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Théo Frazier, Pauline Murail, Arthur Boulangé, Nazim Chalane, Francis Giraud, et al.. Synthesis of diversely substituted pyridin-2(1H)-ones and in vivo evaluation of their anti-allodynic effect on cutaneous inflammatory mechanical allodynia. *RSC Medicinal Chemistry*, 2024, 15 (8), pp.2900-2921. 10.1039/d4md00375f . hal-04742185

**HAL Id: hal-04742185**

**<https://hal.science/hal-04742185v1>**

Submitted on 17 Oct 2024

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**Synthesis of diversely substituted pyridin-2(1H)-ones and *in vivo* evaluation of their anti-allodynic effect on cutaneous inflammatory mechanical allodynia**

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## **Abstract**

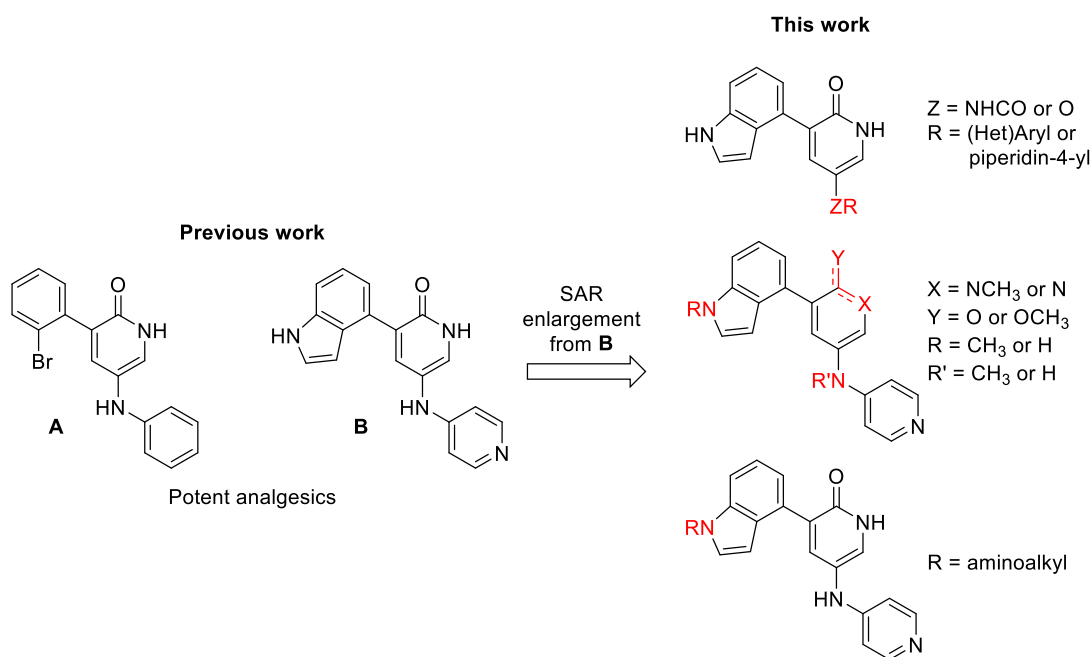
A series of 3,5-disubstituted pyridin-2(1*H*)-ones was synthesized. As part of a structure-activity relationship study performed in this series, structural modifications were based on 3-(indol-4-yl)-5-(pyridin-4-ylamino)pyridin-2(1*H*)-one **B**, that exhibited a potent anti-allodynic effect in a rat model of inflammatory pain. In this study, new compounds were assessed for their ability to inhibit cutaneous mechanical allodynia in rats by using the capsaicin pain model. Compound **36**, a 2-methoxypyridine derivative, yielded the most promising outcome, demonstrating an enhanced analgesic effect.

**Keywords:** Pyridin-2(1*H*)-ones; Cutaneous mechanical allodynia; Analgesics

## 1. Introduction

Chronic pain is a worldwide health problem that affects a significant portion of the population. Mechanical allodynia (MA), a common symptom of chronic pain caused by normally non-painful mechanical stimuli, remains incompletely understood, although some biological targets involved have been identified.<sup>1</sup> Furthermore, there are limited effective medical treatments for alleviating pain without side-effects or risk of abuse potential, as illustrated by opioid analgesics. Therefore, there is still an urgent need to develop new chemical agents that could enhance our understanding of the physiological mechanisms underlying pain and facilitate the identification of novel therapeutical approaches.

As part of our research on the development of new heteroaromatic compounds with biological applications, we recently reported on a pyridin-2(1*H*)-one series with potent analgesic properties. Indeed, we initially reported that intracisternal injection of compound **A** (5  $\mu$ L at 100  $\mu$ M) rapidly and strongly prevented the development of inflammatory MA on the facial Complete Freund's Adjuvant (CFA) model in rat, as well as reversed neuropathic MA induced by the chronic constriction injury of the rat's infraorbital nerve (IoN-CCI).<sup>2</sup> Further development in this series led to compound **B** that completely prevented MA on the rat facial inflammatory model at 10-fold lower concentration (i.e., 5  $\mu$ L at 10  $\mu$ M) (Figure 1).<sup>3</sup> Accordingly, compound **B** was selected as a starting point for further development, to expand the structure-activity relationship (SAR) study performed around this pyridin-2(1*H*)-one scaffold. One of the objectives was to highlight the structural requirements essential to analgesic activity. Thus, based on compound **B** structure, new derivatives were synthesized in which the nitrogen atom linking the pyridine and pyridinone rings was replaced by either an oxygen atom or an amide function (Figure 1). In addition, to get an insight into the role of the hydrogen donor positions, the corresponding heteroatoms were methylated. This included pyridinone oxygen, considering the hydroxypyridine tautomer of this heterocycle. Finally, substitution of the indolic nitrogen atom by aminoalkyl groups was undertaken with the objective to improve water solubility in this series (Figure 1). New compounds were evaluated for their potency to inhibit cutaneous MA in rats.

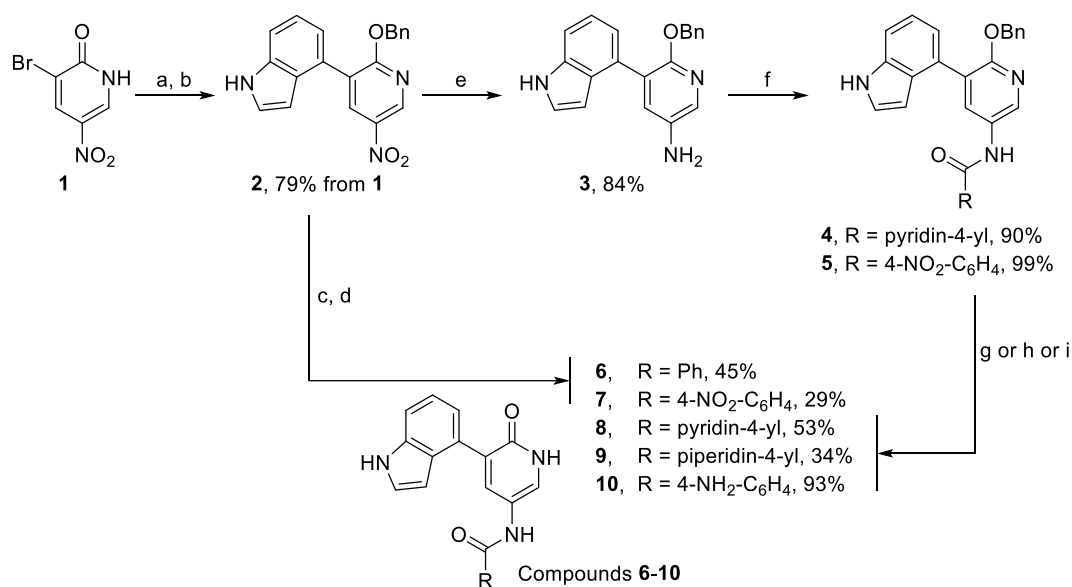


**Figure 1.** Structure of compounds **A** and **B** previously identified as potent analgesics. General formula of new pyridin-2(1*H*)-ones prepared to enlarge the SAR study in this series.

## 2. Results and Discussion

### 2.1. Synthesis of diversely substituted pyridin-2(1*H*)-ones

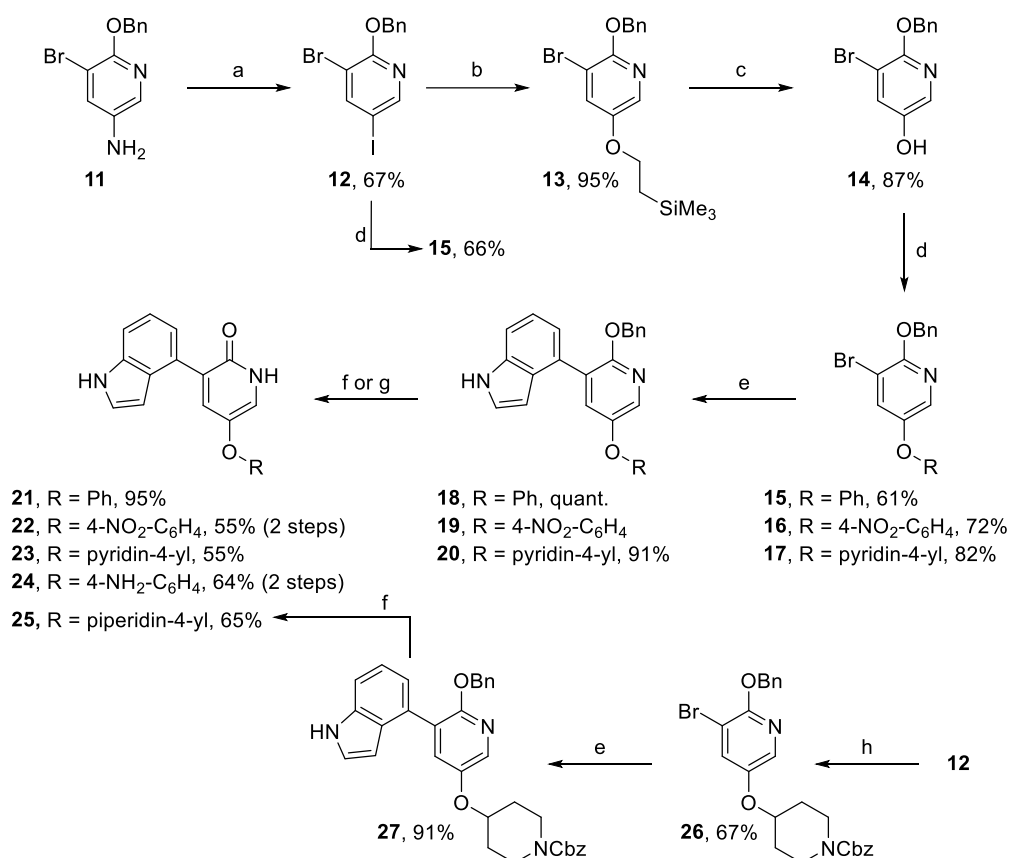
The synthesis of amide analogues of compound **B** was achieved from either intermediate **2** or **3** which were prepared from commercially available **1** (Scheme 1).<sup>3</sup> First, *O*-benzylation of compound **1** and Suzuki-Miyaura coupling with indole-4-boronic acid pinacol ester led to **2** in similar yields to those we previously reported.<sup>3</sup> Improved reduction of the nitro group by catalytic hydrogenation led to **3** in 84% yield, instead of 70% yield by using Fe/NH<sub>4</sub>Cl.<sup>3</sup> From compound **2**, amides **6** and **7** were straightforwardly synthesized after nitro reduction/debenzylation by catalytic hydrogenation and acylation step. However, this procedure did not allow us to prepare pyridinyl derivative **8** due to difficulties in the acylation step. Therefore, this analogue was prepared from **3**, after acylation to give **4** and debenzylation using BBr<sub>3</sub>. Interestingly, catalytic hydrogenation of **4** using palladium hydroxide did not provide **8**, possibly due to a catalyst poisoning effect of the pyridine moiety. In addition, when the hydrochloride salt of **4** was prepared first, reduction of the pyridine moiety led to piperidine **9**.<sup>4</sup> Finally, compound **10**, the nitro-reduced analogue of **7**, was similarly prepared from **3**, after acylation leading to **5**, and nitro reduction/debenzylation under catalytic hydrogenation.<sup>2,3</sup>



Reagents and Conditions: a) BnBr, Ag<sub>2</sub>CO<sub>3</sub>, toluene, 94%; b) indole-4-boronic acid pinacol ester, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, aq. Na<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane, 84%; c) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, CH<sub>2</sub>Cl<sub>2</sub>; d) acyl chloride, NEt<sub>3</sub>, THF/DMF; e) Fe, NH<sub>4</sub>Cl, *i*PrOH/H<sub>2</sub>O; f) acyl chloride, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; g) for prep. of **8**, BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; h) for prep. of **9** and **10**, H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH; i) for prep. of **9**, 1) HCl, MeOH, 2) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH.

### Scheme 1. Synthesis of amide analogues **6–10**.

Preparation of ether analogues of compound **B** took advantage of an Ullmann-type coupling using aryl/heteroaryl iodides from compound **14** (Scheme 2). The latter was prepared in three steps from previously reported compound **11**.<sup>3</sup> Firstly, Sandmeyer reaction produced iodopyridine derivative **12** that was then easily and regioselectively converted to hydroxypyridine **14**.<sup>5,6</sup> Ullmann ether synthesis with aryl/heteroaryl iodides produced compounds **15–17**.<sup>7</sup> It should be noted that our attempts to perform an Ullmann-type coupling directly from **12** and phenol derivatives was not satisfying. Only compound **15** could be obtained through this method, with 66% yield. From **15–17**, subsequent steps were introduction of the indol-4-yl moiety *via* Suzuki-Miyaura cross-coupling to give **18–20** and then debenylation leading to **21–23**. As for the amide series depicted in Scheme 1, reduced analogues **24** and **25** were also synthesized. The first was prepared from **19** by catalytic hydrogenation to reduce the nitro group and cleave the benzyl protecting group. Regarding **25**, the pyridine moiety of compound **23** could not be easily hydrogenated. Therefore **25** was prepared from **12**: coupling of benzyl 4-hydroxypiperidine-1-carboxylate under copper catalysis led to compound **26**,<sup>6</sup> then the indol-4-yl moiety was introduced before cleavage of the protecting groups.



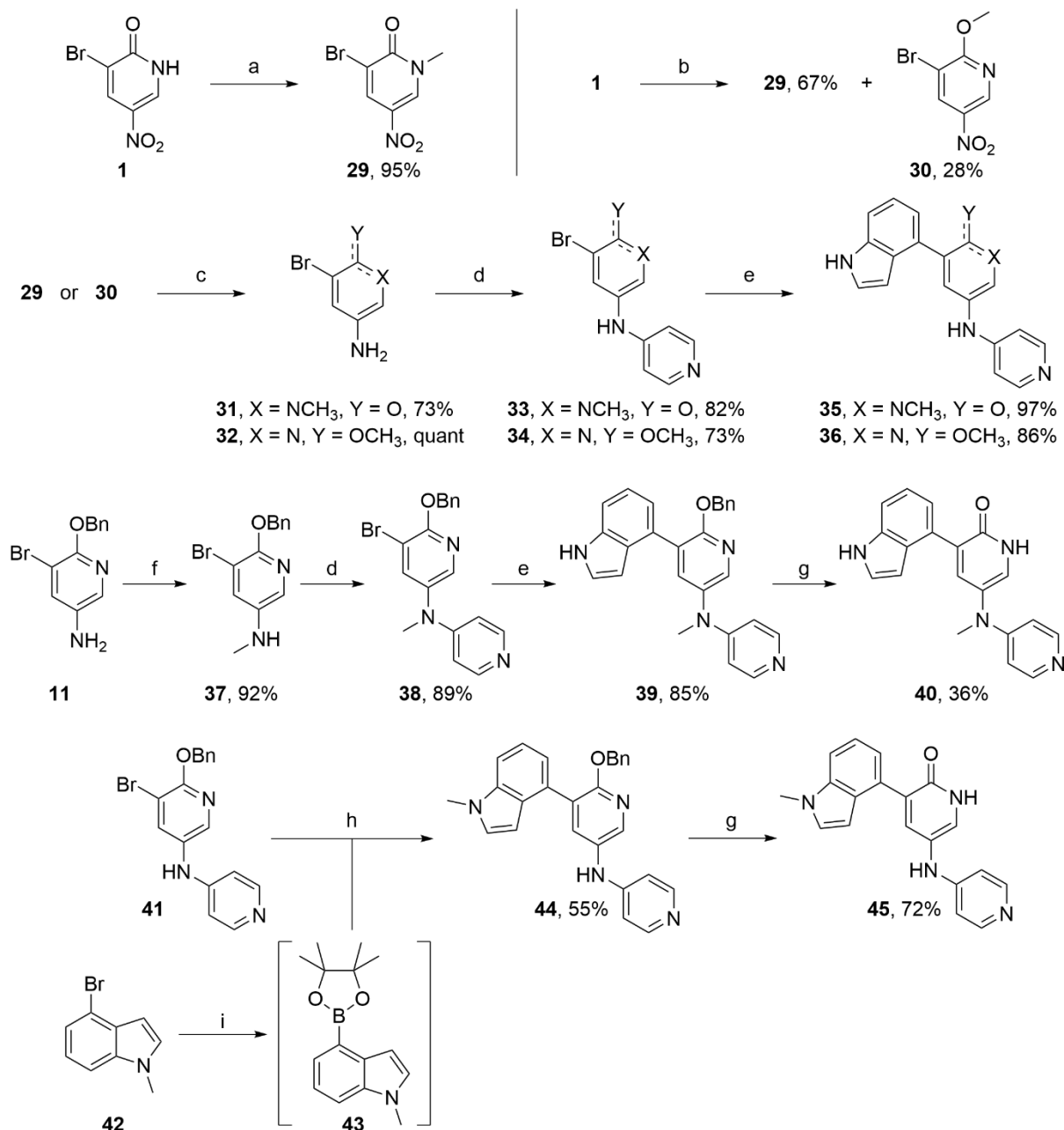
Reagents and Conditions: a) PTSA, NaNO<sub>2</sub>, KI, CH<sub>3</sub>CN, H<sub>2</sub>O; b) 2-(trimethylsilyl)ethanol, CuI, 1,10-phenanthroline, Cs<sub>2</sub>CO<sub>3</sub>, toluene; c) CsF, DMF; d) CuI, 2,2,6,6-tetramethylheptane-2,5-dione, Cs<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane, phenol from **12** or aryl/heteroaryl iodide from **14**; e) indole-4-boronic acid pinacol ester, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, aq. Na<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane; f) for prep. of **21**, **24** and **25**, H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, MeOH, CH<sub>2</sub>Cl<sub>2</sub>; g) for prep. of **22** and **23**, BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; h) Benzyl 4-hydroxypiperidine-1-carboxylate, CuI, 1,10-phenanthroline, Cs<sub>2</sub>CO<sub>3</sub>, toluene.

