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Synthesis of 3,5-bis(2-indolyl)pyridine and 3-[(2-indolyl)-5-phenyl]-pyridine derivatives as CDK inhibitors and cytotoxic agents

Ulrich Jacquemard,[a] Nathalie Dias,[b] Amélie Lansiaux,[b] Christian Bailly,[b,†] Cédric Logé,[c] Jean-Michel Robert,[c] Olivier Lozach,[d] Laurent Meijer,[d] Jean-Yves Mérour[a] and Sylvain Routier[a,*]

[a]*Institut de Chimie Organique et Analytique, (1) Université d'Orléans, (2) CNRS UMR 6005, Rue de Chartres, BP 6759, 45067 Orléans Cedex 2, France*
[b]*INSERM U-837, IRCL, Place de Verdun, 59045 Lille, France*
[c]*Université de Nantes, Nantes Atlantique Universités, Biomolécules et Cibles Thérapeutiques, Département de Pharmacochimie, BioCiT-EA 1155, UFR Sciences Pharmaceutiques, 1 rue Gaston Veil, Nantes F-44000, France*
[d]*CNRS, Amyloids & Cell Division Cycle Group, 29680 Roscoff, France*

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Abstract—We here report the synthesis and biological evaluation of new 3,5-bis(2-indolyl)pyridine and 3-[(2-indolyl)-5-phenyl]pyridine designed as potential CDK inhibitors. Indole, 5-hydroxyindole, and phenol derivatives were used to generate three substitutions of the pyridine. The resulting skeletons were successively exploited to introduce various dimethylaminoalkyl side chains by Williamson type reactions. The synthesis includes Stille or Suzuki type reactions, which were realized on the 3,5-dibromopyridine. The preparation and the use of stannylindoles in mono or bis cross-coupling reactions were also described and each step was optimized and detailed. Kinase assays were realized and shown that nude compounds **7**, **18**, and **25** inhibited CDK1 in the 0.3–0.7 micromolar range with a good selectivity over GSK-3. Cytotoxicity against CEM human leukemia cells was evaluated with IC_{50} values in the 5–15 micromolar range. Precise structure–activity relationships were delineated. Molecular modeling and docking solutions were proposed to complete the studies and to explain the observed SAR in the CDK assays.

1. Introduction

Numerous marine indole alkaloids have been isolated and among them certain bis(indole) secondary metabolites containing an imidazole- or a piperazine-derived spacer unit[1] exhibit a broad spectrum of biological activities, with potent cytotoxic effects toward cancer cells in some cases. As an example, dragmacidin D (Fig. 1),[2] extracted from deep-water sponges, was described as a potent inhibitor of serine/threonine protein phosphatases. In this case, a piperazinone ring separates the two indoles units. This compound shows a structural analogy with hamacanthin A and asterriquinone, isolated from Aspergillus terreus, which both possess a bis indolic structure, spaced by a piperidinone or a quinonic system.[3] Structure of these cytotoxic natural products can also be compared to some extent to synthetic 3-substituted indole derivatives of type **I** (Fig. 1) acting as anti-angiogenic inhibitors of the KDR kinase.[4]

These indole structures provide an interesting framework for the design of novel targeted anticancer agents. Mixing the structure of the related compound in Figure 1, suggested also that a pyridine heterocycle substituted with one or two indoles units apparently should represent a suitable core to interact with the ATP-binding sites of enzymes.[5]

In an ongoing program devoted to the design of DNA-binding anticancer agents we have developed non-fused tris-aromatic compounds containing either a carbazole **II**[6,7] or pyridine **III**[8] or pyrazine **IV**[9] central ring. All of them were disubstituted in positions 3 and 5 by aryl groups. SAR studies showed that in the three series

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* Corresponding author. Tel.: +33 2 38 49 48 53; fax: +33 2 38 41 72 81; e-mail: sylvain.routier@univ-orleans.fr
† Present address: Centre de Recherche en Oncologie Expérimentale, Institut de Recherche Pierre Fabre, 3 rue des satellites, 31140 Toulouse, France.

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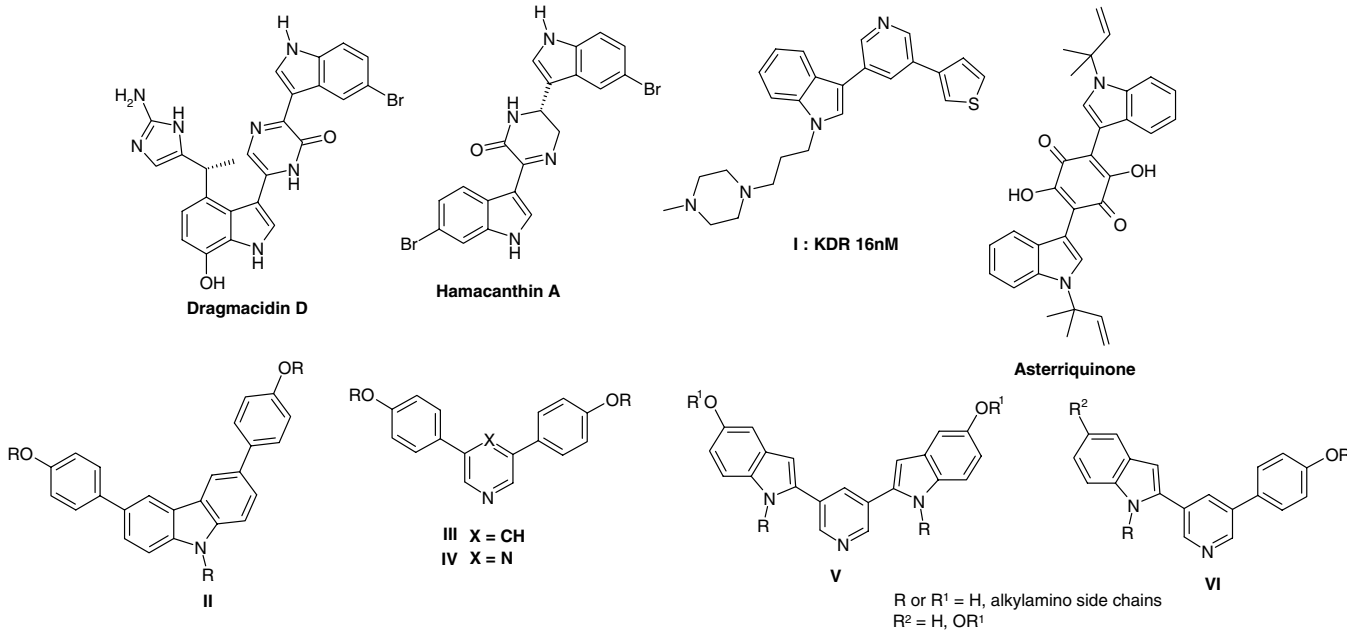


Figure 1. 3-Substituted indolic structures and general structures of synthesized compounds.

the introduction of lateral basic side chains led to strong DNA binders whereas the absence of side chains generally reduced or abolished the DNA sequence recognition property. A few compounds in those series also revealed modest kinase inhibitory activities. First molecular modeling studies indicated that the absence of a crucial donor acceptor hydrogen bond system in the medium size of the tricyclic structure was for us the major reason to explain this result.[10] As we were interested in the design of new CDK inhibitors, we focused our new effort on V-shaped pyridinyl derivatives bearing as substituents one or two indole rings. The lack of one of the two indoles was corrected by the introduction of a phenol. These compounds (types **V** and **VI**), could be considered as mimics of the related compounds in Figure 1 and were certainly able to promote binding to the ATP sites by a supplementary hydrogen bond. 2-Substituted indoles close to the pyridinyl hydrogen acceptor atom should achieve this donor/acceptor strategy. In addition, based on our previous experiences with molecules of types **II**–**IV**, we used the free OH to introduce alkyl basic side chains to enhance solubility, and to introduce molecular diversity in order to verify our hypothesis (Fig. 1).

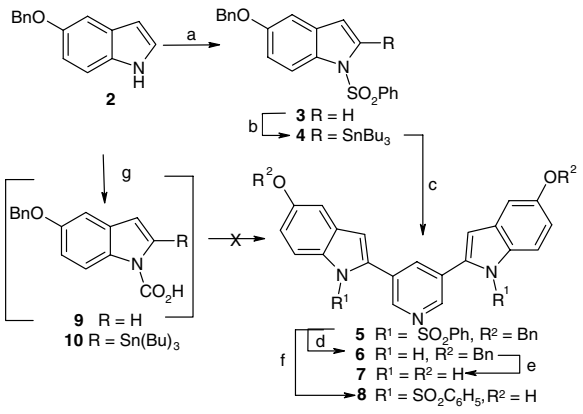
Bis-indoles linked by position-2 to a spacer such as in compound of type **V** are scarcely described.[11] Most of them have been developed as polyaza cavity-shaped molecules.[12–15] A reported synthesis of unsubstituted compounds of type **V** is the result of a double Fischer reaction on 3,5-diacetylpyridine.[16] A different strategy was applied in the present case.

2. Chemistry

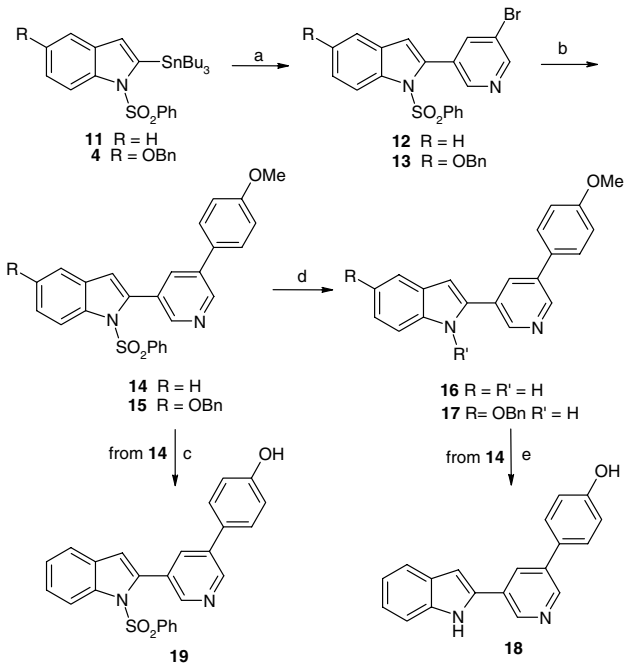
In order to produce symmetrical and unsymmetrical aromatic heterocyclic structures of types **V** and **VI**, we performed a retrosynthetic analysis, which led us to choose a one pot double Stille procedure in the case of **V** and a Stille/Suzuki tandem cross-coupling strategy for **VI**. In both cases, the starting material was the 3,5-dibromopyridine **1**.

2.1. Synthesis of symmetrical compounds type V

5-Benzyloxyindole **2** was protected with a phenylsulfonyl group to give **3** (95% yield), which then was treated with LDA (1.5 equiv) in THF at −20 °C for 30 min (Scheme 1). Tributylstannyl chloride was added at −78 °C to rt to give the stannyl derivative **4** in a good yield (78%). The synthetic sequence was completed with a Stille reaction involving **4** in a slight excess (2.3 equiv) and 3,5-dibromopyridine **1** in the presence of $Pd(PPh_3)_4$



Scheme 1. Reagents and conditions: (a) NaH (2.3 equiv), $PhSO_2Cl$ (2.0 equiv), THF, 0 °C to rt, 4 h, 95%; (b) LDA (1.5 equiv), THF, −20 °C, 30 min then Bu_3SnCl (1.7 equiv), −78 °C to rt, 2 h, 78%; (c) 3,5-dibromopyridine **1**, **4** (2.3 equiv), $Pd(PPh_3)_4$ (0.1 equiv), CuI (0.2 equiv), THF, 8 h, reflux, 89%; (d) Bu_4NF (5 equiv), THF, reflux, 2.5 h, 74%; (e) BBr_3 (2.1 equiv), CH_2Cl_2, rt, 3 h, 33%; (f) BBr_3 (7 equiv), idem, 68%. (g) i—CO_2, BuLi, THF, −78 °C; ii—*t*-BuLi, Bu_3SnCl (1.2 equiv), −78 °C, 1 h 30.



Scheme 2. Reagents and conditions: (a) 3,5-dibromopyridine **1**, $Pd(PPh_3)_4$ (0.05 equiv) CuI (0.1 equiv), THF, reflux, from **11**, 4 h, **12**, 88%; from ***4***, 8 h, **13** 78%; (b) 4-methoxyboronic acid (1.2 equiv), toluene/ethanol 5/3, aq. satd. $NaHCO_3$, reflux, 18 h, from **12**, $Pd(PPh_3)_4$ (0.1 equiv), **14** 97%; from ***13***, $Pd(PPh_3)_4$ (0.05 eq), **15** 81%; (c) BBr_3 (4.1 equiv), CH_2Cl_2, 0 °C to rt, 3 h, from**14**, **19** 77%; (d) Bu_4NF (3.5 equiv), THF, reflux, 2 h, from **14**, **16** 83%; from **15**, **17** quant.; (e) HBr 47%, AcOH, reflux, 5 h, from **16**, **18** 83%.

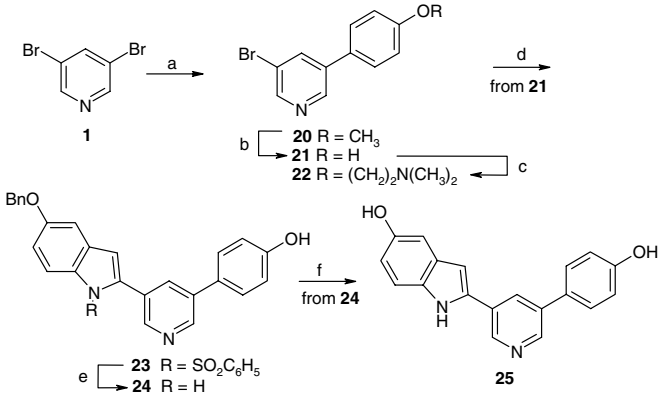
(10 %) and CuI (20%) in refluxing THF. The two simultaneous coupling procedures led after 8 h to the bis indolic compound **5** in an 89% yield. A selective deprotection of the protecting groups was next successfully realized. The phenylsulfonyl group of **5** was removed using Bu_4NF (5 equiv) in refluxing THF to afford **6** (74% yield). The cleavage of the benzyl groups occurred by treating **5** or **6** at room temperature with an excess of BBr_3. A satisfactory yield of **8** was obtained (68%) from **5**, whereas similar conditions led to **7** in only 33% yield from **6**. In order to synthesize compound **7** directly from **2**, we next prepared the 5-benzyloxy-1-carboxy-2-stannylindole **10** (obtained by reacting Bu_3SnCl on the dilithium salt of 5-benzyloxy-1-carboxyindole **9**) which was used in a Stille reaction with 3,5-dibromopyridine **1** but we were unable to isolate the desired compound and only the 5-benzyloxyindole **2** was recovered in a quantitative manner.

2.2. Synthesis of dissymmetrical structure type VI

The second framework was the disubstituted pyridine in positions 3 and 5, respectively, with an indole and a 4-hydroxyphenyl ring. We used a similar approach to that described for **5** (Scheme 1), starting from the stannyl derivatives **4** and **11**.

The mono Stille coupling of **4** and **11** with 3,5-dibromopyridine **1** was carefully controlled using only stoichiometric amount of stannylated derivatives. In this case only 5% of catalyst was necessary to isolate compounds **12** and **13** in 88% and 78% yields from **11** and **4**, respectively (see Scheme 2).

Then the second aryl unit was introduced by a Suzuki reaction on **12** and **13** with the commercially available 4-methoxyphenylboronic acid to afford **14** and **15** in 97% and 81% yield, respectively. The experimental conditions required $Pd(PPh_3)_4$ as catalyst and aqueous $NaHCO_3$ in a refluxing mixture of toluene and ethanol. Deprotection of the phenylsulfonyl group of **14** and **15** was achieved with Bu_4NF in THF at room temperature and afforded **16** in 83% yield and **17** quantitatively. The methoxy group of **16** was then removed with HBr in acetic acid leading to **18** in an 83% yield. In addition, starting from compound **14**, the ether deprotection occurred, using BBr_3, to give **19** in a 77% yield. At this stage, it must be pointed out that the cleavage of the ethers of **15** and **17** was unproductive. So we envisaged another way and began by the Suzuki palladium catalyzed reaction involving the 3,5-dibromopyridine **1** and a slight default of 4-methoxyphenylboronic acid (Scheme 3). Thus, compound **20** was isolated after 18 h in a 77% yield. After a quantitative demethylation leading to **21**, the Stille reaction with indole **4** led to **23** in only 33% yield.



Scheme 3. Reagents and conditions: (a) 4-methoxyphenylboronic acid (0.95 equiv), $Pd(PPh_3)_4$,(0.1 equiv), toluene/ethanol 5/1, aq. satd. $NaHCO_3$, reflux, 18 h, 77%; (b) BBr_3, CH_2Cl_2, 0 °C to rt, 3 h, quant; (c) Cs_2CO_3, **26**, DMF, 100 °C, 8 h, 57%; (d) **4** (1.1 equiv), $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.1 equiv), THF, reflux, 4 h, 33%; (e) Bu_4NF (5 equiv), THF, reflux, 1h, 80%; (f) BBr_3 (1.2 equiv), CH_2Cl_2, 0 °C to rt, 3 h, 52%.

Table 1. Conditions for the synthesis of **28**–**35**

Entry	Starting material	Conditions	Compound	R^1	R^2	Yield[a] (%)
1	**6**	(a) NaH (8 equiv), **26** (2.25 equiv), DMF, 0 °C to 100 °C, 2 h	**28**	$(CH_2)_2N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	55
2	**6**	Idem (a) with **27** (2.5 equiv)	**29**	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	52
3	**6**	(b) Idem, NaH (2.5 equiv), **26** (1.2 equiv)	**30**	$(CH_2)_2N(CH_3)_2$	H	58
4	**6**	Idem (b) with **27**	**31**	$(CH_2)_3N(CH_3)_2$	H	60
5	**28**	(c) BBr_3, (1.25 equiv), CH_2Cl_2, 0 °C to rt, 2 h	**32**	$(CH_2)_2N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	49
6	**29**	Idem (c) with **29**	**33**	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	47
7	**30**	Idem (c) with and BBr_3 (2eq)	**34**	$(CH_2)_2N(CH_3)_2$	H	52
8	**31**	Idem (c) with **31**	**35**	$(CH_2)_3N(CH_3)_2$	H	48

SM, starting material.
[a] Yields in purified products.

Step by step deprotection afforded first **24** in an 83% yield and then **25** in a 52% yield.

2.3. Synthesis of symmetrical alkylated compounds of type V

Direct alkylation of symmetrical compounds of type **V** was performed under Williamson type alkylations involving the 2-chloroethyl or 3-chloropropyl dimethylamine hydrochloride salts **26** and **27**. In order to direct successfully all the reactions on the two nitrogen indolic atoms, compound **6** was treated with an excess of NaH at 0 °C. After 30 min, hydrochlorides **26/27** were added and the temperature adjusted to 100 °C for the desired time. All results are indicated in Table 1 and Scheme 4. Using a large excess of **26** or **27**, disubstituted compounds **28** and **29**were obtained whereas in the presence of 1.0 equiv of the same reagents only mono alkylated products **30** and **31** were isolated. Cleavages of the residual ether groups were carried out with BBr_3 at room temperature. All alkylation and deprotection steps were quantitative on TLC but numerous difficulties appeared during aqueous treatment and chromatographic purification, decreasing also the yields in isolated compounds **28**–**35**.

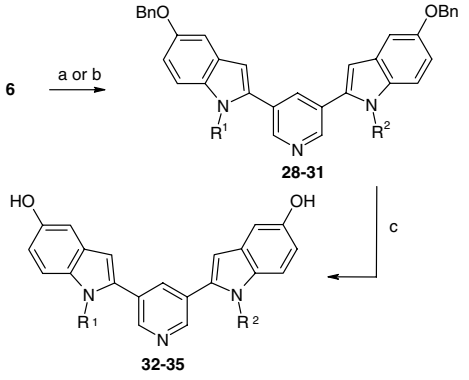
All our efforts concerning the use of fully unprotected compound **7** in such alkylation reactions or Mitsunobu reaction using the corresponding alcohol failed. To circumvent this problem, we decided to introduce the dimethylaminoethyl side chain at the beginning of the synthesis.

