 3235, 2958, 2925, 2843, 1719, 1610, 1544, 1512, 1444, 1375, 1227, 1171, 1043, 835, 775;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 6.73 (dd, 1H, $J = 5.5$ Hz, $J' = 1.5$ Hz, H6), 6.90 (d, 1H, $J = 1.0$ Hz, H3), 6.94 (d, 2H, $J = 5.5$ Hz, 2 × H3″), 7.16 (d, 1H, $J = 0.8$ Hz, H4), 7.33 (d, 1H, $J = 5.5$ Hz, H7), 8.24 (d, 2H, $J = 5.5$ Hz, 2 × H2″), 8.20 (s, 1H, OH), 8.96 (s, 1H, H3′), 9.02 (s, 1H,H5′), 9.95 (s, 1H, OH), 11.45 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 101.2 (CH), 104.0 (CH), 112.6 (Cq), 113.9 (CH), 115.6 (2 × CH), 118.7 (Cq), 126.5 (Cq), 127.5 (Cq), 128.5 (2 × CH), 129.0 (Cq), 131.8 (Cq), 132.2 (Cq), 134.5 (CH), 150.2 (CH), 151.1 (CH), 159.4 (Cq); HRMS (EI-MS) *m*/*z* calculated for C18H14 N3O2 304.1086 found 304.1091.

*7.1.42. 4-[6-(5-Hydroxy-1H-indol-2-yl)-pyrazin-2-yl]-benzonitrile (**40**)*

Compound **40** was obtained following the general procedure **C**. A solution of compound **35** (145 mg, 0.36 mmol) in CH2Cl2 (10 mL) and 10.0 eq. of BBr3 (3.6 mL, 3.6 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 12 h. After flash chromatography (dichloromethane/MeOH 98/02), compound **40** was obtained as a red solid (111 mg, 99%). Rf: 0.25 (dichloromethane/MeOH 98/02); mp 195 °C; IR (ATR Diamond, cm^{-1}) ν 3358, 2222, 1542, 1518, 1448, 1383, 1227, 1180, 1159, 1107, 1011, 839, 787, 728, 688;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 6.76 (dd, 1H, $J = 8.8$ Hz, $J' = 2.3$ Hz, H6), 6.92 (d, 1H, $J = 2.0$ Hz, H3), 7.25 (d, 1H, $J = 1.0$ Hz, H4), 6.34 (d, 2H, $J = 8.8$ Hz, H7), 8.07 (d, 2H, $J = 8.5$ Hz, 2 × H3″), 8.62 (d, 2H, $J = 8.5$ Hz, 2 × H2″), 8.83 (s, 1H, OH), 9.20 (s, 1H, H3′), 9.23 (s, 1H, H5′), 11.60 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 101.9 (CH), 104.0 (CH), 112.3 (Cq), 112.5 (CH), 114.3 (CH), 127.6 (2 × CH), 128.9 (Cq), 132.3 (2 × Cq), 132.7 (2 × CH), 133.9 (Cq), 139.2 (CH), 139.9 (Cq), 141.1 (CH), 145.6 (Cq), 148.0 (Cq), 151.2 (Cq); HRMS (EI-MS): *m*/*z* calculated for C19H13 N4O 313.1089 found 313.1078.

*7.1.43. 2-[6-(4-Methanesulfonyl-phenyl)-pyrazin-2-yl]-1H-indol-5-ol (**41**)*

Compound **6** was obtained following the general procedure **C**. A solution of compound **36** (300 mg, 0.65 mmol) in CH2Cl2 (10 mL) and 6.0 eq. of BBr3 (3.94 mL, 3.94 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 7 h. After flash chromatography (dichloromethane/MeOH 90/10), compound **41** was obtained as a brown solid (110 mg, 41%). Rf: 0.25 (CH2Cl2/MeOH 90/10); mp 248 °C; IR (ATR Diamond, cm^{-1}) ν 3346, 2929, 1542, 1450, 1380, 1286, 1233, 1185, 1145, 1089, 1011, 956, 840, 802, 772, 729;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.31 (s, 3H, SO2CH3), 6.76 (dd, 1H, $J = 8.8$ Hz, $J' = 2.3$ Hz, H6), 6.93 (d, 1H, $J = 1.8$ Hz, H4), 7.25 (d, 1H, $J = 1.2$ Hz, H3), 7.35 (d, 1H, $J = 8.8$ Hz, H7), 8.11 (d, 2H, $J = 8.5$ Hz, 2 × H3″), 8.66 (d, 2H, $J = 8.5$ Hz, 2 × H2″), 9.21 (s, 1H, H3′), 9.22 (s, 1H,H5′), 9.80 (s, 1H, OH), 11.60 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 43.4 (CH3), 101.9 (CH), 104.1 (CH), 112.5 (CH), 114.3 (CH), 127.4 (2 × CH), 127.7 (2 × CH), 128.9 (Cq), 132.4 (Cq), 133.9 (Cq), 139.3 (CH), 140.4 (Cq), 141.1 (CH), 141.7 (Cq), 145.6 (Cq), 148.3 (Cq), 151.2 (Cq); HRMS (EI-MS): *m*/*z* calculated for C19H16 N3O3S 366.0912 found 366.0907.

*7.1.44. 1-Benzenesulfonyl-5-benzyloxy-2-(4-chloro-pyridin-2-yl)-1H-indole (**42**)*