## Scheme 2. Synthesis of ether analogues **21–25**.

The next part of this synthetic work was to introduce a methyl group on heteroatoms of compound **B**, except the nitrogen atom of the pyridine ring. First, commercially available **1** was methylated using CH<sub>3</sub>I and silver carbonate in acetonitrile under microwave irradiation to give regioselectively *N*-methylated **29**, in 95% yield (Scheme 3). However, *O*-methylated regioisomer **30** was isolated in only 28% yield in similar alkylation conditions in toluene, together with **29** in 67% yield.<sup>8</sup> Next steps were those already reported<sup>2</sup>: reduction of the nitro group, Buchwald-Hartwig coupling with 4-iodopyridine and Suzuki-Miyaura reaction with indole-4-boronic acid pinacol ester, to give compounds **35** and **36**.

Methylation of the nitrogen atom linking the two heterocycles started from compound **11** with a 3-step monomethylation of the amino group: **11** was trifluoroacetylated, methylated and then the trifluoroacetyl group was removed to give **37**.<sup>9</sup> Introduction of the pyridinyl and indolyl substituents and final benzyl cleavage produced compound **40**.

Finally, *N*-methylated indole derivative was obtained from previously reported compound **41**.<sup>2</sup> Suzuki-Miyaura cross-coupling with boronic acid pinacol ester **43**, prepared by borylation of commercially available **42**,<sup>10</sup> gave **44** that was subsequently deprotected to obtain **45**.

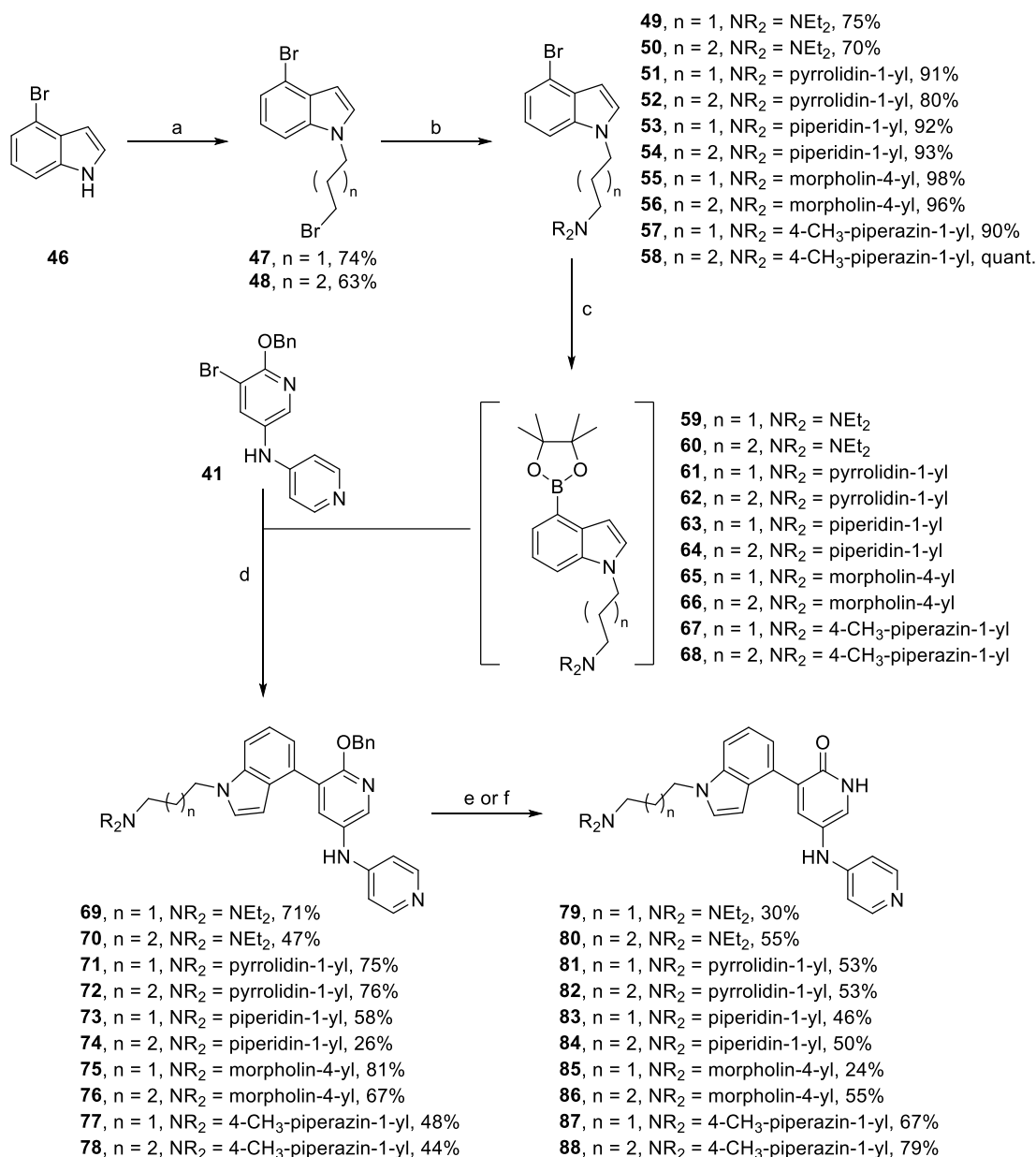


Reagents and Conditions: a) CH<sub>3</sub>I, Ag<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN,  $\mu$ w; b) CH<sub>3</sub>I, Ag<sub>2</sub>CO<sub>3</sub>, toluene; c) Fe, NH<sub>4</sub>Cl, *i*PrOH, H<sub>2</sub>O; d) 4-iodopyridine, Pd(OAc)<sub>2</sub>, Xantphos, Cs<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane; e) indole-4-boronic acid pinacol ester, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, aq. Na<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane; f) 1) TFAA, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 2) CH<sub>3</sub>I, K<sub>2</sub>CO<sub>3</sub>, acetone, 3) aq. NaOH, MeOH, CH<sub>3</sub>CN; g) H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, CH<sub>3</sub>CO<sub>2</sub>H, MeOH (for prep. of **40**) or CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:1 (for prep. of **45**); h) 1-methylindole-4-boronic acid pinacol ester, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, aq. Na<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane; i) bis(pinacolato)diboron, Pd(dppf)Cl<sub>2</sub>, KOAc, 1,4-dioxane,  $\mu$ w.

**Scheme 3.** Synthesis of methylated analogues **35**, **36**, **40** and **45**.



Analogues substituted on the indole nitrogen by aminoalkyl chains were prepared in a similar pathway to the one used for synthesizing **45** (Scheme 4). Thus, starting from 4-bromoindole, *N*-alkylation with either 1,3-dibromopropane or 1,4-dibromobutane led to compounds **47** and **48**.<sup>11</sup> Nucleophilic substitution with various secondary amines (Et<sub>2</sub>NH, pyrrolidine, piperidine, morpholine, *N*-methylpiperazine) gave aminopropyl and aminobutyl compounds **49–58**.<sup>12</sup> Further borylation,<sup>10</sup> Suzuki coupling with **41** and final deprotection provided derivatives **79–88**.



Reagents and Conditions: a) 1,3 dibromopropane or 1,4-dibromobutane, NaOH, TBAB, H<sub>2</sub>O, toluene; b) R<sub>2</sub>NH, DMF; c) bis(pinacolato)diboron, Pd(dppf)Cl<sub>2</sub>, KOAc, 1,4-dioxane,  $\mu\text{w}$ ; d) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, aq. Na<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane; e) for prep. of **79**, **83**, **85**, BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; f) for prep. of **80-82**, **84**, **86-88**, H<sub>2</sub>, Pd(OH)<sub>2</sub>/C, AcOH, CH<sub>2</sub>Cl<sub>2</sub>/MeOH.

#### Scheme 4. Synthesis of aminopropyl and aminobutyl analogues 79–88.

### 2.2. *In vivo* assessment of anti-allodynic effect

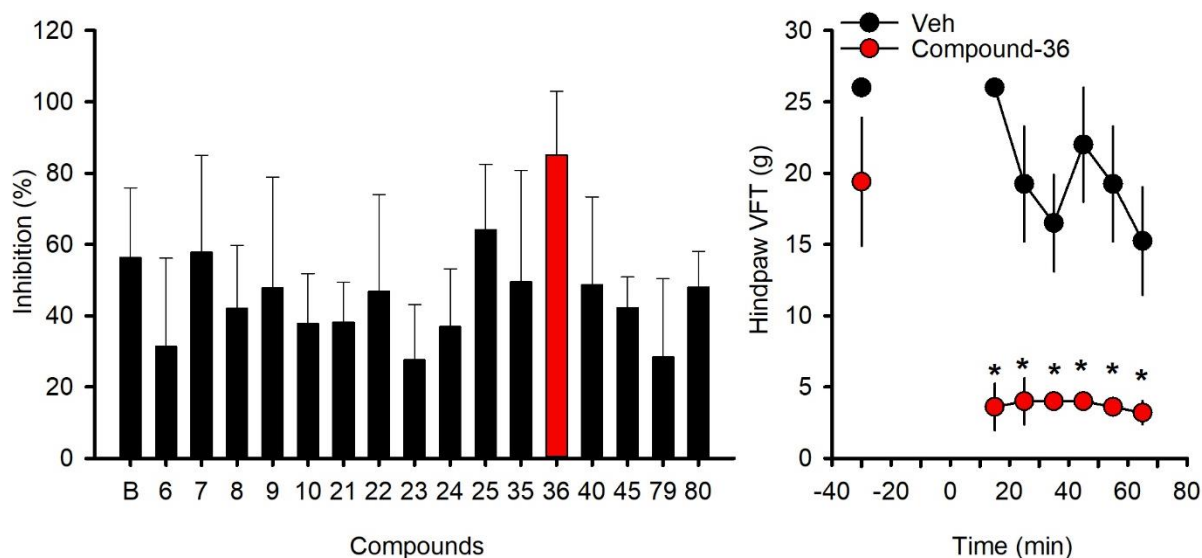
We evaluated *in vivo* the analgesic efficacy of new compounds **6–10**, **21–25**, **35**, **36**, **40**, **45**, **79**, and **80** in rats by using the hindpaw capsaicin model, where animals were administered a subcutaneous injection of capsaicin (25  $\mu\text{g}$  in 25  $\mu\text{L}$ ) into the plantar surface of the right hindpaw to induce cutaneous MA. All compounds were intrathecally administered at a concentration of 5  $\mu\text{M}$ , 30 min before the capsaicin injection. Their analgesic efficacy is

compared with that of compound **B**, which was selected as a starting point in this SAR study enlargement<sup>3</sup> (Fig. 1).

Substitution of the indole nitrogen of compound **B** by a methyl (**45**), diethylaminopropyl (**79**) or diethylaminobutyl (**80**) groups led to decreased activity toward capsaicin-induced MA (Fig. 2, left), suggesting that substitution at this position is detrimental to the desired biological activity. This indicates that the indole NH may act as a hydrogen bond donor in the interactions of compound **B** with its biological target. Analogues **81–88** substituted at the indole nitrogen by aminoalkyl groups were not behaviorally assessed to avoid unnecessary use of animals, and because some of the other prepared analogues showed improved activity. Indeed, among the other tested compounds, seven showed effective analgesic effect. Notably, compared with compound **B** (56% MA inhibition), three (compounds **7**, **25**, and **36**) exhibited similar or superior MA inhibition (Fig. 2, left).

When the NH of the (pyridin-4-yl)amino group in compound **B** was methylated (**40**) or replaced by an amide function (**8**) or an oxygen atom (**23**), the MA inhibitory activity was reduced. However, in the amide and ether series, the 4-nitrophenyl (**7**, **22**) and piperidinyl derivatives (**9**, **25**) led to similar or slightly superior activities to that of compound **B**. The best results were obtained for **7** and **25**, with 58% and 64% MA inhibition, respectively. These findings show that the replacement of the NH group at the pyridinone 5-position by an amide function or an oxygen atom is not detrimental to the analgesic activity. In addition, in line with our previous results, the nature of the ring attached to the amide or ether function has a significant effect, with 4-nitrophenyl and piperidinyl being the best substituents.

Finally, only one of these newly synthesized compounds, *O*-methylated compound **36**, demonstrated a larger MA inhibition (85 % inhibition) (red bar in Fig. 2, left and Fig. 2, right). This suggests that methylation at the pyridinone oxygen atom produces a striking positive effect, while *N*-methylation only leads to slightly reduced potency.



**Figure 2.** Intrathecal (i.t.) application of new pyridinones effectively mitigates mechanical allodynia (MA) in inflammatory paw pain induced by capsaicin. Left: Bar histograms summarizing MA inhibitions by compound **B**, and new compounds **6–10**, **21–25**, **35**, **36**, **40**, **45**, **79**, and **80**. Compound **36** effectively prevents inflammatory MA (85%). Right: Time course of the paw von Frey threshold (VFT) after a subcutaneous injection of capsaicin (25 µg in 25 µL) in compound **36** (10 µL at 5 µM) and vehicle-treated male rats. Compound **36** significantly attenuated capsaicin induced MA (two-way RM ANOVA followed by Tukey’s *post-hoc* test,  $P = 0.004$  on treatment,  $P < 0.001$  on time, and  $P = 0.008$  on time×treatment,  $n = 5$ /group). \*  $P < 0.05$  compared to vehicle with two-way repeated measures ANOVA followed by Tukey’s *post-hoc* test.

### 3. Conclusion

In conclusion, the initial SAR study around 3,5-disubstituted pyridine-2(1*H*)-one derivatives was extended. We show that the NH linking group at the 5-position can be replaced by an aminocarbonyl group or an oxygen atom, with good activity reached for compounds **7** and **25**. On the contrary, methylation or aminoalkylation of the indole nitrogen produces compounds with lower potency. The best result within the newly prepared compounds is obtained with *O*-methylated derivative **36**. Methoxypyridine **36** exhibited 85% inhibition of capsaicin-induced mechanical allodynia, instead of 56% for previously reported compound **B**.

In addition to previously reported inhibition of inflammatory pain on the facial CFA model in rat, and neuropathic pain induced by the IoN-CCI of the rat’s infraorbital nerve, we demonstrate in this work the potency of this series toward capsaicin-induced inflammatory

mechanical allodynia. These results confirm that 3,5-disubstituted pyridin-2(1*H*)-ones and their derivatives are of high interest for the development of novel analgesics.

## 4. Experimental section

### 4.1 Chemistry

#### 4.1.1. General.

Starting materials were obtained from commercial suppliers and used without further purification. IR spectra were recorded on a Perkin-Elmer Spectrum 65 FT-IR spectrometer ( $\bar{\nu}$  in  $\text{cm}^{-1}$ ). NMR spectra, performed on a Bruker AVANCE 400 III HD ( $^1\text{H}$ : 400 MHz,  $^{13}\text{C}$ : 101 MHz) or Bruker AVANCE 500 III HD ( $^1\text{H}$ : 500 MHz,  $^{13}\text{C}$ : 126 MHz) are reported in ppm using the solvent residual peak as an internal standard; the following abbreviations are used: singlet (s), doublet (d), triplet (t), quadruplet (q), quintuplet (quint), doublet of doublets (dd), multiplet (m), broad signal (br s). Coupling constants are expressed in Hertz. High resolution mass spectra were determined on a Thermo Scientific Q Exactive Q-Orbitrap apparatus (UCA Partner, Université Clermont Auvergne, Clermont-Ferrand, France). Chromatographic purifications were performed by column chromatography using 40–63  $\mu\text{m}$  silica gel or by flash column chromatography using puriFlash® XS 520 Plus with IR-50SI-F0004, IR-50SI-F0012, IR-50SI-F0025 or IR-50SI-F0040 columns. Reactions were monitored by TLC using fluorescent silica gel plates (60 F254 from Macherey Nagel). Melting points were measured on a Stuart SMP3 apparatus and are uncorrected.

The purity of compounds **6-10**, **21-25**, **35**, **36**, **40**, **45**, **79-88** was established by HPLC analysis using a VWR Hitachi chromatograph with DAD detector and a Macherey Nagel Nucleodur C18 Gravity column (4.6 mm  $\times$  250 mm, 5  $\mu\text{m}$ ). Flow rate was 0.5 mL/min and analysis were performed at 25 °C. Detection wavelength is indicated for each compound. Solvents were (A) water/0.1% trifluoroacetic acid (B) acetonitrile (C) water. Method A: gradient was 95:5 A/B for 5 min, then 95:5 A/B to 5:95 A/B in 20 min and then 5:95 A/B for 10 min. Method B: gradient was 95:5 C/B for 5 min, then 95:5 C/B to 5:95 C/B in 20 min and then 5:95 C/B for 10 min. Method C: 70:30 A/B for 10 min. Method D: 60:40 A/B for 10 min.

#### 4.1.2. General procedures

**Procedure A** for the preparation of compounds **6** and **7**.

To a solution of **2** (100 mg, 0.290 mmol) in MeOH (3 mL) and  $\text{CH}_2\text{Cl}_2$  (0.5 mL) degassed with argon was added 20%  $\text{Pd}(\text{OH})_2/\text{C}$  (3.3 mg, 4.7  $\mu\text{mol}$ , 0.02 eq.). The mixture was then

hydrogenated at room temperature for 6 h in the dark. After filtration through a pad of Celite, the solid was washed with MeOH. The filtrate was evaporated under reduced pressure to give crude 5-amino-3-(1*H*-indol-4-yl)pyridin-2(1*H*)-one as a green-dark solid ( $R_f = 0.16$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N)) that was used for the next step without further purification. To a solution under argon, in the dark, of crude 5-amino-3-(1*H*-indol-4-yl)pyridin-2(1*H*)-one in 3:1 THF/DMF mixture (amount for 0.072 M starting material concentration) was added Et<sub>3</sub>N (1.2 eq.). The mixture was cooled to 0 °C before the addition of acid chloride derivative (1.1 eq.). The solution was stirred 1 h in an ice bath in the dark. Water was added and the resulting mixture was extracted three times with ethyl acetate. The organic phase was washed with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub> and with brine, then dried over MgSO<sub>4</sub> and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography.

**Procedure B.** Debenzylation using BBr<sub>3</sub>, for the preparation of compounds **8**, **22**, **23**, **79**, **83** and **85**.

A solution under argon of benzylated derivative in dry dichloromethane (amount for 0.02 M starting material concentration) was cooled to -10 °C (for **8**, **22**, **23**) or to 0 °C (for **79**, **83**, **85**). A solution of BBr<sub>3</sub> in dichloromethane (1 M, 4 eq.) was added dropwise. The mixture was stirred at 0 °C (unless otherwise indicated) until reaction completion. The reaction mixture was then quenched by addition of excess of Et<sub>3</sub>N and then methanol. After evaporation under reduced pressure, the crude mixture was purified by column chromatography.

**Procedure C.** Hydrogenation/hydrogenolysis, for the preparation of compounds **10**, **21**, **24**, **25**. To a solution under argon of benzylated derivative in MeOH or CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1) degassed with argon was added 20% Pd(OH)<sub>2</sub>/C (0.02 eq.). The mixture was then hydrogenated at room temperature for several hours. The mixture was filtered through a pad of Celite which was then washed with methanol. The filtrate was evaporated under reduced pressure and the crude was purified by column chromatography.

**Procedure D.** Ullmann ether synthesis, for the preparation of compounds **15–17**.

A screw-cap tube was charged with **14**, CuI (0.05 eq.), Cs<sub>2</sub>CO<sub>3</sub> (2 eq.). The tube was flushed with argon and 1,4-dioxane (amount for 0.25 M starting material concentration), 2,2,6,6-tetramethylheptane-3,5-dione (0.1 eq.) and iodide derivative (2 eq.) were added. The tube was then sealed with a screw cap and heated in oil bath at 60 °C for 24 h. The resulting mixture was

filtered through a pad of Celite which was then washed with EtOAc. The filtrate was evaporated under reduced pressure and the crude was purified by column chromatography.