The 5-[2-dimethylamino(ethoxy)]indole **36** was prepared in a global yield of 54% from **3** by (i) a cleavage of the benzyl group with BBr_3 (ii) an alkylation using **26** and Cs_2CO_3 as base (Scheme 5).

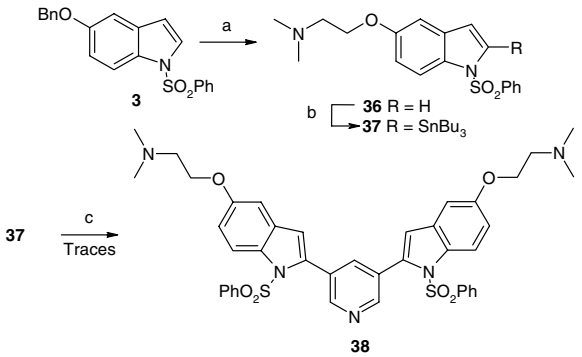
The best conditions for obtaining the stannyl derivative **37** were the use of LDA (3 equiv) at −20 °C followed by the addition of Bu_3SnCl (3.4 equiv) at −78 °C to rt (60% yield). A large excess of LDA (4.5 equiv) gave a lower yield (50%). In spite of our numerous efforts, the Stille coupling of **37** with 3,5-dibromopyridine gave unfortunately only traces (<4%) of the targeted bis-indole **38**.

2.4. Synthesis of disymmetrical alkylated compounds of type VI

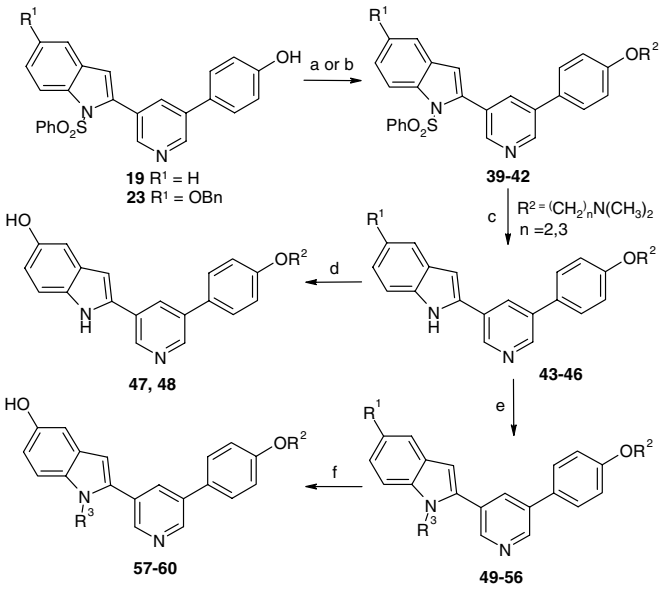
Having in our hands the two main frameworks **24** and **25**, the introduction of the 2-dimethylaminoethyl and 3-dimethylaminopropyl residues was tentatively performed on the nitrogen and oxygen atoms simultaneously with the corresponding chlorides **26** and **27**. However, despite numerous efforts, all attempts failed. In contrast, alkylations of the phenol group of the partially protected compounds **19** and **23** were successfully performed (Scheme 6, Table 2 entries 1–4).



Scheme 4. Reagents and conditions: see also Table 1.



Scheme 5. Reagents and conditions: (a) i—BBr_3 (1.2 equiv), CH_2Cl_2, 0 °C to rt, 2 h, 80%; ii—**26** (1.2 equiv), Cs_2CO_3 (2.7 equiv), DMF, rt to 100 °C, 3.5 h, 67%; (b) i—LDA (3 equiv), THF, −20 °C, 30 min then Bu_3SnCl (3.4 equiv), −78 °C to rt, 18 h, 60%; (c) $Pd(PPh_3)_4$ (0.1 equiv), CuI (0.2 equiv), THF, reflux, 24 h, traces.



Scheme 6. Reagents and conditions: For details see also Table 2.

Table 2. Synthesis of compounds **39**–**60**

Entry	Starting material	Conditions	Compound	R^1	R^2	R^3	Yield[a] (%)
1	**19**	(a) **26** (1.5 equiv), Cs_2CO_3 (2.9 equiv), DMF, rt, 2 h	**39**	H	$(CH_2)_2N(CH_3)_2$	—	77
2	**19**	(b) **27** (1.5 equiv), Cs_2CO_3 (2.9 equiv), DMF, rt, 2 h	**40**	H	$(CH_2)_3N(CH_3)_2$	—	80
3	**23**	Idem (a) with Cs_2CO_3 (2.7 equiv), 4 h	**41**	OBn	$(CH_2)_2N(CH_3)_2$	—	69
4	**23**	Idem (b) with Cs_2CO_3 (2.7 equiv), 4 h	**42**	OBn	$(CH_2)_3N(CH_3)_2$	—	72
5	**39**	(c) Bu_4NF (1.5 equiv), THF, rflx, 3 h	**43**	H	$(CH_2)_2N(CH_3)_2$	—	64
6	**40**	Idem	**44**	H	$(CH_2)_3N(CH_3)_2$	—	87
7	**41**	Idem	**45**	OBn	$(CH_2)_2N(CH_3)_2$	—	84
8	**42**	Idem	**46**	OBn	$(CH_2)_3N(CH_3)_2$	—	85
9	**45**	(d) BBr_3 (1.1 equiv), CH_2Cl_2, rt, 2 h	**47**	OH	$(CH_2)_2N(CH_3)_2$	—	60
10	**46**	Idem	**48**	OH	$(CH_2)_3N(CH_3)_2$	—	54
11	**43**	(e) **26** (1.5 equiv), NaH (4 equiv), DMF, 100 °C	**49**	H	$(CH_2)_2N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	83
12	**27**	Idem	**50**	H	$(CH_2)_2N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	81
13	**44**	Idem	**51**	H	$(CH_2)_3N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	53
14	**44**	Idem (e) with **27**	**52**	H	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	45
15	**45**	Idem (e) with **26**	**53**	OBn	$(CH_2)_2N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	53
16	**45**	Idem (e) with **27**	**54**	OBn	$(CH_2)_2N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	69
17	**46**	Idem (e) with **26**	**55**	OBn	$(CH_2)_3N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	70
18	**46**	Idem (e) with **27**	**56**	OBn	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	67
19	**53**	(f) BBr_3 (1.1 equiv), CH_2Cl_2, rt, 2 h	**57**	—	$(CH_2)_2N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	55
20	**54**	Idem	**58**	—	$(CH_2)_2N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	50
21	**55**	Idem	**59**	—	$(CH_2)_3N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	52
22	**56**	Idem	**60**	—	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	49

SM, starting material.
[a] Yields in purified products.

Mono O-alkylation of **19** or **23** being the only possibility, we used an excess of the electrophile **26** and **27**, in the presence of Cs_2CO_3 as base to afford **39**–**42** in 69–80% yields. The indolic nitrogen atom was first deprotected using Bu_4NF for 2 h in refluxing THF giving access to **43**–**46** in fairly good yields (entries 5–8). As a last step, cleavage of the benzyl ether groups of **45** and **46** with BBr_3 (2.1 equiv) led to compounds **47** and **48** (entries 9–10). Here again, all reactions appeared as quantitative on TLC.

Following a similar strategy, the indolic nitrogen atom of **43**–**46** was reacted with the corresponding chlorides **26** and **27** and an excess of NaH in DMF at rt. Compounds **49**–**56** were thus obtained in 45–83% yields (entries 11–18). As a final reaction, the *O*-benzyl group of **53**–**56** was cleaved with BBr_3 in dichloro-

methane to afford compounds **57**–**60**in 49–55% yields (entries 19–22).

3. Results and discussion

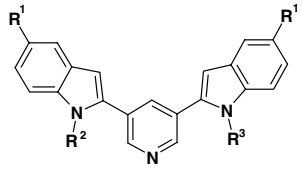
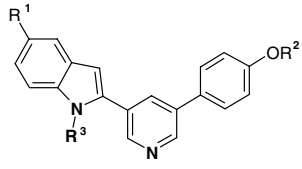
Several compounds were evaluated for inhibition of protein kinases. Cytotoxicity and cell cycle analyses were also performed. In addition, a molecular modeling study was performed to support the experimental results of the best compounds. Kinases activities assays were performed according to our previously published methodology (all experimental details were indicated).[9]

Compounds with two indole rings and *N*-aminoalkyl side chains (**32**–**35**), which were certainly charged at physiologic pHs, have no effect on the tested kinases, whatever the length of the side chain (2 or 3 carbons). The same is true for the monoindolic compounds substituted on the indole NH and bearing a phenol function (**49**–**52**, **57**–**60**). In the bis indolic series, the best activities appeared when all the *O*- and *N*- heteroatoms were unsubstituted, indicating also the crucial role of donor/acceptor hydrogen bonds to generate the CDK binding. Nevertheless compound **7** exhibits a moderate inhibition of CDK1 with an IC_{50} of 0.54 μM (Table 3, entry 1). The two indoles should be also too bulky to give full inhibition of the enzyme at low concentration. This hypothesis was confirmed with compounds **34** and **35** bearing an indolic side chain, which certainly modified the conformation of the molecule and dramatically decreased the activities (entries 4–5).

In the second mono indolyl series, the size of one of the pyridine satellites was reduced to a 4-hydroxyphenyl moiety (entries 6–19). As attempted all the unsubstituted NH indolic compounds exhibited quantifiable inhibition of the enzyme (**18**, **43**, **44**, **25**, **47**, and **48**, $IC_{50} < 10$ μM). The best activity was found with the unsubstituted compound **25** ($IC_{50} = 0.31$ μM, entry 13). Suppression of the hydroxyl group on the indole ring decreases the activity (**18**, entry 6), suggesting that this OH function is essential for enzyme binding through hydrogen-bonding, leading to inhibition. The same behavior was observed by alkylation of the phenol by a hydrophilic chain. Activities of compounds **43** and (**47**, **48**) were significantly reduced by a factor of 5- to 10-fold compared to **18** and **25**, respectively. There is no doubt that the donor/acceptor hydrogen bond system (NH of indole/N of pyridine) and the two OH groups are key elements for the kinase inhibition.

Preliminary information about kinase selectivity was obtained by testing the compounds for inhibition of two related kinases, CDK5 and GSK-3. Interestingly, the three most potent molecules **7**, **18**, and **25** were also slightly less active toward CDK5. In addition, these compounds were 30- to 100-fold more active toward CDK1 versus GSK-3. This excellent selectivity could be explained by the substitution of the phenol. Addition of an hydrophilic side chain (i) decreased the inhibition of CDK1, (ii) enhanced the inhibition of GSK-3, and (iii) decreased also the selectivity [(**43**, **44**), and (**47**, **48**) compared to **18** and **25**, respectively]. The aminoalkyl chain should interfere with an hydrophilic pocket in the ATP site of GSK-3. The observed selectivity of

Table 3. Biological activities

Entry	Formula	Compound	R^1	R^2	R^3	CEM IC_{50}	CDK1 IC_{50}	CDK5 IC_{50}	GSK-3 α/β IC_{50}
1		**7**	OH	H	H	7.99	**0.54**	1.2	30
2		**32**	OH	$(CH_2)_2N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	14.8	>10	ND	>10
3		**33**	OH	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	11.1	>10	ND	>10
4		**34**	OH	$(CH_2)_2N(CH_3)_2$	H	5.76	>10	ND	>10
5	**7, 32-35**	**35**	OH	$(CH_2)_3N(CH_3)_2$	H	14.21	>10	ND	>10
6		**18**	H	H	H	4.67	**0.7**	0.9	>100
7		**43**	H	$(CH_2)_2N(CH_3)_2$	H	9.02	2.5	3.1	4.8
8		**44**	H	$(CH_2)_3N(CH_3)_2$	H	5.4	**0.9**	1	31
9		**49**	H	$(CH_2)_2N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	7.97	>10	ND	>10
10		**50**	H	$(CH_2)_2N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	3.72	>10	ND	>10
11		**51**	H	$(CH_2)_3N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	4.13	>10	ND	>10
12		**52**	H	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	4.19	>10	ND	>10
13		**25**	OH	H	H	14.45	**0.31**	1.5	40
14		**47**	OH	$(CH_2)_2N(CH_3)_2$	H	12.33	3.6	6.7	4.6
15		**48**	OH	$(CH_2)_3N(CH_3)_2$	H	5.35	1.9	5	3.8
16	**18, 25, 43, 44, 47-52, 57-60**	**57**	OH	$(CH_2)_2N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	31.94	>10	ND	>10
17		**58**	OH	$(CH_2)_2N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	59.26	>10	ND	>10
18		**59**	OH	$(CH_2)_3N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	20.76	>10	ND	>10
19		**60**	OH	$(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	12.67	>10	ND	>10

ND, not determined. All IC_{50} were expressed in μM and were linked to cytotoxicity for CEM and to kinase inhibition for CDK 1, 5 and GSK-3. IC_{50} values are averaged from two experiments.

our compounds prompted us to investigate further their binding to the enzyme using molecular modeling.

3.1. Cytotoxicity

The compounds were evaluated for cytotoxicity using CEM human leukemia cells. In parallel, we measured the DNA binding (data not shown) but no strict correlation could be established with the cytotoxicity. IC_{50} values in the 3–5 μM range were obtained for the best compounds. A marked cytotoxic effect was also measured with the CDK1 inhibitor **18**, which is more cytotoxic than **7** and much more potent than **25**. Nevertheless the inhibition of the tumor cell proliferation and the cytotoxicity are limited to the micromolar range. This result is also in agreement with the other published results,[17] which indicate that potent inhibition of the CDKs led rarely to strong cytotoxic agents.

3.2. Molecular modeling

Several forms of CDK2 have been crystallized in the last years. In sharp contrast, the 3D structure of CDK1 has not been reported. As our compounds were evaluated for biochemical activity against CDK1-cyclin B, we decided to create a homology model of human CDK1-cyclin B from the crystal structure of human CDK2-cyclin A in complex with indirubin-5-sulfonate.[18] Our goal was to obtain a working model of CDK1 able to illustrate some features of the binding of a new class of inhibitors into the ATP-binding site cavity. Indeed, molecular modeling studies of the compounds shown in Table 3 were conducted *a posteriori* to understand the observed structure–activity relationships. Sequence alignment was performed as described in Section 5, and the results are shown in Figure 2. Sequence identity between CDK1 and CDK2 is about 65% and reaches 90% within the ATP-binding site.

The binding poses found by the docking program GOLD for the most active compounds **18** and **25** into the ATP pocket of our homology model of human CDK1 are shown in Figure 3. These compounds have a similar docking mode and make two key hydrogen-bonding interactions with the backbone of the kinase at the hinge region; the NH group of Leu83 donates a hydrogen bond to the pyridine nitrogen, the carbonyl oxygen of Leu83 acts as a hydrogen bond acceptor to the indole nitrogen NH of the inhibitors. This typical pattern of hydrogen-bonding has previously been observed in the complexes of CDK2 with several inhibitors.[19,20] Moreover, the *para*-phenol moiety is involved in a hydrogen-bonding interaction with the terminal amino group of Lys33 and exploit an aromatic stacking interaction at residue Phe80, located at the bottom of the pocket. Interestingly, compound **25**, which has a hydroxyl moiety at the *C*-5 position of the indole, is more potent than the parent indole analogue **18**. The hydroxyl group of compound **25** forms three additional hydrogen bonds with the Asp86 backbone NH and its carboxylic side chain and with the side chain NH of Lys89, similar to those observed in other series of CDK inhibitors suggesting an importance of those interactions in binding affinity (Fig. 3).[20–24]