Compound **6** was obtained following the general procedure **A**. A solution of compound **24** (1.5 g, 2.29 mmol), 2,4-dichloropyridine (0.37 mL, 3.43 mmol) and CuI (43.8 mg, 0.23 mmol) in THF (32 mL) were used. The reaction was carried out under μWave irradiation for 30 min at 100 °C. After flash chromatography (petroleum ether/EtOAc 70/30), compound **42** was obtained as yellow solid (789 g, 72%). Rf: 0.35 (petroleum ether/EtOAc 60/40); mp 165 °C; IR (ATR Diamond, cm^{-1}) ν 3068, 3023, 1582, 1543, 1454, 1361, 1262, 1205, 1176, 1147, 1077, 1009, 877, 860, 809, 746, 724, 700.^{1}H NMR (CDCl3, 250 MHz) δ 5.05 (s, 2H, OCH2), 6.84 (s, 1H, H3), 6.98 (d, 1H, $J = 2.3$ Hz, H4), 7.06 (dd, 1H, $J = 9.0$ Hz, $J' = 2.5$ Hz, H6), 7.29–7.45 (m, 9H, Harom + H5′), 7.59 (d, 2H, $J = 7.2$ Hz, Harom), 7.72 (s, 1H, H3′), 8.09 (d, 1H, $J = 9.0$ Hz, H7), 8.57 (d, 1H, $J = 5.5$ Hz, H6′);^{13}C NMR(CDCl3, 100.6 MHz) δ 69.4 (CH2), 104.1 (CH), 114.5 (CH), 115.6 (CH), 116.5 (CH), 122.4 (CH), 125.4 (CH), 125.9 (CH), 126.5 (CH), 127.0 (CH), 127.6 (2 × CH), 127.7 (2 × CH), 130.3 (Cq), 132.0 (Cq), 132.6 (CH), 133.7 (CH), 133.8 (CH), 135.5 (Cq), 136.7 (Cq), 142.5 (Cq), 146.3 (Cq), 148.5 (CH), 151.5 (Cq), 155.4 (Cq); HRMS (EI-MS): *m*/*z* calculated for C26H20 N2O3SCl: 475.0883 found 475.0880.

*7.1.45. 1-Benzenesulfonyl-2-(4-chloro-pyridin-2-yl)-6-methoxy-1H-indole (**43**)*

Compound **6** was obtained following the general procedure **A**. A solution of compound **3** (828 mg, 1.47 mmol), 2,4-dichloropyridine (0.24 mL, 2.20 mmol) and CuI (28 mg, 0.147 mmol) in THF (15 mL) were used. The reaction mixture was charged in a microwave vial equipped with a stirring bar and subjected to irradiation for 30 min at 100 °C. After flash chromatography (petroleum ether/EtOAc 70/30), compound **43** was obtained as yellow oil (414 g, 70%). Rf: 0.3 (petroleum ether/EtOAc 60/40); IR (ATR Diamond, cm^{-1}) ν 2955, 2923, 2853, 1614, 1586, 1460, 1371, 1277, 1173, 1112, 1090, 1027, 843, 726, 688;^{1}H NMR (CDCl3, 250 MHz) δ 3.92 (s, 3H, OCH3), 6.84 (s, 1H, H3), 6.88 (dd, 1H, $J = 8.8$ Hz, $J' = 2.5$ Hz, H5), 7.30–7.37 (m, 5H, 3 × Harom + H5′ + H4), 7.63 (d, 2H, $J = 7.2$ Hz, 2 × Harom), 7.70 (d, 1H, $J = 1.7$ Hz, H3′), 7.73 (d, 1H, $J = 2.3$ Hz, H7), 8.55 (d, 1H, $J = 5.3$ Hz, H6′);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.8 (CH3), 100.7 (CH), 113.8 (CH), 116.5 (CH), 122.0 (CH), 123.0 (CH), 124.0 (Cq), 126.1 (CH), 126.9 (2 × CH), 128.7 (2 × CH), 133.7 (CH), 135.7 (Cq), 138.6 (Cq), 139.7 (Cq), 143.5 (Cq), 149.5 (CH), 152.7 (Cq), 158.8 (Cq); HRMS (EI-MS): *m*/*z* calculated for C20H16 N2O3SCl: 399.0570 found 399.0574.

*7.1.46. 1-Benzenesulfonyl-5-benzyloxy-2-[4-methoxy-phenyl)-pyridin-2-yl]-1H-indole (**44**)*

Compound **6** was obtained following the general procedure **B**. A solution of compound **42** (1.7 g, 3.57 mmol) and 4-methoxyphenylboronic acid (797.8 mg, 5.25 mmol) in a mixture of toluene (9 mL), ethanol (5.7 mL) and aqueous saturated NaHCO3 solution (4.6 mL) was added. The reaction was carried out under μWave irradiation for 30 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 60/40) yielded compound **44** as a yellow oil (1.5 g, 77%). Rf: 0.25 (petroleum ether/EtOAc 60/40); IR (ATR Diamond, cm^{-1}) ν 3068, 2929, 2831, 1603, 1515, 1449, 1367, 1252, 1202, 1176, 1146, 1090, 1025, 825, 724;^{1}H NMR (CDCl3, 250 MHz) δ 3.86 (s, 3H, OCH3), 5.05 (s, 2H, OCH2), 6.88 (s, 1H, H3), 6.99–7.05 (m, 3H, 2 × H3″ + H6), 7.28–7.50 (m, 10H, Harom + H5′ + H4),7.60 (d, 2H, $J = 7.2$ Hz, Harom), 7.70 (d, 2H, $J = 8.8$ Hz, 2 × H2″), 7.92 (s, 1H, H3′), 8.15 (d, 1H, $J = 9.0$ Hz, H7), 8.67 (d, 1H, $J = 5.2$ Hz, H6′);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.3 (CH3), 70.4 (CH2), 104.9 (CH), 114.5 (2 × CH), 114.9 (CH), 115.9 (CH), 117.5 (CH), 120.4 (CH), 124.0 (CH), 126.9 (CH), 127.5 (2 × CH), 127.9 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 128.6 (2 × CH), 130.1 (Cq), 131.6 (Cq), 132.0 (CH), 133.0 (Cq), 133.5 (CH), 136.6 (Cq), 136.8 (Cq), 142.2 (Cq), 147.2 (Cq), 149.2

(CH), 151.3 (Cq), 156.3 (Cq), 160.6 (Cq); HRMS (EI-MS): *m*/*z* calculated for C33H27 N2O4S: 547.1692 found 547.1702.