**Procedure E.** Suzuki-Miyaura cross-coupling, for the preparation of compounds **18–20, 27, 35, 36, 39, 44** and **69–78**.

To a solution under argon of brominated derivative in 1,4-dioxane (amount for 0.1 M starting material concentration) were added indole-4-boronic acid pinacol ester or derivatives (1.5 eq. of indole-4-boronic acid pinacol ester or 1–2 eq. based on starting material of borylation procedure) and 2 M aqueous solution of Na<sub>2</sub>CO<sub>3</sub> (5 eq.). The mixture was degassed with argon for 10 min before the addition of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 eq.). The solution was refluxed overnight. The resulting mixture was filtered through a pad of Celite which was then washed with EtOAc. The organic layer was washed with water and then with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by column chromatography.

**Procedure F.** Reduction of nitro derivatives, for the preparation of compounds **31** and **32**.

To a solution of nitro derivative (1 eq.) in a 10:1 propan-2-ol/water mixture (amount for 0.045 M starting material concentration) were added Fe powder (6 eq.) and NH<sub>4</sub>Cl (0.4 eq.). The mixture was refluxed for several hours. Then, the mixture was filtered through a pad of Celite which was then washed with ethyl acetate. The filtrate was washed with water, and the aqueous phase was extracted with ethyl acetate. Combined organic phases were dried over MgSO<sub>4</sub>, filtered and then evaporated. The obtained crude was purified by column chromatography.

**Procedure G.** Buchwald-Hartwig cross-coupling, for the preparation of compounds **33, 34** and **38**.

A screw-cap tube under argon was charged with amine derivative (1 eq.), Pd(OAc)<sub>2</sub> (0.05 eq.), Xantphos (0.05 eq.) and Cs<sub>2</sub>CO<sub>3</sub> (2 eq.). Then, anhydrous 1,4-dioxane (amount for 0.2 M starting material concentration) degassed with argon and 4-iodopyridine (1 eq.) were added. The tube was sealed and the mixture was stirred at 100 °C for several hours. The resulting suspension was filtered through a pad of Celite which was then washed with ethyl acetate. After evaporation of the filtrate, the brown residue was purified by column chromatography.

**Procedure H.** Debenzylation by catalytic hydrogenolysis, for preparation of compounds **45**, **80–82**, **84** and **86–88**.

To a solution under argon of benzylation derivative (1 eq.) and acetic acid (5 eq.) in CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:1 degassed with argon was added 20% Pd(OH)<sub>2</sub>/C (0.2 eq.). The mixture was then hydrogenated at room temperature overnight. Et<sub>3</sub>N (200 μL) was added and the mixture was filtered through a pad of Celite which was then washed with methanol. The filtrate was evaporated under reduced pressure and the crude was purified by column chromatography.

**Procedure I.** Amination of bromoalkylindoles **47** and **48**, for the preparation of compounds **49–58**

To a solution under argon of **47** or **48** (1 eq.) in DMF (amount for 0.25 M starting material concentration) was added amine derivative (5.0 eq.). The mixture was stirred for 1.5 h at room temperature. The resulting mixture was diluted in water and extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. Combined organic phases were dried over MgSO<sub>4</sub>, filtered, and evaporated under reduced pressure. After evaporation, the crude was purified by column chromatography.

**Procedure J.** Borylation of 4-bromo-1*H*-indole derivatives, for the preparation of compounds **59–68**.

A microwave tube under argon was charged with 4-bromo-1*H*-indole derivative (1 eq., ~100 mg per 10 mL tube), Pd(dppf)Cl<sub>2</sub> (0.1 eq.), KOAc (3.0 eq.) and bis(pinacolato)diboron (1.1 eq.). Then, anhydrous 1,4-dioxane (1 mL for 100 mg of starting material) degassed with argon was added. The tube was sealed and the mixture was heated under microwave irradiation for 30 min (Dynamic control, P<sub>max</sub> = 150 W, T = 80 °C). The resulting mixture was concentrated under reduced pressure and the crude was purified by column chromatography.

#### **4.1.3. 4-(2-(Benzyloxy)-5-nitropyridin-3-yl)-1*H*-indole 2**

To a solution under argon of crushed **1** (1.90 g, 8.68 mmol, 1 eq.) in anhydrous toluene (26 mL), benzyl bromide (2.2 mL, 18.5 mmol, 2.1 eq.) was added. The mixture was stirred at room temperature for 5 min. Then, the mixture was stirred at 70 °C and crushed Ag<sub>2</sub>CO<sub>3</sub> was added in three portions of 0.35 eq. every hour (3 x 840 mg, 3 x 3.05 mmol, 3 x 0.35 eq.). After 3 h 30 min at 70 °C, the mixture was filtered through a pad of Celite which was then washed with ethyl acetate. The obtained yellow solid was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 100:0 to 5:95) to give the desired product with a residual impurity which was removed by washing with cyclohexane, to give 2-(benzyloxy)-3-bromo-5-nitropyridine



(2.51 g, 8.12 mmol, 94%) as a white solid.  $R_f = 0.40$  (cyclohexane/EtOAc 98:2). For characterization data, see Ref. 3.

To a solution under argon of 2-(benzyloxy)-3-bromo-5-nitropyridine (500 mg, 1.62 mmol) in 1,4-dioxane (16 mL) were added the indole-4-boronic acid pinacol ester (587 mg, 2.41 mmol, 1.5 eq.) and 2 M aqueous solution of  $\text{Na}_2\text{CO}_3$  (4 mL, 8 mmol, 5 eq.). The mixture was degassed with argon for 10 min before the addition of  $\text{PdCl}_2(\text{PPh}_3)_2$  (56 mg, 0.08 mmol, 0.05 eq.). The solution was refluxed overnight. Ethyl acetate was added and the resulting mixture was washed with water. The organic phase was dried over  $\text{MgSO}_4$  and filtered. After evaporation under reduced pressure, the crude oil was purified by column chromatography ( $\text{SiO}_2$ , cyclohexane/EtOAc 95:5 to 80:20) to give **2** (472 mg, 1.37 mmol, 84%) as a yellow solid.  $R_f = 0.25$  (cyclohexane/EtOAc 8:2). For characterization data, see Ref. 3.

#### 4.1.4. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)pyridin-3-amine **3**

To a solution of compound **2** (465 mg, 1.35 mmol) in a 10:1 propan-2-ol/water mixture (33 mL) were added Fe powder (455 mg, 8.15 mmol, 6 eq.) and  $\text{NH}_4\text{Cl}$  (29 mg, 0.54 mmol, 0.4 eq.). The mixture was refluxed for 2 h and then filtered through a Celite pad. The solid was washed with EtOAc, and the filtrate was evaporated. The obtained oil was purified by column chromatography ( $\text{SiO}_2$ , cyclohexane/EtOAc 7:3 to 5:5) to give **3** (358 mg, 1.14 mmol, 84%) as a brown solid.  $R_f = 0.13$  (cyclohexane/EtOAc 7:3). For characterization data, see Ref. 3.

#### 4.1.5. *N*-[6-Benzyloxy-5-(1*H*-indol-4-yl)pyridin-3-yl]pyridine-4-carboxamide **4**

To a solution of 4-isonicotinoyl chloride hydrochloride (51 mg, 0.286 mmol, 1.5 eq.) in dichloromethane (3 mL) under argon atmosphere was added triethylamine (32  $\mu\text{L}$ , 0.230 mmol, 1.2 eq.) and then dropwise a second solution of **3** (60 mg, 0.190 mmol) and triethylamine (32  $\mu\text{L}$ , 0.230 mmol, 1.2 eq.) in dichloromethane (2 mL). The resulting solution was stirred 30 min at rt. The solvent was removed and water was added. The aqueous phase was extracted three times with ethyl acetate and combined organic extracts were washed with a saturated aqueous solution of  $\text{Na}_2\text{CO}_3$  and then with brine. The organic phase was dried over  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure. The obtained yellow solid was purified by column chromatography ( $\text{Et}_3\text{N}$ -treated  $\text{SiO}_2$ , EtOAc 100%) to give **4** (72 mg, 0.171 mmol, 90%) as a yellow solid.  $R_f = 0.29$  (EtOAc 100%); Mp > 205 °C (decomposition); IR (ATR) 3261, 1611, 1588, 1488, 1324, 1220, 853, 748, 729, 690  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.22 (s, 1H), 10.64 (s, 1H), 8.80 (m, 2H), 8.59 (d,  $J = 2.6$ , 1H), 8.25 (d,  $J = 2.6$ , 1H), 7.89 (m, 2H), 7.42 (dd,  $J_1 = 7.1$ ,  $J_2 = 1.7$ , 1H), 7.39 (t,  $J = 2.8$ , 1H), 7.37–7.22 (m, 5H), 7.20–7.13 (m, 2H), 6.39

(m, 1H), 5.41 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  164.0 (C), 156.5 (C), 150.3 (2CH), 141.5 (C), 137.5 (C), 137.2 (CH), 136.1 (C), 132.9 (CH), 129.7 (C), 128.2 (2CH), 127.47 (2CH), 127.44 (C), 127.43 (CH), 126.5 (C), 125.7 (CH), 123.2 (C), 121.5 (2CH), 120.7 (CH), 120.1 (CH), 111.2 (CH), 100.6 (CH), 67.1 ( $\text{CH}_2$ ); HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{26}\text{H}_{21}\text{N}_4\text{O}_2$  ( $\text{M} + \text{H}$ ) $^+$  421.1659, found 421.1650.

#### 4.1.6. *N*-[6-Benzyloxy-5-(1*H*-indol-4-yl)pyridin-3-yl]-4-nitrobenzamide **5**

To a solution of 4-nitro benzoyl chloride (48 mg, 0.259 mmol, 1.6 eq.) in dichloromethane (3 mL) under argon atmosphere was added a solution of triethylamine (23  $\mu\text{L}$ , 0.165 mmol, 1.04 eq.) and **3** (50 mg, 0.159 mmol) in dichloromethane (2 mL). The resulting solution was stirred 2 h at rt. The solvent was removed under reduced pressure and water was added. The aqueous phase was extracted three times with ethyl acetate and combined organic extracts were washed with a saturated aqueous solution of  $\text{Na}_2\text{CO}_3$  and then with brine. The organic phase was dried over  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure to give **5** (73 mg, 0.157 mmol, 99%) as a yellow solid.  $R_f$  = 0.12 (cyclohexane/EtOAc 8:2); Mp > 220  $^\circ\text{C}$  (decomposition); IR (ATR) 3432, 3342, 2922, 1654, 1514, 1341, 1266, 1214, 755, 718, 695  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.22 (s, 1H), 10.70 (s, 1H), 8.60 (d,  $J$  = 2.4 Hz, 1H), 8.39 (d,  $J$  = 8.7 Hz, 2H), 8.26 (d,  $J$  = 2.4 Hz, 1H), 8.22 (d,  $J$  = 8.7 Hz, 2H), 7.45–7.38 (m, 2H), 7.37–7.22 (m, 5H), 7.20–7.13 (m, 2H), 6.39 (m, 1H), 5.41 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  163.9 (C), 156.5 (C), 149.2 (C), 140.1 (C), 137.5 (C), 137.2 (CH), 136.1 (C), 132.9 (CH), 129.9 (C), 129.2 (2CH), 128.2 (2CH), 127.48 (2CH), 127.45 (C), 127.43 (CH), 126.5 (C), 125.7 (CH), 123.6 (2CH), 123.2 (C), 120.7 (CH), 120.1 (CH), 111.2 (CH), 100.6 (CH), 67.1 ( $\text{CH}_2$ ); HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{27}\text{H}_{21}\text{N}_4\text{O}_4$  ( $\text{M} + \text{H}$ ) $^+$  465.1557, found 465.1547.

#### 4.1.7. *N*-[5-(1*H*-Indol-4-yl)-6-oxo-1,6-dihydropyridin-3-yl]benzamide **6**

Compound **6** was prepared according to general procedure A, starting from **2** (100 mg, 0.290 mmol). The crude oil was purified by column chromatography ( $\text{Et}_3\text{N}$ -treated  $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  98:2 to 9:1 + 0.5%  $\text{Et}_3\text{N}$ ). The obtained solid was washed with  $\text{CH}_2\text{Cl}_2$  to give **6** (43 mg, 0.131 mmol, 45%) as a purple solid.  $R_f$  = 0.35 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5 + 0.5%  $\text{Et}_3\text{N}$ ); Mp > 250  $^\circ\text{C}$ ; IR (ATR) 3241, 1647, 1351, 1254, 1119, 747, 684, 607  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.60 (br s, 1H), 11.15 (s, 1H), 10.12 (s, 1H), 8.01 (d,  $J$  = 2.6, 1H), 7.99 (d,  $J$  = 2.7, 1H), 7.97–7.92 (m, 2H), 7.61–7.56 (m, 1H), 7.55–7.50 (m, 2H), 7.40–7.36 (m, 2H), 7.32 (d,  $J$  = 7.2, 1H), 7.11 (t,  $J$  = 7.7, 1H), 6.51 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  165.2 (C), 159.5 (C), 136.2 (C), 135.6 (CH), 134.4 (C), 131.6 (CH), 129.9 (C), 128.4 (2CH),

128.2 (C), 127.5 (2CH), 126.2 (C), 125.3 (CH), 125.2 (CH), 120.4 (CH), 119.9 (CH), 119.7 (C), 110.9 (CH), 100.8 (CH); HRMS (ESI+)  $m/z$  calcd for  $C_{20}H_{16}N_3O_2$  (M + H)<sup>+</sup> 330.1237, found 330.1230. HPLC purity  $\geq$  99%, Method A:  $t_R$  = 22.53 min,  $\lambda$  = 280 nm.

#### 4.1.8. *N*-[5-(1*H*-Indol-4-yl)-6-oxo-1,6-dihydropyridin-3-yl]-4-nitrobenzamide **7**

Compound **7** was prepared according to general procedure A, starting from **2** (100 mg, 0.290 mmol). The crude oil was purified by column chromatography (Et<sub>3</sub>N-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 to 92:8 + 0.5 % Et<sub>3</sub>N). The obtained solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **7** (31 mg, 0.0828 mmol, 29%) as a beige solid.  $R_f$  = 0.40 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N); Mp > 250 °C; IR (ATR) 3434, 1568, 1524, 1465, 1341, 853, 751, 712, 619 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.69 (br s, 1H), 11.17 (s, 1H), 10.45 (s, 1H), 8.38 (d,  $J$  = 8.7, 2H), 8.18 (d,  $J$  = 8.8, 2H), 8.03 (d,  $J$  = 2.7 1H), 7.99 (d,  $J$  = 2.7, 1H), 7.43–7.35 (m, 2H), 7.32 (d,  $J$  = 7.2, 1H), 7.11 (t,  $J$  = 7.7, 1H), 6.51 (s, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  163.5 (C), 159.6 (C), 149.2 (C), 140.0 (C), 136.2 (C), 135.3 (CH), 130.0 (C), 129.1 (2CH), 128.0 (C), 126.1 (C), 125.5 (CH), 125.4 (CH), 123.6 (2CH), 120.4 (CH), 119.9 (CH), 119.4 (C), 111.0 (CH), 100.8 (CH); HRMS (ESI+)  $m/z$  calcd for  $C_{20}H_{15}N_4O_4$  (M + H)<sup>+</sup> 375.1088, found 375.1077. HPLC purity  $\geq$  96%, Method A:  $t_R$  = 23.40 min,  $\lambda$  = 280 nm.

#### 4.1.9. *N*-[5-(1*H*-Indol-4-yl)-6-oxo-1,6-dihydropyridin-3-yl]pyridine-4-carboxamide **8**

Compound **8** was prepared according to general procedure B, starting from **4** (100 mg, 0.238 mmol). The mixture was stirred 7.5 h at 0 °C. The crude oil was purified by column chromatography (Et<sub>3</sub>N-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 93:7 to 90:10). The obtained solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **8** (42 mg, 0.127 mmol, 53%) as an ochre solid.  $R_f$  = 0.15 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N); Mp > 250 °C; IR (ATR) 3276, 1611, 1588, 1488, 1324, 1220, 853, 748, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.66 (br s, 1H), 11.16 (s, 1H), 10.37 (s, 1H), 8.78 (d,  $J$  = 4.0, 2H), 8.01 (s, 1H), 7.98 (s, 1H), 7.85 (d,  $J$  = 4.0, 2H), 7.41–7.35 (m, 2H), 7.32 (d,  $J$  = 7.1, 1H), 7.11 (t,  $J$  = 7.4, 1H), 6.50 (s, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  163.6 (C), 159.6 (C), 150.3 (2CH), 141.4 (C), 136.1 (C), 135.3 (CH), 130.0 (C), 128.0 (C), 126.1 (C), 125.5 (CH), 125.4 (CH), 121.4 (2CH), 120.4 (CH), 119.9 (CH), 119.2 (C), 111.0 (CH), 100.8 (CH); HRMS (ESI+)  $m/z$  calcd for  $C_{19}H_{15}N_4O_2$  (M + H)<sup>+</sup> 331.1190, found 331.1194. HPLC purity  $\geq$  99%, Method C:  $t_R$  = 3.63 min,  $\lambda$  = 346 nm.

#### 4.1.10. *N*-[5-(1*H*-Indol-4-yl)-6-oxo-1,6-dihydropyridin-3-yl]piperidine-4-carboxamide **9**

To compound **4** (100 mg, 0.238 mmol) was added a solution of 37% HCl (80  $\mu$ L) in MeOH (5 mL). The mixture was concentrated under reduced pressure to obtain the corresponding hydrochloride salt. The salt was solubilized in MeOH (5 mL) and the solution was degassed with argon. 20% Pd(OH)<sub>2</sub>/C (33 mg, 0.05 mmol, 0.2 eq.) was added and the mixture was hydrogenated at room temperature for 24 h. Et<sub>3</sub>N (0.2 mL, 1.43 mmol, 6.0 eq.) was added and the mixture was filtered through a pad of Celite and the solid was washed with methanol. After evaporation under reduced pressure, the crude solid was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:1 + 2% Et<sub>3</sub>N). The obtained solid was solubilized in acetonitrile and filtered to remove SiO<sub>2</sub>. After evaporation, the solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **9** (27 mg, 0.080 mmol, 34%) as a white solid.  $R_f$  = 0.06 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:1 + 2% Et<sub>3</sub>N); Mp > 241 °C (decomposition); IR (ATR) 3253, 2927, 2849, 1652, 1623, 1562, 1535, 1339, 1189, 1113, 958 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.14 (s, 1H), 9.63 (s, 1H), 7.88 (d,  $J$  = 2.6, 1H), 7.73 (d,  $J$  = 2.7, 1H), 7.39–7.34 (m, 2H), 7.28 (d,  $J$  = 7.2, 1H), 7.09 (t,  $J$  = 7.7 Hz, 1H), 6.43 (m, 1H), 3.00–2.92 (m, 2H), 2.51–2.41 (m, 2H), 2.38–2.27 (m, 1H), 1.70–1.61 (m, 2H), 1.56–1.43 (m, 2H), two exchangeable NH protons were not observed; <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  173.4 (C), 159.3 (C), 136.1 (C), 134.6 (CH), 129.9 (C), 128.2 (C), 126.1 (C), 125.3 (CH), 123.8 (CH), 120.4 (CH), 120.0 (C), 119.9 (CH), 110.9 (CH), 100.7 (CH), 45.5 (2CH<sub>2</sub>), 43.4 (CH), 29.4 (2CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>19</sub>H<sub>21</sub>N<sub>4</sub>O<sub>2</sub> (M + H)<sup>+</sup> 337.1659, found 337.1652. HPLC purity  $\geq$  99%, Method A:  $t_R$  = 17.91 min,  $\lambda$  = 280 nm.