Replacement of the *para*-hydroxyl moiety by aminoalkyloxy analogues **43**, **47**, and **48** seems to be detrimental for high potency (Table 3). Inspection of the CDK1/compound **25** complex model can provide an explanation. The *para*-phenol moiety is positioned in a small cavity due to the bulkiness of the Phe80 side chain. As this part of the binding site appears to be compatible only with small substituents, sterically encumbering compounds would be expected to encounter unfavorable steric interactions with the enzyme. Therefore, the docking studies suggest a change in binding conformation compared to compounds **18** and **25** leading to a lack of a key hydrogen-bonding interaction with the backbone carbonyl of Leu83 (Fig. 4). The indole nitrogen NH is directed toward the backbone carbonyl of residue Glu81 of the hinge region but the distance is too large (higher than 4 Å) to allow the formation of an appropri-

```
                    15             30             45             60             76
          **    * ************* * * ** *** *****  * ****************  **** * **      *
CDK2   -MENFQKVEKIGEGTYGVVYKARNKLTGEVVALKKIRLDTETEGVPSTAIREISLLKELNHPNIVKLLDVIHTENKL
CDK1   -MEDYTKIEKIGEGTYGVVYKGRHKTTGQVVAMKKIRLESEEEGVPSTAIREISLLKELRHPNIVSLQDVLMQDSRL

                  90            105            120            135            152
       ** ****  ****  *          * **** * ***  **** ***************   * ************
CDK2   YLVFEFLHQDLKKFMDASALTG-IPLPLIKSYLFQLLQGLAFCHSHRVLHRDLKPQNLLINTEGAIKLADFGLARAF
CDK1   YLIFEFLSMDLKKYLDSIPPGQYMDSSLVKSYLYQILQGIVFCHSRRVLHRDLKPQNLLIDDKGTIKLADFGLARAF

                165            180            195            210                229
       * * * ********** ** ***   *** ***** * ****  *   ** ************* ****   ***
CDK2   GVPVRTYTHEVVTLWYRAPEILLGCKYYSTAVDIWSLGCIFAEMVTRRALFPGDSEIDQLFRIFRTLGTPDEVVWPG
CDK1   GIPIRVYTHEVVTLWYRSPEVLLGSARYSTPVDIWSIGTIFAELATKKPLFHGDSEIDQLFRIFRALGTPNNEVWPE

                240            255            270            285        296
       * *  ***  ****        *  *** *  *** ** *** **** * ** ** * * *
CDK2   VTSMPDYKPSFPKWARQDFSKVVPPLDEDGRSLLSQMLHYDPNKRISAKAALAHPFFQDVTKPVPHL
CDK1   VESLQDYKNTFPKWKPGSLASHVKNLDENGLDLLSKMLIYDPAKRISGKMALNHPYFNDLDNQIKKM
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Figure 2. Sequence alignment of human CDK2 and CDK1. Asterisks indicate residues, which are completely conserved in the two sequences. Residues corresponding to the ATP-binding site are marked in bold red type.

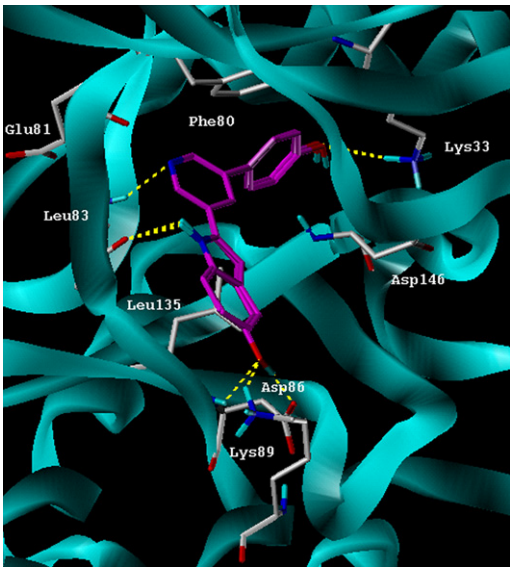


Figure 3. Docking solutions of compounds **18** and **25** in the ATP-binding site of the homology model of human CDK1. The hydrogen bonds are indicated as yellow dotted lines.

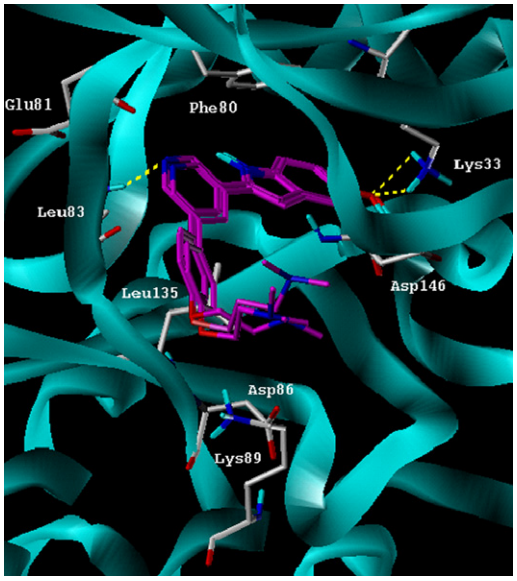


Figure 4. Docking solutions of compounds **43**, **47**, and **48** in the ATP-binding site of the homology model of human CDK1.

ate hydrogen bond (Fig. 4). The reported weak activities for these compounds are consistent with that expectation.

As evocated in the kinase inhibition part, we showed that the bis-indole product **7** was less efficient as its phenol analogue **25**, suggesting that the two indoles moieties modified mainly the approach of the inhibitor in the active site. Modeling of **7** suggests also interactions analogous to hydrogen bonds between compound **25** and CDK1 (Fig. 5). Precisely, key interactions with the hinge segment are remarkably conserved by two direct hydrogen bonds with Leu83. Perhaps more importantly, the hydroxyl group at C-5 position of the

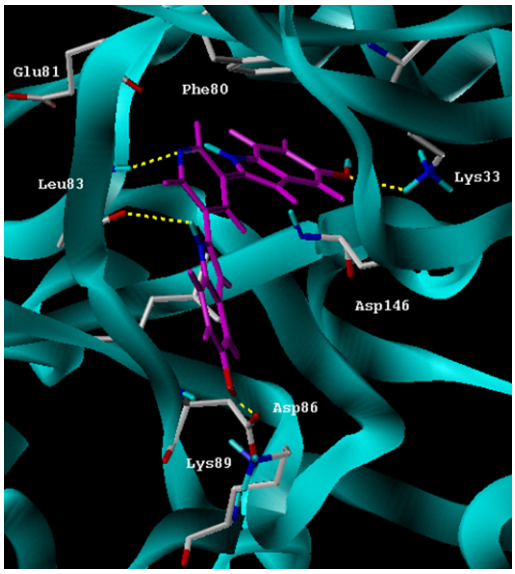


Figure 5. Docking solution of compound **7** in the ATP-binding site of the homology model of human CDK1.

indole ring is involved in a hydrogen bond with the terminal carboxylate group of Asp86 (Fig. 5). The loss of the interaction with Lys89 could explain the slight decrease of the inhibition of CDK1 of **7**.

Of particular interest are indoles bearing *N*-aminoalkyl groups, which were completely inactive against CDK1 (compounds **49**–**52**, **57**–**60**, and **32**–**35**; Table 3). The dimension of the pocket in this area constituted of Phe80, Glu81, and Leu83 (Figs. 4 and 5) is not suitable to accept bulky substituents, leading to a steric clash.

The result of this steric hindrance is probably the loss of any hydrogen-bonding interactions at the hinge region crucial for a good inhibitory activity.

The properties and activities of our compounds have been characterized in more detail. Inhibitors **18**, **25**, and **7** show selectivity for CDK1 over GSK-3 (Table 3). As mentioned before, several potent CDK inhibitors also inhibit GSK-3, due mainly to the high degree of homology (~86%) between the ATP-binding site of the two kinases.[25] Nevertheless, other papers have shown that specificity among kinases can be achieved utilizing structural differences of the ATP-binding sites even if competition with ATP does not seem to be favorable for high selectivity.[26–31] In such case, the gain in selectivity can be associated with the main differences in the ATP pocket between the enzymes. Phe80 in CDK1, the so-called gatekeeper residue, is replaced by Leu132 in GSK-3. Moreover, the negative-charged side chain of Asp86 is replaced by Thr138 and the positive-charged side chain of Lys89 by Arg141. Interactions with these residues have already been mentioned in some papers and seem to be especially relevant for the binding affinity and selectivity of the ligands.[20,32,33] However, only optimization of this series including further pharmacological evaluation of selected compounds against a large panel of functionally diverse kinases are necessary to confirm this hypothesis.

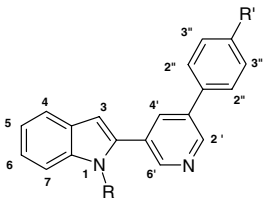
4. Conclusion

We have synthesized a novel series of mono- and bis-indole-pyridine derivatives via an efficient widely, applicable chemical procedure. Concerning their mechanism of action, two major conclusions can be drawn from this study. First, a number of DNA-binding ligands were identified, in particular those bearing one or two cationic side chains. In terms of DNA recognition, the most interesting molecule is compound **33**, which behaves as a conventional DNA minor groove binder. Indeed, circular dichroism experiments revealed that this molecule exhibits a positive CD at 345 nm upon complex formation with DNA and footprinting studies indicated preferential binding to some AT-rich sequences. A binding affinity of 6.8×10^5 M^{-1} was measured with this compound (data not shown) but it showed only a modest cytotoxic effect and did not affect the cell cycle of CEM leukemia cells. Second, we have identified and characterized three CDK1 inhibitors: **7**, **18**, and **25**, which exhibit selectivity over GSK-3. A docking study performed with a homology model for human CDK1 strongly suggests that these compounds can fit into the ATP pocket of the enzyme. Several potential hydrogen bonds have been identified. This study may be very helpful to guide the rational design of more potent CDK1 targeted therapeutic agents. For example, based on the suggested binding mode of these compounds, structural modifications could be carried out toward the surface-exposed front area or the ribose pocket.

5. Experimental

5.1. Chemistry

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 250 Avance instrument using $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm (δ scale) and all J values are in Hz. The following abbreviations are used: singlet (s), doublet (d), doubled doublet (dd), triplet (t), quintuplet (qt), multiplet (m), quaternary carbon (Cq). Melting points are uncorrected. IR absorptions were recorded on a Perkin Elmer PARAGON 1000 PC or on Avatar 320 using an ATR (Ge) technique and values were reported in cm^{-1}. MS spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI 300. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F_{254}). Spots were visualized by UV light at 254 and 356 nm. Flash chromatography columns were performed using silica gel 60 (0.063–0.200 mm, Merck) (Scheme 7).



Scheme 7. Atom labeling scheme for NMR spectra.

5.1.1. 1-Phenylsulfonyl-5-benzyloxy-2-tributylstannyl-1*H*-indole (4). To a solution of 1-phenylsulfonyl-5-benzyloxy-1*H*-indole[34] **3** (1.62 g, 4.48 mmol) in dry THF (25 mL) under argon at −20 °C was added dropwise an LDA solution in hexane (2 M, 3.36 mL, 6.72 mmol). After 30 min stirring at −20 °C, the resulting red solution was cooled to −78 °C and treated with Bu_3SnCl (2.06 mL, 7.61 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 ethyl acetate (3× 100 mL), the combined organic layers were successively washed with a saturated solution of KF (100 mL), water (100 mL) then dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/ethyl acetate 9:1) to afford compound **4** as a white solid (2.26 g, 78%). Mp: 67–69 °C; R_f (petroleum ether/ethyl acetate 94:6) : 0.68; IR (KBr, cm^{-1}) ν 2955, 2923, 2850, 1605, 1503, 1446, 1365, 1233, 1147, 843, 725; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.89 (t, 9H, J = 7.1 Hz, 3× CH_3), 1.15–1.20 (m, 5H, CH_2), 1.25–1.41 (m, 7H, CH_2), 1.49–1.59 (m, 6H, CH_2), 5.05 (s, 2H, OCH_2), 6.73 (s, 1H, H_3), 6.88 (dd, 1H, J = 2.4 Hz, J = 8.9 Hz, H_6), 7.02 (d, 1H, J = 2.4 Hz, H_4), 7.30–7.60 (m, 8H, H_{arom}), 7.59–7.62 (m, 3H, H_{arom}), 7.72 (d, 1H, J = 8.9 Hz, H_7); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 11.9 (3× CH_2), 13.8 (3× CH_3), 27.5 (3× CH_2), 29.1 (3× CH_2), 70.6 (CH_2), 103.9 (CH), 113.8 (CH), 114.5 (CH), 120.7 (CH), 126.3 (2× CH), 127.6 (2× CH), 128.0 (CH), 128.7 (2× CH), 129.1 (2× CH), 133.0 (Cq), 133.4 (CH), 133.5 (Cq), 137.3 (Cq), 139.5 (Cq), 144.7 (Cq), 155.5 (Cq); MS (IS): 654 $(M+1)^+$.

5.1.2. 3,5-Bis(1-phenylsulfonyl-5-benzyloxy-1*H*-indole) pyridine (5). A solution of compound **4** (730 mg, 1.12 mmol), 3,5-dibromopyridine (115 mg, 0.49 mmol) and CuI (19 mg, 0.097 mmol) in dry THF (15 mL) was degassed by argon bubbling for 30 min $Pd(PPh_3)_4$ (10% mol, 56 mg, 0.049 mmol) was then added and the mixture was immediately transferred to a pre-heated oil bath and was refluxed for 8 h. After hydrolysis (20 mL), the mixture was extracted with ethyl acetate (3 × 20 mL), washed with brine (20 mL) then dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/ethyl acetate 7:3) to afford compound **5** as a red solid (346 mg, 89%). Mp: 211–213 °C; R_f (petroleum ether/ethyl acetate 1:1): 0.62; IR (KBr, cm^{-1}) ν 3444, 2370, 1609, 1448, 1368, 1177, 1147, 1023, 686; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.08 (s, 4H, 2× OCH_2), 6.67 (s, 2H, H_3), 7.00 (d, 2H, J = 2.4 Hz, H_4), 7.09 (dd, 2H, J = 2.4 Hz, J = 9.1 Hz, H_6), 7.27–7.47 (m, 2H, H_{arom}), 8.19 (s, 1H, $H_{4'}$), 8.22 (d, 2H, J = 9.1 Hz, H_7); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 70.6 (2× CH_2), 104.9 (2× CH), 115.4 (CH), 117.8 (2× CH), 126.0 (2× CH), 126.9 (2× CH), 127.6 (8× CH), 128.2 (2× CH), 128.8 (8× CH), 129.1 (2× CH), 131.7 (2× Cq), 133.4 (2× Cq), 134.0 (2× CH), 136.7 (2× Cq), 136.9 (4× Cq), 156.6 (4× Cq); MS (IS): 802 $(M+1)^+$; Anal. Calcd for $C_{47}H_{35}N_3O_6S_2$: C 70.39, H 4.40, N 5.24. Found: C 70.73, H 4.56, N 5.12.

5.1.3. 3,5-Bis(5-benzyloxy-1*H*-indole)pyridine (6). To a solution of compound **5** (400 mg, 0.50 mmol) in dry THF (20 mL), a solution of Bu_4NF in dry THF (1 M, 2.50 mL, 2.50 mmol) was added. The solution was stirred to reflux for 2.5 h and the reaction mixture was concentrated under reduced pressure. After hydrolysis (20 mL), the mixture was extracted with ethyl acetate (3 × 20 mL), washed with brine (20 mL) then dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/ethyl acetate 2:8) to afford compound **6** as a yellow solid (230 mg, 74%). Mp: 209–211 °C; R_f (petroleum ether/ethyl acetate 1:1): 0.17; IR (KBr, cm^{-1}) ν 3444, 2904, 1619, 1578, 1483, 1451, 1295, 1206, 1135, 1015, 845, 794; ^1H NMR ($CDCl_3$, 250 MHz): δ 5.09 (s, 4H, 2× OCH_2), 6.79 (s, 2H, H_3), 6.97 (dd, 2H, J = 1.6 Hz, J = 8.3 Hz, H_6), 7.14 (d, 2H, J = 1.6 Hz, H_4), 7.29–7.49 (m, 13H, H_{arom}), 8.04 (s, 1H, $H_{4'}$), 8.71 (br s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 70.9 (2× CH_2), 101.5 (2× CH), 104.0 (2× CH), 112.2 (2× CH), 114.5 (2× CH), 126.0 (2× CH), 127.7 (4× CH), 128.0 (2× CH), 128.7 (4× CH), 128.8 (2× Cq), 129.5 (2× Cq), 132.9 (2× Cq), 134.9 (2× Cq), 137.6 (2× Cq), 144.6 (CH), 154.0 (2× Cq); MS (IS): 522 $(M+1)^+$; Anal. Calcd for $C_{35}H_{27}N_3O_2$: C 80.59, H 5.22, N 8.06. Found: C 80.18, H 5.13, N 8.19.

5.1.4. 3,5-Bis(5-hydroxy-1H-indol)pyridine (7). To a solution of compound **6** (230 mg, 0.44 mmol) in CH_2Cl_2 (15 mL) at 0 °C, a solution of BBr_3 in CH_2Cl_2 (1 M, 0.92 mL, 0.92 mmol) was added dropwise. After 3 h at room temperature, the reaction mixture was poured into ice (50 g), extracted with ethyl acetate (2× 50 mL) then dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (dichloromethane/methanol 9:1) to afford compound **7** as a yellow solid (50 mg, 33%). Mp: 150–152 °C; R_f (dichloromethane/methanol 9:1): 0.30; IR (KBr, cm^{-1}) ν 3422, 3270, 2955, 1636, 1625, 1560, 1458, 1372, 1200, 783; ^1H NMR (DMSO-d_6, 250 MHz): δ 6.69 (dd, 2H, J = 2.2 Hz, J = 8.5 Hz, H_6), 6.89 (d, 2H, J = 2.2 Hz, H_4), 6.95 (d, 2H, J = 1.4 Hz, H_3), 7.25 (d, 2H, J = 8.7 Hz, H_7), 8.58 (s, 1H, $H_{4'}$), 8.75 (s, 2H, 2× OH), 8.92 (d, 2H, J = 2.0 Hz, $H_{2'}$, $H_{6'}$), 11.41 (s, 2H, 2× NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 99.5 (2× CH), 103.4 (2× CH), 111.8 (2× CH), 112.8 (2× CH), 128.3 (2× Cq), 129.2 (2× CH), 132.0 (2× Cq), 134.6 (2× Cq), 139.2 (2× Cq), 144.1 (CH), 151.1 (2× Cq); MS (IS): 342 $(M+1)^+$; Anal. Calcd for $C_{21}H_{15}N_3O_2$: C 73.89, H 4.43, N 12.31. Found: C 74.07, H 4.52, N 12.18.