*7.1.47. 1-Benzenesulfonyl-6-methoxy-2-[4-4-methoxy-phenyl)-pyridin-2-yl]-1H-indole (**45**)*

Compound **6** was obtained following the general procedure **B**. A solution of compound **43** (420 mg, 1.05 mmol) and 4-methoxyphenylboronic acid (239.3 mg, 1.57 mmol) in a mixture of toluene (3 mL), ethanol (2 mL) and aqueous saturated $NaHCO_3$ solution (1.65 mL) was added. The reaction was carried out under μWave irradiation for 40 min at 150 °C. Flash chromatography (petroleum ether/EtOAc 70/30) afforded compound **45** as yellow oil (394 mg, 79%). Rf: 0.25 (petroleum ether/EtOAc 70/30); IR (ATR Diamond,cm^{-1}) ν 3407, 2962, 2929, 2839, 1601, 1515, 1462, 1442, 1279, 1249, 1177, 1113, 1089, 1027, 824, 752, 723;^{1}H NMR (CDCl3, 250 MHz) δ 3.88 (s, 3H, OCH3), 3.92 (s, 3H, OCH3), 6.87 (m, 2H, H3 + H5), 7.03 (d, 2H, J = 9.0 Hz, 2 × H3″), 7.29–7.50 (m, 5H, Harom + H5′ + H4),7.61–7.65 (m, 2H, Harom), 7.69 (d, 2H, J = 8.8 Hz, 2 × H2″), 7.79 (d, 1H, J = 2.0 Hz, H7), 7.88 (d, 1H, J = 1.0 Hz, H3′), 8.66 (d, 1H, J = 5.3 Hz, H6′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 55.8 (CH3), 100.9 (CH), 113.6 (CH), 114.5 (2 × CH), 115.7 (CH), 120.2 (CH), 121.9 (CH), 123.8 (CH), 124.3 (Cq), 126.9 (2 × CH), 128.4 (2 × CH), 128.7 (2 × CH), 130.4 (Cq), 133.6 (CH), 136.9 (Cq), 139.7 (Cq), 140.3 (Cq), 147.3 (Cq), 149.2 (CH), 151.6 (Cq), 158.5 (Cq), 160.6 (Cq); HRMS (EI-MS): *m*/*z* calculated for C27H23 N2O4S: 471.1379 found 471.1386.

*7.1.48. 5-Benzyloxy-2-[4-(4-methoxy-phenyl)-pyridin-2-yl]-1H-indole (**46**)*

Compound **46** was obtained following the general procedure **D**. A solution of compound **44** (430 mg, 0.78 mmol) in THF (20 mL) and 3.0 eq. of Bu4NF (2.36 mL, 1 M in THF, 2.36 mmol) were used. The reaction was refluxed for 12 h. Flash chromatography (petroleum ether/EtOAc 60/40) afforded compound **46** as a yellow solid (254 mg, 80%). Rf: 0.25 (petroleum ether/EtOAc 60/40); mp 144 °C; IR (ATR Diamond, cm^{-1}) ν 3411, 3068, 2929, 2831, 1597, 1515, 1446, 1252, 1202, 1178, 1150, 1023, 826, 783, 724, 694;^{1}H NMR (CDCl3, 250 MHz) δ 3.89 (s, 3H, OCH3), 5.13 (s, 2H, OCH2), 6.96–7.01 (m, 2H, H3 + H6), 7.05 (d, 2H, J = 8.8 Hz, 2 × H3″), 7.19 (d, 1H, J = 2.3 Hz, H4), 7.30–7.43 (m, 7H, Harom + H5′ + H7), 7.66 (d, 2H, J = 8.8 Hz, 2 × H2″), 7.94 (d, 1H, J = 1.0 Hz, H3′), 8.56 (d, 1H, J = 5.2 Hz, H6′), 9.60 (s, 1H, NH) ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 70.8 (CH2), 100.2 (CH), 104.0 (CH), 112.1 (CH), 114.5 (CH), 114.6 (2 × CH), 117.1 (CH), 119.6 (CH), 127.5 (2 × CH), 127.8 (CH), 128.2 (2 × CH), 128.5 (2 × CH), 129.5 (Cq), 130.5 (Cq), 132.0 (Cq), 137.5 (Cq), 137.7 (Cq), 148.6 (Cq), 149.5 (CH), 150.7 (Cq), 153.6 (Cq), 160.6 (Cq); HRMS (EI-MS): *m*/*z* calculated for C27H23 N2O2: 407.1760 found 407.1772.

*7.1.49. 6-Methoxy-2-[4-(4-methoxy-phenyl)-pyridin-2-yl]-1H-indole (**47**)*

Compound **47** was obtained following the general procedure **D**. A solution of compound **45** (275 mg, 0.58 mmol) in THF (10 mL) and 3.0 eq. of Bu4NF (1.75 mL, 1 M in THF, 1.75 mmol) were used. The reaction was refluxed for 4 h. Flash chromatography (petroleum ether/EtOAc 80/20) afforded compound **47** as a yellow solid (153 mg, 80%). Rf: 0.45 (petroleum ether/EtOAc 70/30); mp 145 °C; IR (ATR Diamond, cm^{-1}) ν 3407, 3068, 2929, 2835, 1621, 1596, 1519, 1507, 1437, 1282, 1249, 1218, 1180, 1156, 1109, 1022, 959, 812, 788;^{1}H NMR (CDCl3, 250 MHz) δ 3.88 (s, 3H, OCH3), 3.89 (s, 3H, OCH3), 6.80 (dd, 1H, J = 8.5 Hz, J' = 2.2 Hz, H5), 6.90 (s, 1H, H3), 7.01 (s, 1H, H7), 7.04 (d, 2H, J = 9.0 Hz, 2 × H3″), 7.31 (dd, 1H, J = 5.2 Hz, J' = 1.8 Hz, H5′), 7.53 (d, 1H, J = 8.8 Hz, H4), 7.66 (d, 2H, J = 9.0 Hz, 2 × H2″), 7.91 (d, 1H, J = 0.8 Hz, H3′), 8.54 (d, 1H, J = 5.3 Hz, H6′), 9.45 (s, 1H, NH);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.4 (CH3), 55.6 (CH3), 94.2 (CH), 100.5 (CH), 110.6 (CH), 112.5 (CH), 114.5 (2 × CH), 116.6 (CH), 119.2 (CH), 121.81 (CH), 123.5 (Cq), 128.1 (2 × CH), 130.5 (Cq), 135.9 (Cq), 137.3 (Cq), 139.1 (Cq), 148.5 (Cq), 149.4 (CH), 160.6 (Cq); HRMS (EI-MS): *m*/*z* calculated for C21H19 N2O2: 331.1447 found 331.1446.