#### 4.1.11. 4-Amino-*N*-[5-(1*H*-indol-4-yl)-6-oxo-1,6-dihydropyridin-3-yl]benzamide **10**

Compound **10** was prepared according to general procedure C in MeOH, starting from **5** (45 mg, 0.097 mmol) during 3 h. The crude was purified by column chromatography (Et<sub>3</sub>N-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 93:7 + 0.5% Et<sub>3</sub>N to 90:10 + 0.5% Et<sub>3</sub>N). The obtained solid was washed with chloroform to give **10** (31 mg, 0.090 mmol, 93%) as a beige solid.  $R_f$  = 0.19 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 92:8 + 0.5% Et<sub>3</sub>N); Mp > 199 °C (decomposition); IR (ATR) 3215, 1599, 1498, 1337, 1268, 1178, 838, 752 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.53 (br s, 1H), 11.13 (s, 1H), 9.64 (s, 1H), 7.96 (d,  $J$  = 2.6, 1H), 7.93 (d,  $J$  = 2.5, 1H), 7.68 (d,  $J$  = 8.3, 2H), 7.41–7.33 (m, 2H), 7.30 (d,  $J$  = 7.2, 1H), 7.10 (t,  $J$  = 7.7 Hz, 1H), 6.59 (d,  $J$  = 8.4 Hz, 2H), 6.50 (s, 1H), 5.73 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  165.3 (C), 159.5 (C), 152.2 (C), 136.2 (C), 136.0 (CH), 129.7 (C), 129.2 (2CH), 128.4 (C), 126.3 (C), 125.3 (CH), 124.8 (CH), 120.7 (C), 120.5 (CH), 120.3 (C), 120.0 (CH), 112.6 (2CH), 110.9 (CH), 101.0 (CH); HRMS (ESI+)  $m/z$

calcd for C<sub>20</sub>H<sub>17</sub>N<sub>4</sub>O<sub>2</sub> (M + H)<sup>+</sup> 345.1346, found 345.1338. HPLC purity ≥ 99%, Method A: t<sub>R</sub> = 19.11 min, λ = 280 nm.

#### 4.1.12. 2-(Benzyloxy)-3-bromo-5-iodopyridine **12**

To a solution of **11** (100 mg, 0.358 mmol) in acetonitrile (1.4 mL) and water (0.25 mL) in an ice bath was added *p*-toluenesulfonic acid monohydrate (204 mg, 1.07 mmol, 3 eq.). The resulting solution was stirred for 10 min and then a solution of sodium nitrite (49 mg, 0.71 mmol, 2 eq.) and KI (149 mg, 0.90 mmol, 2.5 eq.) in water (0.25 mL) was added dropwise. The mixture was stirred for 10 min in an ice bath and then at room temperature. The reaction was monitored by release of N<sub>2</sub>. After addition of water, saturated aqueous solutions of NaHCO<sub>3</sub> and Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> were added. The aqueous phase was extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. Combined organic phases were dried over MgSO<sub>4</sub>, filtered and evaporated. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane 100%) to give the desired product **12** (94 mg, 0.241 mmol, 67%) as a white solid. *R*<sub>f</sub> = 0.19 (toluene/cyclohexane 1:9); Mp 83 °C; IR (ATR) 2923, 1559, 1466, 1428, 1352, 1309, 1300, 1238, 1048, 1014, 891, 730, 719, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.40 (d, *J* = 2.0, 1H), 8.38 (d, *J* = 2.0, 1H), 7.47–7.43 (m, 2H), 7.42–7.36 (m, 2H), 7.36–7.30 (m, 1H), 5.40 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 158.5 (C), 151.2 (CH), 148.6 (CH), 136.4 (C), 128.4 (2CH), 127.9 (CH), 127.6 (2CH), 107.8 (C), 83.5 (C), 68.1 (CH<sub>2</sub>); HRMS (ESI+) *m/z* calcd for C<sub>12</sub>H<sub>10</sub>BrINO (M + H)<sup>+</sup> 389.8985, found 389.8986.

#### 4.1.13. 2-(Benzyloxy)-3-bromo-5-[2-(trimethylsilyl)ethoxy]pyridine **13**

A screw-cap tube was charged with CuI (17 mg, 0.089 mmol, 0.1 eq.), 1,10-phenanthroline (33 mg, 0.183 mmol, 0.2 eq.), Cs<sub>2</sub>CO<sub>3</sub> (593 mg, 1.82 mmol, 2 eq.), **12** (355 mg, 0.91 mmol). The tube was flushed with argon and 2-(trimethylsilyl)ethanol (391 μL, 2.73 mmol, 3 eq.) and dry toluene (450 μL) were added. The tube was then sealed with a screw cap and placed in a pre-heated oil bath at 110 °C and stirred overnight. The resulting suspension was cooled to room temperature and concentrated under reduced pressure. The crude was purified by column chromatography (SiO<sub>2</sub>, toluene/cyclohexane 1:1) to give the desired product **13** (328 mg, 0.86 mmol, 95%) as a white solid. *R*<sub>f</sub> = 0.30 (toluene/cyclohexane 4:6); Mp 82 °C; IR (ATR) 3052, 2940, 1426, 1351, 1310, 1301, 1240, 731, 720, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.87 (d, *J* = 2.4, 1H), 7.79 (d, *J* = 2.4, 1H), 7.44 (d, *J* = 7.4, 2H), 7.38 (t, *J* = 7.4, 2H), 7.31 (t, *J* = 7.1, 1H), 5.35 (s, 2H), 4.09 (t, *J* = 8.1, 2H), 1.05 (t, *J* = 8.1, 2H), 0.05 (s, 9H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 153.1 (C), 150.4 (C), 137.1 (C), 131.7 (CH), 129.7 (CH), 128.4 (2CH),

127.7 (CH), 127.4 (2CH), 105.9 (C), 67.7 (CH<sub>2</sub>), 66.8 (CH<sub>2</sub>), 17.2 (CH<sub>2</sub>), -1.3 (3CH<sub>3</sub>); HRMS (ESI+) *m/z* calcd for C<sub>17</sub>H<sub>23</sub>BrNO<sub>2</sub>Si (M + H)<sup>+</sup> 380.0676, found 380.0674.

#### 4.1.14. 6-(Benzyloxy)-5-bromopyridin-3-ol **14**

To a solution of **13** (525 mg, 1.38 mmol) in dry DMF (2.8 mL) under argon was added cesium fluoride (630 mg, 4.15 mmol, 3 eq.) and heated at 60 °C for 2 h 30 min. Reaction mass was diluted with water and extracted three times with ethyl acetate. Combined organic phases were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 9:1 to 8:2) to give the desired product **14** (338 mg, 1.21 mmol, 87%) as a yellow solid. *R<sub>f</sub>* = 0.38 (cyclohexane/EtOAc 8:2); Mp 145 °C; IR (ATR) 3250–2500, 1434, 1344, 1229, 1208, 1059, 1022, 736, 694 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 9.74 (s, 1H), 7.71 (d, *J* = 2.6, 1H), 7.51 (d, *J* = 2.6, 1H), 7.45–7.41 (m, 2H), 7.40–7.35 (m, 2H), 7.33–7.28 (m, 1H), 5.32 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 152.1 (C), 149.2 (C), 137.3 (C), 131.7 (CH), 129.9 (CH), 128.4 (2CH), 127.6 (CH), 127.4 (2CH), 105.6 (C), 67.6 (CH<sub>2</sub>); HRMS (ESI+) *m/z* calcd for C<sub>12</sub>H<sub>11</sub>BrNO<sub>2</sub> (M + H)<sup>+</sup> 279.9968, found 279.9970.

#### 4.1.15. 2-(Benzyloxy)-3-bromo-5-phenoxy pyridine **15**

Compound **15** was prepared according to general procedure D, starting from **14** (60 mg, 0.143 mmol). The mixture was heated for 24 h. The crude was purified by column chromatography (SiO<sub>2</sub>, toluene/cyclohexane 2:8) to give **15** (31 mg, 0.087 mmol, 61%) as a colorless oil.

Alternatively, compound **15** can be prepared from **12**: a screw-cap tube was charged with **12** (100 mg, 0.256 mmol), CuI (2.5 mg, 0.013 mmol, 0.05 eq.), Cs<sub>2</sub>CO<sub>3</sub> (167 mg, 0.513 mmol, 2 eq.) and phenol (25 mg, 0.266 mmol, 1 eq.). The tube was flushed with argon and 1,4-dioxane (1 mL) and 2,2,6,6,6-tetramethyl-3,5-heptanedione (5 μL, 0.024 mmol, 0.1 eq.) were added. The tube was then sealed with a screw cap and heated in oil bath at 100 °C for 41 h. The resulting mixture was diluted with water and extracted three time with EtOAc. Combined organic phases were washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated under reduced pressure. The crude oil was purified by column chromatography (SiO<sub>2</sub>, toluene/cyclohexane 1:9 to 2:8) to give **15** (60 mg, 0.168 mmol, 66%) as a colorless oil. *R<sub>f</sub>* = 0.25 (toluene/cyclohexane 2:8); Aspect: colorless oil; IR (ATR) 1587, 1436, 1212, 855, 729, 691 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.04 (d, *J* = 2.6, 1H), 7.93 (d, *J* = 2.6, 1H), 7.48 (d, *J* = 7.4, 2H), 7.43–7.31 (m, 5H), 7.14 (t, *J* = 7.3, 1H), 7.02 (d, *J* = 8.0, 2H), 5.41 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 157.3 (C), 155.4 (C), 147.5 (C), 136.8 (1C+1CH), 134.5 (CH),

130.1 (2CH), 128.4 (2CH), 127.9 (CH), 127.6 (2CH), 123.5 (CH), 117.4 (2CH), 106.2 (C), 68.2 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>18</sub>H<sub>15</sub>BrNO<sub>2</sub> (M + H)<sup>+</sup> 356.0281, found 356.0272.

#### 4.1.16. 2-Benzyloxy-3-bromo-5-(4-nitrophenoxy)pyridine **16**

Compound **16** was prepared according to general procedure D, starting from **14** (60 mg, 0.214 mmol). The mixture was heated for 24 h. The crude was purified by column chromatography (SiO<sub>2</sub>, toluene/cyclohexane 1:1) to give **16** (62 mg, 0.155 mmol, 72%) as a yellow-orange solid.  $R_f$  = 0.17 (toluene/cyclohexane 1:1); Mp 130 °C; IR (ATR) 1427, 1347, 1311, 1240, 1044, 891, 731, 721, 692, 605 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.25 (d,  $J$  = 9.1, 2H), 8.19 (d,  $J$  = 2.4, 1H), 8.18 (d,  $J$  = 2.4, 1H), 7.49 (d,  $J$  = 7.2, 2H), 7.41 (t,  $J$  = 7.3, 2H), 7.35 (t,  $J$  = 7.0, 1H), 7.19 (d,  $J$  = 9.1, 2H), 5.44 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 163.0 (C), 156.5 (C), 145.6 (C), 142.5 (C), 138.1 (CH), 136.6 (C), 135.8 (CH), 128.5 (2CH), 127.9 (CH), 127.6 (2CH), 126.2 (2CH), 117.0 (2CH), 106.5 (C), 68.4 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>18</sub>H<sub>14</sub>BrN<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 401.0131, found 401.0126.

#### 4.1.17. 2-Benzyloxy-3-bromo-5-[(pyridin-4-yl)oxy]pyridine **17**

Compound **17** was prepared according to general procedure D, starting from **14** (100 mg, 0.357 mmol). The mixture was heated for 24 h. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 8:2 to 7:3) to give **17** (105 mg, 0.294 mmol, 82%) as a white solid.  $R_f$  = 0.18 (cyclohexane/EtOAc 7:3); Mp 99 °C; IR (ATR) 3027, 3004, 2939, 2924, 1576, 1466, 1433, 1358, 1251, 1207, 1056, 901, 865, 816 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.48 (br s, 2H), 8.17 (s, 2H), 7.49 (d,  $J$  = 6.9, 2H), 7.41 (t,  $J$  = 7.1, 2H), 7.35 (t,  $J$  = 6.8, 1H), 6.98 (d,  $J$  = 4.3, 2H), 5.44 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 164.2 (C), 156.5 (C), 151.5 (2CH), 144.9 (C), 138.2 (CH), 136.6 (C), 135.9 (CH), 128.4 (2CH), 127.9 (CH), 127.6 (2CH), 111.6 (2CH), 106.5 (C), 68.4 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>17</sub>H<sub>14</sub>BrN<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 357.0233, found 357.0228.

#### 4.1.18. 4-(2-Benzyloxy-5-phenoxy)pyridin-3-yl)-1H-indole **18**

Compound **18** was prepared according to general procedure E, starting from **15** (114 mg, 0.32 mmol). The mixture was refluxed overnight. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 95:5 to 90:10) to give **18** (126 mg, 0.32 mmol, quantitative) as a white-green solid.  $R_f$  = 0.38 (cyclohexane/EtOAc 8:2); Mp 116 °C; IR (ATR) 3427, 3308, 1423, 1353, 1217, 731, 718, 686, 666, 624, 611 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.21 (s, 1H), 8.06 (d,  $J$  = 2.9, 1H), 7.50 (d,  $J$  = 2.9, 1H), 7.43–7.22 (m, 9H), 7.16–7.06

(m, 5H), 6.25 (m, 1H), 5.39 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  157.6 (C), 156.3 (C), 147.6 (C), 137.3 (C), 136.01 (C), 135.98 (CH), 131.3 (CH), 130.1 (2CH), 128.2 (2CH), 127.53 (2CH), 127.47 (CH), 127.0 (C), 126.4 (C), 125.7 (CH), 124.7 (C), 123.2 (CH), 120.7 (CH), 120.1 (CH), 117.5 (2CH), 111.4 (CH), 100.3 (CH), 67.3 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>26</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 393.1598, found 393.1592.

#### 4.1.19. 4-[2-Benzyloxy-5-(4-nitrophenoxy)pyridin-3-yl]-1H-indole 19

Compound **19** was prepared according to general procedure E, starting from **16** (170 mg, 0.424 mmol). The mixture was refluxed overnight. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 9:1 to 8:2) to give impure **19** (196 mg) as a brown solid. **19** was used in the next step (preparation of **22** and **24**) without further purification.  $R_f$  = 0.28 (cyclohexane/EtOAc 8:2);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.22 (s, 1H), 8.27 (d,  $J$  = 9.3, 2H), 8.19 (d,  $J$  = 2.9, 1H), 7.70 (d,  $J$  = 2.9, 1H), 7.44–7.11 (m, 11H), 6.31 (m, 1H), 5.42 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  163.3 (C), 157.4 (C), 145.7 (C), 142.3 (C), 137.3 (CH), 137.2 (C), 136.0 (C), 132.7 (CH), 128.2 (2CH), 127.6 (2CH), 127.5 (CH), 126.8 (C), 126.4 (C), 126.3 (2CH), 125.8 (CH), 125.2 (C), 120.7 (CH), 120.2 (CH), 116.9 (2CH), 111.5 (CH), 100.5 (CH), 67.5 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>26</sub>H<sub>20</sub>N<sub>3</sub>O<sub>4</sub> (M + H)<sup>+</sup> 437.1448, found 438.1435.

#### 4.1.20. 4-{2-Benzyloxy-5-[(pyridin-4-yl)oxy]pyridin-3-yl}-1H-indole 20

Compound **20** was prepared according to general procedure E, starting from **17** (80 mg, 0.224 mmol). The mixture was refluxed 1 h 30 min. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 5:5 to 6:4). The obtained solid was solubilized in EtOAc and the solution was washed with a 0.1 M aqueous solution of HCl and then with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub> to remove a residual impurity. The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give **20** (80 mg, 0.203 mmol, 91%) as a grey solid.  $R_f$  = 0.23 (cyclohexane/EtOAc 1:1); Mp > 162 °C (decomposition); IR (ATR) 3055, 2919, 2853, 1577, 1438, 1418, 1242, 1206, 989, 825 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.22 (s, 1H), 8.48 (d,  $J$  = 5.1, 2H), 8.17 (s, 1H), 7.68 (s, 1H), 7.41 (d,  $J$  = 7.1, 1H), 7.39–7.22 (m, 6H), 7.19–7.10 (m, 2H), 7.04 (d,  $J$  = 5.2, 2H), 6.30 (s, 1H), 5.41 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  164.5 (C), 157.4 (C), 151.6 (2CH), 145.0 (C), 137.4 (CH), 137.2 (C), 136.0 (C), 132.8 (CH), 128.2 (2CH), 127.6 (2CH), 127.5 (CH), 126.8 (C), 126.5 (C), 125.8 (CH), 125.1 (C), 120.7 (CH), 120.2 (CH), 111.6 (2CH), 111.5 (CH), 100.4 (CH), 67.5 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>25</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub> (M + H)<sup>+</sup> 394.1550, found 394.1541.



#### 4.1.21. 3-(1*H*-Indol-4-yl)-5-phenoxy pyridin-2(1*H*)-one **21**

Compound **21** was prepared according to general procedure C in CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1), starting from **18** (100 mg, 0.255 mmol). The mixture was stirred for 3 h 30 min. The crude was purified by column chromatography (Et<sub>3</sub>N-treated SiO<sub>2</sub>, cyclohexane/EtOAc 3:7 to 0:10) to give **21** (73 mg, 0.241 mmol, 95%) as a white solid. *R*<sub>f</sub> = 0.10 (EtOAc 100% + 0.5% Et<sub>3</sub>N); Mp > 165 °C (decomposition); IR (ATR) 3285, 1652, 1613, 1588, 1557, 1488, 1464, 1323, 1220, 873, 852, 747, 726, 689, 616 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.68 (br s, 1H), 11.15 (s, 1H), 7.48–7.30 (m, 6H), 7.26 (d, *J* = 6.9, 1H), 7.14–7.02 (m, 4H), 6.28 (s, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 159.7 (C), 158.2 (C), 137.5 (C), 136.1 (C), 134.6 (CH), 130.8 (C), 130.0 (2CH), 127.8 (C), 126.1 (C), 125.7 (CH), 125.5 (CH), 122.7 (CH), 120.4 (CH), 120.0 (CH), 116.5 (2CH), 111.1 (CH), 100.3 (CH); HRMS (ESI+) *m/z* calcd for C<sub>19</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub> (M + H)<sup>+</sup> 303.1128, found 303.1122. HPLC purity ≥ 96%, Method A: *t*<sub>R</sub> = 25.43 min, λ = 280 nm.