5.1.5. 3,5-Bis(1-phenylsulfonyl-5-hydroxy-1*H*-indol) pyridine (8). Same procedure as described for compound **7** starting from compound **5** and BBr_3 (7 equiv). Compound **8** was purified by flash chromatography (dichloromethane/methanol 9:1) and isolated as a white solid (68%). Mp: 164–166 °C; R_f (ethyl acetate/petroleum ether 1:1): 0.10; IR (KBr, cm^{-1}) ν 3388, 1611, 1448, 1366, 1371, 1207, 1175, 1089, 723, 685; ^1H NMR ($CDCl_3$, 250 MHz): δ 6.87–6.91 (m, 4H, H_{arom}), 6.99 (s, 2H, H_3), 7.43–7.45 (m, 8H, H_{arom}), 7.57–7.62 (m, 2H, H_{arom}), 7.96 (d, 2H, J = 8.5 Hz, H_7), 8.15 (s, 1H, $H_{4'}$), 8.81 (s, 2H, $H_{2'}$, $H_{6'}$), 9.51 (s large, 2H, 2× OH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 106.0 (2× CH), 114.7 (2× CH), 116.4 (2× CH), 117.2 (2× CH), 126.4 (4× CH), 127.3 (2× Cq), 129.3 (4× CH), 131.3 (2× Cq), 131.8 (2× Cq), 134.4 (2× CH), 135.4 (2× Cq), 137.3 (CH), 138.4 (2× Cq), 149.0 (2× CH), 155.0 (2× Cq); MS (IS): 622 $(M+1)^+$; Anal. Calcd for $C_{33}H_{23}N_3O_6S_2$: C 63.76, H 3.73, N 6.76. Found: C 64.02, H 3.58, N 6.89.

5.1.6. 1-Phenylsulfonyl-2-tributylstannyl-1*H*-indole (11). To a solution of 1-phenylsulfonyl-1*H*-indole (5 g, 19.43 mmol) in dry THF (70 mL) under argon at −20 °C was added dropwise a solution of LDA in dry THF (2 M, 14.6 mL, 29.15 mmol). After 30 min at −20 °C, the resulting red solution was cooled to −78 °C and treated with Bu_3SnCl (8.97 mL, 33.07 mmol). The mixture was warmed up to room temperature within 2 h and then hydrolyzed with cold water (100 mL). The mixture was extracted with ethyl acetate (3× 100 mL), the combined organic layers were successively washed with a saturated solution of KF (100 mL), water (100 mL) then dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/ethyl acetate 9:1) to afford compound **11** as a pale brown oil (9.00 g, 85%), which was conserved by freezing under argon and rapidly used. R_f (ether petroleum/ethyl acetate 9:1): 0.68; IR (NaCl, cm^{-1}) ν 2962, 2923, 2853, 1465, 1361, 1228, 1169, 1129, 1092, 747, 727; ^1H NMR ($CDCl_3$, 250 MHz): δ 0.89 (t, 9H, J = 7.0 Hz, 3× CH_3), 1.16–1.20 (m, 5H, CH_2), 1.25–1.43 (m, 7H, CH_2), 1.50–1.66 (m, 6H, CH_2), 6.82 (s, 1H, H_3), 7.17 (m, 2H, H_{arom}), 7.38 (m, 2H, H_{arom}), 7.45–7.51 (m, 2H, H_{arom}), 7.63 (m, 2H, H_{arom}), 7.80–7.83 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 11.9 (3× CH_2), 13.8 (3× CH_3), 27.4 (3× CH_2), 29.1 (3× CH_2), 113.7 (CH), 120.4 (CH), 120.7 (CH), 123.1 (CH), 124.0 (CH), 126.3 (2× CH), 129.1 (2× CH), 133.2 (Cq), 133.4 (CH), 138.5 (Cq), 139.4 (Cq), 143.6 (Cq); MS (IS): 546 $(M+1)^+$.

5.1.7. 1-Phenylsulfonyl-2-(5-bromopyridin-3-yl)-1*H*-indole (12). Same procedure as described for compound **5** starting from compound **11** and 3,5-dibromopyridine (1.05 equiv). Compound **12** was purified by flash chromatography (petroleum ether/ethyl acetate 7:3) and isolated as an orange solid (88%). Mp: 153–155 °C; R_f (petroleum ether/ethyl acetate 7:3): 0.36; IR (KBr, cm^{-1}) ν 1561, 1448, 1373, 1172, 1059, 987, 835, 724; ^1H NMR ($CDCl_3$, 250 MHz): δ 5.97 (s, 1H, H_3), 7.31–7.51 (m, 8H, H_{arom}), 8.01 (t, 1H, J = 1.8 Hz, $H_{4'}$), 8.32 (d, 1H, J = 8.3 Hz, H_7), 8.57 (d, 1H, J = 1.8 Hz, $H_{2'}$), 8.73 (d, 1H, J = 2.1 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 115.6 (CH), 116.6 (CH), 119.7 (Cq), 121.4 (CH), 124.9 (CH), 125.9 (CH), 126.6 (2× CH), 129.0 (2× CH), 130.1 (2× Cq), 134.1 (CH), 136.4 (Cq), 137.3 (Cq), 138.5 (Cq), 140.3 (CH), 147.9 (CH), 150.7 (CH); MS (IS): 413 (M+1, $^{79}Br)^+$ and 415 (M+1, $^{81}Br)^+$; Anal. Calcd for $C_{19}H_{13}B_rN_2O_2S$: C 55.22, H 3.17, N 6.78. Found: C 55.57, H 3.03, N 6.63.

5.1.8. 1-Phenylsulfonyl-5-benzyloxy-2-(5-bromopyridin-3-yl)-1*H*-indole (13). Same procedure as described for compound **5** starting from compound **4** and 3,5-dib-

romopyridine (1.05 equiv). Compound **13** was purified by flash chromatography (petroleum ether/ethyl acetate 7:3) and isolated as a yellow solid (78%). Mp: 84–86 °C; R_f (petroleum ether/ethyl acetate 1:1): 0.72; IR (KBr, cm^{-1}) ν 3416, 1609, 1473, 1447, 1371, 1207, 1184, 1089, 1019, 869, 723; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.06 (s, 2H, 2× OH), 6.54 (s, 1H, H_3), 6.97 (d, 1H, J = 2.3 Hz, H_4), 7.09 (dd, 1H, J = 2.6 Hz, J = 9.1 Hz, H_6), 7.24–7.48 (m, 10H, H_{arom}), 7.99 (t, 1H, J = 2.1 Hz, H_4), 8.19 (d, 1H, J = 9.1 Hz, H_7), 8.57 (d, 1H, J = 1.8 Hz, $H_{2'}$), 8.70 (d, 1H, J = 2.1 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 70.6 (CH_2), 104.8 (CH), 115.5 (CH), 115.9 (CH), 117.7 (CH), 126.6 (2× CH), 127.6 (2× CH), 128.2 (CH), 128.7 (2× CH), 129.0 (2× CH), 131.2 (2× Cq), 133.2 (Cq), 134.0 (CH), 136.8 (2× Cq), 137.0 (Cq), 137.3 (Cq), 140.3 (CH), 147.8 (CH), 150.7 (CH), 156.6 (Cq); MS (IS): 519 [M+1, ^{79}Br] and 521 [M+1, ^{81}Br]; Anal. Calcd for $C_{26}H_{19}B_rN_2O_3S$: C 60.12, H 3.69, N 5.39. Found: C 59.75, H 3.87, N 5.54.

5.1.9. 1-Phenylsulfonyl-2-[5-(4-methoxyphenyl)-pyridin-3-yl]-1*H*-indole (14). A solution of compound **12** (2 g, 4.84 mmol) and 4-methoxyphenylboronic acid (888 mg, 5.81 mmol) in a mixture of toluene (80 mL), ethanol (48 mL), and aqueous saturated $NaHCO_3$ solution (32 mL) was degassed by argon bubbling for 30 min $Pd(PPh_3)_4$ (10% mol, 0.48 mmol) was added and the mixture was immediately transferred to a pre-heated oil bath and was refluxed for 18 h. After hydrolysis (150 mL), the mixture was extracted with ethyl acetate (2× 150 mL), washed with brine (150 mL) then dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/ethyl acetate 1:1) to afford compound **14** as a white solid (1.45 g, 97%). Mp: 161–163 °C; R_f (ether petroleum/ethyl acetate 1:1): 0.59; IR (KBr, cm^{-1}) ν 1608, 1515, 1430, 1369, 1250, 1172, 1025, 825; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.86 (s, 3H, CH_3), 6.67 (s, 1H, H_3), 7.03 (d, 2H, J = 8.8 Hz, $H_{3''}$), 7.22–7.50 (m, 8H, H_{arom}), 7.60 (d, 2H, J = 8.6 Hz, $H_{2'}$), 8.06 (t, 1H, J = 2.1 Hz, $H_{4'}$), 8.34 (d, 1H, J = 8.3 Hz, H_7), 8.53 (s, 1H, $H_{6'}$), 8.86 (s, 1H, $H_{2'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 55.4 (CH_3), 114.7 (CH), 114.8 (CH), 116.6 (CH), 121.2 (CH), 124.7 (CH), 125.5 (Cq), 125.9 (2× CH), 126.6 (2× CH), 128.5 (2× CH), 128.9 (2× CH), 129.7 (Cq), 130.3 (Cq), 133.9 (CH), 135.0 (Cq), 136.5 (CH), 137.4 (Cq), 138.2 (Cq), 138.5 (Cq), 147.5 (CH), 147.8 (CH), 160.0 (Cq); MS (IS): 441 $(M+1)^+$; Anal. Calcd for $C_{26}H_{20}N_2O_3S$: C 70.89, H 4.58, N 6.36. Found: C 70.54, H 4.73, N 6.54.

5.1.10. 1-Phenylsulfonyl-5-benzyloxy-2-[5-(4-methoxy phenyl)-pyridin-3-yl]-1*H*-indole (15). Same procedure as described for compound **14** starting from compound **13** and 4-methoxyphenylboronic acid (1.2 equiv). Compound **15** was purified by flash chromatography (petroleum ether/ethyl acetate 1:1 to 7:3) and isolated as a white solid (81%). Mp: 184–186 °C; R_f (ether petroleum/ethyl acetate 6:4): 0.19; IR (KBr, cm^{-1}) ν 3430, 1609, 1515, 1448, 1371, 1251, 1181, 1089, 1025, 831, 725; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.87 (s, 3H, CH_3), 5.08 (s, 2H, OCH_2), 6.59 (s, 1H, H_3), 6.99–7.11 (m, 4H, H_{arom}), 7.29–7.45 (m, 12H, H_{arom}), 7.61 (d, 2H, J = 8.5 Hz, $H_{2''}$), 8.03 (t, 1H, J = 2.1 Hz, $H_{4'}$), 8.24 (d, 1H, J = 8.9 Hz, H_7), 8.51 (d, 1H, J = 1.8 Hz, $H_{6'}$), 8.85 (d, 1H, J = 2.1 Hz, $H_{2'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 55.4 (CH_3), 70.5 (CH_2), 104.7 (CH), 114.7 (2× CH), 114.9 (CH), 115.0 (CH), 117.7 (CH), 126.6 (2× CH), 127.5 (2× CH), 128.1 (CH), 128.3 (Cq), 128.4 (2× CH), 128.6 (2× CH), 128.8 (2× CH), 129.7 (Cq), 131.4 (Cq), 133.2 (Cq), 133.8 (CH), 134.9 (Cq). (Cq), 136.3 (CH), 136.9 (Cq), 137.1 (Cq), 139.1 (Cq), 147.4 (CH), 147.8 (CH), 156.5 (Cq), 160.1 (Cq); MS (IS): 547 $(M+1)^+$; Anal. Calcd for $C_{33}H_{26}N_2O_4S$: C 72.51; H 4.79, N 5.12. Found: C 72.83, H 4.62, N 5.30.

5.1.11. 2-[5-(4-Methoxyphenyl)-pyridin-3-yl]-1*H*-indole (16). Same procedure as described for compound **6**starting from compound **14** (1.22 g, 2.78 mmol) and Bu_4NF (3.5 equiv). The mixture was refluxed for 2 h. Compound **16** was purified by flash chromatography (petroleum ether/ethyl acetate 4:6) and isolated as a white solid (83%). Mp: 209–211 °C; R_f (petroleum ether/ethyl acetate 6:4): 0.46; IR (KBr, cm^{-1}) ν 3418, 1596, 1515, 1455, 1249, 1184, 1027, 837, 803; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 3.83 (s, 3H, CH_3), 7.00–7.18 (m, 5H, H_{arom}), 7.45 (d, 1H, J = 7.8 Hz, H_4), 7.58 (d, 1H, J = 7.8 Hz, H_7), 7.81 (d, 2H, J = 8.5 Hz, $H_{2''}$), 8.47 (t, 1H, J = 1.9 H, $H_{4'}$), 8.78 (d, 1H, J = 1.9 Hz, $H_{6'}$), 9.05 (d, 1H, J = 1.9 Hz, $H_{2'}$), 11.74 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 55.3 (CH_3), 100.1 (CH), 111.4 (CH), 114.6 (2× CH), 119.6 (CH), 120.3 (CH), 122.2 (CH), 128.1 (Cq), 128.2 (2× CH), 128.5 (Cq), 129.0 (Cq), 129.1 (CH), 134.5 (Cq), 135.2 (Cq), 137.3 (Cq), 144.6 (CH), 145.6 (CH), 159.6 (Cq); MS (IS): 301 $(M+1)^+$; Anal. Calcd for $C_{20}H_{16}N_2O$: C 79.98; H 5.37, N 9.33. Found: C 80.24, H 5.25, N 9.18.

5.1.12. 5-Benzyloxy-2-[5-(4-methoxyphenyl)pyridin-3-yl]-1*H*-indole (17). Same procedure as described for compound **6** starting from compound **15** and Bu_4NF (1.5 equiv). The mixture was refluxed for 2 h. Compound 17 was purified by flash chromatography (petroleum ether/ethyl acetate 1:1) and isolated as a white solid (99%). Mp: 164–166 °C; R_f (petroleum ether/ethyl acetate 1:1): 0.54; IR (KBr, cm^{-1}) ν 3450, 2942, 1608, 1515, 1455, 1284, 1241, 1184, 1060, 801; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.86 (s, 3H, CH_3), 5.12 (s, 2H, OCH_2), 6.85 (s, 1H, H_3), 6.95–7.04 (m, 3H, H_{arom}), 7.18 (d, 1H, J = 1.8 Hz, H_4), 7.31–7.57 (m, 8H, H_{arom}), 8.04 (t, 1H, J = 2.1 Hz, $H_{4'}$), 8.71 (d, 1H, J = 1.8 Hz, $H_{6'}$), 8.80 (s large, 1H, NH), 8.86 (d, 1H, J = 1.8 Hz, $H_{2'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 55.5 (CH_3), 71.0 (CH_2), 101.4 (CH), 104.0 (CH), 112.0 (CH), 114.3 (CH), 114.8 (2× CH), 126.0 (CH), 127.7 (2× CH), 128.0 (Cq), 128.4 (2× CH), 128.7 (2× CH), 129.6 (Cq), 129.9 (Cq), 130.3 (CH), 132.8 (Cq), 135.3 (Cq), 136.7 (Cq), 137.7 (Cq), 144.4 (CH), 146.7 (CH), 154.0 (Cq), 160.1 (Cq); MS (IS): 407 $(M+1)^+$; Anal. Calcd for $C_{27}H_{22}N_2O_2$: C 79.78, H 5.46, N 6.89. Found: C 80.05, H 5.33, N 6.98.

5.1.13. 5-(1H-Indol-2-yl)pyridin-3-yl]phenol (18). A solution of compound **16** (200 mg, 0.67 mmol) in HBr (10 mL, 47% in acetic acid) was refluxed for 5 h. The

reaction mixture was cooled to room temperature, neutralized with an aqueous saturated $NaHCO_3$ solution, and extracted with ethyl acetate (3 × 20 mL) then dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (ethyl acetate/petroleum ether 1:1) to afford compound **18** as a white solid (191 mg, 83%). Mp: >250 °C; R_f (ethyl acetate/petroleum ether 6:4): 0.45; IR (KBr, cm^{-1}) ν 3390, 3367, 2576, 1597, 1518, 1445, 1269, 837, 803; ^1H NMR (DMSO-d_6, 250 MHz): δ 6.93 (d, 2H, J = 8.6 Hz, $H_{3''}$), 7.00–7.17 (m, 4H, H_{arom}), 7.44 (d, 1H, J = 7.9 Hz, H_4), 7.57 (d, 1H, J = 7.6 Hz, H_7), 7.68 (d, 2H, J = 8.4 Hz, $H_{2''}$), 8.43 (s, 1H, $H_{4'}$), 8.73 (s, 1H, $H_{6'}$), 9.00 (s, 1H, $H_{2'}$), 11.75 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 100.0 (CH), 111.4 (CH), 116.0 (2× CH), 119.6 (CH), 120.3 (CH), 122.1 (CH), 127.4 (Cq), 128.0 (Cq), 128.2 (2× CH), 128.5 (Cq), 128.8 (CH), 134.6 (Cq), 135.6 (Cq), 137.3 (Cq), 144.3 (CH), 145.5 (CH), 157.9 (Cq); MS (IS): 287 $(M+1)^+$; Anal. Calcd for $C_{19}H_{14}N_2O$: C 79.70, H 4.93, N 9.78. Found: C 79.43, H 4.86, N 9.93.

5.1.14. 4-[5-(1-Phenylsulfonyl-1H-indol-2-yl)pyridin-3-yl]phenol (19). Same procedure as described for compound **7** starting from compound **14** (1.44 g, 3.28 mmol) and BBr_3 (4.2 equiv). Compound **19** was purified by flash chromatography (ethyl acetate/petroleum ether 1:1) and isolated as a white solid (77%). Mp: 119–121 °C; R_f (ethyl acetate/petroleum ether 1:1): 0.64; IR (KBr, cm^{-1}) ν 3054, 1610, 1517, 1447, 1371, 1175, 1270, 831; ^1H NMR ($CDCl_3$, 250 MHz): δ 4.41 (s, 1H, OH), 6.88 (s, 1H, H_3), 7.07 (d, 2H, J = 8.5 Hz, $H_{3''}$), 7.33–7.63 (m, 9H, H_{arom}), 8.37 (d, 2H, J = 8.5 Hz, $H_{2''}$), 8.63 (s, 1H, $H_{4'}$), 9.32 (s, 1H, $H_{2'}$), 9.75 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 114.8 (CH), 114.9 (CH), 116.6 (CH), 116.7 (CH), 121.2 (CH), 124.8 (CH), 125.7 (CH), 126.7 (2× CH), 128.6 (CH), 128.7 (CH), 129.0 (2× CH), 129.6 (Cq), 130.3 (2× Cq), 134.0 (CH), 136.9 (CH), 137.5 (Cq), 138.1 (Cq), 138.6 (Cq), 147.1 (CH), 147.5 (CH), 157.8 (Cq), 160.2 (Cq); MS (IS): 427 $(M+1)^+$; Anal. Calcd for $C_{25}H_{18}N_2O_3S$: C 70.41, H 4.25, N 6.57. Found: C 70.02, H 4.37, N 6.46.

5.1.15. 3-Bromo-5-(4-methoxyphenyl)pyridine (20).[35] Same procedure as described for compound **14** starting from 3,5-dibromopyridine **1** (3 g, 12.66 mmol) and 4-methoxyphenylboronic acid (0.95 equiv). Compound **20** was purified by flash chromatography (petroleum ether/ethyl acetate 7:3) and isolated as a white solid (77%). Mp: 119–121 °C R_f (petroleum ether/ethyl acetate 7/ 3): 0.49; IR (KBr, cm^{-1}) ν 3021, 1608, 1510, 1428, 1248, 1184, 1024, 1015, 840; ^1H NMR ($CDCl_3$, 250 MHz): δ 7.01 (dd, 2H, J = 2.2 Hz, J = 6.5 Hz, $H_{3'}$), 7.50 (dd, 2H, J = 2.2 Hz, J = 6.7 Hz, $H_{2'}$), 7.97 (t, 1H, J = 2.2 Hz, H_4), 8.60 (d, 1H, J = 2.2 Hz, H_6), 8.72 (d, 1H, J = 1.8 Hz, H_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 55.3 (CH_3), 114.6 (2× CH), 120.8 (Cq), 120.8 (2× CH), 128.4 (Cq), 136.1 (CH), 137.7 (Cq), 145.9 (CH), 148.6 (CH), 160.1 (Cq); MS (IS): 264 (M+1, ^{79}Br) and 266 (M+1, ^{81}Br); Anal. Calcd for $C_{12}H_{10}BrNO$: C 54.57, H 3.82, N 5.30. Found: C 54.13, H 3.98, N 5.17.

5.1.16. 4-(5-Bromopyridin-3-yl)phenol (21). Same procedure as described for compound **7** starting from compound **20** (1.10 g, 4.16 mmol) and BBr_3 (3.2 equiv). Compound **21** was purified by flash chromatography (petroleum ether/ethyl acetate 7:3) and isolated as a white solid (99%). Mp: >250 °C; R_f (petroleum ether/ethyl acetate 7:3): 0.27; IR (KBr, cm^{-1}) ν 3514, 3089, 1607, 1553, 1442, 1273, 1182, 1067, 836; ^1H NMR (DMSO-d_6, 250 MHz): δ 6.97 (d, 2H, J = 8.5 Hz, $H_{3'}$), 7.70 (d, 2H, J = 8.7 Hz, $H_{2'}$), 9.09 (s, 1H, H_4), 9.35 (s, 1H, H_6), 9.46 (s, 1H, H_2), 10.16 (s large, 1H, OH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 116.6 (2× CH), 122.9 (Cq), 129.1 (2× CH), 140.0 (CH), 140.9 (Cq), 142.8 (CH), 144.5 (CH), 159.8 (2× Cq); MS (IS): 250 (M+1, ^{79}Br) and 252 (M+1, ^{81}Br); Anal. Calcd for $C_{11}H_8BrNO$: C 52.83, H 3.22, N 5.60. Found: C 52.48, H 3.40, N 5.46.