*7.1.50. 2-[4-(4-Hydroxy-phenyl)-pyridin-2-yl]-1H-indol-5-ol (**48**)*

Compound **48** was obtained following the general procedure **C**. A solution of compound **46** (220 mg, 0.54 mmol) in CH2Cl2 (10 mL) and 8.0 eq. of BBr3 (4.3 mL, 4.32 mmol, 1 M in CH2Cl2) were used. The reaction mixture was stirred for 12 h. After flash chromatography (petroleum ether/EtOAc 50/50), compound **48** was obtained as a green solid (162 mg, 99%). Rf: 0.25 (petroleum ether/EtOAc 50/50); mp 166 °C; IR (ATR Diamond, cm^{-1}) ν 3411, 3270, 2929, 2831, 1599, 1544, 1517, 1433, 1374, 1270, 1205, 1176, 1143, 1008, 947, 822, 774;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 6.66 (dd, 1H, J = 8.8 Hz, J' = 2.3 Hz, H6), 6.87 (d, 1H, J = 2.3 Hz, H3), 6.93 (d, 2H, J = 8.5 Hz, 2 × H3″), 7.09 (d, 1H, J = 1.5 Hz, H4), 7.26 (d, 1H, J = 8.7 Hz, H7), 7.50 (dd, 1H, J = 5.2 Hz, J = 1.5 Hz, H5′), 7.78 (d, 2H, J = 8.8 Hz, 2 × H2″), 7.15 (s, 1H, H3′), 8.56 (d, 1H, J = 5.5 Hz, H6′), 8.69 (s, 1H, OH), 9.85 (s, 1H, OH), 11.36 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 100.0 (CH), 103.8 (CH), 112.2 (CH), 113.0 (CH), 115.7 (CH), 115.8 (2 × CH), 118.3 (CH), 127.5 (Cq), 128.1 (2 × CH), 128.9 (2 × CH), 131.7 (Cq), 147.5 (Cq), 149.5 (CH), 150.8 (Cq), 151.0 (Cq), 158.7 (Cq); HRMS (EI-MS): *m*/*z* calculated for C19H15 N2O2: 303.1134 found 303.1139.

*7.1.51. 2-[4-(4-Hydroxy-phenyl)-pyridin-2-yl]-1H-indol-6-ol (**49**)*

Compound **6** was obtained following the general procedure **C**. A solution of compound **47** (140 mg, 0.42 mmol) in CH2Cl2 (10 mL) and 5.0 eq. of BBr3 (2.1 mL, 2.1 mmol, 1 M dans CH2Cl2) were used. The reaction mixture was stirred for 5 h. After flash chromatography (dichloromethane/MeOH 95/05), compound **49** was obtained as a red solid (125 mg, 97%). Rf: 0.32 (dichloromethane/MeOH 98/02); mp 199 °C; IR (ATR Diamond, cm^{-1}) ν 3403, 3272, 2929, 2831, 1598, 1544, 1516, 1445, 1355, 1222, 1176, 1114, 1043, 1002, 812, 725, 679;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 6.54 (dd, 1H, J = 8.5 Hz, J' = 2.3 Hz, H5), 6.84 (d, 1H, J = 1.2 Hz, H3), 6.92 (d, 2H, J = 8.8 Hz, 2 × H3″), 7.14 (d, 1H, J = 1.0 Hz, H7), 7.23 (d, 1H, J = 8.5 Hz, H4),7.46 (dd, 1H, J = 5.2 Hz, J = 1.5 Hz, H5′), 7.77 (d, 2H, J = 8.8 Hz, 2 × H2″), 8.11 (s, 1H, H3′), 8.53 (d, 1H, J = 5.5 Hz, H6′), 9.05 (s, 1H, OH), 9.84 (s, 1H, OH), 11.28 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 96.6 (CH), 100.9 (CH), 110.4 (CH), 115.2 (CH), 115.8 (2 × CH), 117.9 (CH), 121.0 (CH), 121.8 (Cq), 127.5 (Cq), 128.0 (2 × CH), 135.6 (Cq), 138.4 (Cq), 147.4 (Cq), 149.4 (CH), 151.2 (Cq), 153.9 (Cq), 158.7 (Cq); HRMS (EI-MS): *m*/*z* calculated for C19H15 N2O2: 303.1134 found 303.1145.

*7.1.52. [5-(1-Benzenesulfonyl-5-benzyloxy-1H-indol-2-yl)-pyridin-3-yl]-(4-methoxy-phenyl)-amine (**50**)*

Compound **6** was obtained following the general procedure **E**. A solution of compound **25** (100 mg, 0.19 mmol) and *p*-anisidine (35.4 mg, 0.28 mmol) in 1,4-dioxane (8 mL) was used under microwave irradiation. After flash chromatography (petroleum ether/EtOAc 50/50), compound **50** was obtained as yellow solid (93 mg, 87%). Rf: 0.25 (petroleum ether/EtOAc 30/70); mp 90 °C; IR (ATR Diamond, cm^{-1}) ν 3378, 2161, 2042, 1977, 1605, 1505, 1438, 1369, 1174, 1118, 1091, 1025, 852, 820, 741, 726, 686;^{1}H NMR (CDCl3, 250 MHz) δ 3.81 (s, 3H, OCH3), 5.06 (s, 2H, OCH2), 5.71 (s, 1H, NH), 6.51 (s, 1H, H3), 6.91 (d, 2H, J = 9.0 Hz, 2 × H3″), 6.96 (d, 1H, J = 2.5 Hz, H4), 7.06 (dd, 1H, J = 9.0 Hz, J' = 2.5 Hz, H6), 7.18 (d, 2H, J = 9.0 Hz, 2 × H2″), 7.27–7.55 (m, 8H, Harom), 7.63–7.71 (m, 3H, Harom + H4′), 8.02 (s, 1H, H2′), 8.19 (d, 1H, J = 9.0 Hz, H7), 8.29 (s, 1H, H6′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.6 (CH3), 70.5 (CH2), 104.6 (CH), 114.7 (CH), 114.8 (CH), 114.9 (CH), 117.6 (2 × CH), 122.7 (CH), 126.6 (CH), 127.5 (2 × CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 128.6 (2 × CH), 128.7

(CH), 131.4 (Cq), 131.8 (CH), 131.9 (CH), 132.0 (CH), 132.3 (Cq), 132.1(CH), 133.1 (Cq), 133.7 (CH), 134.0 (Cq), 136.2 (Cq), 136.9 (Cq), 137.1 (Cq), 156.0 (Cq), 156.2 (Cq), 156.4 (Cq); HRMS (EI-MS): *m*/*z* calculated for C33H28 N3O4S 562.1801 found 562.1799.