#### 4.1.22. 3-(1*H*-Indol-4-yl)-5-(4-nitrophenoxy)pyridin-2(1*H*)-one **22**

Compound **22** was prepared according to general procedure B, starting from **19** (80 mg). The mixture was stirred for 1 h at 0 °C. The crude was purified by column chromatography (Et<sub>3</sub>N-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99:1 to 97:3). The obtained solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **22** (33 mg, 0.095 mmol, 55% in two steps from **16**) as a pale-yellow solid. *R*<sub>f</sub> = 0.31 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); Mp > 245 °C (decomposition); IR (ATR) 3258, 1607, 1512, 1467, 1331, 1239, 1109, 845 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.88 (br s, 1H), 11.15 (s, 1H), 8.27 (d, *J* = 8.5, 2H), 7.60 (s, 1H), 7.53 (s, 1H), 7.38 (d, *J* = 7.5, 1H), 7.34 (s, 1H), 7.30–7.22 (m, 3H), 7.10 (t, *J* = 7.5, 1H), 6.32 (s, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 163.6 (C), 160.0 (C), 142.1 (C), 136.1 (C), 135.9 (C), 134.5 (CH), 131.4 (C), 127.7 (C), 127.0 (CH), 126.2 (2CH), 126.1 (C), 125.5 (CH), 120.4 (CH), 120.0 (CH), 116.4 (2CH), 111.2 (CH), 110.5 (CH); HRMS (ESI+) *m/z* calcd for C<sub>19</sub>H<sub>14</sub>N<sub>3</sub>O<sub>4</sub> (M + H)<sup>+</sup> 348.0979, found 348.0970. HPLC purity ≥ 98%, Method D: *t*<sub>R</sub> = 4.33 min, λ = 318 nm.

#### 4.1.23. 3-(1*H*-Indol-4-yl)-5-[(pyridin-4-yl)oxy]pyridin-2(1*H*)-one **23**

Compound **23** was prepared according to general procedure B, starting from **20** (57 mg, 0.145 mmol). The mixture was stirred for 5 h 30 min at 0 °C. The crude was purified by column chromatography (Et<sub>3</sub>N-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 97:3 to 94:6). The obtained solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **23** (24 mg, 0.079 mmol, 55%) as a pale-yellow solid. *R*<sub>f</sub> = 0.22 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); Mp > 250 °C; IR (ATR) 3200–2700, 1615, 1586, 1473, 1326, 1255,

1237, 1208, 875, 828  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.84 (br s, 1H), 11.15 (s, 1H), 8.47 (m, 2H), 7.57 (d,  $J = 2.5$  Hz, 1H), 7.50 (d,  $J = 3.0$ , 1H), 7.37 (d,  $J = 8.0$ , 1H), 7.33 (t,  $J = 2.6$ , 1H), 7.25 (d,  $J = 7.0$ , 1H), 7.10 (t,  $J = 7.7$ , 1H), 7.05 (m, 2H), 6.31 (s, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  164.7 (C), 160.0 (C), 151.5 (2CH), 136.1 (C), 135.3 (C), 134.6 (CH), 131.2 (C), 127.7 (C), 127.0 (CH), 126.1 (C), 125.5 (CH), 120.4 (CH), 120.0 (CH), 111.3 (2CH), 111.2 (CH), 100.4 (CH); HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{14}\text{N}_3\text{O}_2$  ( $\text{M} + \text{H}$ ) $^+$  304.1081, found 304.1075. HPLC purity  $\geq 99\%$ , Method C:  $t_{\text{R}} = 2.75$  min,  $\lambda = 346$  nm.

#### 4.1.24. 5-(4-Aminophenoxy)-3-(1H-indol-4-yl)pyridin-2(1H)-one **24**

Compound **24** was prepared according to general procedure C in  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (1:1), starting from **19** (80 mg). The mixture was stirred for 24 h. The crude was purified by column chromatography ( $\text{Et}_3\text{N}$ -treated  $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  96:4 to 93:7). The obtained solid was washed with  $\text{CH}_2\text{Cl}_2$  to give **24** (35 mg, 0.110 mmol, 64% in two steps from **16**) as a beige solid.  $R_{\text{f}} = 0.22$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5); Mp  $> 152$  °C (decomposition); IR (ATR) 3379, 3332, 3106, 2849, 1619, 1502, 1468, 1329, 1209, 852  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.48 (br s, 1H), 11.14 (s, 1H), 7.40 (d,  $J = 2.6$ , 1H), 7.36 (d,  $J = 8.0$ , 1H), 7.32 (m, 1H), 7.23 (d,  $J = 7.2$ , 1H), 7.17 (d,  $J = 2.6$ , 1H), 7.09 (t,  $J = 7.7$ , 1H), 6.80 (d,  $J = 8.5$ , 2H), 6.56 (d,  $J = 8.4$ , 2H), 6.26 (s, 1H), 4.89 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  159.3 (C), 147.7 (C), 144.8 (C), 140.3 (C), 136.1 (C), 133.6 (CH), 130.3 (C), 128.0 (C), 126.1 (C), 125.4 (CH), 123.3 (CH), 120.4 (CH), 119.9 (CH), 118.8 (2CH), 114.8 (2CH), 111.0 (CH), 100.3 (CH); HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}_2$  ( $\text{M} + \text{H}$ ) $^+$  318.1237, found 318.1230. HPLC purity  $\geq 98\%$ , Method B:  $t_{\text{R}} = 21.32$  min,  $\lambda = 240$  nm.

#### 4.1.25. 3-(1H-Indol-4-yl)-5-[(piperidin-4-yl)oxy]pyridin-2(1H)-one **25**

Compound **25** was prepared according to general procedure C in  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (1:1), starting from **27** (120 mg, 0.225 mmol). The mixture was stirred for 24 h. The crude was purified by column chromatography ( $\text{Et}_3\text{N}$ -treated  $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  85:15 + 1%  $\text{Et}_3\text{N}$ ). The obtained solid was washed with  $\text{CH}_2\text{Cl}_2$  to give **25** (45 mg, 0.145 mmol, 65%) as a white solid.  $R_{\text{f}} = 0.10$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  8:2 + 1%  $\text{Et}_3\text{N}$ ); Mp  $> 167$  °C (decomposition); IR (ATR) 3240, 2944, 1650, 1604, 1559, 1465, 1334, 1208, 1152, 1000, 819  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  11.13 (s, 1H), 7.43 (d,  $J = 2.9$ , 1H), 7.39–7.33 (m, 2H), 7.20 (d,  $J = 7.2$ , 1H), 7.14 (d,  $J = 2.7$ , 1H), 7.09 (t,  $J = 7.7$ , 1H), 6.31 (s, 1H), 4.12–4.04 (m, 1H), 2.98–2.89 (m, 2H), 2.50 (2H under solvent residual signal), 1.93–1.84 (m, 2H), 1.48–1.37 (m, 2H), two exchangeable NH protons were not observed;  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  159.0 (C), 139.6 (C), 136.1 (C), 134.3 (CH), 130.2

(C), 128.4 (C), 126.2 (C), 125.3 (CH), 122.0 (CH), 120.4 (CH), 119.9 (CH), 110.9 (CH), 100.6 (CH), 76.4 (CH), 43.5 (2CH<sub>2</sub>), 32.2 (2CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>18</sub>H<sub>20</sub>N<sub>3</sub>O<sub>2</sub> (M + H)<sup>+</sup> 310.1550, found 310.1541. HPLC purity ≥ 98%, Method A: *t<sub>R</sub>* = 18.21 min, λ = 280 nm.

#### 4.1.26. Benzyl 4-[(6-benzyloxy-5-bromopyridin-3-yl)oxy]piperidine-1-carboxylate **26**

A screw-cap tube was charged with CuI (5 mg, 0.026 mmol, 0.1 eq.), 1,10-phenanthroline (10 mg, 0.055 mmol, 0.2 eq.), Cs<sub>2</sub>CO<sub>3</sub> (167 mg, 0.51 mmol, 2 eq.), **12** (100 mg, 0.256 mmol) and benzyl 4-hydroxy-1-piperidinecarboxylate (181 mg, 0.77 mmol, 3 eq.). The tube was flushed with argon and dry toluene (1 mL) was added. The tube was then sealed with a screw cap and placed in a pre-heated oil bath at 110 °C and stirred for 24 h. The resulting mixture was filtered through a pad of Celite which was then washed with EtOAc. The filtrate was evaporated under reduced pressure. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 9:1 to 8:2) to give the desired product **26** (85 mg, 0.171 mmol, 67%) as a white wax. *R<sub>f</sub>* = 0.35 (cyclohexane/EtOAc 8:2); IR (ATR) 2948, 2868, 1693, 1430, 1357, 1221, 1196, 1046, 1026 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.94 (d, *J* = 2.6, 1H), 7.90 (d, *J* = 2.6, 1H), 7.44 (d, *J* = 7.3, 2H), 7.41–7.29 (m, 8H), 5.36 (s, 2H), 5.08 (s, 2H), 4.60–4.52 (m, 1H), 3.76–3.67 (m, 2H), 3.32–3.19 (m, 2H), 1.94–1.85 (m, 2H), 1.59–1.48 (m, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 154.4 (C), 153.5 (C), 148.7 (C), 137.05 (C), 136.96 (C), 133.9 (CH), 131.5 (CH), 128.42 (2CH), 128.38 (2CH), 127.8 (CH), 127.7 (CH), 127.53 (2CH), 127.47 (2CH), 105.9 (C), 73.9 (CH), 67.8 (CH<sub>2</sub>), 66.2 (CH<sub>2</sub>), 40.7 (2CH<sub>2</sub>), 30.1 (2CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>25</sub>H<sub>26</sub>BrN<sub>2</sub>O<sub>4</sub> (M + H)<sup>+</sup> 497.1070, found 497.1070.

#### 4.1.27. Benzyl 4-[[6-benzyloxy-5-(1*H*-indol-4-yl)pyridin-3-yl]oxy]piperidine-1-carboxylate **27**

Compound **27** was prepared according to general procedure E, starting from **26** (200 mg, 0.402 mmol). The mixture was refluxed overnight. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 85:5 to 75:25) to give **27** (195 mg, 0.365 mmol, 91%) as a white solid. *R<sub>f</sub>* = 0.36 (cyclohexane/EtOAc 7:3); Mp 62 °C; IR (ATR) 3421, 2928, 2861, 1678, 1421, 1222, 1198, 1024 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.19 (s, 1H), 7.95 (d, *J* = 2.5, 1H), 7.50 (d, *J* = 2.5, 1H), 7.43–7.20 (m, 12H), 7.17–7.08 (m, 2H), 6.26 (s, 1H), 5.32 (s, 2H), 5.08 (s, 2H), 4.61–4.53 (m, 1H), 3.79–3.67 (m, 2H), 3.36–3.19 (m, 2H), 1.99–1.88 (m, 2H), 1.66–1.53 (m, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 154.6 (C), 154.4 (C), 148.5 (C), 137.6 (C), 137.0 (C), 136.0 (C), 133.3 (CH), 129.0 (CH), 128.4 (2CH), 128.1 (2CH), 127.8 (CH), 127.7 (C), 127.5 (2CH), 127.4 (2CH), 127.3 (CH), 126.6 (C), 125.6 (CH), 124.2 (C),

120.7 (CH), 120.1 (CH), 111.1 (CH), 100.6 (CH), 73.4 (CH), 67.0 (CH<sub>2</sub>), 66.2 (CH<sub>2</sub>), 40.7 (2CH<sub>2</sub>), 30.3 (2CH<sub>2</sub>); HRMS (ESI+) *m/z* calcd for C<sub>33</sub>H<sub>32</sub>N<sub>3</sub>O<sub>4</sub> (M + H)<sup>+</sup> 534.2387, found 534.2379.

#### 4.1.28. 3-Bromo-1-methyl-5-nitropyridin-2(1H)-one **29**

To a microwave tube (CEM, 10 mL) charged with **1** (126 mg, 0.58 mmol) in acetonitrile (3 mL) under argon atmosphere were added Ag<sub>2</sub>CO<sub>3</sub> (189 mg, 0.68 mmol, 1.2 eq.) and then MeI (70 μL, 1.12 mmol, 2 eq.). The tube was sealed and the mixture was irradiated for 2 x 1 h (Dynamic control type, P<sub>max</sub> = 150 W, T = 60 °C). Then, the mixture was filtered through a pad of Celite which was then washed with ethyl acetate. After evaporation under reduced pressure, the crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 98:2 to 7:3) to give **29** (128 mg, 0.55 mmol, 95%) as a white solid. *R*<sub>f</sub> = 0.11 (cyclohexane/EtOAc 8:2); For characterization data, see Ref. 8.

#### 4.1.29. 3-Bromo-2-methoxy-5-nitropyridine **30**

To a solution of **1** (1.26 g, 5.75 mmol) in anhydrous toluene (57 mL) under argon atmosphere were added crushed Ag<sub>2</sub>CO<sub>3</sub> (2.15 g, 7.8 mmol, 1.4 eq.) and MeI (3.52 mL, 57 mmol, 10 eq.). The mixture was stirred at room temperature overnight. The mixture was filtered through a pad of Celite which was then washed with ethyl acetate. After evaporation under reduced pressure, the crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 95:5 to 6:4) to give the desired O-methylated product **30** (378 mg, 1.62 mmol, 28%) as a pale-yellow solid but also the N-methylated product **29** (897 mg, 3.85 mmol, 67%) as a pale-yellow solid. *R*<sub>f</sub> = 0.55 (cyclohexane/EtOAc 9:1); For characterization data, see Ref. 8.

#### 4.1.30. 5-Amino-3-bromo-1-methylpyridin-2(1H)-one **31**

Compound **31** was prepared according to general procedure F, starting from **29** (478 mg, 2.05 mmol). The mixture was refluxed for 4 h. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 to 97:3) to give **31** (305 mg, 1.50 mmol, 73%) as a green solid. *R*<sub>f</sub> = 0.73 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); Mp > 162 °C (decomposition); IR (ATR) 3313, 3185, 1565, 1532, 1408, 1256, 1121, 771, 743 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.56 (d, *J* = 2.8, 1H), 6.95 (d, *J* = 2.8, 1H), 4.39 (br s, 2H), 3.40 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 155.3 (C), 136.2 (CH), 129.0 (C), 120.8 (CH), 114.8 (C), 38.1 (CH<sub>3</sub>); HRMS (ESI+) *m/z* calcd for C<sub>6</sub>H<sub>8</sub>BrN<sub>2</sub>O (M + H)<sup>+</sup> 202.9815, found 202.9814.

#### 4.1.31. 5-Bromo-6-methoxypyridin-3-amine **32**

Compound **32** was prepared according to general procedure F, starting from **30** (473 mg, 2.03 mmol). The mixture was refluxed for 1.5 h. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 7:3) to give **32** (413 mg, 2.03 mmol, quantitative) as a yellow solid.  $R_f = 0.34$  (cyclohexane/EtOAc 7:3); Mp 58 °C; IR (ATR) 3413, 3333, 3217, 2933, 1474, 1403, 1246, 1219, 1052, 1011, 864 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.50 (d,  $J = 2.5$ , 1H), 7.30 (d,  $J = 2.5$ , 1H), 4.98 (s, 2H), 3.77 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 151.0 (C), 140.9 (C), 130.1 (CH), 128.2 (CH), 105.4 (C), 53.6 (CH<sub>3</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>6</sub>H<sub>8</sub>BrN<sub>2</sub>O (M + H)<sup>+</sup> 202.9815, found 202.9815.

#### 4.1.32. 3-bromo-1-methyl-5-[(pyridin-4-yl)amino]pyridin-2(1H)-one **33**

Compound **33** was prepared according to general procedure G, starting from **31** (150 mg, 0.74 mmol). The mixture was heated for 6 h. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 + 0.5% Et<sub>3</sub>N) to give **33** (169 mg, 0.60 mmol, 82%) as a green solid.  $R_f = 0.22$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 + 0.5% Et<sub>3</sub>N); Mp > 198 °C (decomposition); IR (ATR) 3273, 1663, 1571, 1512, 1211, 990, 806 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.20 (s, 1H), 8.11 (m, 2H), 7.85 (d,  $J = 2.7$ , 1H), 7.81 (d,  $J = 2.7$ , 1H), 6.60 (m, 2H), 3.51 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 157.1 (C), 152.4 (C), 149.8 (2CH), 141.8 (CH), 135.7 (CH), 118.9 (C), 114.6 (C), 108.2 (2CH), 38.3 (CH<sub>3</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>11</sub>H<sub>11</sub>BrN<sub>3</sub>O (M + H)<sup>+</sup> 280.0080, found 280.0078.

#### 4.1.33. 5-Bromo-6-methoxy-*N*-(pyridin-4-yl)pyridin-3-amine **34**

Compound **34** was prepared according to general procedure G, starting from **32** (300 mg, 1.48 mmol). The mixture was heated for 2 h. The crude was purified by column chromatography (SiO<sub>2</sub>, EtOAc + 0.5% Et<sub>3</sub>N) to give **34** (303 mg, 1.08 mmol, 73%) as a yellow solid.  $R_f = 0.17$  (EtOAc + 0.5% Et<sub>3</sub>N); Mp 172 °C; IR (ATR) 3280–2700, 1602, 1593, 1524, 1472, 1416, 1290, 1214, 1054, 990, 810, 738 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.68 (s, 1H), 8.17 (m, 2H), 8.07 (d,  $J = 2.4$ , 1H), 7.91 (d,  $J = 2.4$ , 1H), 6.75 (m, 2H), 3.92 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 155.7 (C), 150.7 (C), 150.1 (2CH), 139.0 (CH), 136.3 (CH), 131.9 (C), 108.6 (2CH), 105.8 (C), 54.3 (CH<sub>3</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>11</sub>H<sub>11</sub>BrN<sub>3</sub>O (M + H)<sup>+</sup> 280.0080, found 280.0083.

#### 4.1.34. 3-(1*H*-Indol-4-yl)-1-methyl-5-[(pyridin-4-yl)amino]pyridin-2(1*H*)-one **35**

Compound **35** was prepared according to general procedure E, starting from **33** (100 mg, 0.357 mmol). The mixture was refluxed overnight. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 97:3 + 0.5% Et<sub>3</sub>N) to give **35** (110 mg, 0.348 mmol, 97%) as a beige solid. *R*<sub>f</sub> = 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N); Mp > 230 °C (decomposition); IR (ATR) 3261, 1586, 1574, 1519, 999, 802, 760 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.15 (s, 1H), 8.30 (s, 1H), 8.12 (d, *J* = 5.8, 2H), 7.76 (d, *J* = 2.6, 1H), 7.47 (d, *J* = 2.8, 1H), 7.37 (d, *J* = 8.0, 1H), 7.34 (t, *J* = 2.5, 1H), 7.24 (d, *J* = 7.2, 1H), 7.10 (t, *J* = 7.7, 1H), 6.68 (d, *J* = 6.0, 2H), 6.33 (s, 1H), 3.54 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 159.6 (C), 152.8 (C), 149.4 (2CH), 137.8 (CH), 136.1 (C), 134.0 (CH), 130.3 (C), 128.3 (C), 126.2 (C), 125.4 (CH), 120.5 (CH), 120.0 (CH), 118.5 (C), 111.0 (CH), 108.2 (2CH), 100.6 (CH), 37.6 (CH<sub>3</sub>); HRMS (ESI+) *m/z* calcd for C<sub>19</sub>H<sub>17</sub>N<sub>4</sub>O (M + H)<sup>+</sup> 317.1397, found 317.1395. HPLC purity ≥ 98%, Method A: *t*<sub>R</sub> = 18.43 min, λ = 280 nm.