5.1.17. {2-[4-(5-Bromopyridin-3-yl)phenoxy]-ethyl}dimethylamine (22). To a solution of 4-(5-bromo-pyridin-3-yl)-phenol**21** in dry DMF (30 mL), Cs_2CO_3 (1.72 g, 5.28 mmol) was added under argon at room temperature. At the same time, a solution of 2-chloroethyldimethylamine hydrochloride **26** (950 mg, 6.60 mmol) in DMF (30 mL) was stirred in the presence of Cs_2CO_3 (2.44 g, 7.48 mmol). After 30 min, this solution was added to the solution containing the 4-(5-bromo-pyridin-3-yl)-phenol **21**. The mixture was heated to 100 °C for 8 h. After cooling to room temperature, hydrolysis was performed with water (100 mL) and the reaction mixture was extracted with ethyl acetate (3× 100 mL) then dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) to afford compound **22** as a white solid (800 mg, 57%). Mp: 97–99 °C; R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.40; IR (KBr, cm^{-1}) ν 3444, 2940, 2766, 2366, 1607, 1509, 1436, 1234, 1192, 1044, 1002, 837; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.91 (s, 6H, 2× CH_3), 3.47 (t, 2H, J = 4.2 Hz, CH_2), 4.56 (t, 2H, J = 4.5 Hz, CH_2), 7.04 (d, 2H, J = 8.7 Hz, $H_{3'}$), 7.51 (d, 2H, J = 8.7 Hz, $H_{2'}$), 7.97 (s, 1H, H_4), 8.62 (s, 1H, H_6), 8.70 (s, 1H, H_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 45.6 (2× CH_3), 57.9 (CH_2), 65.7 (CH_2), 115.2 (2× CH), 120.8 (Cq), 128.2 (2× CH), 128.6 (Cq), 136.2 (CH), 137.8 (Cq), 145.8 (CH), 148.5 (CH), 159.2 (Cq); MS (IS): 321 (M+1, ^{79}Br) and 323 (M+1, ^{81}Br); Anal. Calcd for $C_{15}H_{17}BrN_2O$: C 56.09, H 5.33, N 8.72. Found: C 56.32, H 5.18, N 8.65.

5.1.18. 4-[5-(1-Phenylsulfonyl-5-benzyloxy-1*H*-indol-2-yl)pyridin-3-yl]phenol (23). Same procedure as described for compound **5** starting from 4-(5-bromo-pyridin-3-yl)-phenol **21** (1 g, 4.00 mmol) and compound **4** (1.5 equiv). The reaction mixture was refluxed for 4 h. Compound **23** was purified by flash chromatography (petroleum ether/ethyl acetate 7:3) and isolated as a white solid (33%). Mp: 143–145 °C; R_f (petroleum ether/ethyl acetate 7:3): 0.43; IR (KBr, cm^{-1}) ν 3440, 3090, 1609, 1518, 1448, 1371, 1247, 1182, 1152, 1090, 1039, 831, 799, 729; ^1H NMR ($CDCl_3$, 250 MHz): δ 5.05 (s, 2H, CH_2), 6.47 (s, 1H, H_3), 6.92–7.08 (m, 4H, H_{arom}),

7.26–7.43 (m, 11H, H_{arom}), 7.59 (d, 2H, $J = 8.3$ Hz, $H_{2''}$), 8.03 (s, 1H, $H_{4'}$), 8.21 (d, 1H, $J = 8.8$ Hz, H_7), 8.49 (d, 1H, $J = 1.7$ Hz, $H_{2'}$), 8.81 (d, 1H, $J = 1.8$ Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 70.2 (CH_2), 103.9 (CH), 113.9 (2× CH), 114.2 (CH), 115.1 (CH), 117.1 (CH), 125.9 (2× CH), 126.9 (2× CH), 128.5 (CH), 128.7 (Cq), 128.9 (2× CH), 129.1 (2× CH), 129.4 (2× CH), 129.7 (Cq), 131.2 (Cq), 133.2 (Cq), 133.6 (CH), 134.2 (Cq), 136.7 (CH), 136.9 (Cq), 137.6 (Cq), 140.2 (Cq), 147.5 (CH), 147.8 (CH), 155.4 (Cq), 159.8 (Cq); MS (IS): 533 $(M+1)^+$; Anal. Calcd for $C_{32}H_{24}N_2O_4S$: C 72.16, H 4.54, N 5.26. Found: C 72.53, H 4.39, N 5.41.

5.1.19. 4-[5-(5-Benzyloxy-1H-indol-2-yl)pyridin-3-yl] phenol (24). To a solution of compound **23** (100 mg, 0.19 mmol) in dry THF (10 mL), Bu_4NF (0.94 mL, 1 M in THF, 0.94 mmol) was added. The solution was stirred to reflux for 1 h. The reaction mixture was concentrated under reduced pressure. After hydrolysis (20 mL), the mixture was extracted with ethyl acetate (3× 20 mL), washed with brine (20 mL) then dried over $MgSO_4$, and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (ethyl acetate/petroleum ether 6:4) to afford compound **24** as a yellow solid (60 mg, 80%). Mp: 165–167 °C; R_f (ethyl acetate/petroleum ether 1:1): 0.23; IR (NaCl, cm^{-1}) ν 3322, 2965, 1611, 1595, 1518, 1467, 1265, 1221, 1175, 1124, 1018, 738; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 5.08 (s, 2H, OCH_2), 6.81 (s, 1H, H_3), 6.85 (dd, 1H, $J = 2.4$, 8.9 Hz, H_6), 7.03 (d, 2H, $J = 8.5$ Hz, $H_{3''}$), 7.11 (d, 1H, $J = 2.4$ Hz, H_4), 7.27–7.56 (m, 9H, H_{arom}), 8.37 (s, 1H, $H_{4'}$), 8.60 (s, 1H, $H_{2'}$), 8.92 (s, 1H, $H_{6'}$), 11.11 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 70.9 (CH_2), 99.7 (CH), 103.3 (CH), 113.3 (CH), 116.6 (CH), 126.0 (CH), 126.1 (2× CH), 127.6 (CH), 127.8 (CH), 127.9 (Cq), 128.0 (2× CH), 128.3 (CH), 128.6 (CH), 129.2 (Cq), 129.3 (CH), 130.1 (Cq), 133.5 (Cq), 135.6 (Cq), 137.8 (Cq), 145.2 (2× CH), 146.9 (Cq), 153.5 (Cq), 158.4 (Cq); MS (IS): 393 $(M+1)^+$; Anal. Calcd for $C_{26}H_{20}N_2O_2$: C, H, N. Found: C, 79.57; H, 5.14; N, 7.14. Found C 79.57, H 5.14, N 7.14. Found C 79.21, H 5.25, N 7.02.

5.1.20. 2-[5-(4-Hydroxyphenyl) pyridin-3-yl]-5-hydroxy-1*H*-indole (25). Same procedure as described for compound **7** starting from compound **24** and BBr_3 (1.2 equiv). Compound **25** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a pale brown solid (52%). Mp: 112–115 °C; R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.42; IR (NaCl, cm^{-1}) ν 3514, 3089, 1607, 1553, 1442, 1273, 1182, 1067, 836; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 6.91 (d, 2H, $J = 8.4$ Hz, $H_{3''}$), 6.99–7.14 (m, 4H, H_{arom}), 7.42 (d, 1H, $J = 7.8$ Hz, H_6), 7.53 (d, 1H, $J = 7.8$ Hz, H_7), 7.59 (d, 2H, $J = 8.1$ Hz, $H_{2''}$), 8.41 (s, 1H, $H_{4'}$), 8.71 (s, 1H, $H_{6'}$), 8.97 (s, 1H, $H_{2'}$), 11.72 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 100.0 (CH), 111.4 (CH), 116.0 (2× CH), 119.6 (CH), 120.3 (CH), 127.4 (Cq), 128.0 (Cq), 128.2 (2× CH), 128.5 (Cq), 128.8 (CH), 134.6 (Cq), 135.6 (Cq), 137.3 (Cq), 138.9 (Cq), 144.3 (CH), 145.5 (CH), 157.9 (Cq); MS (IS): 303 $(M+1)^+$; Anal. Calcd for $C_{19}H_{14}N_2O_2$: C 75.48, H 4.67, N 9.27. Found: C 75.16, H 4.53, N 9.40.

5.1.21. [2-(5-Benzyloxy-2-{5-[5-benzyloxy-1-(2-dimethyl aminoethyl)-1*H*-indol-2-yl]pyridin-3-yl}indol-1-yl) ethyl]dimethylamine (28). A solution of 3,5-bis-(5-benzyloxy-1*H*-indole)-pyridine **6** (162 mg, 0.31 mmol) in DMF (10 mL) was cooled to 0 °C, under argon, then NaH (60% dispersion in oil, 100 mg, 2.48 mmol) was portion wise added and the solution was stirred for 30 min. 2-Chloroethyldimethylamine hydrochloride **26** (112 mg, 0.77 mmol) was added and the resulting mixture was heated for 2 h at 100 °C. Water (10 mL) was added, the mixture was extracted with dichloromethane (3× 20 mL), the combined organic layers were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure and the crude material was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) to afford compound **28** as a yellow oil (113 mg, 55%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.67; IR (NaCl, cm^{-1}) ν 2953, 2825, 2777, 2249, 1620, 1479, 1454, 1292, 1197, 1023, 909, 734; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.13 (s, 12H, 4× CH_3), 2.58 (t, 4H, $J = 7.1$ Hz, 2× CH_2), 4.24 (t, 4H, $J = 7.1$ Hz, 2× CH_2), 5.11 (s, 4H, 2× CH_2), 6.56 (s, 2H, H_3), 7.02 (dd, 2H, $J = 2.2$ Hz, $J = 8.8$ Hz, H_6), 7.19 (d, 2H, $J = 2.4$ Hz, H_4), 7.31–7.49 (m, 14H, H_{arom}), 8.80 (s, 1H, $H_{4'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 43.0 (2× CH_2), 45.8 (4× CH_3), 58.7 (2× CH_2), 70.9 (2× CH_2), 103.6 (2× CH), 104.1 (2× CH), 110.9 (2× CH), 113.6 (2× CH), 127.6 (2× CH), 127.9 (2× CH), 128.5 (2× Cq), 128.6 (4× CH), 128.9 (2× Cq), 133.4 (2× Cq), 136.8 (2× CH), 137.6 (2× Cq), 137.7 (2× Cq), 148.9 (CH), 153.8 (2× Cq); MS (IS): 665 $(M+1)^+$; Anal. Calcd for $C_{43}H_{45}N_5O_2$: C 77.80, H 6.83, N 10.55. Found: C 78.17, H 6.91, N 10.40.

5.1.22. [3-(5-Benzyloxy-2-{5-[5-benzyloxy-1-(3-dimethyl aminopropyl)-1H-indol-2-yl]pyridin-3-yl}indol-1-yl)propyl]dimethylamine (29). Same procedure as described for compound **28** starting from compound **6** and 3-chloropropyldimethylamine hydrochloride **27** (2.5 equiv). Compound **29** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a pale yellow oil (52%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01) : 0. 32; IR (NaCl, cm^{-1}) ν 2934, 2857, 2251, 2218, 1620, 1478, 1455, 1379, 1195, 1025, 909, 733; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.79–1.90 (m, 4H, 2× CH_2), 2.11 (s, 12H, 4× CH_3), 2.17 (t, 4H, $J = 6.9$ Hz, 2× CH_2), 4.26 (t, 4H, $J = 7.5$ Hz, 2× CH_2), 5.13 (s, 4H, 2× OCH_2), 6.57 (s, 2H, H_3), 7.02 (dd, 2H, $J = 2.4$ Hz, $J = 8.9$ Hz, H_6), 7.19 (d, 2H, $J = 2.4$ Hz, H_4), 7.31–7.50 (m, 14H, H_{arom}), 8.77 (s, 1H, $H_{4'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 28.1 (2× CH_2), 42.3 (2× CH_2), 45.1 (4× CH_3), 56.4 (2× CH_2), 70.8 (2× CH_2), 103.7 (2× CH), 103.9 (2× CH), 111.1 (2× CH), 113.6 (2× CH), 127.5 (4× CH), 127.8 (2× CH), 128.4 (2× Cq), 128.5 (4× CH), 129.1 (2× Cq), 133.5 (2× Cq), 136.3 (2× CH), 137.3 (2× Cq), 137.6 (2× Cq), 148.7 (CH), 153.7 (2× Cq); MS (IS): 693 $(M+1)^+$; Anal. Calcd for $C_{45}H_{49}N_5O_2$: C 78.12, H 7.14, N 10.12. Found: C 77.70, H 7.33, N 10.27.

5.1.23. (2-{5-Benzyloxy-2-[5-(5-benzyloxy-1*H*-indol-2-yl)pyridin-3-yl]indol-1-yl}ethyl)dimethylamine (30). Same procedure as described for compound **28** starting from compound **6** and 2-chloroethyldimethylamine hydrochloride **26** (1.2 equiv). Compound **30** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a pale brown oil (58%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.32; IR (NaCl, cm^{-1}) ν 3398, 2867, 2424, 1601, 1485, 1392, 1227, 1007, 727; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.10–2.13 (m, 8H), 4.24 (t, 2H, J = 7.1 Hz, 2× CH_2), 5.12 (s, 4H, 2× OCH_2), 6.56 (s, 2H, H_3), 7.02 (dd, 2H, J = 2.2 Hz, J = 8.8 Hz, H_6), 7.19 (d, 2H, J = 2.4 Hz, H_4), 7.25–7.49 (m, 14H, H_{arom}), 8.04 (d, 1H, J = 20.8 Hz), 8,80 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 42.5 (CH_2), 46.4 (2× CH_3), 58.9 (CH_2), 70.9 (2× CH_2), 102.4 (2× CH), 103.0 (2× CH), 109.7 (2× CH), 112.5 (2× CH), 126.5 (4× CH), 126.8 (2× CH), 127.3 (2× Cq), 127.6 (4× CH), 127.9 (2× Cq), 132.1 (2× Cq), 135.6 (2× CH), 136.6 (2× Cq), 136.9 (2× Cq), 147.6 (CH), 152.9 (2× Cq); MS (IS): 593 $(M+1)^+$; Anal. Calcd for $C_{39}H_{36}N_4O_2$: C 79.03, H, 6.12, N 9.45. Found: C 78.76, H 6.30, N 9.32.

5.1.24. (3-{5-Benzyloxy-2-[5-(5-benzyloxy-1H-indol-2-yl)pyridin-3-yl]indol-1-yl}propyl)dimethylamine (31). Same procedure as described for compound **30** starting from compound **6** and 3-chloropropyldimethylamine hydrochloride **27** (1.2 equiv). Compound **31** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a pale brown oil (60%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.33; IR (NaCl, cm^{-1}) ν 3408, 2873, 2436, 1607, 1498, 1460, 1235, 1019, 743; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.78 (m, 2H, CH_2), 2.10–2.13 (m, 8H), 4.24 (t, 2H, J = 7.1 Hz, 2× CH_2), 5.12 (s, 4H, 2× CH_2), 6.56 (s, 2H, H_3), 7.02 (dd, 2H, J = 2.2, 8.8 Hz, H_6), 7.19 (d, 2H, J = 2.4 Hz, H_4), 7.25–7.49 (m, 14H, H_{arom}), 8.04 (d, 1H, J = 20.8 Hz), 8.80 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 27.4 (CH_2), 42.2 (CH_2), 46.7 (2× CH_3), 58.2 (CH_2), 70.3 (2× CH_2), 102.2 (2× CH), 103.3 (2× CH), 109.5 (2× CH), 112.8 (2× CH), 126.2 (4× CH), 126.6 (2× CH), 127.7 (2× Cq), 127.9 (4× CH), 128.1 (2× Cq), 132.6 (2× Cq), 135.9 (2× CH), 136.8 (2× Cq), 137.3 (2× Cq), 147.9 (CH), 153.4 (2× Cq); MS (IS): 607 $(M+1)^+$; Anal. Calcd for $C_{40}H_{38}N_4O_2$: C 79.18; H, 6.31, N 9.23. Found: C 79.44, H 6.12, N 9.07.

5.1.25. 3,5-Bis-(1-(2-dimethylaminoethyl)-5-hydroxy-1*H*-indol)pyridine (32). Same procedure as described for compound **7** starting from compound **28** and BBr_3 (1.25 equiv). The reaction mixture was stirred at room temperature for 2 h. Compound **32** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a colorless oil (49%). R_f dichloromethane/methanol/triethylamine 9:1:0.01): 0.40; IR (NaCl, cm^{-1}) ν 3254, 3214, 2795, 2822, 1634, 1495, 1427, 1212, 1054, 815, 747; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.12 (s, 12H, 4× CH_3), 2.59 (t, 4H, J = 6.8 Hz, 2× CH_2), 4.24 (t, 4H, J = 7.0 Hz, 2× CH_2), 6.48 (s, 2H, H_3), 6.95 (dd, 2H, J = 2.0 Hz, J = 8.7 Hz, H_6), 7.02 (d, 2H, J = 2.2 Hz, H_4), 7.27 (d, 2H, J = 8.9 Hz, H_7), 8.06 (s, 1H, $H_{4'}$), 8.62 (s large, 2H, 2× OH), 8.79 (s, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 42.4 (2× CH_2), 45.4 (4× CH_3), 58.1 (2× CH_2), 102.8 (2× CH), 105.0 (2× CH), 110.2 (2× CH), 112.8 (2× CH), 127.9 (2× CH), 128.7 (2× Cq), 132.6 (2× Cq), 137.1 (2× Cq), 141.2 (2× Cq), 148.2 (CH), 151.1 (2× Cq); MS (IS): 484 $(M+1)^+$; Anal. Calcd for $C_{29}H_{33}N_5O_2$: C 72.02, H 6.88, N 14.48. Found: C 72.31, H 6.70, N 14.35.

5.1.26. 3,5-Bis-(1-(3-dimethylaminopropyl)-5-hydroxy-1*H*-indol)pyridine (33). Same procedure as described for compound **32** starting from **29**. Compound **33** was isolated as a pale brown oil (47%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.20; IR (NaCl, cm^{-1}) ν 3276, 3225, 2823, 2810, 1617, 1498, 1454, 1227, 1086, 829, 756; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.78–1.92 (m, 4H), 2.12 (s, 12H, 4× CH_3), 2.21 (t, 4H, J = 7.0 Hz, 2× CH_2), 4.19 (t, 4H, J = 7.1 Hz, 2× CH_2), 6.47 (s, 2H, H_3), 6.70 (dd, 2H, J = 2.0 Hz, J = 8.5 Hz, H_6), 6.96 (d, 2H, J = 2.0 Hz, H_4), 7.15 (d, 2H, J = 9.1 Hz, H_7), 7.90 (s, 1H, $H_{4'}$), 8.62 (s large, 2H, 2× OH), 8.74 (s, 2H, $H_{2'}$, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 28.2 (2× CH_2), 42.5 (2× CH_2), 45.2 (4× CH_3), 56.6 (2× CH_2), 103.4 (2× CH), 105.3 (2× CH), 111.0 (2× CH), 113.2 (2× CH), 128.6 (2× Cq), 129.5 (2× Cq), 133.2 (2× CH), 136.6 (2× Cq), 137.3 (2× Cq), 148.5 (CH), 153.2 (2× Cq); MS (IS): 512 $(M+1)^+$; Anal. Calcd for $C_{31}H_{37}N_5O_2$: C 72.77, H 7.29, N 13.69. Found: C 73.06, H 7.12, N 13.75.

5.1.27. 1-(2-Dimethylaminoethyl)-2-[5-(5-hydroxy-1*H*-indol-2yl)pyridin-3-yl]-5-hydroxy-1*H*-indole (34). Same procedure as described for **32** starting from **30** and BBr_3 (2.0 equiv). Compound **34** was isolated as a pale brown oil (52%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.35; IR (NaCl, cm^{-1}) ν 3289, 3238, 2877, 2834, 2665, 2101, 1623, 1502, 1423, 1201, 1098, 887, 714; ^1H NMR (DMSO-d_6, 250 MHz): δ 2.09–2.12 (m, 8H), 4.15 (t, 2H, J = 6.9 Hz, CH_2), 6.58 (dd, 2H, J = 1.9 Hz, J = 8.1 Hz, H_6), 6.87 (m, 4H, H_{arom}), 7.12 (d, 2H, J = 8.2 Hz, H_7), 8.16 (s, 1H, $H_{4'}$), 8.68 (s, 2H, 2× OH), 8.74 (d, 2H, J = 1.7 Hz, $H_{2'}$, $H_{6'}$), 11.32 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 41.3 (CH_2), 45.2 (2× CH_3), 57.6 (CH_2), 100.1 (2× CH), 102.8 (2× CH), 111.6 (2× CH), 112.2 (2× CH), 127.8 (2× Cq), 128.7 (2× CH), 132.3 (2× Cq), 134.5 (2× Cq), 139.2 (2× Cq), 144.7 (CH), 150.8 (2× Cq); MS (IS): 413 $(M+1)^+$; Anal. Calcd for $C_{25}H_{24}N_4O_2$: C 72.80, H 5.86, N 13.58. Found: C 72.41, H 5.99, N 13.41.