*7.1.53. [6-(1-Benzenesulfonyl-5-benzyloxy-1H-indol-2-yl)-pyrazin-2-yl]-(4-methoxy-phenyl)-amine (**51**)*

Compound **6** was obtained following the general procedure **E**. A solution of compound **26** (400 mg, 0.84 mmol) and *p*-anisidine (155.1 mg, 1.26 mmol) in 1,4-dioxane (8 mL) was used under microwave irradiation. After flash chromatography (petroleum ether/EtOAc 50/50), compound **51** was obtained as yellow solid (392 mg, 83%). Rf: 0.25 (petroleum ether/EtOAc50/50); mp 82 °C; IR (ATR Diamond, cm^{-1}) ν 3436, 2165, 1617, 1548, 1507, 1452, 1367, 1237, 1199, 1177, 1151, 1093, 1028, 998, 830, 726, 684;^{1}H NMR (CDCl3, 250 MHz) δ 3.82 (s, 3H, OCH3), 5.06 (s, 2H, OCH2), 6.15 (s, 1H, NH), 6.78 (s, 1H, H3), 6.92 (d, 2H, J = 9.0 Hz, 2 × H3″), 6.99 (d, 1H, J = 2.3 Hz, H4), 7.07 (dd, 1H, J = 9.0 Hz, J' = 2.5 Hz, H6), 7.29–7.45 (m, 10H, Harom + 2 × H2″), 7.64 (d, 2H, J = 9.5 Hz, Harom), 8.10 (d, 1H, J = 9.5 Hz, H7), 8.11 (s, 1H, H3′), 8.21 (s, 1H, H5′);^{13}C NMR (CDCl3, 100.6 MHz) δ 55.6 (CH3), 70.5 (CH2), 105.0 (CH), 114.7 (2 × CH), 115.3 (CH), 115.9 (CH), 117.3 (CH), 123.6 (2 × CH), 127.0 (2 × CH), 127.5 (2 × CH), 128.0 (CH), 128.6 (2 × CH), 128.7 (2 × CH), 131.0 (CH), 131.2 (Cq), 131.9 (Cq), 133.0 (Cq), 133.6 (CH), 135.3 (CH), 136.8 (Cq), 137.2 (Cq), 139.0 (Cq), 144.4 (Cq), 151.8 (Cq), 156.3 (Cq), 156.6 (Cq); HRMS (EI-MS): *m*/*z* calculated for C32H27 N4O4S 563.1753 found 563.1766.

*7.1.54. [6-(1-Benzenesulfonyl-6-methoxy-1H-indol-2-yl)-pyrazin-2-yl]-(4-methoxy-phenyl)-amine (**52**)*

Compound **6** was obtained following the general procedure **E**. A solution of compound **14** (400 mg, 1.0 mmol) and 4-methoxyaniline (184.72 mg, 1.5 mmol) in 1,4-dioxane (8 mL) was used. After flash chromatography (petroleum ether/EtOAc 50/50), compound **52** was obtained as yellow oil (415 mg, 86%). Rf: 0.25 (petroleum ether/EtOAc 50/50); IR (ATR Diamond, cm^{-1}) ν 3436, 2230, 2165, 1732, 1617, 1505, 1439, 1377, 1363, 1275, 1231, 1175, 1155, 1094, 1034, 997, 865, 831, 727, 686; ^{1}H NMR (CDCl3, 250 MHz) δ 3.82 (s, 3H, OCH3), 3.91 (s, 3H, OCH3), 6.51 (s, 1H, NH), 6.79 (s, 1H, H3), 6.87–6.92 (m, 3H, 2 × H3″ + H4), 6.27–7.49 (m, 6H, Harom + H5), 7.67 (d, 2H, J = 8.5 Hz, 2 × H2″), 7.74 (d, 1H, J = 2.0 Hz, H7), 8.10 (s, 1H, H2′), 8.21 (s, 1H, H6′). ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.5 (CH3), 55.8 (CH3), 100.5 (CH), 113.7 (CH), 114.7 (2 × CH), 115.7 (CH), 121.9 (CH), 123.5 (CH), 123.9 (Cq), 126.9 (2 × CH), 128.7 (2 × CH), 130.7 (2 × CH), 132.0 (Cq), 133.6 (CH), 135.1 (CH), 136.9 (Cq), 137.4 (Cq), 139.6 (Cq), 151.7 (Cq), 1356.5 (Cq), 158.6 (2 × Cq). HRMS (EI-MS): *m*/*z* calculated for C26H23 N4O4S 487.1440 found 487.1449.

*7.1.55. [5-(5-Benzyloxy-1H-indol-2-yl)-pyridin-2-yl]-(4-methoxy-phenyl)-amine (**53**)*

A solution of NaOH (0.23 mL, 2 M in H2O, 0.46 mmol) was added to a solution of compound **50** (164 mg, 0.29 mmol) in methanol (5 mL). The reaction was refluxed under stirring for 12 h. After cooling, the reaction mixture was concentrated under reduced pressure. After hydrolysis with water (15 mL), the crude product was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with brine (10 mL) then dried with MgSO4, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/EtOAc 50/50), compound **53** was obtained as a white solid (85 mg, 70%). Rf: 0.5 (dichloromethane/MeOH 90/10); mp 211 °C; IR (ATR Diamond, cm^{-1}) ν 3448, 3423, 3048, 2165, 1973, 1580, 1512, 1453, 1360, 1343, 1282, 1227, 1199, 1177, 1142, 1032, 794; 727; 691. ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.74 (s, 3H, OCH3), 5.09 (s, 2H, OCH2), 6.78 (s, 1H, H3), 6.84 (dd, 1H, J = 8.8 Hz, J' = 2.3 Hz, H6), 6.94 (d, 2H, J = 8.8 Hz, 2 × H3″), 7.12 (d, 2H, J = 8.8 Hz, 2 × H2″), 7.16 (s, 1H, H4), 7.29 (d, 1H, J = 9.0 Hz, H7), 7.34–7.48 (m, 5H, Harom), 7.63 (s, 1H, H4′), 8.12 (s, 1H, H2′), 8.18 (s, 1H, NH), 8.41 (s, 1H, H6′), 11.44 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 55.2 (CH3), 69.6 (CH2), 99.3 (CH), 103.1 (CH), 112.0 (CH), 112.8 (CH), 112.9 (CH), 114.7 (2 × CH), 115.3 (CH), 120.9 (2 × CH), 127.5 (2 × CH), 128.3 (2 × CH), 128.7 (Cq), 132.5 (Cq), 134.8 (Cq), 135.6 (Cq), 136.2 (CH), 136.6 (CH), 137.6 (2 × Cq), 141.6 (Cq), 152.6 (Cq), 154.4 (Cq); HRMS (EI-MS): *m*/*z* calculated for C27H24 N3O2 422.1869 found 422.1883.