#### 4.1.35. 5-(1*H*-Indol-4-yl)-6-methoxy-*N*-(pyridin-4-yl)pyridin-3-amine **36**

Compound **36** was prepared according to general procedure E, starting from **34** (100 mg, 0.357 mmol). The mixture was refluxed overnight. The crude was purified by two column chromatographies (SiO<sub>2</sub>, EtOAc + 0.5% Et<sub>3</sub>N, then CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99:1 + 0.5% Et<sub>3</sub>N) to give **36** (97 mg, 0.307 mmol, 86%) as a beige solid. *R*<sub>f</sub> = 0.15 (EtOAc + 0.5% Et<sub>3</sub>N); Mp 132 °C; IR (ATR) 3300–2700, 1605, 1591, 1465, 1396, 1213, 996, 808, 748, 731 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.21 (s, 1H), 8.67 (s, 1H), 8.15 (m, 2H), 8.11 (d, *J* = 2.7, 1H), 7.60 (d, *J* = 2.7, 1H), 7.42 (d, *J* = 8.0, 1H), 7.37 (m, *J* = 2.8, 1H), 7.15 (t, *J* = 7.7, 1H), 7.08 (dd, *J* = 7.2, 0.9, 1H), 6.79 (m, 2H), 6.25 (m, 1H), 3.84 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 157.0 (C), 151.2 (C), 150.1 (2CH), 138.6 (CH), 136.0 (C), 133.9 (CH), 130.9 (C), 127.6 (C), 126.5 (C), 125.7 (CH), 124.0 (C), 120.8 (CH), 120.1 (CH), 111.2 (CH), 108.5 (2CH), 100.4 (CH), 53.3 (CH<sub>3</sub>); HRMS (ESI+) *m/z* calcd for C<sub>19</sub>H<sub>17</sub>N<sub>4</sub>O (M + H)<sup>+</sup> 317.1397, found 317.1393. HPLC purity ≥ 99%, Method A: *t*<sub>R</sub> = 20.67 min, λ = 280 nm.

#### 4.1.36. 6-Benzyloxy-5-bromo-*N*-methylpyridin-3-amine **37**

To a solution of **11** (100 mg, 0.358 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.2 mL) were added Et<sub>3</sub>N (91 μL, 0.65 mmol, 1.8 eq.) and trifluoroacetic acid anhydride (100 μL, 0.72 mmol, 2 eq.) at 0 °C. The mixture was stirred for 30 min at 0 °C and then concentrated under reduced pressure. The residue was solubilized in acetone (1.15 mL), then K<sub>2</sub>CO<sub>3</sub> (247 mg, 1.790 mmol, 5 eq.) and MeI (110 μL, 1.77 mmol, 5 eq.) were added. The mixture was stirred at 40 °C for 2 h. After cooling, the suspension was filtered and the filtrate was concentrated under reduced pressure to

give a white solid. The intermediate was dissolved in MeOH (1.15 mL) and ACN (0.5 mL), and NaOH (1 M, 537  $\mu$ L, 0.537 mmol, 1.5 eq.) was added. The mixture was stirred for 1.5 h, diluted in water and extracted three times with ethyl acetate. Combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 9:1) to give **37** (97 mg, 0.331 mmol, 92% in three steps from **11**) as a colorless oil.  $R_f$  = 0.16 (cyclohexane/EtOAc 9:1); IR (ATR) 3413, 2927, 2881, 2814, 1490, 1472, 1445, 1424, 1358, 1286, 1229, 1044, 992, 862, 728, 694 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.47 (d,  $J$  = 2.6, 1H), 7.44–7.40 (m, 2H), 7.39–7.34 (m, 2H), 7.32–7.27 (m, 1H), 7.30 (d,  $J$  = 2.6, 1H), 5.59 (q,  $J$  = 5.0, 1H), 5.29 (s, 2H), 2.65 (d,  $J$  = 5.2, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  150.2 (C), 142.6 (C), 137.6 (C), 128.3 (2CH), 127.8 (CH), 127.5 (CH), 127.3 (2CH), 126.2 (CH), 106.2 (C), 67.3 (CH<sub>2</sub>), 30.1 (CH<sub>3</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>13</sub>H<sub>14</sub>BrN<sub>2</sub>O (M + H)<sup>+</sup> 293.0284, found 293.0282.

#### 4.1.37. 6-Benzyloxy-5-bromo-*N*-methyl-*N*-(pyridin-4-yl)pyridin-3-amine **38**

Compound **38** was prepared according to general procedure G, starting from **37** (171 mg, 0.58 mmol). The mixture was heated for 4 h. The crude was purified by column chromatography (SiO<sub>2</sub>, EtOAc + 0.5% Et<sub>3</sub>N) to give **38** (192 mg, 0.52 mmol, 89%) as an orange oil.  $R_f$  = 0.18 (EtOAc + 0.5% Et<sub>3</sub>N); IR (ATR) 3029, 1587, 1442, 1222, 1049, 985, 806, 732, 695 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  8.17–8.14 (m, 3H), 8.12 (d,  $J$  = 2.3, 1H), 7.52–7.47 (m, 2H), 7.44–7.39 (m, 2H), 7.38–7.32 (m, 1H), 6.58 (m, 2H), 5.45 (s, 2H), 3.26 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  157.0 (C), 153.5 (C), 149.7 (2CH), 144.3 (CH), 141.3 (CH), 137.3 (C), 136.7 (C), 128.4 (2CH), 127.9 (CH), 127.6 (2CH), 108.1 (CH), 106.4 (C), 68.2 (CH<sub>2</sub>), 39.4 (CH<sub>3</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>18</sub>H<sub>17</sub>BrN<sub>3</sub>O (M + H)<sup>+</sup> 370.0550, found 370.0551.

#### 4.1.38. 6-Benzyloxy-5-(1*H*-indol-4-yl)-*N*-methyl-*N*-(pyridin-4-yl)pyridin-3-amine **39**

Compound **39** was prepared according to general procedure E, starting from **38** (173 mg, 0.467 mmol). The mixture was refluxed overnight. The crude was purified by column chromatography (SiO<sub>2</sub>, EtOAc + 0.5% Et<sub>3</sub>N) to give **39** (162 mg, 0.399 mmol, 85%) as a beige solid.  $R_f$  = 0.17 (EtOAc + 0.5% Et<sub>3</sub>N); Mp > 224 °C (decomposition); IR (ATR) 3250–2980, 2940, 1591, 1506, 1456, 1237, 1220, 988, 818, 749, 736, 723, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.21 (s, 1H), 8.17 (d,  $J$  = 2.6, 1H), 8.16 (m, 2H), 7.71 (d,  $J$  = 2.6, 1H), 7.42–7.23 (m, 7H), 7.18–7.11 (m, 2H), 6.64 (m, 2H), 6.29 (m, 1H), 5.43 (s, 2H), 3.32 (s, 3H, under H<sub>2</sub>O signal); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>), not recorded due to low solubility in DMSO-*d*<sub>6</sub>; HRMS (ESI+)  $m/z$  calcd for C<sub>26</sub>H<sub>23</sub>N<sub>4</sub>O (M + H)<sup>+</sup> 407.1866, found 407.1870.

#### 4.1.39. 3-(1*H*-Indol-4-yl)-5-[methyl(pyridin-4-yl)amino]pyridin-2(1*H*)-one **40**

To a solution under argon of **39** (25 mg, 0.062 mmol) and acetic acid (23  $\mu$ L, 0.40 mmol, 6.5 eq.) in MeOH (1.6 mL) degassed with argon was added 20% Pd(OH)<sub>2</sub>/C (11 mg, 0.016 mmol, 0.25 eq.). The mixture was then hydrogenated (balloon) at room temperature overnight. The mixture was evaporated under reduced pressure and the crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 96:4 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was washed with chloroform to give **40** (7 mg, 0.022 mmol, 36%) as a beige solid.  $R_f$  = 0.11 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 96:4 + 0.5% Et<sub>3</sub>N); Mp > 250 °C; IR (ATR) 3150–2600, 1648, 1624, 1597, 997, 821, 754 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  11.88 (br s, 1H), 11.14 (s, 1H), 8.16 (d,  $J$  = 5.3, 2H), 7.49–7.46 (m, 2H), 7.36 (d,  $J$  = 8.1, 1H), 7.33 (t,  $J$  = 2.7, 1H), 7.26 (d,  $J$  = 7.3, 1H), 7.10 (t,  $J$  = 7.7, 1H), 6.63 (d,  $J$  = 5.7, 2H), 6.31 (m, 1H), 3.23 (s, 3H); <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  160.3 (C), 154.0 (C), 149.7 (2CH), 139.8 (CH), 136.1 (C), 132.9<sup>a</sup> (CH), 131.6<sup>a</sup> (C), 128.0 (C), 126.1 (C), 125.4 (CH), 125.3<sup>a</sup> (C), 120.4 (CH), 119.9 (CH), 111.0 (CH), 107.9 (2CH), 100.5 (CH), 39.5 (CH<sub>3</sub>), <sup>a</sup> determined from <sup>1</sup>H-<sup>13</sup>C HSQC and HMBC experiments; HRMS (ESI+)  $m/z$  calcd for C<sub>19</sub>H<sub>17</sub>N<sub>4</sub>O (M + H)<sup>+</sup> 317.1397, found 317.1394. HPLC purity  $\geq$  97%, Method A:  $t_R$  = 18.44 min,  $\lambda$  = 280 nm.

#### 4.1.40. 6-(Benzyloxy)-5-(1-methyl-1*H*-indol-4-yl)-*N*-(pyridin-4-yl)pyridin-3-amine **44**

A microwave tube under argon was charged with **42** (50 mg, 0.238 mmol), Pd(dppf)Cl<sub>2</sub> (17 mg, 0.023 mmol, 0.1 eq.), KOAc (70 mg, 0.71 mmol, 3 eq.) and bis(pinacolato)diboron (91 mg, 0.36 mmol, 1.5 eq.). Then, anhydrous 1,4-dioxane (1 mL) degassed with argon was added. The tube was sealed and the mixture was heated under microwave irradiation for 30 min (Dynamic control, P<sub>max</sub> = 150 W, T = 80 °C). The resulting mixture was concentrated under reduced pressure and the crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 8:2 to 5:5), but some starting material remained in the product **43** (60 mg).  $R_f$  = 0.73 (cyclohexane/acetone 1:1). Compound **43** was used for the next step without further purification.

Compound **44** was prepared according to general procedure E, starting from **41** (76 mg, 0.213 mmol) in 1.5 mL of 1,4-dioxane and **43** (60 mg). The solution was refluxed overnight. After Celite filtration, the solution was washed with water and then with brine, dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 95:5 + 0.5% Et<sub>3</sub>N to 50:50 + 0.5% Et<sub>3</sub>N) to give **44** (48 mg, 0.118 mmol, 55%) as a white solid.  $R_f$  = 0.25 (cyclohexane/acetone 1:1 + 0.5%



Et<sub>3</sub>N); Mp 85 °C; IR (ATR) 3029, 2921, 2848, 1591, 1425, 1413, 1287, 1213, 992, 813 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.70 (s, 1H), 8.15 (d, *J* = 5.9, 2H), 8.11 (d, *J* = 2.6, 1H), 7.62 (d, *J* = 2.5, 1H), 7.45 (d, *J* = 7.5, 1H), 7.38–7.17 (m, 8H), 6.80 (d, *J* = 5.9, 2H), 6.29 (d, *J* = 2.9, 1H), 5.38 (s, 2H), 3.81 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 156.3 (C), 151.0 (C), 150.1 (2CH), 138.4 (CH), 137.5 (C), 136.5 (C), 134.0 (CH), 131.2 (C), 129.9 (CH), 128.2 (2CH), 127.7 (C), 127.5 (2CH), 127.4 (CH), 126.8 (C), 123.8 (C), 120.8 (CH), 120.3 (CH), 109.5 (CH), 108.5 (2CH), 99.7 (CH), 67.1 (CH<sub>2</sub>), 32.6 (CH<sub>3</sub>); HRMS (ESI+) *m/z* calcd for C<sub>26</sub>H<sub>23</sub>N<sub>4</sub>O (M+H)<sup>+</sup> 407.1866, found 407.1859.

#### 4.1.41. 3-(1-Methyl-1*H*-indol-4-yl)-5-(pyridin-4-ylamino)pyridin-2(1*H*)-one 45

Compound **45** was prepared according to general procedure H, starting from **44** (80 mg, 0.197 mmol) in CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:1 (4 mL). The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N to 90:10 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **45** (45 mg, 0.142 mmol, 72%) as a pale-yellow solid. *R*<sub>f</sub> = 0.34 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 + 0.5% Et<sub>3</sub>N); Mp 183 °C; IR (ATR) 3300–2150, 1592, 1470, 1353, 1284, 1043, 1000 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.73 (br s, 1H), 8.22 (s, 1H), 8.11 (d, *J* = 6.0, 2H), 7.49 (d, *J* = 2.7, 1H), 7.41 (d, *J* = 8.1, 1H), 7.35–7.32 (m, 2H), 7.30 (d, *J* = 7.2, 1H), 7.17 (t, *J* = 7.7, 1H), 6.64 (d, *J* = 6.0, 2H), 6.34 (d, *J* = 2.8, 1H), 3.80 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 159.9 (C=O), 152.5 (C), 149.9 (2CH), 138.7 (CH), 136.6 (C), 130.6 (C), 129.7 (CH), 129.5 (CH), 128.3 (C), 126.5 (C), 120.6 (CH), 120.1 (CH), 119.5 (C), 109.2 (CH), 108.1 (2CH), 99.7 (CH), 32.6 (CH<sub>3</sub>); HRMS (ESI+) *m/z* calcd C<sub>19</sub>H<sub>17</sub>ON<sub>4</sub> (M + H)<sup>+</sup> 317.1397, found 317.1390. HPLC purity ≥ 99%, Method A: *t*<sub>R</sub> = 18.96 min, λ = 280 nm.

#### 4.1.42. 4-Bromo-1-(3-bromopropan-1-yl)-1*H*-indole 47

To a solution of NaOH (3.8 g) in water (5 mL) were added toluene (10 mL), TBAB (5.9 g, 18.3 mmol, 3.6 eq.), 4-bromoindole (1.00 g, 5.1 mmol) and 1,3-dibromopropane (3.10 mL, 30.5 mmol, 6 eq.). The solution was stirred at room temperature for 16 h. The resulting mixture was diluted with water and extracted three times with dichloromethane. Combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 100:0 to 95:5) to give **47** (1.20 g, 3.78 mmol, 74%) as a colorless oil. *R*<sub>f</sub> = 0.26 (cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 8:2); IR (ATR) 2935, 1432, 1244, 1165, 888 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.55 (d, *J* = 8.2, 1H), 7.51 (d, *J* = 3.2, 1H), 7.25 (d, *J* = 7.6, 1H), 7.09 (t, *J* = 7.8, 1H), 6.42 (dd, *J* = 3.2, 0.7, 1H), 4.32 (t, *J* = 6.8, 2H), 3.42 (t, *J* = 6.5, 2H), 2.29 (quint, *J* = 6.7, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ

136.1 (C), 129.7 (CH), 128.3 (C), 122.4 (CH), 121.8 (CH), 113.7 (C), 109.5 (CH), 100.7 (CH), 44.3 (CH<sub>2</sub>), 32.8 (CH<sub>2</sub>), 31.5 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>11</sub>H<sub>12</sub>Br<sub>2</sub>N (M + H)<sup>+</sup> 315.9331, found 315.9325.

#### 4.1.43. 4-Bromo-1-(4-bromobutan-1-yl)-1*H*-indole 48

To a solution of NaOH (5.7 g) in water (7.5 mL) were added toluene (15 mL), TBAB (8.85 g, 27.5 mmol, 3.6 eq.), 4-bromoindole (1.50 g, 7.65 mmol) and 1,4-dibromobutane (5.48 mL, 45.9 mmol, 6 eq). The solution was stirred at room temperature for 16 h. The resulting mixture was diluted with water and extracted three times with dichloromethane. Combined organic phases were dried over MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 100:0 to 95:5) to give **48** (1.60 g, 4.82 mmol, 63%) as a colorless oil. *R*<sub>f</sub> = 0.26 (cyclohexane/CH<sub>2</sub>Cl<sub>2</sub> 8:2); IR (ATR) 2939, 2871, 1478, 1433, 1336, 1282, 1131, 888 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.56 (d, *J* = 8.2, 1H), 7.52 (d, *J* = 3.1, 1H), 7.24 (d, *J* = 7.6, 1H), 7.07 (t, *J* = 7.9, 1H), 6.40 (d, *J* = 2.9, 1H), 4.24 (t, *J* = 6.8, 2H), 3.53 (t, *J* = 6.5, 2H), 1.92–1.82 (m, 2H), 1.78–1.69 (m, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 136.1 (C), 129.7 (CH), 128.3 (C), 122.2 (CH), 121.6 (CH), 113.6 (C), 109.6 (CH), 100.4 (CH), 45.0 (CH<sub>2</sub>), 34.5 (CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 28.5 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>12</sub>H<sub>14</sub>Br<sub>2</sub>N (M + H)<sup>+</sup> 329.9488, found 329.9481.

#### 4.1.44. 4-Bromo-1-[3-(diethylamino)propan-1-yl]-1*H*-indole 49

Compound **49** was prepared according to general procedure I, starting from **47** (144 mg, 0.454 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:0 to 9:1) to give **49** (106 mg, 0.343 mmol, 75%) as an orange oil. *R*<sub>f</sub> = 0.54 (cyclohexane/acetone 1:1 + 0.5% Et<sub>3</sub>N); IR (ATR) 2966, 2802, 1433, 1336, 1162, 1069, 889 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.51 (d, *J* = 8.3, 1H), 7.49 (d, *J* = 3.2, 1H), 7.23 (d, *J* = 7.5, 1H), 7.07 (t, *J* = 7.9, 1H), 6.39 (d, *J* = 2.8, 1H), 4.20 (t, *J* = 6.9, 2H), 2.41 (q, *J* = 7.1, 4H), 2.29 (t, *J* = 6.9, 2H), 1.85 (quint, *J* = 6.9, 2H), 0.89 (t, *J* = 7.1, 6H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 136.1 (C), 129.8 (CH), 128.3 (C), 122.1 (CH), 121.6 (CH), 113.6 (C), 109.5 (CH), 100.3 (CH), 49.2 (CH<sub>2</sub>), 46.1 (2CH<sub>2</sub>), 44.0 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 11.5 (2CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>15</sub>H<sub>22</sub>BrN<sub>2</sub> (M+H)<sup>+</sup> 309.0961, found 309.0958.