5.1.28. 1-(3-Dimethylaminopropyl)-2-[5-(5-hydroxy-1H-indol-2-yl)pyridin-3-yl]-5-hydroxy-1*H*-indole (35). Same procedure as described for compound **32** starting from **31**. Compound **35** was isolated as a pale brown oil (48%) R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.39; IR (NaCl, cm^{-1}) ν 3312, 3267, 2948, 2817, 2657, 2058, 1617, 1487, 1432, 1205, 1023, 901, 726; ^1H NMR (DMSO-d_6, 250 MHz): δ 1.67 (m, 2H, CH_2), 2.07–2.11 (m, 8H), 4.15 (t, 2H, J = 7.1 Hz, CH_2), 6.59 (dd, 2H, J = 1.8 Hz, J = 8.4 Hz, H_6), 6.88 (dd, 4H, J = 1.5 Hz, J = 12.7 Hz), 7.24 (d, 2H, J = 8.6 Hz, H_7), 8.14 (s, 1H, $H_{4'}$), 8.69 (s, 2H, 2× OH), 8.76 (d, 2H, J = 1.9 Hz, $H_{2'}$, $H_{6'}$), 11.36 (s, 1H, NH);; ^{13}C NMR

(DMSO-d_6, 62.5 MHz): δ 39.6 (CH_2), 42.9 (2× CH_3), 45.9 (CH_2), 54.8 (CH_2), 103.8 (CH), 104.4 (CH), 111.3 (CH), 112.7 (CH), 125.4 (CH), 127.4 (2× Cq), 128.0 (2× CH), 128.5 (2× CH), 132.1 (2× Cq), 134.3 (2× Cq), 136.1 (CH), 139.7 (2× Cq), 148.4 (CH), 150.4 (2× Cq); MS (IS): 427 $(M+1)^+$; Anal. Calcd for $C_{26}H_{26}N_4O_2$: C 73.22, H 6.14, N 13.14. Found: C 73.58, H 6.01, N 13.03.

5.1.29. [2-(1-Phenylsulfonyl-1*H*-indol-5-yloxy)ethyl]dimethylamine (36). Same procedure as described for compound **7** starting from 1-phenylsulfonyl-5-benzyloxy-1*H*-indole **3**(500 Hz, 1.38 mmol) and BBr_3 (1.2 equiv). The mixture was stirred for 2 h at room temperature. *1-Phenylsulfonyl-5-hydroxy-1H-indole* was purified by flash chromatography (ethyl acetate/petroleum ether 3:7 to 1:1) and isolated as a white solid (80%). R_f (ethyl acetate/petroleum ether 3:7): 0.31; IR (KBr, cm^{-1}) ν 3494, 2366, 1589, 1449, 1350, 1221, 1143, 997, 807; ^1H NMR ($CDCl_3$, 250 MHz): δ 5.44 (s, 1H, OH), 6.52 (d, 1H, J = 3.6 Hz, H_3), 6.84 (dd, 1H, J = 2.6 Hz, J = 8.8 Hz, H_6), 6.92 (d, 1H, J = 2.3 Hz, H_4), 7.36–7.50 (m, 4H, H_{arom}), 7.80–7.84 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 106.5 (CH), 109.3 (CH), 113.8 (CH), 114.5 (CH), 126.8 (2× CH), 127.4 (CH), 129.3 (2× CH), 129.7 (Cq), 132.1 (Cq), 133.9 (CH), 138.1 (Cq), 152.4 (Cq). MS (IS): 274 $(M+1)^+$; the previously obtained *1-phenylsulfonyl-5-hydroxy-1H-indole* was then used following the same procedure as described for compound **22** and 2-chloroethyldimethylamine hydrochloride **26** (1.2 equiv). The reaction was heated at 100 °C for 3.5 h. Compound **36** was purified by flash chromatography (dichloromethane/methanol/triethylamine 8:2:0.01) and isolated as a colorless hygroscopic solid (250 m 67%). R_f (dichloromethane/methanol/triethylamine 8:2:0.01): 0.43; IR (NaCl, cm^{-1}) ν 2952, 2660, 1485, 1396, 1205, 1161, 1036, 786; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.32 (s, 6H, 2× CH_3), 2.72 (t, 2H, J = 5.7 Hz, CH_2), 4.05 (t, 2H, J = 5.7 Hz, CH_2), 6.57 (d, 1H, J = 3.6 Hz, H_3), 6.94–6.97 (m, 3H, H_{arom}), 7.36–7.51 (m, 4H, H_{arom}), 7.81–7.89 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 45.8 (2× CH_3), 58.2 (CH_2), 66.3 (CH_2), 104.5 (CH), 109.4 (CH), 114.3 (2× CH), 126.5 (2× CH), 127.0 (CH), 129.1 (2× CH), 129.5 (Cq), 131.7 (Cq), 133.7 (CH), 138.0 (Cq), 155.6 (Cq); MS (IS): 345 $(M+1)^+$; Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C 62.77, H 5.85, N 8.13. Found: C 63.13, H 5.69, N 7.99.

5.1.30. [2-(1-Phenylsulfonyl-2-tributylstannyl-1H-indol-5-yloxy)ethyl]dimethylamine (37). An LDA solution (0.44 mL, 0.87 mmol, 2 M in THF) was added dropwise to compound **36** (100 mg, 0.29 mmol) in THF (10 mL), at −20 °C and stirred 30 min. Then, a solution of tributylstannyl chloride (0.27 mL, 0.99 mmol) in THF (1 mL) was added dropwise at −78 °C and stirred for 2 h at room temperature. Water (20 mL) was added and the mixture was extracted with ethyl acetate (3× 50 mL). The combined organic layers were washed with a saturated solution of KF (3× 50 mL) and dried over $MgSO_4$. After evaporation the residue was purified by flash chromatography (dichloromethane/methanol 9:1) to afford compound **37** as a pale brown oil (110 mg, 67%). ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.89 (t, 9H, J = 7.1 Hz, 3× CH_3), 1.15–1.20 (m, 5H, CH_2), 1.25–1.41 (m, 7H, CH_2), 1.49–1.59 (m, 6H, CH_2), 2.37 (s, 6H, 2× CH_3), 2.78 (t, 2H, J = 5.7 Hz, CH_2), 4.09 (t, 2H, J = 5.7 Hz, CH_2), 6.73 (s, 1H, H_3), 6.83 (dd, 1H, J = 2.6 Hz, J = 9.1 Hz, H_6), 6.96 (d, 1H, J = 2.3 Hz, H_4), 7.34–7.62 (m, 5H, H_{arom}), 7.70 (d, 1H, J = 9.1 Hz, H_7).

5.1.31. [2-(1-Benzenesulfonyl-2-{5-[1-benzenesulfonyl-5-(2-dimethylaminoethoxy)-1*H*-indol-2-yl]pyridin-3-yl}-1*H*-indol-5-yloxy)ethyl]dimethylamine (38). Same procedure as described for compound **5** starting from compound **37** (110 mg, 0.17 mmol) and 3,5-dibromopyridine (18 mg, 0.07 mmol). The mixture was refluxed for 18 h. Compound **38** was purified by flash chromatography (dichloromethane/methanol 9:1) and isolated as a colorless oil (2 mg, 4%). R_f (dichloromethane/methanol 9:1): 0.17; IR (NaCl, cm^{-1}) ν 3431, 2370, 2332, 1802, 1652, 1450, 1375, 1219, 1166, 1092; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.39 (s, 6H, 2× CH_3); 2.40 (s, 6H, 2× CH_3), 2.81 (t, 4H, J = 5.5 Hz, 2× CH_2), 4.12 (t, 4H, J = 4.2 Hz, 2× CH_2), 6.58 (d, 2H, J = 2.8 Hz, 2× CH), 6.92–6.99 (m, 4H), 7.05 (dd, 1H, J = 2.6 Hz, J = 8.9 Hz, CH), 7.27–7.52 (m, 7H), 7.82–7.89 (m, 3H), 8.01 (t, 1H, J = 1.8 Hz, CH), 8.19 (d, 1H, J = 9.1 Hz, CH), 8.56 (d, 1H, J = 1.4 Hz, CH), 8.72 (d, 1H, J = 2.0 Hz, CH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 45,6 (2× CH_3); 45.8 (2× CH_3), 58.1 (2× CH_2), 58.2 (2× CH_2), 66.0 (2× CH_2), 66.1 (2× CH_2), 104.4 (CH), 104.8 (CH), 114.4 (CH), 114.5 (CH), 115.3 (CH), 115.9 (CH), 117.7 (CH),119.7 (Cq), 126.0 (Cq), 126.6 (2× CH), 126.8 (2× CH), 127.2 (CH), 129.0 (2× CH), 129.3 (2× CH), 129.8 (Cq), 130.0 (Cq), 131.3 (Cq), 131.8 (Cq), 133.2 (Cq), 133.9 (CH), 134.1 (CH), 137.0 (Cq), 137.4 (Cq), 138.3 (Cq), 140.2 (CH), 147.8 (CH), 150.7 (CH), 155.5 (Cq), 156.5 (Cq).

5.1.32. (2-{4-[5-(1-Phenylsulfonyl-1*H*-indol-2-yl)pyridin-3-yl] phenoxy}ethyl)dimethylamine (39). Same procedure as described for compound **22** starting from compounds **19** and **26**. Compound **39** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a white solid (77%). Mp: 134–136 °C; R_f (dichloromethane/methanol 9:1): 0.33; IR (KBr, cm^{-1}) ν 3770, 1605, 1517, 1369, 1186, 1035, 843; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.37 (s, 6H, 2× CH_3), 2.78 (t, 2H, J = 5.6 Hz, CH_2), 4.14 (t, 2H, J = 5.6 Hz, CH_2), 6.68 (s, 1H, H_3), 7.06 (d, 2H, J = 8.5 Hz, $H_{3''}$), 7.24–7.51 (m, 8H, H_{arom}), 7.60 (d, 2H, J = 8.3 Hz, $H_{2''}$), 8.06 (t, 1H, J = 2.0 Hz, $H_{4'}$), 8.35 (d, 1H, J = 8.3 Hz, H_7), 8.52 (d, 1H, J = 1.6 Hz, $H_{2'}$), 8.85 (d, 1H, J = 1.6 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 46.0 (2× CH_3), 58.4 (CH_2), 66.2 (CH_2), 114.8 (CH), 115.4 (2× CH), 116.7 (CH), 121.2 (CH), 124.8 (CH), 125.6 (CH), 126.7 (2× CH), 128.4 (Cq), 128.5 (2× CH), 128.9 (2× CH), 129.9 (Cq), 130.3 (Cq), 134.0 (CH), 135.0 (Cq), 136.5 (CH), 137.5 (Cq), 138.3 (Cq), 138.6 (Cq), 147.6 (CH), 147.9 (CH), 159.3 (Cq); MS (IS): 498 $(M+H)^+$; Anal. Calcd for $C_{29}H_{27}N_3O_3S$: C 70.00, H 5.47, N 8.44. Found: C 69.67, H 5.62, N 8.58.

5.1.33. (3-{4-[5-(1-Phenylsulfonyl-1*H*-indol-2-yl)pyridin-3-yl]phenoxy}propyl)dimethylamine (40). Same procedure as described for **22** starting from compounds **19**

and **27**. Compound **40** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a white solid (80%). Mp: 131–133 °C; R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.43; IR (KBr, cm^{-1}) ν 3408, 2758, 1605, 1515, 1433, 1368, 1250, 1186, 1171, 834, 760; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.02–2.07 (m, 2H, CH_2), 2.34 (s, 6H, 2× CH_3), 2.58 (t, 2H, J = 7.2 Hz, CH_2), 4.09 (t, 2H, J = 6.4 Hz, CH_2), 6.67 (s, 1H, H_3), 7.03 (d, 2H, J = 8.8 Hz, $H_{3''}$), 7.23–7.51 (m, 8H, H_{arom}), 7.59 (d, 2H,J = 8.7 Hz, $H_{2''}$), 8.05 (t, 1H, J = 2 Hz, $H_{4'}$), 8.35 (d, 1H, J = 8.3 Hz, H_7), 8.52 (d, 1H, J = 1.8 Hz, $H_{2'}$), 8.85 (d, 1H, J = 2 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 27.3 (CH_2), 45.3 (2× CH_3), 56.4 (CH_2), 66.3 (CH_2), 114.8 (CH), 115.3 (2× CH), 116.6 (CH), 121.2 (CH), 124.8 (CH), 125.6 (CH), 126.7 (2× CH), 128.9 (Cq), 128.5 (2× CH), 128.9 (2× CH), 129.8 (Cq), 130.3 (Cq), 134.0 (CH), 135.0 (Cq), 136.5 (CH), 137.5 (Cq), 138.3 (Cq), 138.6 (Cq), 147.5 (CH), 147.9 (CH), 159.4 (Cq); MS (IS): 512 $(M+H)^+$; Anal. Calcd for $C_{30}H_{29}N_3O_3S$: C 70.43, H 5.71, N 8.21. Found: C 70.76, H 5.63, N 8.08.

5.1.34. (2-{4-[5-(1-Phenylsulfonyl-5-benzyloxy-1*H*-indol-2-yl)pyridin-3-yl]phenoxy}ethyl)dimethylamine (41). Same procedure as described for **22** starting from compounds **23** and **26**. Compound **41** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a brown solid (69%). Mp: 97 °C; R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.51; IR (KBr, cm^{-1}) ν 3056, 2360, 1675, 1610, 1515, 1449, 1373, 1265, 1183, 1091, 1025; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.36 (s, 6H, 2× CH_3), 2.76 (t, 2H, J = 5.6 Hz, CH_2), 4.12 (t, 2H, J = 5.9 Hz, CH_2), 5.06 (s, 2H, CH_2), 6.58 (s, 1H, H_3), 6.98–7.10 (m, 5H, H_{arom}), 7.21–7.45 (m, 10H, H_{arom}), 7.59 (d, 2H, J = 8.5 Hz, $H_{2''}$), 8.23 (d, 1H, J = 9.1 Hz, H_7), 8.51 (d, 1H, J = 1.7 Hz, $H_{2'}$), 8.84 (d, 1H, J = 2.0 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 45.9 (2× CH_3), 58.3 (CH_2), 66.1 (CH_2), 70.5 (CH_2), 104.7 (CH), 114.9 (CH), 115.0 (CH), 115.3 (2× CH), 117.7 (CH), 126.6 (2× CH), 127.5 (2× CH), 128.0 (CH), 128.3 (Cq), 128.4 (2× CH), 128.6 (2× CH), 128.8 (2× CH), 129.7 (Cq), 131.4 (Cq), 133.2 (Cq), 133.8 (CH), 134.9 (Cq), 136.3 (CH), 136.8 (Cq), 137.1 (Cq), 139.1 (Cq), 147.3 (CH), 147.8 (CH), 156.5 (Cq), 159.2 (Cq); MS (IS): 604 $(M+H)^+$; Anal. Calcd for $C_{36}H_{33}N_3O_4S$: C 71.62, H 5.51, N 6.96. Found: C 71.35, H 5.40, N 7.15.

5.1.35. (3-{4-[5-(1-Phenylsulfonyl-5-benzyloxy-1*H*-indol-2-yl)pyridin-3-yl]phenoxy}propyl)dimethyl-amine (42). Same procedure as described for **22** starting from compounds **23** and **27**. Compound **42** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a pale brown oil (72%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.40; IR (NaCl, cm^{-1}) ν 3417, 2951, 1674, 1610, 1515, 1465, 1373, 1265, 1183, 1091, 1025; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.03 (qt, 2H, J = 6.2 Hz, CH_2), 2.32 (s, 6H, 2× CH_3), 2.55 (t, 2H, J = 6.9 Hz, CH_2), 4.09 (t, 2H, J = 6.3 Hz, CH_2), 5.08 (s, 2H, CH_2), 6.59 (s, 1H, H_3), 6.99–7.12 (m, 5H, H_{arom}), 7.23–7.61 (m, 10H, H_{arom}), 8.03 (d, 2H, J = 9.1 Hz, $H_{2''}$), 8.24 (d, 1H, J = 9.1 Hz, H_7), 8.51 (s, 1H, $H_{2'}$), 8.85 (d, 1H, J = 1,8 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 27.5 (CH_2), 45.5 (2× CH_3), 56.4 (CH_2), 66.4 (CH_2), 70.5 (CH_2), 104.7 (CH), 115.0 (CH), 115.1 (CH), 115.2 (2× CH), 117.7 (CH), 126.6 (2× CH), 127.6 (2× CH), 128.1 (CH), 128.3 (Cq), 128.4 (2× CH), 128.7 (2× CH), 128.9 (2× CH), 129.6 (Cq), 131.5 (Cq), 133.2 (Cq), 133.9 (CH), 135.0 (Cq), 136.3 (CH), 136.9 (Cq), 137.1 (Cq), 139.1 (Cq), 147.3 (CH), 147.8 (CH), 156.5 (Cq), 159.4 (Cq); MS (IS): 618 $(M+H)^+$; Anal. Calcd for $C_{37}H_{35}N_3O_4S$: C 71.94, H 5.71, N 6.80. Found: C 71.63, H 5.83, N 6.94.

5.1.36. (2-{4-[5-(1*H*-Indol-2-yl)pyridin-3-yl]phenoxy} ethyl)-dimethyl-amine (43). Same procedure as described for compound **6** starting from compound **39** and Bu_4NF (1.5 equiv) was added. The solution was stirred to reflux, for 3 h. Compound **43** was purified by flash chromatography (dichloromethane/methanol 9:1) and isolated as a white solid (64%). Mp: 182–184 °C; R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.34; IR (KBr, cm^{-1}) ν 3450, 2942, 1608, 1515, 1455, 1284, 1241, 1184, 1060, 801; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.25 (s, 6H, 2× CH_3), 2.68 (t, 2H, J = 5.7 Hz, CH_2), 4.13 (t, 2H, J = 5.6 Hz, CH_2), 7.03–7.15 (m, 5H, H_{arom}), 7.46 (d, 1H, J = 8.0 Hz, H_4), 7.58 (d, 1H, J = 7.8 Hz, H_7), 7.81 (d, 2H, J = 8.4 Hz, $H_{2''}$), 8.51 (s, 1H, $H_{4'}$), 8.78 (s, 1H, $H_{2'}$), 9.06 (s, 1H, $H_{6'}$), 11.86 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 45.5 (2× CH_3), 57.6 (CH_2), 65.8 (CH_2), 100.0 (CH), 111.4 (CH), 115.1 (2× CH), 119.6 (CH), 120.3 (CH), 122.1 (CH), 128.1 (Cq), 128.2 (2× CH), 128.4 (Cq), 129.0 (Cq), 129.1 (CH), 134.5 (Cq), 135.2 (Cq), 137.4 (Cq), 144.6 (CH), 145.5 (CH), 158.8 (Cq); MS (IS): 357 $(M+1)^+$; Anal. Calcd for $C_{23}H_{23}N_3O$: C 77.28, H 6.49, N 11.76. Found: C 77.64, H 6.59, N 11.61.

5.1.37. (3-{4-[5-(1*H*-Indol-2-yl)pyridin-3-yl]phenoxy} propyl)dimethylamine (44). Same procedure as described for compound **43** starting from compound **40**. Compound **44** was isolated as a white solid (87%). Mp: 178–180 °C; IR (KBr, cm^{-1}) 3424, 1610, 1515, 1444, 1285, 1243, 1192, 831, 791; ^{1}H NMR (DMSO-d_6, 250 MHz): δ 1.89 (qt, 2H, J = 6.0 Hz, CH_2), 2.21 (s, 6H, 2× CH_3), 2.45 (t, 2H, J = 7.1 Hz, CH_2), 4.06 (t, 2H, J = 6.3 Hz, CH_2), 7.00–7.18 (m, 5H, H_{arom}), 7.46 (d, 1H, J = 8.1 Hz, H_4), 7.58 (d, 1H, J = 7.5 Hz, H_7), 7.79 (d, 2H, J = 8.7 Hz, $H_{2''}$), 8.49 (s, 1H, $H_{4'}$), 8.77 (d, 1H, J = 1.8 Hz, $H_{2'}$), 9.05 (d, 1H, J = 1.8 Hz, $H_{6'}$), 11.81 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 26.6 (CH_2), 44.9 (2× CH_3), 55.5 (CH_2), 65.8 (CH_2), 100.0 (CH), 111.4 (CH), 115.1 (2× CH), 119.6 (CH), 120.3 (CH), 122.1 (CH), 128.1 (Cq), 128.1 (2× CH), 128.5 (Cq), 128.9 (Cq), 129.0 (CH), 134.5 (Cq), 135.2 (Cq), 137.3 (Cq), 144.6 (CH), 145.5 (CH), 159.0 (Cq); MS (IS): 372 $(M+1)^+$; Anal. Calcd for $C_{24}H_{25}N_3O$: C 77.60, H 6.78, N 11.31. Found: C 77.28, H 6.95, N 11.17.

5.1.38. (2-{4-[5-(5-Benzyloxy-1*H*-indol-2-yl)pyridin-3-yl]phenoxy}ethyl)dimethylamine (45). Same procedure as described for compound **43** starting from compound **41**. Compound **45** was isolated as a pale brown oil (84%).