*7.1.56. [6-(5-Benzyloxy-1H-indol-2-yl)-pyrazin-2-yl]-(4-methoxy-phenyl)-amine (**54**)*

Compound **54** was obtained following the general procedure **D**. A solution of compound **51** (270 mg, 0.48 mmol) in THF (12 mL) and 10.0 eq. of Bu4NF (4.8 mL, 1 M in THF, 4.8 mmol) were used. The reaction was refluxed for 12 h. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **54** as a green solid (200 mg, 99%). Rf: 0.22 (petroleum ether/EtOAc50/50); mp 227 °C; IR (ATR Diamond, cm^{-1}) ν 3452, 2238, 2161, 1981, 1617, 1543, 1509, 1450, 1366, 1294, 1226, 1190, 1173, 1151, 1092, 1019, 833, 798, 728, 689;^{1}H NMR (DMSO-*d6*, 250 MHz) δ 3.76 (s, 3H, OCH3), 5.11 (s, 2H, OCH2), 6.90 (dd, 1H, J = 9.0 Hz, J' = 2.5 Hz, H6), 6.97 (d, 2H, J = 9.0 Hz, 2 × H3″), 7.07 (s, 1H, H3), 7.12 (d, 1H, J = 1.7 Hz, H4), 7.32–7.49 (m, 6H, Harom + H7), 7.76 (d, 2H, J = 9.0 Hz, 2 × H2″), 8.03 (s, 1H, H3′), 8.42 (s, 1H, H5′), 9.35 (s, 1H, NH), 11.31 (s, 1H, NH);^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 55.1 (CH3), 69.5 (CH2), 101.6 (CH), 103.2 (CH), 112.7 (CH), 113.8 (CH), 114.1 (2 × CH), 119.9 (2 × CH), 127.5 (3 × CH), 128.3 (3 × CH), 128.4 (Cq), 132.5 (CH), 133.7 (Cq), 135.6 (Cq), 137.6 (Cq), 142.5 (Cq), 145.6 (Cq), 151.6 (Cq), 152.7 (Cq), 154.1 (Cq); HRMS (EI-MS): *m*/*z* calculated for C26H23 N4O2 423.1821 found 423.1822.

*7.1.57. [6-(5-methoxy-1H-indol-2-yl)-pyrazin-2-yl]-(4-methoxy-phenyl)-amine (**55**)*

Compound **56** was obtained following the general procedure **D**. A solution of compound **52** (385 mg, 0.79 mmol) in THF (15 mL) and 10.0 eq. of Bu4NF (7.49 mL, 1 M in THF, 7.49 mmol) were used. The reaction was refluxed for 12 h. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **55** as a green solid (236 mg, 86%). Rf: 0.25 (petroleum ether/EtOAc 50/50); mp 206 °C; IR (ATR Diamond, cm^{-1}) ν 3455, 2116, 2030, 1981, 1613, 1498, 1448, 1424, 1360, 1343, 1176, 1151, 1112, 1093, 1027, 998, 813, 728, 689; ^{1}H NMR (CDCl3, 250 MHz) δ 3.87 (s, 3H, OCH3), 3.89 (s, 3H, OCH3), 6.40 (s, 1H, NH), 6.83 (dd, 1H, J = 8.5 Hz, J' = 2.0 Hz, H5), 6.90 (s, 1H, H3), 6.99 (d, 2H, J = 9.0 Hz, 2 × H3″), 7.04 (d, 1H, J = 1.2 Hz, H7), 7.35 (d, 2H, J = 9.0 Hz, 2 × H2″), 7.55 (d, 1H, J = 8.8 Hz, H4), 7.92 (s, 1H, H2′), 8.45 (s, 1H, H6′), 9.10 (s, 1H, NH); ^{13}C NMR (CDCl3, 100.6 MHz) δ 55.6 (2 × CH3), 94.2 (CH), 101.8 (CH), 111.0 (CH), 114.7 (2 × CH), 122.1 (CH), 123.4 (Cq), 124.1 (2 × CH), 128.5 (CH), 131.0 (CH), 131.8 (Cq), 133.1 (Cq), 137.5 (2 × Cq), 152.0 (Cq), 156.8 (Cq), 157.6 (Cq); HRMS (EI-MS): *m*/*z* calculated for C20H19 N4O2 347.1508 found 347.1496.

*7.1.58. 1-Benzenesulfonyl-6-benzyloxy-2-(6-chloro-pyrazin-2-yl)-1H-indole (**57**)*

Compound **57** was obtained following the general procedure **A**. A solution of compound **56** (1.5 g, 2.29 mmol), 2,6-dichloropyrazine (409.4 mg, 2.75 mmol) and CuI (43.6 mg, 0.22 mmol) in THF (20 mL) were used. The reaction was carried out under μWave irradiation for 30 min at 100 °C. After flash chromatography (petroleum ether/EtOAc 80/20), compound **57** was obtained as an orange solid (989 mg, 91%). Rf: 0.25 (petroleum ether/EtOAc 80/20); mp 57 °C; IR (ATR Diamond, cm^{-1}) ν 3387, 2949, 2909, 2872, 1604, 1506, 1450, 1368, 1234, 1170, 1118, 1086, 1025, 1004, 812, 722, 689; ^{1}H NMR (CDCl3, 250 MHz) δ 5.23 (s, 2H, OCH2), 6.94 (s, 1H, H3), 6.99 (dd, 1H, J = 8.5 Hz, J' = 2.3 Hz, H5), 7.33 (d, 1H, J = 9.7 Hz, H4), 7.37–7.54 (m,

10H, Harom), 7.79 (d, 1H, J = 2.3 Hz, H7), 8.55 (s, 1H, H3′), 8.84 (s, 1H, H5′). ^{13}C NMR (CDCl3, 100.6 MHz) δ 70.5 (CH2), 101.5 (CH), 115.2 (CH), 118.1 (CH), 122.4 (CH), 123.9 (Cq), 127.0 (2 × CH), 127.5 (2 × CH), 128.1 (CH), 128.7 (2 × CH), 128.8 (2 × CH), 133.8 (CH), 134.9 (Cq), 136.4 (Cq), 136.7 (Cq), 139.9 (Cq), 142.6 (CH), 143.8 (CH), 146.9 (Cq), 147.8 (Cq), 158.0 (Cq); HRMS (EI-MS): m/z calculated for C25H19ClN3O3S 476.0836 found 476.0851.