#### 4.1.45. 4-Bromo-1-[4-(diethylamino)butan-1-yl]-1*H*-indole 50

Compound **50** was prepared according to general procedure I, starting from **48** (527 mg, 1.59 mmol). The mixture was stirred for 3 h at room temperature. The crude oil was purified by

column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:0 + 0.5% Et<sub>3</sub>N to 98:2 + 0.5% Et<sub>3</sub>N) to give **50** (359 mg, 1.11 mmol, 70%) as a brown oil.  $R_f = 0.35$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 + 0.5% Et<sub>3</sub>N); IR (ATR) 2966, 2798, 1434, 1336, 1290, 888 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.53 (d,  $J = 8.2$ , 1H), 7.50 (d,  $J = 3.1$ , 1H), 7.23 (d,  $J = 7.5$ , 1H), 7.06 (t,  $J = 8.0$ , 1H), 6.39 (d,  $J = 3.1$ , 1H), 4.19 (t,  $J = 6.9$ , 2H), 2.36 (q,  $J = 7.1$ , 4H), 2.31 (t,  $J = 7.2$ , 2H), 1.73 (quint,  $J = 7.3$ , 2H), 1.32 (quint,  $J = 7.2$ , 2H), 0.88 (t,  $J = 7.1$ , 6H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 136.1 (C), 129.7 (CH), 128.3 (C), 122.1 (CH), 121.5 (CH), 113.6 (C), 109.6 (CH), 100.2 (CH), 51.7 (CH<sub>2</sub>), 46.2 (2CH<sub>2</sub>), 45.9 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 24.0 (CH<sub>2</sub>), 11.7 (2CH<sub>3</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>16</sub>H<sub>24</sub>BrN<sub>2</sub> (M+H)<sup>+</sup> 323.1117, found 323.1115.

#### 4.1.46. 4-Bromo-1-[3-(pyrrolidin-1-yl)propan-1-yl]-1H-indole **51**

Compound **51** was prepared according to general procedure I, starting from **47** (395 mg, 1.25 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:0 to 97:3) to give **51** (349 mg, 1.14 mmol, 91%) as an orange oil.  $R_f = 0.21$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); IR (ATR) 2954, 2791, 1435, 1346, 1172, 1127, 890 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.52 (d,  $J = 8.2$ , 1H), 7.48 (d,  $J = 3.1$ , 1H), 7.23 (d,  $J = 7.5$ , 1H), 7.06 (t,  $J = 7.8$ , 1H), 6.39 (d,  $J = 3.1$ , 1H), 4.22 (t,  $J = 6.8$ , 2H), 2.40–2.31 (m, 4H), 2.27 (t,  $J = 7.0$ , 2H), 1.89 (quint,  $J = 6.8$ , 2H), 1.72–1.60 (m, 4H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 136.2 (C), 129.8 (CH), 128.2 (C), 122.1 (CH), 121.5 (CH), 113.5 (C), 109.5 (CH), 100.3 (CH), 53.4 (2CH<sub>2</sub>), 52.3 (CH<sub>2</sub>), 43.9 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 23.1 (2CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>15</sub>H<sub>20</sub>BrN<sub>2</sub> (M+H)<sup>+</sup> 307.0804, found 307.0796.

#### 4.1.47. 4-Bromo-1-[4-(pyrrolidin-1-yl)butan-1-yl]-1H-indole **52**

Compound **52** was prepared according to general procedure I, starting from **48** (527 mg, 1.59 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:0 to 98:2) to give **52** (409 mg, 1.27 mmol, 80%) as an orange oil.  $R_f = 0.26$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); IR (ATR) 2932, 2787, 1433, 1336, 1172, 1128, 888 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.53 (d,  $J = 8.2$ , 1H), 7.50 (d,  $J = 3.2$ , 1H), 7.23 (d,  $J = 7.6$ , 1H), 7.06 (t,  $J = 7.9$ , 1H), 6.39 (d,  $J = 3.0$ , 1H), 4.19 (t,  $J = 7.0$ , 2H), 2.39–2.28 (m, 6H), 1.77 (quint,  $J = 7.3$ , 2H), 1.68–1.57 (m, 4H), 1.36 (quint,  $J = 7.5$ , 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 136.1 (C), 129.8 (CH), 128.3 (C), 122.1 (CH), 121.6 (CH), 113.6 (C), 109.6 (CH), 100.2 (CH), 54.9 (CH<sub>2</sub>), 53.5 (2CH<sub>2</sub>), 45.8 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 23.0 (2CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>16</sub>H<sub>22</sub>BrN<sub>2</sub> (M+H)<sup>+</sup> 321.0961, found 321.0957.

#### 4.1.48. 4-Bromo-1-[3-(piperidin-1-yl)propan-1-yl]-1H-indole 53

Compound **53** was prepared according to general procedure I, starting from **47** (395 mg, 1.25 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:0 to 98:2) to give **53** (368 mg, 1.15 mmol, 92%) as an orange oil.  $R_f = 0.10$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2); IR (ATR) 2923, 2771, 1429, 1302, 1172, 1118, 891 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.53 (d,  $J = 8.2$ , 1H), 7.48 (d,  $J = 3.1$ , 1H), 7.22 (dd,  $J = 7.5, 0.7$ , 1H), 7.06 (t,  $J = 7.9$ , 1H), 6.39 (dd,  $J = 3.1, 0.8$ , 1H), 4.21 (t,  $J = 6.8$ , 2H), 2.28–2.18 (br s, 4H), 2.10 (t,  $J = 6.8$ , 2H), 1.88 (quint,  $J = 6.8$ , 2H), 1.52–1.45 (m, 4H), 1.40–1.32 (m, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  136.2 (C), 129.8 (CH), 128.2 (C), 122.1 (CH), 121.5 (CH), 113.5 (C), 109.6 (CH), 100.3 (CH), 55.0 (CH<sub>2</sub>), 53.9 (2CH<sub>2</sub>), 43.8 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.6 (2CH<sub>2</sub>), 24.1 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>16</sub>H<sub>22</sub>BrN<sub>2</sub> (M + H)<sup>+</sup> 321.0961, found 321.0958.

#### 4.1.49. 4-Bromo-1-[4-(piperidin-1-yl)butan-1-yl]-1H-indole 54

Compound **54** was prepared according to general procedure I, starting from **48** (450 mg, 1.36 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:0 to 98:2) to give **54** (422 mg, 1.26 mmol, 93%) as an orange oil.  $R_f = 0.21$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); IR (ATR) 2930, 2850, 2799, 2763, 1433, 1336, 1298, 1167, 1121, 888 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.54 (d,  $J = 8.2$ , 1H), 7.50 (d,  $J = 3.2$ , 1H), 7.23 (dd,  $J = 7.5, 0.7$ , 1H), 7.06 (t,  $J = 7.9$ , 1H), 6.39 (dd,  $J = 3.1, 0.8$ , 1H), 4.19 (t,  $J = 7.1$ , 2H), 2.32–2.15 (m, 6H), 1.74 (quint,  $J = 7.4$ , 2H), 1.48–1.40 (m, 4H), 1.40–1.30 (m, 4H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  136.1 (C), 129.8 (CH), 128.3 (C), 122.1 (CH), 121.5 (CH), 113.6 (C), 109.6 (CH), 100.2 (CH), 57.7 (CH<sub>2</sub>), 53.9 (2CH<sub>2</sub>), 45.8 (CH<sub>2</sub>), 27.7 (2CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 24.1 (CH<sub>2</sub>), 23.4 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>17</sub>H<sub>24</sub>BrN<sub>2</sub> (M + H)<sup>+</sup> 335.1117, found 335.1115.

#### 4.1.50. 4-Bromo-1-[3-(morpholin-4-yl)propan-1-yl]-1H-indole 55

Compound **55** was prepared according to general procedure I, starting from **47** (144 mg, 0.454 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:0 to 95:5) to give **55** (144 mg, 0.446 mmol, 98%) as a colorless oil.  $R_f = 0.66$  (cyclohexane/acetone 1:1 + 1% Et<sub>3</sub>N); Aspect: colorless oil; IR (ATR) 2947, 2851, 2809, 1433, 1269, 1115 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  7.54 (d,  $J = 8.2$ , 1H), 7.49 (d,  $J = 3.0$ , 1H), 7.23 (d,  $J = 7.5$ , 1H), 7.06 (t,  $J = 7.9$ , 1H), 6.39 (d,  $J = 3.1$ , 1H), 4.22 (t,  $J = 6.6$ , 2H), 3.61–3.51 (m, 4H), 2.32–2.22 (br s, 4H), 2.15 (t,  $J = 6.8$ , 2H), 1.89 (quint,  $J = 6.7$ , 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  136.2 (C), 129.8 (CH), 128.2 (C), 122.1 (CH), 121.5 (CH), 113.5 (C), 109.6 (CH), 100.3 (CH),

66.2 (2CH<sub>2</sub>), 54.8 (CH<sub>2</sub>), 53.2 (2CH<sub>2</sub>), 43.7 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>15</sub>H<sub>20</sub>BrN<sub>2</sub>O (M+H)<sup>+</sup> 323.0754, found 323.0749.

#### 4.1.51. 4-Bromo-1-[4-(morpholin-4-yl)butan-1-yl]-1*H*-indole **56**

Compound **56** was prepared according to general procedure I, starting from **48** (160 mg, 0.483 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 1:0 to 95:5) to give **56** (157 mg, 0.466 mmol, 96%) as a colorless oil. *R<sub>f</sub>* = 0.45 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 + 0.5% Et<sub>3</sub>N); IR (ATR) 2941, 2852, 2807, 1434, 1115 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.53 (d, *J* = 8.2, 1H), 7.49 (d, *J* = 3.1, 1H), 7.23 (d, *J* = 7.5, 1H), 7.06 (t, *J* = 7.9, 1H), 6.38 (d, *J* = 2.9, 1H), 4.19 (t, *J* = 7.0, 2H), 3.53–3.48 (m, 4H), 2.29–2.19 (m, 6H), 1.75 (quint, *J* = 7.2, 2H), 1.35 (quint, *J* = 7.2, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 136.1 (C), 129.8 (CH), 128.3 (C), 122.1 (CH), 121.6 (CH), 113.6 (C), 109.6 (CH), 100.2 (CH), 66.2 (2CH<sub>2</sub>), 57.4 (CH<sub>2</sub>), 53.2 (2CH<sub>2</sub>), 45.8 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 23.0 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>16</sub>H<sub>22</sub>BrN<sub>2</sub>O (M+H)<sup>+</sup> 337.0910, found 337.0908.

#### 4.1.52. 4-Bromo-1-[3-(4-methylpiperazin-1-yl)propan-1-yl]-1*H*-indole **57**

Compound **57** was prepared according to general procedure I, starting from **47** (395 mg, 1.25 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:0 to 98:2) to give **57** (377 mg, 1.12 mmol, 90%) as a colorless oil. *R<sub>f</sub>* = 0.08 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2); IR (ATR) 2935, 2792, 1433, 1282, 1173, 1162, 1139, 1013, 889, 817 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.53 (d, *J* = 8.2, 1H), 7.48 (d, *J* = 3.2, 1H), 7.23 (dd, *J* = 7.6, 0.6, 1H), 7.06 (t, *J* = 7.9, 1H), 6.39 (dd, *J* = 3.1, 0.7, 1H), 4.21 (t, *J* = 6.8, 2H), 2.40–2.20 (br s, 8H), 2.16–2.12 (m, 2H), 2.14 (s, 3H), 1.88 (quint, *J* = 6.8, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 136.2 (C), 129.8 (CH), 128.2 (C), 122.1 (CH), 121.5 (CH), 113.5 (C), 109.6 (CH), 100.3 (CH), 54.7 (2CH<sub>2</sub>), 54.3 (CH<sub>2</sub>), 52.5 (2CH<sub>2</sub>), 45.7 (CH<sub>3</sub>), 43.7 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) *m/z* calcd for C<sub>16</sub>H<sub>23</sub>BrN<sub>3</sub> (M + H)<sup>+</sup> 336.1070, found 336.1067.

#### 4.1.53. 4-Bromo-1-[4-(4-methylpiperazin-1-yl)butan-1-yl]-1*H*-indole **58**

Compound **58** was prepared according to general procedure I, starting from **48** (527 mg, 1.6 mmol). The crude oil was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 100:0 + 0.5% Et<sub>3</sub>N to 98:2 + 0.5% Et<sub>3</sub>N) to give **58** (564 mg, 1.6 mmol, quantitative) as a yellow oil. *R<sub>f</sub>* = 0.26 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 + 0.5% Et<sub>3</sub>N); IR (ATR) 2927, 2815, 2794, 1436, 1339, 1371, 1282, 1165, 1010, 812 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 7.54 (d, *J* = 8.2, 1H), 7.50 (d, *J* = 3.1, 1H), 7.23 (d, *J* = 7.5, 1H), 7.06 (t, *J* = 7.9, 1H), 6.38 (d, *J* = 3.1, 1H), 4.19 (t, *J* = 7.0,

2H), 2.37–2.15 (m, 8H), 2.22 (t,  $J = 7.2$ , 1H), 2.11 (s, 3H), 1.74 (quint,  $J = 7.3$ , 2H), 1.35 (quint,  $J = 7.4$ , 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  136.1 (C), 129.8 (CH), 128.3 (C), 122.1 (CH), 121.5 (CH), 113.6 (C), 109.6 (CH), 100.2 (CH), 57.0 (CH<sub>2</sub>), 54.7 (2CH<sub>2</sub>), 52.6 (2CH<sub>2</sub>), 45.8 (CH<sub>2</sub>), 45.7 (CH<sub>3</sub>), 27.6 (CH<sub>2</sub>), 23.4 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>17</sub>H<sub>25</sub>BrN<sub>3</sub> (M + H)<sup>+</sup> 350.1226, found 350.1222.

#### 4.1.54. 6-(Benzyloxy)-5-{1-[3-(diethylamino)propan-1-yl]-1H-indol-4-yl}-N-(pyridin-4-yl)pyridin-3-amine **69**

Compound **59** was first prepared according to general procedure J, starting from **49** (100 mg, 0.323 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 10:0 + 0.5% Et<sub>3</sub>N to 5:5 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained brown oil **59** (104 mg).  $R_f = 0.47$  (cyclohexane/acetone 1:1 + 0.5% Et<sub>3</sub>N). Compound **59** was used for the next step without further purification.

Compound **69** was prepared according to general procedure E, starting from **41** (168 mg, 0.472 mmol) and **59** (185 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 to 85:15). Evaporation gave compound **69** (170 mg, 0.336 mmol, 71%) as a beige solid.  $R_f = 0.19$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1); Mp 89 °C; IR (ATR) 2962, 2931, 1592, 1445, 1418, 1213, 988, 816 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.80 (s, 1H), 8.16 (d,  $J = 5.6$ , 2H), 8.13 (d,  $J = 2.6$ , 1H), 7.64 (d,  $J = 2.5$ , 1H), 7.52 (d,  $J = 7.5$ , 1H), 7.42 (d,  $J = 3.0$ , 1H), 7.35–7.17 (m, 7H), 6.82 (d,  $J = 6.0$ , 2H), 6.33 (d,  $J = 3.0$ , 1H), 5.38 (s, 2H), 4.25 (t,  $J = 6.9$ , 2H), 2.76–2.56 (m, 6H), 1.97 (quint,  $J = 6.9$ , 2H), 1.00 (t,  $J = 7.1$ , 6H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  156.4 (C), 151.3 (C), 149.7 (2CH), 138.6 (CH), 137.4 (C), 135.8 (C), 134.1 (CH), 131.1 (C), 129.0 (CH), 128.1 (2CH), 127.9 (C), 127.5 (2CH), 127.4 (CH), 126.9 (C), 123.7 (C), 120.9 (CH), 120.3 (CH), 109.6 (CH), 108.5 (2CH), 100.1 (CH), 67.1 (CH<sub>2</sub>), 48.8 (CH<sub>2</sub>), 46.3 (2CH<sub>2</sub>), 43.4 (CH<sub>2</sub>), 26.2 (CH<sub>2</sub>), 10.4 (2CH<sub>3</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>32</sub>H<sub>37</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 253.6494, found 253.6489.

#### 4.1.55. 6-(Benzyloxy)-5-{1-[4-(diethylamino)butan-1-yl]-1H-indol-4-yl}-N-(pyridin-4-yl)pyridin-3-amine **70**

Compound **60** was first prepared according to general procedure J, starting from **50** (340 mg, 1.05 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 9:1 + 0.5% Et<sub>3</sub>N to 7:3 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained brown oil **60** (331 mg).  $R_f = 0.44$  (cyclohexane/acetone 1:1 + 0.5% Et<sub>3</sub>N). Compound **60** was used for the next step without further purification.

Compound **70** was prepared according to general procedure E, starting from **41** (326 mg, 0.92 mmol) and **60** (330 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, acetone + 0.5% Et<sub>3</sub>N) to give **70** (224 mg, 0.43 mmol, 47%) as a yellow-white solid.  $R_f = 0.14$  (acetone + 0.5% Et<sub>3</sub>N); Mp 122–124 °C; IR (ATR) 2964, 2929, 2801, 1591, 1417, 1213 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.70 (s, 1H), 8.16 (d,  $J = 6.0$ , 2H), 8.12 (d,  $J = 2.6$ , 1H), 7.64 (d,  $J = 2.5$ , 1H), 7.50 (d,  $J = 7.6$ , 1H), 7.41 (d,  $J = 3.0$ , 1H), 7.34–7.15 (m, 7H), 6.80 (d,  $J = 6.0$ , 2H), 6.31 (d,  $J = 3.0$ , 1H), 5.38 (s, 2H), 4.21 (t,  $J = 6.9$ , 2H), 2.46–2.30 (m, 6H), 1.77 (quint,  $J = 7.0$ , 2H), 1.37 (quint,  $J = 7.2$ , 2H), 0.90 (t,  $J = 7.0$ , 6H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 156.3 (C), 151.1 (C), 150.1 (2CH), 138.5 (CH), 137.4 (C), 135.8 (C), 134.0 (CH), 131.2 (C), 129.0 (CH), 128.2 (2CH), 127.9 (C), 127.5 (2CH), 127.4 (CH), 126.9 (C), 123.8 (C), 120.8 (CH), 120.2 (CH), 109.7 (CH), 108.5 (2CH), 99.9 (CH), 67.1 (CH<sub>2</sub>), 51.8 (CH<sub>2</sub>), 46.2 (2CH<sub>2</sub>), 45.6 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 24.0 (CH<sub>2</sub>), 11.6 (2CH<sub>3</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>33</sub>H<sub>39</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 260.6572, found 260.6572.

#### 4.1.56. 6-(Benzyloxy)-5-{1-[3-(Pyrrolidin-1-yl)propan-1-yl]-1H-indol-4-yl}-N-(pyridin-4-yl)pyridin-3-amine **71**

Compound **61** was first prepared according to general procedure J, starting from **51** (752 mg, 2.45 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 9:1 + 0.5% Et<sub>3</sub>N to 7:3 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained brown oil **61** (702 mg).  $R_f = 0.53$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 8:2 + 0.5% Et<sub>3</sub>N). Compound **61** was used for the next step without further purification.