R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.37; IR (NaCl, cm^{-1}) ν 3056, 2360, 1675, 1610, 1515, 1449, 1373, 1265, 1183, 1091, 1025; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.40 (s, 6H, 2× CH_3), 2.81 (t, 2H, J = 5.4 Hz, CH_2), 4.04 (t, 2H, J = 5.4 Hz, CH_2), 5.07 (s, 2H, CH_2), 6.80–6.92 (m, 5H, H_{arom}), 7.11 (d, 1H, J = 1.9 Hz, H_4), 7.28–7.59 (m, 7H, H_{arom}), 8.34 (s, 1H, $H_{4'}$), 8.61 (s, 1H, $H_{2'}$), 8.95 (s, 1H, $H_{6'}$), 11.05 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 45.3 (2× CH_3), 57.7 (CH_2), 65.2 (CH_2), 70.7 (CH_2), 99.5 (CH), 103.2 (CH), 113.3 (CH), 113.4 (CH), 115.1 (2× CH), 127.5 (2× CH), 127.7 (CH), 127.9 (2× CH), 128.4 (2× CH), 128.7 (Cq), 129.0 (Cq), 129.7 (Cq), 129.9 (CH), 133.4 (Cq), 135.5 (Cq), 136.0 (Cq), 137.6 (Cq), 144.6 (CH), 145.3 (CH), 153.3 (Cq), 158.7 (Cq); MS (IS): 464 $(M+1)^+$; Anal. Calcd for $C_{30}H_{29}N_3O_2$: C 77.73, H 6.31, N 9.06. Found: C 77.97, H 6.44, N 8.92.

5.1.39. (3-{4-[5-(5-Benzyloxy-1*H*-indol-2-yl)pyridin-3-yl] phenoxy}propyl)dimethylamine (46). Same procedure as described for compound **43** starting from compound **42**. Compound 46 was isolated as a pale brown oil (85%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.34; IR (NaCl, cm^{-1}) ν 3417, 2951, 1674, 1610, 1515, 1465, 1373, 1265, 1183, 1091, 1025; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.97 (qt, 2H, J = 4.6 Hz, CH_2), 2.36 (s, 6H, 2× CH_3), 2.62 (t, 2H, J = 7.3 Hz, CH_2), 3.87 (t, 2H, J = 6.1 Hz, CH_2), 5.07 (s, 2H, CH_2), 6.80–6.92 (m, 5H, H_{arom}), 7.13 (d, 1H, J = 2.2 Hz, H_4), 7.27–7.51 (m, 7H, H_{arom}), 8.25 (s, 1H, $H_{4'}$), 8.60 (s, 1H, $H_{2'}$), 8.94 (s, 1H, $H_{6'}$), 10.76 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 44.3 (2× CH_3); 45.9 (CH_2), 55.9 (CH_2), 58.5 (CH_2), 65.5 (CH_2), 100.3 (CH), 103.7 (CH), 112.5 (CH), 113.8 (CH), 115.0 (2× CH), 127.6 (2× CH), 127.8 (CH), 128.2 (2× CH), 128.5 (2× CH), 128.8 (Cq), 129.3 (Cq), 129.7 (Cq), 130.1 (CH), 133.2 (Cq), 135.4 (Cq), 136.2 (Cq), 137.6 (Cq), 144.5 (CH), 145.7 (CH), 153.6 (Cq), 158.9 (Cq); MS (IS): 478 $(M+1)^+$; Anal. Calcd for $C_{31}H_{31}N_3O_2$: C 77.96, H 6.54, N 8.80. Found: C 78.37, H 6.61, N 8.68.

5.1.40. 2-{5-[4-(2-Dimethylaminoethoxy)phenyl]pyridin-3-yl}-5-hydroxy-1*H*-indole (47). Same procedure as described for compound **7** starting from compound **45** and BBr_3 (1.1 equiv). The reaction was stirred at room temperature for 2 h. Compound **47** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a brown solid (60%). Mp: 190–192 °C; R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.34; IR (KBr, cm^{-1}) ν 3412, 1644, 1617, 1504, 1456, 1388, 1277, 1234, 1208, 1179, 789; ^1H NMR (DMSO-d_6, 250 MHz): δ 2.37 (s, 6H, 2× CH_3), 2.85 (t, 2H, J = 5.1 Hz, CH_2), 4.19 (t, 2H, J = 5.6 Hz, CH_2), 6.68 (d, 1H, J = 7.1 Hz, H_6), 6.88 (s, 1H, H_4), 6.96 (s, 1H, H_3), 7.12 (d, 2H, J = 8.5 Hz, $H_{3''}$), 7.24 (d, 1H, J = 8.5 Hz, H_7), 7.80 (d, 2H, J = 8.5 Hz, $H_{2''}$), 8.43 (s, 1H, $H_{4'}$), 8.74 (s, 2H, $H_{2'}$, OH), 8.99 (s, 1H, $H_{6'}$), 11.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 45.0 (2× CH_3), 57.2 (CH_2), 65.2 (CH_2), 99.3 (CH), 103.8 (CH), 111.8 (CH), 112.7 (CH), 115.2 (2× CH), 125.5 (Cq), 128.1 (2× CH), 128.3 (Cq), 128.8 (CH), 129.2 (Cq), 132.0 (Cq), 134.7 (Cq), 135.1 (Cq), 144.4 (CH), 145.3 (CH), 151.1 (Cq), 158.6 (Cq); MS (IS): 374 $(M+1)^+$; Anal. Calcd for $C_{23}H_{23}N_3O_2$: C 73.97, H 6.21, N 11.25. Found: C 73.63, H 6.40, N 11.34.

5.1.41. 2-{5-[4-(3-Dimethylaminopropoxy)phenyl]pyri-din-3-yl}-5-hydroxy-1*H*-indole (48). Same procedure as described for compound **7** starting from compound **46**. Compound **48** was isolated as a white solid (54%). Mp: 199–201 °C; R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.31; IR (KBr, cm^{-1}) ν 3432, 1654, 1607, 1513, 1466, 1389, 1286, 1247, 1213, 1182, 835, 789; ^1H NMR (DMSO-d_6, 250 MHz): δ 1.89 (qt, 2H, J = 4.3 Hz, CH_2), 2.20 (s, 6H, 2× CH_3), 2.43 (t, 2H, J = 7.3 Hz, CH_2), 4.04 (t, 2H, J = 7.3 Hz, CH_2), 6.68 (dd, 1H, J = 1.9, 8.5 Hz, H_6), 6.88 (d, 1H, J = 1.9 Hz, H_4), 6.96 (s, 1H, H_3), 7.09 (d, 2H, J = 8.8 Hz, $H_{3''}$), 7.24 (d, 1H, J = 8.5 Hz, H_7), 7.78 (d, 2H, J = 8.5 Hz, $H_{2''}$), 8.41 (s, 1H, $H_{4'}$), 8.74 (d, 2H, J = 1.7 Hz, $H_{2'}$, OH), 8.98 (d, 1H, J = 1.7 Hz, $H_{6'}$), 11.44 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 62.5 MHz): δ 26.7 (CH_2), 45.0 (2× CH_3), 55.6 (CH_2), 65.9 (CH_2), 99.4 (CH), 103.9 (CH), 111.8 (CH), 112.7 (CH), 115.1 (2× CH), 128.1 (2× CH), 128.3 (Cq), 128.8 (CH), 129.0 (Cq), 129.2 (Cq), 132.0 (Cq), 134.7 (Cq), 135.2 (Cq), 144.4 (CH), 145.3 (CH), 151.1 (Cq), 159.0 (Cq); MS (IS): 388 $(M+1)^+$; Anal. Calcd for $C_{24}H_{25}N_3O_2$: C 74.39, H 6.50, N 10.84. Found: C 74.13, H 6.37, N 11.02.

5.1.42. 2-(4-{5-[1-(2-Dimethylaminoethyl)-1*H*-indol-2-yl]pyridin-3-yl}phenoxy)ethyl]dimethylamine (49). Same procedure as described for compound **28** starting from compound **43** and 2-chloroethyldimethylamine hydrochloride **26** (1.5 equiv). Compound **49** was purified by flash chromatography (dichloromethane/methanol/triethylamine 9:1:0.01) and isolated as a pale brown oil (83%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.35; IR (NaCl, cm^{-1}) ν 3418, 2934, 2366, 1610, 1514, 1460, 1249, 1037, 751; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.15 (s, 6H, 2× CH_3), 2.45 (s, 6H, 2× CH_3), 2.62 (t, 2H, J = 7.6 Hz, CH_2), 2.88 (t, 2H, J = 5.4 Hz, CH_2), 4.19 (t, 2H, J = 5.6 Hz, CH_2), 4.28 (t, 2H, J = 7.3 Hz, CH_2), 6.64 (s, 1H, H_3), 7.05 (d, 2H, J = 8.6 Hz, $H_{3''}$), 7.16 (t, 1H, J = 7.6 Hz, H_5 or H_6), 7.27 (t, 1H, J = 7.1 Hz, H_5 ou H_6), 7.43 (d, 1H, J = 8.1 Hz, H_4), 7.58 (d, 2H, J = 8.6 Hz, $H_{2''}$), 7.66 (d, 1 Hz J = 7.8 Hz, H_7), 8.04 (t, 1H, J = 1.9 Hz, $H_{4'}$), 8.72 (d, 1H, J = 1.7 Hz, $H_{2'}$), 8.85 (d, 1H, J = 1.7 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 42.6 (CH_2), 45.4 (2× CH_3), 45.7 (2× CH_3), 57.9 (CH_2), 58.5 (CH_2), 65.3 (CH_2), 103.6 (CH), 110.1 (CH), 115.4 (2× CH), 120.4 (CH), 121.0 (CH), 122.4 (CH), 128.2 (Cq), 128.4 (2× CH), 129.0 (Cq), 130.1 (Cq), 134.5 (CH), 135.9 (Cq), 137.6 (Cq), 137.8 (Cq), 147.2 (CH), 148.1 (CH), 158.8 (Cq); MS (IS): 429 $(M+1)^+$; Anal. Calcd for $C_{27}H_{32}N_4O$: C 75.67, H 7.53, N 13.07. Found: C 75.55, H 7.62, N 13.15.

5.1.43. [3-(2-{5-[4-(2-Dimethylaminoethoxy)-phenyl]pyridin-3-yl}indol-1-yl)propyl]dimethylamine (50). Same procedure as described for compound **49** starting from compounds **43** and **27**. Compound **50** was isolated as a pale brown oil (81%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.33; IR (NaCl, cm^{-1}) ν

3430, 3053, 2934, 1610, 1520, 1464, 1265, 1181, 1038, 896; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.85 (qt, 2H, J = 6.8 Hz, CH_2), 2.11 (s, 6H, 2× CH_3), 2.18 (t, 2H, J = 6.8 Hz, CH_2), 2.38 (s, 6H, 2× CH_3), 2.79 (t, 2H, J = 5.6 Hz, CH_2), 4.14 (t, 2H, J = 5.6 Hz, CH_2), 4.28 (t, 2H, J = 7.3 Hz, CH_2), 6.64 (s, 1H, H_3), 7.05 (d, 2H, J = 8.5 Hz, $H_{3''}$), 7.15 (t, 1H, J = 7.6 Hz, H_5 or H_6), 7.26 (t, 1H, J = 8.1 Hz, H_5 or H_6), 7.45 (d, 1H, J = 8.1 Hz, H_4), 7.57 (d, 2H, J = 8.5 Hz, $H_{2''}$), 7.66 (d, 1H, J = 7.8 Hz, H_7), 7.95 (t, 1H, J = 1.9 Hz, $H_{4'}$), 8.69 (d, 1H, J = 1.7 Hz, $H_{2'}$), 8.84 (d, 1H, J = 2.0 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 28.0 (CH_2), 42.1 (CH_2), 45.1 (2× CH_3), 45.8 (2× CH_3), 56.5 (CH_2), 58.2 (CH_2), 66.0 (CH_2), 103.6 (CH), 110.2 (CH), 115.3 (2× CH), 120.1 (CH), 120.8 (CH), 122.2 (CH), 128.1 (Cq), 128.3 (2× CH), 129.1 (Cq), 129.7 (Cq), 134.2 (CH), 136.0 (Cq), 137.3 (Cq), 137.8 (Cq), 147.1 (CH), 147.8 (CH), 159.2 (Cq); MS (IS): 443 $(M+1)^+$; Anal. Calcd for $C_{28}H_{34}N_4O$: C 75.98, H 7.74, N 12.66. Found: C 76.36, H 7.60, N 12.48.

5.1.44. [3-(4-{5-[1-(2-Dimethylaminoethyl)-1*H*-indol-2-yl]pyridin- 3-yl}phenoxy)propyl]dimethylamine (51). Same procedure as described for compound **49** starting from compounds **44** and **26**; Compound **51** was isolated as a pale brown oil (53%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.30; IR (NaCl, cm^{-1}) ν 3396, 3066, 2990, 1618, 1430, 1265, 1052, 912, 739; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.41–1.50 (m, 2H, CH_2), 1.69 (qt, 2H, J = 8.3 Hz, CH_2), 2.02 (t, 2H, J = 7.8 Hz, CH_2), 2.10 (s, 6H, 2× CH_3), 2.15 (s, 6H, 2× CH_3), 4.09 (t, 2H, J = 6.1 Hz, CH_2), 4.28 (t, 2H, J = 7.1 Hz, CH_2), 6.64 (s, 1H, H_3), 7.03 (d, 2H, J = 8.8 Hz, $H_{3''}$), 7.16 (t, 1H, J = 7.3 Hz, H_5 or H_6), 7.27 (t, 1H, J = 7.3 Hz, H_5 or H_6), 7.43 (d, 1H, J = 8.3 Hz, H_4), 7.58 (d, 2H, J = 8.8 Hz, $H_{2''}$), 7.66 (d, 1H, J = 7.6 Hz, H_7), 8.05 (t, 1H, J = 1.9 Hz, $H_{4'}$), 8.71 (d, 1H, J = 1.9 Hz, $H_{2'}$), 8.84 (d, 1H, J = 1.9 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 27.6 (CH_2), 42.8 (CH_2), 45.6 (2× CH_3), 45.8 (2× CH_3), 56.4 (CH_2), 58.6 (CH_2), 66.4 (CH_2), 103.5 (CH), 110.0 (CH), 115.3 (2× CH), 120.3 (CH), 120.9 (CH), 122.3 (CH), 128.2 (Cq), 128.3 (2× CH), 129.0 (Cq), 129.6 (Cq), 134.5 (CH), 135.9 (Cq), 137.7 (Cq), 137.8 (Cq), 147.2 (CH), 148.0 (CH), 159.5 (Cq); MS (IS): 443 $(M+1)^+$; Anal. Calcd for $C_{28}H_{34}N_4O$: C 75.98, H 7.74, N 12.66. Found: C 75.62, H 7.58, N 12.80.

5.1.45. [3-(4-{5-[1-(3-Dimethylaminopropyl)-1*H*-indol-2-yl]pyridin-3-yl}phenoxy)propyl]dimethylamine (52). Same procedure as described for compound **49** starting from compounds **44** and **27**; Compound **52** was isolated as a pale brown oil (45%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.30; IR (NaCl, cm^{-1}) ν 3438, 3066, 2996, 1654, 1515, 1422, 1265, 1058, 896, 741; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.85 (t, 2H, J = 7.1 Hz, CH_2), 2.05–2.12 (m, 8H), 2.19 (t, 2H, J = 6.8 Hz, CH_2), 2.41 (s, 6H, 2× CH_3), 2.67 (t, 2H, J = 7.1 Hz, CH_2), 4.10 (t, 2H, J = 6.1 Hz, CH_2), 4.28 (t, 2H, J = 7.3 Hz, CH_2), 6.64 (s, 1H, H_3), 7.02 (d, 2H, J = 8.5 Hz, $H_{3''}$), 7.16 (td, 1H, J = 1.0, 7.8 Hz, H_5 or H_6), 7.27 (td, 1H, J = 1.2, 7.1 Hz, H_5 or H_6), 7.45 (d, 1H, J = 8.1 Hz, H_4), 7.56 (d, 2H, J = 8.8 Hz, $H_{2''}$), 7.66 (d, 1H, J = 7.6 Hz, H_7), 7.95 (t, 1H, J = 1.9 Hz, $H_{4'}$), 8.69 (s, 1H, $H_{2'}$), 8.83 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 26.9 (CH_2), 28.0 (CH_2), 42.2 (CH_2), 45.0 (2× CH_3), 45.1 (2× CH_3), 56.2 (CH_2), 56.5 (CH_2), 66.1 (CH_2), 103.7 (CH), 110.2 (CH), 115.3 (2× CH), 120.2 (CH), 120.9 (CH), 122.3 (CH), 128.1 (Cq), 128.2 (2× CH), 128.4 (Cq), 129.7 (Cq), 134.3 (CH), 135.9 (Cq), 137.3 (Cq), 137.8 (Cq), 147.2 (CH), 147.8 (CH), 159.3 (Cq); MS (IS): 457 $(M+1)^+$; Anal. Calcd for $C_{29}H_{36}N_4O$: C 76.28, H 7.95, N 12.27. Found: C 76.43, H 8.09, N 12.12.

5.1.46. [2-(4-{5-[5-Benzyloxy-1-(2-dimethylaminoethyl)-1*H*-indol-2-yl]pyridin-3-yl}phenoxy)ethyl]dimethyl amine (53). Same procedure as described for compound **49** from compounds **45** and **26**; Compound **53** was isolated as a pale brown oil (53%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.53; IR (NaCl, cm^{-1}) ν 2934, 1680, 1610, 1515, 1480, 1265, 1185, 1035, 909, 734; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.16 (s, 6H, 2× CH_3), 2.53 (s, 6H, 2× CH_3), 2.62 (t, 2H, J = 7.3 Hz, CH_2), 3.01 (t, 2H, J = 6.8 Hz, CH_2), 4.20–4.24 (m, 4H), 5.12 (s, 2H, CH_2), 6.55 (s, 1H, H_3), 6.99–7.10 (m, 2H, H_{arom}), 7.19 (d, 2H, J = 2.2 Hz, H_4), 7.31–7.41 (m, 4H, H_{arom}), 7.48 (d, 2H, J = 7.1 Hz, $H_{3''}$), 7.58 (d, 2H, J = 8.5 Hz, $H_{2''}$), 8.04 (s, 1H, $H_{4'}$), 8.69 (s, 1H, $H_{2'}$), 8.82 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 43.0 (CH_2), 45.8 (2× CH_3), 46.0 (2× CH_3), 58.3 (CH_2), 58.8 (CH_2), 66.2 (CH_2), 70.9 (CH_2), 103.2 (CH), 104.1 (CH), 110.8 (CH), 113.4 (CH), 115.4 (2× CH), 127.6 (2× CH), 127.8 (CH), 128.3 (2× CH), 128.5 (Cq), 128.6 (2× CH), 128.9 (Cq), 129.8 (Cq), 133.3 (Cq), 134.4 (CH), 135.9 (Cq), 137.7 (Cq), 138.3 (Cq), 147.1 (CH), 147.9 (CH), 153.8 (Cq), 159.3 (Cq); MS (IS): 536 $(M+1)^+$; Anal. Calcd for $C_{34}H_{38}N_4O_2$: C 76.37, H 7.16, N 10.48. Found: C 76.01, H 7.23, N 10.62.

5.1.47. [3-(5-Benzyloxy-2-{5-[4-(2-dimethylaminoethoxy)phenyl]pyridin-3-yl}indol-1-yl)propyl-dimethyl amine (54). Same procedure as described for compound **49** starting from **45** and **27**. Compound **54** was isolated as a pale brown oil (69%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.32; IR (NaCl, cm^{-1}) ν 3431, 2966, 1611, 1515, 1480, 1266, 1187, 1124, 1035, 1088, 737; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.80–1.87 (m, 2H, CH_2), 2.28 (t, 2H, J = 7.0 Hz, CH_2), 2.46 (s, 6H, 2× CH_3), 2.62 (t, 2H, J = 6.9 Hz, CH_2), 2.72 (s, 6H, 2× CH_3), 4.27–4.35 (m, 4H), 5.12 (s, 2H, OCH_2), 7.00 (dd, 1H, J = 2.0, 8.9 Hz, H_6), 7.06 (d, 2H, J = 8.5 Hz, $H_{3''}$), 7.17 (d, 1H, J = 2.2 Hz, H_4), 7.32–7.60 (m, 9H, H_{arom}), 7.92 (s, 1H, $H_{4'}$), 8.65 (s, 1H, $H_{2'}$), 8.81 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 24.0 (CH_2), 42.9 (CH_2), 43.6 (2× CH_3), 44.5 (2× CH_3), 55.3 (CH_2), 57.0 (CH_2), 64.2 (CH_2), 70.8 (CH_2), 103.8 (CH), 104.0 (CH), 111.1 (CH), 113.6 (CH), 115.4 (2× CH), 127.5 (2× CH), 127.8 (CH), 128.4 (2× CH), 128.7 (Cq), 129.4 (2× CH), 129.3 (Cq), 129.7 (Cq), 133.1 (Cq), 134.1 (CH), 135.7 (Cq), 135.9 (Cq), 138.2 (Cq), 147.1 (CH), 147.5 (CH), 153.7 (Cq), 158.4 (Cq); MS (IS): 550 $(M+1)^+$; Anal. Calcd for $C_{35}H_{40}N_4O_2$: C 76.61, H 7.35, N 10.21. Found: C 76.43, H 7.46, N 10.34.

5.1.48. [3-(4-{5-[5-Benzyloxy-1-(2-dimethylaminoethyl)-1*H*-indol-2-yl]pyridin-3-yl}phenoxy)-propyl]dimethyl amine (55). Same procedure as described for compound **49** starting from compounds **46** and **26**. Compound **55** was isolated as a pale brown oil (70%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.61; IR (NaCl, cm^{-1}) ν 3386, 2947, 1610, 1515, 1479, 1453, 1249, 1188, 1033, 909, 831; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.79–1.85 (m, 2H, CH_2), 2.18 (s, 6H, 2× CH_3), 2.31 (t, 2H, J = 7.1 Hz, CH_2), 2.64 (t, 2H, J = 7.0 Hz, CH_2), 2.76 (s, 6H, 2× CH_3), 4.15 (t, 2H, J = 6.7 Hz, CH_2), 4.28 (t, 2H, J = 7.4 Hz, CH_2), 5.13 (s, 2H, OCH_2), 6.56 (s, 1H, H_3), 7.01–7.05 (m, 2H, H_{arom}), 7.19 (d, 1H, J = 2.4 Hz, H_4), 7.32–7.60 (m, 9H, H_{arom}), 8.03 (s, 1H, $H_{4'}$), 8.70 (s, 1H, $H_{2'}$), 8.83 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 27.0 (CH_2), 42.9 (CH_2), 45.1 (2× CH_3), 45.8 (2× CH_3), 56.3 (CH_2), 58.6 (CH_2), 66.1 (CH_2), 70.9 (CH_2), 103.2 (CH), 104.0 (CH), 110.8 (CH), 113.4 (CH), 115.2 (2× CH), 127.6 (2× CH), 127.8 (CH), 128.3 (2× CH), 128.5 (Cq), 128.6 (2× CH), 129.0 (Cq), 129.7 (Cq), 133.3 (Cq), 134.4 (CH), 135.9 (Cq), 137.7 (Cq), 138.2 (Cq), 147.1 (CH), 147.9 (CH), 153.7 (Cq), 159.3 (Cq); MS (IS): 550 $(M+1)^+$; Anal. Calcd for $C_{35}H_{40}N_4O_2$: C 76.61, H 7.35, N 10.21. Found: C 76.24, H 7.51, N 10.37.