7.1.59. 4-[6-(1-Benzenesulfonyl-5-benzyloxy-1H-indol-2-yl)-pyrazin-2-ylamino]-phenol (**58**)

Compound **58** was obtained following the general procedure **E**. A solution of compound **26** (400 mg, 0.84 mmol) and 4-aminophenol (137.5 mg, 1.26 mmol) in 1,4-dioxane (8 mL) was used. After flash chromatography (petroleum ether/EtOAc 50/50), compound **58** was obtained as a green solid (402 mg, 87%). Rf: 0.22 (petroleum ether/EtOAc 50/50); mp 147 °C; IR (ATR Diamond, cm^{-1}) ν 3329, 2161, 1732, 1617, 1507, 1449, 1372, 1240, 1225, 1178, 1150, 1010, 825, 745, 726, 693; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 5.09 (s, 2H, OCH2), 6.38–6.48 (m, 1H, Harom), 6.72 (d, 2H, J = 9.0 Hz, 2 × H3″), 6.98 (s, 1H, H3), 7.07 (dd, 1H, J = 9.2 Hz, J' = 2.5 Hz, H6), 7.19 (d, 1H, J = 2.2 Hz, H4), 7.31–7.42 (m, 7H, Harom), 7.49 (d, 2H, J = 9.0 Hz, 2 × H2″), 7.67 (d, 2H, J = 8.5 Hz, Harom), 7.92 (d, 1H, J = 9.2 Hz, H7), 8.06 (s, 1H, H3′), 8.17 (s, 1H, H5′), 9.12 (s, 1H, OH), 9.34 (s, 1H, NH); ^{13}C NMR (DMSO-d6, 100.6 MHz) δ 69.5 (CH2), 105.1 (CH), 115.0 (CH), 115.1 (CH), 115.2 (2 × CH), 115.4 (CH), 116.3 (CH), 120.7 (2 × CH), 126.5 (2 × CH), 127.6 (2 × CH), 127.7 (CH), 128.3 (2 × CH), 129.2 (2 × CH), 130.9 (Cq), 131.7 (Cq), 132.9 (CH), 133.6 (CH), 134.2 (CH), 136.0 (Cq), 136.8 (Cq), 138.9 (Cq), 148.1 (Cq), 151.3 (Cq), 152.5 (Cq), 155.7 (Cq); HRMS (EI-MS): m/z calculated for C31H25 N4O4S 549.1597 found 549.1607. (Scheme 4 and 5)

7.1.60. [6-(1-Benzenesulfonyl-6-benzyloxy-1H-indol-2-yl)-pyrazin-2-yl]-(4-benzyloxy-phenyl)-amine (**59**)

Compound **59** was obtained following the general procedure **B**E. A solution of compound **57** (700 mg, 1.47 mmol), 4-(benzyloxy)-aniline hydrochloride (519.9 mg, 2.20 mmol) and 3.0 eq. of K2CO3 (609.5 mg, 4.41 mmol) in 1,4-dioxane (10 mL) were used. After flash chromatography (petroleum ether/EtOAc 50/50), compound **59** was obtained as a brown solid (743 mg, 80%). Rf: 0.22 (petroleum ether/EtOAc 50/50); mp 73 °C; IR (ATR Diamond, cm^{-1}) ν 3436, 2157, 1605, 1503, 1448, 1422, 1366, 1270, 1228, 1174, 1153, 1116, 1090, 1001, 828, 726, 685; ^{1}H NMR (CDCl3, 250 MHz) δ 5.08 (s, 2H, OCH2), 5.22 (s, 2H, OCH2), 6.46 (s, 1H, NH), 6.77 (s, 1H, H3), 6.98 (d, 3H, J = 8.8 Hz, H5 + 2 × H3″), 6.20 (d, 1H, J = 7.8 Hz, H4), 7.33–7.71(m, 17H, Harom + 2 × H2″), 7.81 (d, 1H, J = 2.0 Hz, H7), 8.22 (s, 2H, H3′ + H5′); ^{13}C NMR (CDCl3, 100.6 MHz) δ 70.3 (2 × CH2), 101.6 (CH), 114.7 (CH), 115.7 (2 × CH), 115.8 (CH), 121.9 (CH), 123.3 (2 × CH), 124.0 (Cq), 127.9 (2 × CH), 127.4 (3 × CH), 127.5 (3 × CH), 128.0 (2 × CH), 128.5 (2 × CH), 128.6 (Cq), 128.7 (2 × CH), 128.8 (2 × CH), 132.0 (Cq), 132.2 (Cq), 132.6 (Cq), 133.5 (Cq), 136.9 (2 × Cq), 137.1 (Cq), 139.4 (Cq), 155.7 (Cq), 157.5 (Cq); HRMS (EI-MS): m/z calculated for C38H31 N4O4S 639.2066 found 639.2062.

7.1.61. 4-[6-(5-Benzyloxy-1H-indol-2-yl)-pyrazin-2-ylamino]-phenol (**60**)

Compound **60** was obtained following the general procedure **D**. A solution of compound **58** (370 mg, 0.67 mmol) in THF (15 mL) and 4.0 eq. of Bu4NF (2.7 mL, 1 M in THF, 2.7 mmol) were used. The reaction was refluxed for 8 h. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **60** as green solid (102 mg, 37%). Rf: 0.17 (petroleum ether/EtOAc 50/50); mp 250 °C; IR (ATR Diamond, cm^{-1}) ν 3452, 3190, 3031, 1609, 1542, 1507, 1447, 1372, 1226, 1194, 1149, 1023, 832, 796, 727, 690; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 5.11 (s, 2H, OCH2), 6.79 (d, 2H, J = 8.8 Hz, 2 × H3″), 6.89 (dd, 1H, J = 9.0 Hz, J' = 2.5 Hz, H6), 7.04 (s, 1H, H3), 7.19 (d, 1H, J = 2.0 Hz, H4), 7.32–7.49 (m, 6H, Harom + H7), 7.60 (d, 2H, J = 8.8 Hz, 2 × H2″), 7.99 (s, 1H, H3′), 8.39 (s, 1H, H5′), 9.10 (s, 1H, OH), 9.20 (s, 1H, NH), 11.27 (s, 1H, NH); ^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 69.5 (CH2), 105.1 (CH), 105.4 (CH), 108.8 (CH), 109.3 (CH), 115.1 (CH), 115.3 (CH), 116.4 (CH), 126.6 (CH), 127.6 (CH), 127.8 (CH), 128.3 (CH), 129.2 (CH), 129.4 (CH), 130.9 (Cq), 131.4 (Cq), 134.0 (CH), 134.3 (CH), 135.9 (Cq), 136.8 (Cq), 138.8 (Cq), 141.5 (Cq), 151.0 (Cq), 155.7 (Cq), 157.7 (Cq); HRMS (EI-MS): m/z calculated for C25H21 N4O2 409.1679 found 409.1665.