5.1.49. [3-(4-{5-[5-Benzyloxy-1-(3-dimethylaminopro-pyl)-1H- indol-2-yl]pyridin-3-yl}-phenoxy)propyl]di methylamine (56). Same procedure as described for compound **49** starting from compounds **46** and **27**. Compound **56** was isolated as a pale brown oil (67%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.35; IR (NaCl, cm^{-1}) ν 3376, 2945, 1609, 1517, 1482, 1457, 1244, 1192, 1026, 904, 835; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.63–1.71 (m, 2H, CH_2), 1.79–1.85 (m, 2H, CH_2), 2.10 (s, 6H, 2× CH_3), 2.17 (t, 2H, J = 6.9 Hz, CH_2), 2.39 (s, 6H, 2× CH_3), 2.65 (t, 2H, J = 7.1 Hz, CH_2), 4.10 (t, 2H, J = 6.4 Hz, CH_2), 4.25 (t, 2H, J = 7.5 Hz, CH_2), 5.13 (s, 2H, OCH_2), 6.99–7.05 (m, 3H, H_{arom}), 7.19 (d, 1H, J = 2.4 Hz, H_4), 7.32–7.58 (m, 9H, H_{arom}), 7.94 (s, 1H, $H_{4'}$), 8.67 (s, 1H, $H_{2'}$), 9.19 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 27.0 (CH_2), 27.9 (CH_2), 42.8 (CH_2), 45.1 (2× CH_3), 45.7 (2× CH_3), 56.4 (CH_2), 58.5 (CH_2), 66.2 (CH_2), 70.9 (CH_2), 103.2 (CH), 104.1 (CH), 110.5 (CH), 113.3 (CH), 115.2 (2× CH), 127.6 (2× CH), 127.9 (CH), 128.0 (2× CH), 128.4 (Cq), 128.8 (2× CH), 129.0 (Cq), 129.7 (Cq), 133.0 (Cq), 134.9 (CH), 135.6 (Cq), 137.5 (Cq), 138.2 (Cq), 147.1 (CH), 147.6 (CH), 153.8 (Cq), 159.3 (Cq); MS (IS): 564 $(M+1)^+$; Anal. Calcd for $C_{36}H_{42}N_4O_2$: C 76.84, H 7.52, N 9.96. Found: C 77.18, H 7.67, N 10.06.

5.1.50. 2-{5-[4-(2-Dimethylaminoethoxy)phenyl]pyridin-3-yl}-1-(2-dimethylaminoethyl)-5-hydroxy-1*H*-indole (57). Same procedure as described for compound **47** starting from compound **53**. Compound **57** was isolated as a pale brown oil (55%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.43; IR (NaCl, cm^{-1}) ν 3324, 3052, 2973, 2939, 2738, 2673, 2490, 1470, 1397, 1265, 1170, 1035; ^1H NMR ($CDCl_3$, 250 MHz): δ 2.16 (s, 6H, 2× CH_3), 2.53 (s, 6H, 2× CH_3), 2.60 (t, 2H, J = 7.1 Hz, CH_2), 2.84 (t, 2H, J = 6.9 Hz, CH_2), 4.11 (t, 2H, J = 6.1 Hz, CH_2), 4.23 (t, 2H, J = 7.9 Hz, CH_2), 6.47 (s, 1H, H_3), 6.97–7.07 (m, 4H, H_{arom}), 7.16–7.45 (m, 3H, H_{arom}), 7.56 (d, 2H, J = 8.1 Hz, $H_{2''}$), 8.68 (s, 1H, $H_{2'}$), 8.89 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 42.3 (CH_2), 44.2 (2× CH_3), 45.2 (2× CH_3), 55.5 (CH_2), 58.0 (CH_2), 65.4 (CH_2), 102.2 (CH), 104.8 (CH), 110.0 (CH), 112.4 (CH), 114.8 (2× CH), 127.7 (CH), 127.8 (CH), 128.3 (Cq), 128.6 (Cq), 129.1 (Cq), 132.3 (Cq), 133.8 (CH), 135.5 (Cq), 137.5 (Cq), 146.3 (CH), 147.1 (CH), 151.0 (Cq), 158.7 (Cq); MS (IS): 445 $(M+1)^+$; Anal. Calcd for $C_{27}H_{32}N_4O_2$: C 72.95, H 7.26, N 12.60. Found: C 73.29, H 7.17, N 12.75.

5.1.51. 2-{5-[4-(2-Dimethylaminoethoxy)phenyl]pyridin-3-yl}-1-(3-dimethylaminopropyl)-5-hydroxy-1*H*-indole (58). Same procedure as described for compound **47** starting from compound **54**. Compound 58 was isolated as a pale brown oil (50%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.40; IR (NaCl, cm^{-1}) ν 3302, 2928, 1678, 1623, 1506, 1481, 1262, 1191, 1052, 909, 723; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.79 (t, 2H, J = 6.6 Hz, CH_2), 2.26 (s, 6H, 2× CH_3), 2.43–2.52 (m, 8H), 2.96 (t, 2H, J = 5.4 Hz, CH_2), 4.19–4.23 (m, 4H, 2× CH_2), 6.55 (s, 1H, H_3), 6.74 (dd, 1H, J = 2.2, 8.7 Hz, H_6), 6.91 (s, 1H, H_4), 7.11 (d, 2H, J = 8.5 Hz, $H_{3''}$), 7.40 (d, 1H, J = 9.1 Hz, H_7), 7.79 (d, 2H, J = 8.7 Hz, $H_{2''}$), 8.14 (s, 1H, $H_{4'}$), 8.67 (s, 1H, $H_{2'}$), 8.85 (s large, 1H, OH), 8.90 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 23.3 (CH_2), 42.1 (CH_2), 44.1 (2× CH_3), 45.4 (2× CH_3), 56.5 (CH_2), 57.7 (CH_2), 64.5 (CH_2), 102.2 (CH), 104.8 (CH), 110.1 (CH), 112.5 (CH), 115.3 (2× CH), 128.0 (2× CH), 128.5 (Cq), 128.8 (Cq), 129.6 (Cq), 132.1 (Cq), 133.2 (CH), 134.8 (Cq), 137.7 (Cq), 146.1 (CH), 147.9 (CH), 151.4 (CH), 158.1 (Cq); MS (IS): 459 $(M+1)^+$; Anal. Calcd for $C_{28}H_{34}N_4O_2$: C 73.33, H 7.47, N 12.22. Found: C 73.06, H 7.60, N 12.38.

5.1.52. 1-(2-Dimethylaminoethyl)-2-{5-[4-(3-dimethylaminopropoxy)phenyl]pyridin-3-yl}-5-hydroxy-1*H*-indole (59). Same procedure as described for compound **47** starting from compound **55**. Compound **59** was isolated as a pale brown oil (52%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.39; IR (NaCl, cm^{-1}) ν 3322, 2923, 1656, 1617, 1509, 1476, 1298, 1187, 1045, 917, 721; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.81 (t, 2H, J = 6.3 Hz, CH_2), 2.24 (s, 6H, 2× CH_3), 2.41–2.50 (m, 8H), 2.91 (t, 2H, J = 5.7 Hz, CH_2), 4.17–4.26 (m, 4H, 2× CH_2), 6.57 (s, 1H, H_3), 6.71 (dd, 1H, J = 2.0, 8.7 Hz, H_6), 6.90 (s, 1H, H_4), 7.11 (d, 2H, J = 8.1 Hz, $H_{3''}$), 7.40 (d, 1H, J = 8.8 Hz, H_7), 7.76 (d, 2H, J = 8.4 Hz, $H_{2''}$), 8.15 (s, 1H, $H_{4'}$), 8.67 (s, 1H, $H_{2'}$), 8.84 (s large, 1H, OH), 8.89 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 23.1 (CH_2), 41.9 (CH_2), 44.4 (2× CH_3), 45.0 (2× CH_3), 56.7 (CH_2), 57.7 (CH_2), 64.5 (CH_2), 102.3 (CH), 104.1 (CH), 110.9 (CH), 112.3 (CH), 115.3 (2× CH), 128.3 (2× CH), 128.5 (Cq), 128.6 (Cq), 129.1 (Cq), 132.3 (Cq), 133.3 (CH), 134.8 (Cq), 137.5 (Cq), 146.3 (CH), 147.4 (CH), 151.4 (Cq), 158.5 (Cq); MS (IS): 459 $(M+1)^+$; Anal. Calcd for $C_{28}H_{34}N_4O_2$: C 73.33, H 7.47, N 12.22. Found: C 73.74, H 7.35, N 12.37.

5.1.53. 2-{5-[4-(3-Dimethylaminopropoxy) phenyl]pyridin-3-yl}-1-(3-dimethylaminopropyl)-5-hydroxy-1*H*-indole (60). Same procedure as described for compound **47** starting from compound **56**. Compound **60** was isolated as a pale brown oil (49%). R_f (dichloromethane/methanol/triethylamine 9:1:0.01): 0.44; IR (NaCl, cm^{-1}) ν 3312, 2933, 1687, 1608, 1511, 1478, 1268, 1188, 1044, 917, 733; ^1H NMR ($CDCl_3$, 250 MHz): δ 1.63–1.71 (m, 2H, CH_2), 1.79–1.85 (m, 2H, CH_2), 2.15 (s, 6H, 2× CH_3), 2.17 (t, 2H, J = 6.9 Hz, CH_2), 2.25 (s, 6H, 2× CH_3), 2.65 (t, 2H, J = 7.1 Hz, CH_2), 4.10 (t, 2H, J = 6.0 Hz, CH_2), 4.22 (t, 2H, J = 7.9 Hz, CH_2), 6.46 (s, 1H, H_3), 6.95–7.04 (m, 3H, H_{arom}), 7.16–7.47 (m, 2H, H_{arom}), 7.57 (d, 2H, J = 8.3 Hz, $H_{2''}$), 7.84 (s, 1H, $H_{4'}$), 8.67 (s, 1H, $H_{2'}$), 8.75 (s large, 1H, OH), 8.80 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 27.1 (CH_2), 28.1 (CH_2), 42.1 (CH_2), 45.2 (2× CH_3), 45.9 (2× CH_3), 56.5 (CH_2), 58.2 (CH_2), 65.0 (CH_2), 102.1 (CH), 104.7 (CH), 110.0 (CH), 112.4 (CH), 114.5 (2× CH), 127.9 (CH), 128.1 (CH), 128.3 (Cq), 128.6 (Cq), 129.6 (Cq), 132.1 (Cq), 133.5 (CH), 135.5 (Cq), 137.5 (Cq), 146.7 (CH), 147.9 (CH), 153.1 (Cq), 158.9 (Cq); MS (IS): 474 $(M+1)^+$; Anal. Calcd for $C_{29}H_{36}N_4O_2$: C 73.70, H 7.68, N 11.85. Found: C 73.44,H 7.54, N 12.02.

5.2. Computational methods

5.2.1. Homology modeling of CDK1-cyclinB. Molecular modeling studies were performed using Sybyl software version 7.0 running on a Silicon Graphics Octane workstation.[36] The structure of human CDK2-cyclinA complexed with indirubin-5-sulfonate at 2.5 Å resolution (PDB code, 1E9H)[37] was used as the template. The amino acid sequence of human CDK1 was retrieved from the Protein Information Resource (http://pir.georgetown.edu, Accession No. A29539) and aligned to that of human CDK2-cyclinA using ClustalW.[38] The high degree of primary sequence identity between CDK2 and CDK1 (65%, Fig. 4) strongly indicates that CDK2 structures are good models to be used as templates for CDK1. The 3D model of CDK1 was constructed by the Nest program from the protein structure modeling package JACKAL.[39] The resulting model was subjected to energy minimization using the Powell method available in Maximin2 procedure with the Tripos force field[40] and a dielectric constant of 4.0 until the gradient value reached 0.1 kcal/mol Å. Energy minimization was started with the core side chains then the core main chains. The Sybyl ProTable module checked the structure periodically. Where present, bad geometries were manually corrected and the structure minimized again with the above protocol.

5.2.2. Docking. Three-dimensional structures of compounds were built from a standard fragments library, and their geometry was subsequently optimized using the Tripos force field including the electrostatic term calculated from Gasteiger and Hückel atomic charges. Powell's method available in Maximin2 procedure was used for energy minimization until the gradient value was smaller than 0.001 kcal/mol Å. Flexible docking of compounds into the ATP-binding site of CDK1 model was performed using GOLD software.[41] For each compound, the most stable docking model was selected according to the best scored conformation predicted by the GoldScore[41] and X-Score[42] scoring functions. The complexes were energy-minimized using the Powell method available in Maximin2 procedure with the Tripos force field and a dielectric constant of 4.0 until the gradient value reached 0.1 kcal/mol Å.

5.3. Cell cultures and survival assay

CEM human leukemia cells were grown at 37 °C in a humidified atmosphere containing 5% CO_2 in RPMI 1640 medium, supplemented with 10% fetal bovine serum, glutamine (2 mM), penicillin (100 UI/ml), and streptomycin (100 μg/mL). The cytotoxicity of the studied molecules was assessed using a cell proliferation assay developed by Promega (CellTiter 96® AQ_{ueous} one solution cell proliferation assay). Briefly, 2×10^4 exponentially growing cells were seeded in 96-well microculture plates with various drug concentrations in a volume of 100 μL. After 72 h incubation at 37 °C, 20 μL of the tetrazolium dye solution was added to each well and the samples were incubated for a further 2 h at 37 °C. Plates were analyzed on a Labsystems Multiskan MS (type 352) reader at 492 nm.

5.4. Protein kinase assays

5.4.1. Biochemical reagents. Sodium ortho-vanadate, EGTA, EDTA, Mops, β-glycerophosphate, phenylphosphate, sodium fluoride, dithiothreitol (DTT), glutathione–agarose, glutathione, bovine serum albumin (BSA), nitrophenylphosphate, leupeptin, aprotinin, pepstatin, soybean trypsin inhibitor, benzamidine, and histone H1 (type **III**-S) were obtained from Sigma Chemicals. [γ-^{32}P]ATP (PB 168) was obtained from Amersham. The GS-1 peptide (YRRAAVPPSPSLSRHSSPHQSpE-DEEE) was synthesized by the Peptide Synthesis Unit, Institute of Biomolecular Sciences, University of Southampton, Southampton SO16 7PX, UK.

5.4.2. Buffers. *Homogenization buffer:* 60mM β-glycerophosphate, 15 mM *p*-nitrophenylphosphate, 25 mM Mops (pH 7.2), 15 mM EGTA, 15 mM $mgCl_2$, 1 mM DTT, 1 mM sodium vanadate, 1 mM NaF, 1 mM phenylphosphate, 10 μg leupeptin/ml, 10 μg aprotinin/ml, 10 μg soybean trypsin inhibitor/ml, and 100 μM benzamidine. *Bead buffer:* 50 mM Tris, pH 7.4, 5 mM NaF, 250 mM NaCl, 5 mM EDTA, 5 mM EGTA, 0.1% Nonidet P-40, 10 μg leupeptin/ml, 10 μg aprotinin/ml, 10 μg soybean trypsin inhibitor/ml, and 100 μM benzamidine. *Buffer A:* 10 mM $mgCl_2$, 1 mM EGTA, 1 mM DTT, 25 mM Tris–HCl, pH 7.5, 50 μg heparin/ml. *Buffer C:* homogenization buffer but 5 mM EGTA, no NaF and no protease inhibitors. *Tris-buffered saline–Tween 20 (TBST):* 50 mM Tris, pH 7.4, 150 mM NaCl, 0.1% Tween 20. *Hypotonic lysis buffer (HLB):* 50 mM Tris–HCl, pH 7.4, 120 mM NaCl, 10% glycerol, 1% Nonidet-P40, 5 mM DTT, 1 mM EGTA, 20 mM NaF, 1 mM orthovanadate, 5 μM microcystin, 100 μg/ml each of leupeptin, aprotinin, and pepstatin.

5.4.3. Kinase preparations and assays. Kinases activities were assayed in Buffer A or C (unless otherwise stated), at 30 °C, at a final ATP concentration of 15 μM. Blank values were subtracted and activities calculated as pmol of phosphate incorporated for a 10 min incubation. Controls were performed with appropriate dilutions of dimethylsulfoxide. GSK-3α/β was purified from porcine brain.[43] It was assayed, following a 1/100 dilution in 1 mg BSA/ml 10 mM DTT, with 5 μl 40 μM GS-1 peptide as a substrate, in buffer A, in the presence of 15 μM [γ-^{33}P] ATP (3000 Ci/mmol; 1 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. CDK1-cyclin B__was extracted in homogenization buffer from M phase starfish (Marthasterias glacialis) oocytes and purified by affinity chromatography on p9^{CKShs1}-sepharose beads, from which it was eluted by free p9^{CKShs1} as previously described.[25,44] The kinase activity was assayed in buffer C, with 1 mg histone H1/ml, in the presence of 15 μM [[γ-^{33}P] ATP (3000 Ci/mmol; 1 mCi/ml) in a final volume of 30 μl. After 10 min incubation at 30 °C, 25 μl aliquots of supernatant were spotted onto P81 phosphocellulose papers and treated as described above. CDK5/p25 was reconstituted by mixing equivual amounts of recombinant mammalian CDK5 and p25 expressed in *Escherichia coli* as GST (Glutathione-*S*-transferase) fusion proteins and purified by affinity chromatography on glutathione-agarose (vectors kindly provided by Dr. J.H. Wang) (p25 is a truncated version of p35, the 35 kDa CDK5 activator). Its activity was assayed in buffer C as described for CDK1-cyclin B.

5.4.4. Cell culture and cytotoxicity. L1210 and HT29 cells were cultivated in RPMI 1640 (Gibco) supplemented with 10% fetal calf serum, 2 mM L-glutamine, 100 U/mL penicillin, 100 mg/mL streptomycin, and 10 mM HEPES buffer (pH 7.4). Cytotoxicity was measured by the microculture tetrazolium assay (MTA) as described.[43] Cells were exposed to graded concentrations of compound (nine serial dilutions in triplicate) for four doubling times (48 h for L1210 cells and 96 h for HT29 cells). Results are expressed as IC_{50}, the concentration which reduced by 50% the optical density of treated cells with respect to the optical density of untreated controls.z

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