7.1.62. [6-(6-Benzyloxy-1H-indol-2-yl)-pyrazin-2-yl]-(4-benzyloxy-phenyl)-amine (**61**)

Compound **61** was obtained following the general procedure **D.** A solution of compound **59** (700 mg, 1.09 mmol) in THF (20 mL) and 10.0 eq of Bu4NF (10.9 mL, 1 M in THF, 10.9 mmol) were used. The reaction was refluxed for 10 h. Flash chromatography (petroleum ether/EtOAc 50/50) afforded compound **61** as a brown solid (408 mg, 75%). Rf: 0.2 (petroleum ether/EtOAc 50/50); mp 204 °C; IR (ATR Diamond, cm^{-1}) ν 3391, 3035; 2913, 2161, 1597, 1539, 1504, 1435, 1368, 1256, 1231, 1165, 1115, 1024; 815, 722, 691; ^{1}H NMR (DMSO-*d6*, 250 MHz) δ 5.11 (s, 2H, OCH2), 5.16 (s, 2H, OCH2), 6.84 (dd, 1H, J = 8.8 Hz, J' = 2.3 Hz, H5), 7.00–7.33 (m, 4H, H3 + H4 + 2 × H3″), 7.36–7.63 (m, 11H, Harom + H7), 7.76 (d, 2H, J = 9.0 Hz, 2 × H2″), 8.01 (s, 1H, H3′),8.14 (s, 1H, H5′), 9.36 (s, 1H, NH), 11.27 (s, 1H, NH); ^{13}C NMR (DMSO-*d6*, 100.6 MHz) δ 69.4 (2 × CH2), 95.8 (CH), 101.9 (CH), 110.9 (CH), 115.1 (CH), 119.8 (CH), 121.3 (CH), 122.6 (Cq), 127.4 (2 × CH), 127.5 (2 × CH), 127.6 (Cq), 127.7 (2 × CH), 128.3 (3 × CH), 128.6 (CH), 128.7 (CH), 131.3 (CH), 131.4 (CH), 131.9 (CH), 134.0 (Cq), 134.1 (Cq), 137.3 (2 × Cq), 137.4 (Cq), 138.1 (Cq), 153.1 (Cq), 155.5 (Cq); HRMS (EI-MS): m/z calculated for C32H27 N4O2 499.1594 found 299.1605.

7.2. Kinase preparations and assays

Buffer A: 10 mM MgCl2, 1 mM EGTA, 1 mM DTT, 25 mM Tris–HCl pH 7.5, 50 μg heparin/ml. *Buffer C*: 60 mM β-glycerophosphate, 15 mM *p*-nitrophenylphosphate, 25 mM Mops (pH 7.2), 5 Mm EGTA, 15 mM MgCl2, 1 mM DTT, 1 mM sodium vanadate, 1 mM henylphosphate. Kinase activities were assayed in Buffer A or C, at 30 °C, at a final ATP concentration of 15 μM. Blank values were subtracted and activities expressed in% of the maximal activity, i.e. in the absence of inhibitors. Controls were performed with appropriate dilutions of DMSO. *CDK5/p25* (human, recombinant) was prepared as previously described [36]. Its kinase activity was assayed in buffer C, with 1 mg histone H1/mL, in the presence of 15 μM [γ-33P] ATP (3000 Ci/mmol; 10 mCi/mL) in a final volume of 30 μL. After 30 min incubation at 30 °C, 25 μL aliquots of supernatant were spotted onto 2.5 × 3 cm pieces of Whatman P81 phosphocellulose paper, and, 20 s later, the filters were washed five times (for at least 5 min each time) in a solution of 10 ml phosphoric acid/liter of water. The wet filters were counted in the presence of 1 mL ACS (Amersham) scintillation fluid. *GSK-3αβ* (porcine brain, native) was assayed, as described for CDK5/p25 but in Buffer A and using a GSK-3 specific substrate (GS-1: YRRAAVPPSPSLSRHSSPHQSpEDEEE) (pS stands for phosphorylated serine). 15 GS-1 was synthesized by Millegen (Labege, France). *DYRK1A* (rat, recombinant, expressed in *Escherichia coli* as a GST fusion protein) was purified by affinity chromatography on glutathione–agarose and assayed as described for CDK5/p25 using myelin basic protein (1 mg/mL) as a substrate.

7.3. Cell culture and survival assay

Skin diploid fibroblastic cells were provided by BIOPREDIC International Company (Rennes, France). Caco-2 cells and Huh7

cells were obtained from the ECAC collection. Cells were grown according to ECAC recommendations. The RLEC-F1 clone was derived from an established rat biliary epithelial cell line as previously described [37]. The toxicity test of the compounds on these cells was as follows: 4×10^3 cells were seeded in 96 multiwell plates and left for 24 h for attachment, spreading and growing. Then, they were exposed for 48 h to increasing concentrations of the compounds, ranging from 0.1 to 25 μL in a final volume of 80 μL of culture medium. They were fixed with 4% paraformaldehyde solution and nuclei were stained with Hoechst 3342 and counted using automated imaging analysis (Simple PCI software).

7.4. Molecular modeling

Hardware and software: all molecular modeling studies were performed with the Schrodinger Molecular Modeling Suite 2010 [38]. Maestro was 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: complex DYRK1A with 7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (HRM) was retrieved from the protein data bank [34]. 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 Modeling Suite 2010. The protein was preprocessed (hydrogen atoms added, incomplete residues filled …), bond orders and connections of ligands were manually corrected. An exhaustive sampling was done 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 ones co-crystallized, were built within Marvin [39] and were submitted to Corina [40], a 3D structure generator. Next 3D structures were submitted to the LigPrep module of the Schrodinger Molecular Modeling Suite 2010 in order to take into account tautomerization and ionization via Ionizer module. Resulting structures became the starting point of docking simulations.

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

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