Compound **71** was prepared according to general procedure E, starting from **41** (320 mg, 0.898 mmol) with 6.5 mL of dioxane and **61** (350 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 50:50 + 0.5% Et<sub>3</sub>N to 0:100 + 0.5% Et<sub>3</sub>N) to give **71** (339 mg, 0.673 mmol, 75%) as a brown solid.  $R_f = 0.08$  (acetone + 0.5% Et<sub>3</sub>N); Mp 84–85 °C; IR (ATR) 2927, 2791, 1590, 1459, 1407, 1238, 1211, 993, 818 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.71 (s, 1H), 8.16 (d,  $J = 6.0$ , 2H), 8.12 (d,  $J = 2.6$ , 1H), 7.64 (d,  $J = 2.6$ , 1H), 7.49 (d,  $J = 7.5$ , 1H), 7.39 (d,  $J = 3.0$ , 1H), 7.35–7.15 (m, 7H), 6.81 (d,  $J = 6.1$ , 2H), 6.31 (d,  $J = 2.9$ , 1H), 5.38 (s, 2H), 4.24 (t,  $J = 6.7$ , 2H), 2.44–2.37 (m, 4H), 2.34 (t,  $J = 6.9$ , 2H), 1.92 (quint,  $J = 6.7$ , 2H), 1.74–1.64 (4H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 156.3 (C), 151.0 (C), 150.1 (2CH), 138.5 (CH), 137.4 (C), 135.8 (C), 134.0 (CH), 131.2 (C), 129.1 (CH), 128.1 (2CH), 127.8 (C), 127.5 (2CH), 127.4 (CH), 126.8 (C), 123.8 (C), 120.8 (CH), 120.2 (CH), 109.6 (CH), 108.5 (2CH), 99.9 (CH), 67.1 (CH<sub>2</sub>), 53.5 (2CH<sub>2</sub>), 52.5 (CH<sub>2</sub>), 43.6 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 23.1 (2CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>32</sub>H<sub>35</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 252.6415, found 252.6412.

#### 4.1.57. 6-(Benzyloxy)-5-{1-[4-(Pyrrolidin-1-yl)butan-1-yl]-1H-indol-4-yl}-N-(pyridin-4-yl)pyridin-3-amine **72**

Compound **62** was first prepared according to general procedure J, starting from **52** (358 mg, 1.11 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 9:1 + 0.5% Et<sub>3</sub>N to 7:3 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained yellow oil **62** (292 mg). *R<sub>f</sub>* = 0.23 (cyclohexane/acetone 7:3 + 0.5% Et<sub>3</sub>N). Compound **62** was used for the next step without further purification.

Compound **72** was prepared according to general procedure E, starting from **41** (100 mg, 0.281 mmol) and **62** (114 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/EtOAc 50:50 + 0.5% Et<sub>3</sub>N to 0:100 + 0.5% Et<sub>3</sub>N) to give **72** (110 mg, 0.212 mmol, 76%) as a white powder. *R<sub>f</sub>* = 0.09 (acetone/MeOH 95:5 + 0.5% Et<sub>3</sub>N); Mp 109 °C; IR (ATR) 2925, 1593, 1424 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.70 (s, 1H), 8.16 (d, *J* = 5.9, 2H), 8.12 (d, *J* = 2.5, 1H), 7.64 (d, *J* = 2.5, 1H), 7.50 (d, *J* = 7.3, 1H), 7.41 (d, *J* = 3.0, 1H), 7.34–7.14 (m, 7H), 6.81 (d, *J* = 6.1, 2H), 6.31 (d, *J* = 2.7, 1H), 5.38 (s, 2H), 4.21 (t, *J* = 6.7, 2H), 2.41–2.31 (m, 6H), 1.79 (quint, *J* = 7.0, 2H), 1.67–1.59 (4H), 1.41 (quint, *J* = 7.3, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 156.3 (C), 151.0 (C), 150.1 (2CH), 138.4 (CH), 137.4 (C), 135.8 (C), 134.0 (CH), 131.2 (C), 129.0 (CH), 128.1 (2CH), 127.8 (C), 127.43 (2CH), 127.38 (CH), 126.9 (C), 123.8 (C), 120.7 (CH), 120.2 (CH), 109.7 (CH), 108.5 (2CH), 99.8 (CH), 67.1 (CH<sub>2</sub>), 55.0 (CH<sub>2</sub>), 53.5 (2CH<sub>2</sub>), 45.5 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub>), 23.0 (2CH<sub>2</sub>); HRMS (ESI+) *m/z* calcd for C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 259.6494, found 259.6489.

#### 4.1.58. 6-(Benzyloxy)-5-{1-[3-(piperidin-1-yl)propan-1-yl]-1H-indol-4-yl}-N-(pyridin-4-yl)pyridin-3-amine **73**

Compound **63** was first prepared according to general procedure J, starting from **53** (350 mg, 1.09 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 9:1 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained brown solid **63** (406 mg). *R<sub>f</sub>* = 0.37 (cyclohexane/acetone 7:3 + 0.5% Et<sub>3</sub>N). Compound **63** was used for the next step without further purification.

Compound **73** was prepared according to general procedure E, starting from **41** (390 mg, 1.09 mmol) and **63** (404 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, acetone + 0.5% Et<sub>3</sub>N) to give **73** (329 mg, 0.64 mmol, 58%) as a white solid. *R<sub>f</sub>* = 0.19 (acetone + 0.5% Et<sub>3</sub>N); Mp 77 °C; IR (ATR) 2931, 1591, 1446, 1419, 1214, 993 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.70 (s, 1H), 8.16 (d, *J* = 6.0, 2H), 8.12 (d, *J* = 2.5, 1H), 7.64 (d, *J* = 2.5, 1H), 7.50



(d,  $J = 7.5$ , 1H), 7.38 (d,  $J = 3.0$ , 1H), 7.34–7.14 (m, 7H), 6.81 (d,  $J = 6.1$ , 2H), 6.31 (d,  $J = 2.9$ , 1H), 5.38 (s, 2H), 4.22 (t,  $J = 6.6$ , 2H), 2.33–2.21 (br s, 4H), 2.17 (t,  $J = 6.6$ , 2H), 1.90 (quint,  $J = 6.8$ , 2H), 1.55–1.45 (m, 2H), 1.42–1.33 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  156.3 (C), 151.0 (C), 150.1 (2CH), 138.5 (CH), 137.4 (C), 135.8 (C), 134.0 (CH), 131.2 (C), 129.1 (CH), 128.1 (2CH), 127.8 (C), 127.44 (2CH), 127.39 (CH), 126.8 (C), 123.8 (C), 120.7 (CH), 120.2 (CH), 109.6 (CH), 108.5 (2CH), 99.9 (CH), 67.1 (CH<sub>2</sub>), 55.1 (CH<sub>2</sub>), 53.9 (2CH<sub>2</sub>), 43.5 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.6 (2CH<sub>2</sub>), 24.1 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 259.6494, found 259.6489.

#### 4.1.59. 6-(Benzyloxy)-5-{1-[4-(piperidin-1-yl)butan-1-yl]-1H-indol-4-yl}-N-(pyridin-4-yl)pyridin-3-amine **74**

Compound **64** was first prepared according to general procedure J, starting from **54** (135 mg, 0.40 mmol). The tube was sealed and the mixture was heated under microwave irradiation for 60 min. The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 9:1 + 0.5% Et<sub>3</sub>N to 7:3 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained brown solid **64** (135 mg).  $R_f = 0.32$  (cyclohexane/acetone 7:3 + 0.5% Et<sub>3</sub>N). Compound **64** was used for the next step without further purification.

Compound **74** was prepared according to general procedure E, starting from **41** (143 mg, 0.40 mmol) and **64** (135 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, acetone + 0.5% Et<sub>3</sub>N) to give **74** (56 mg, 0.105 mmol, 26%) as a white solid.  $R_f = 0.16$  (acetone + 0.5% Et<sub>3</sub>N); Mp 71 °C; IR (ATR) 2927, 1591, 1445, 1418, 1358, 1285, 1213, 993, 746, 695 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.70 (s, 1H), 8.16 (d,  $J = 5.6$ , 2H), 8.12 (d,  $J = 2.5$ , 1H), 7.64 (d,  $J = 2.6$ , 1H), 7.51 (d,  $J = 7.5$ , 1H), 7.41 (d,  $J = 3.1$ , 1H), 7.34–7.15 (m, 7H), 6.81 (d,  $J = 5.6$ , 2H), 6.30 (d,  $J = 3.0$ , 1H), 5.38 (s, 2H), 4.21 (t,  $J = 6.9$ , 2H), 2.29–2.18 (m, 6H), 1.76 (quint,  $J = 7.1$ , 2H), 1.48–1.30 (m, 8H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  156.3 (C), 151.0 (C), 150.1 (2CH), 138.4 (CH), 137.4 (C), 135.7 (C), 133.9 (CH), 131.2 (C), 129.0 (CH), 128.1 (2CH), 127.8 (C), 127.42 (2CH), 127.37 (CH), 126.9 (C), 123.8 (C), 120.7 (CH), 120.2 (CH), 109.7 (CH), 108.5 (2CH), 99.8 (CH), 67.1 (CH<sub>2</sub>), 57.9 (CH<sub>2</sub>), 54.0 (2CH<sub>2</sub>), 45.5 (CH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 25.5 (2CH<sub>2</sub>), 24.1 (CH<sub>2</sub>), 23.5 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>34</sub>H<sub>39</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 266.6572, found 266.6564.

#### 4.1.60. 6-(Benzyloxy)-5-{1-[3-(morpholin-4-yl)propan-1-yl]-1*H*-indol-4-yl}-*N*-(pyridin-4-yl)pyridin-3-amine 75

Compound **65** was first prepared according to general procedure J, starting from **55** (500 mg, 1.55 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 100:0 + 0.5% Et<sub>3</sub>N to 50:50 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained grey powder **65** (391 mg). *R*<sub>f</sub> = 0.71 (cyclohexane/acetone 1:1 + 1% Et<sub>3</sub>N). Compound **65** was used for the next step without further purification.

Compound **75** was prepared according to general procedure E, starting from **41** (466 mg, 1.31 mmol) and **65** (532 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N to 90:10 + 0.5% Et<sub>3</sub>N) to give **75** (554 mg, 1.07 mmol, 81%) as a pink solid. *R*<sub>f</sub> = 0.46 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 + 0.5% Et<sub>3</sub>N); Mp 88 °C; IR (ATR) 2944, 2807, 1591, 1417, 1213, 1115, 988, 814 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.70 (s, 1H), 8.16 (d, *J* = 5.8, 2H), 8.12 (d, *J* = 2.5, 1H), 7.64 (d, *J* = 2.5, 1H), 7.50 (d, *J* = 7.6, 1H), 7.40 (d, *J* = 3.0, 1H), 7.34–7.14 (m, 7H), 6.80 (d, *J* = 6.0, 2H), 6.31 (d, *J* = 2.9, 1H), 5.38 (s, 2H), 4.24 (t, *J* = 6.7, 2H), 3.60–3.54 (m, 4H), 2.34–2.26 (br s, 4H), 2.20 (t, *J* = 6.8, 2H), 1.92 (quint, *J* = 6.6, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 156.3 (C), 151.0 (C), 150.1 (2CH), 138.5 (CH), 137.4 (C), 135.8 (C), 134.0 (CH), 131.2 (C), 129.1 (CH), 128.1 (2CH), 127.8 (C), 127.45 (2CH), 127.40 (CH), 126.8 (C), 123.8 (C), 120.7 (CH), 120.2 (CH), 109.6 (CH), 108.5 (2CH), 99.9 (CH), 67.1 (CH<sub>2</sub>), 66.2 (2CH<sub>2</sub>), 54.9 (CH<sub>2</sub>), 53.2 (2CH<sub>2</sub>), 43.4 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>); HRMS (ESI+) *m/z* calcd for C<sub>32</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub> (M+2H)<sup>2+</sup> 260.6390, found 260.6386.

#### 4.1.61. 6-(Benzyloxy)-5-{1-[4-(morpholin-4-yl)butan-1-yl]-1*H*-indol-4-yl}-*N*-(pyridin-4-yl)pyridin-3-amine 76

Compound **66** was first prepared according to general procedure J, starting from **56** (829 mg, 2.46 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 100:0 + 0.5% Et<sub>3</sub>N to 50:50 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained brown powder **66** (513 mg). *R*<sub>f</sub> = 0.65 (cyclohexane/acetone 1:1 + 1% Et<sub>3</sub>N). Compound **66** was used for the next step without further purification.

Compound **76** was prepared according to general procedure E, starting from **41** (432 mg, 1.21 mmol) and **66** (513 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, acetone + 0.5% Et<sub>3</sub>N) to give **76** (431 mg, 0.81 mmol, 67%) as a beige-orange solid. *R*<sub>f</sub> = 0.18 (acetone + 0.5% Et<sub>3</sub>N); Mp 93 °C; IR (ATR) 2929, 2856, 2807, 1591, 1418, 1213, 1115, 991, 814 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.74 (s, 1H), 8.16 (d, *J* = 6.2, 2H), 8.12 (d, *J* = 2.6, 1H), 7.64 (d, *J* = 2.7, 1H), 7.51 (d, *J* = 7.5, 1H), 7.41 (d, *J* = 3.1, 1H), 7.35–7.15 (m, 7H), 6.81 (d, *J* = 6.3,

2H), 6.31 (d,  $J = 2.9$ , 1H), 5.38 (s, 2H), 4.21 (t,  $J = 6.9$ , 2H), 3.52 (t,  $J = 4.5$ , 4H), 2.30–2.22 (m, 6H), 1.79 (quint,  $J = 7.2$ , 2H), 1.40 (quint,  $J = 7.4$ , 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  156.3 (C), 151.2 (C), 149.8 (2CH), 138.5 (CH), 137.4 (C), 135.7 (C), 134.0 (CH), 131.1 (C), 129.0 (CH), 128.1 (2CH), 127.8 (C), 127.43 (2CH), 127.39 (CH), 126.9 (C), 123.8 (C), 120.7 (CH), 120.2 (CH), 109.7 (CH), 108.5 (2CH), 99.8 (CH), 67.1 (CH<sub>2</sub>), 66.2 (2CH<sub>2</sub>), 57.5 (CH<sub>2</sub>), 53.2 (2CH<sub>2</sub>), 45.5 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 23.1 (2CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>33</sub>H<sub>37</sub>N<sub>5</sub>O<sub>2</sub> (M+2H)<sup>2+</sup> 267.6468, found 267.6469.

#### 4.1.62. 6-(Benzyloxy)-5-{1-[3-(4-methylpiperazin-1-yl)propan-1-yl]-1H-indol-4-yl}-N-(pyridin-4-yl)pyridin-3-amine 77

Compound **67** was first prepared according to general procedure J, starting from **57** (350 mg, 1.04 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 9:1 + 0.5% Et<sub>3</sub>N to 3:7 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained colorless oil **67** (310 mg).  $R_f = 0.21$  (cyclohexane/acetone 6:4 + 0.5% Et<sub>3</sub>N). Compound **67** was used for the next step without further purification.

Compound **77** was prepared according to general procedure E, starting from **41** (370 mg, 1.04 mmol) and **67** (308 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, acetone/MeOH 100:0 + 0.5% Et<sub>3</sub>N to 85:15 + 0.5% Et<sub>3</sub>N) to give **77** (268 mg, 0.503 mmol, 48%) as a beige solid.  $R_f = 0.13$  (acetone/MeOH 85:15 + 0.5% Et<sub>3</sub>N); Mp 94 °C; IR (ATR) 2935, 2792, 1591, 1446, 1418, 1359, 1282, 1214, 1164, 993, 814 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.69 (s, 1H), 8.16 (d,  $J = 6.0$ , 2H), 8.12 (d,  $J = 2.6$ , 1H), 7.64 (d,  $J = 2.6$ , 1H), 7.49 (d,  $J = 7.4$ , 1H), 7.38 (d,  $J = 3.1$ , 1H), 7.34–7.14 (m, 7H), 6.80 (d,  $J = 6.2$ , 2H), 6.31 (d,  $J = 3.0$ , 1H), 5.38 (s, 2H), 4.22 (t,  $J = 6.6$ , 2H), 2.41–2.22 (br s, 8H), 2.19 (t,  $J = 6.8$ , 2H), 2.14 (s, 3H), 1.90 (quint,  $J = 6.5$ , 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  156.3 (C), 151.0 (C), 150.1 (2CH), 138.5 (CH), 137.4 (C), 135.8 (C), 134.0 (CH), 131.2 (C), 129.1 (CH), 128.1 (2CH), 127.8 (C), 127.44 (2CH), 127.39 (CH), 126.8 (C), 123.8 (C), 120.7 (CH), 120.2 (CH), 109.6 (CH), 108.5 (2CH), 99.9 (CH), 67.1 (CH<sub>2</sub>), 54.8 (2CH<sub>2</sub>), 54.4 (CH<sub>2</sub>), 52.6 (2CH<sub>2</sub>), 45.7 (CH<sub>3</sub>), 43.4 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>33</sub>H<sub>38</sub>N<sub>6</sub>O (M+2H)<sup>2+</sup> 267.1548, found 267.1547.

#### 4.1.63. 6-(Benzyloxy)-5-{1-[4-(4-methylpiperazin-1-yl)butan-1-yl]-1H-indol-4-yl}-N-(pyridin-4-yl)pyridin-3-amine 78

Compound **68** was first prepared according to general procedure J, starting from **58** (540 mg, 1.54 mmol). The crude was purified by column chromatography (SiO<sub>2</sub>, cyclohexane/acetone 9:1 + 0.5% Et<sub>3</sub>N to 4:6 + 0.5% Et<sub>3</sub>N), but some starting material remained in the obtained

colorless oil **68** (470 mg).  $R_f = 0.24$  (cyclohexane/acetone 6:4 + 0.5% Et<sub>3</sub>N). Compound **68** was used for the next step without further purification.

Compound **78** was prepared according to general procedure E, starting from **41** (548 mg, 1.54 mmol) and **68** (469 mg). The crude was purified by column chromatography (SiO<sub>2</sub>, acetone/MeOH 100:0 + 0.5% Et<sub>3</sub>N to 85:15 + 0.5% Et<sub>3</sub>N) to give **78** (370 mg, 0.68 mmol, 44%) as a beige solid.  $R_f = 0.23$  (acetone/MeOH 8:2 + 0.5% Et<sub>3</sub>N); Mp 86 °C; IR (ATR) 2932, 2792, 1591, 1445, 1418, 1358, 1281, 1213, 1163, 991, 813 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.70 (s, 1H), 8.17 (d,  $J = 6.1$ , 2H), 8.13 (d,  $J = 2.6$ , 1H), 7.65 (d,  $J = 2.6$ , 1H), 7.52 (d,  $J = 7.4$ , 1H), 7.41 (d,  $J = 3.1$ , 1H), 7.36–7.15 (m, 7H), 6.81 (d,  $J = 6.2$ , 2H), 6.31 (d,  $J = 3.0$ , 1H), 5.39 (s, 2H), 4.21 (t,  $J = 6.9$ , 2H), 2.39–2.17 (br s, 8H), 2.25 (t,  $J = 7.1$ , 2H), 2.12 (s, 3H), 1.78 (quint,  $J = 7.1$ , 2H), 1.40 (quint,  $J = 7.2$ , 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 156.3 (C), 151.0 (C), 150.1 (2CH), 138.4 (CH), 137.4 (C), 135.7 (C), 134.0 (CH), 131.2 (C), 129.0 (CH), 128.1 (2CH), 127.9 (C), 127.42 (2CH), 127.38 (CH), 126.9 (C), 123.8 (C), 120.7 (CH), 120.2 (CH), 109.7 (CH), 108.5 (2CH), 99.8 (CH), 67.1 (CH<sub>2</sub>), 57.1 (CH<sub>2</sub>), 54.8 (2CH<sub>2</sub>), 52.6 (2CH<sub>2</sub>), 45.8 (CH<sub>3</sub>), 45.5 (CH<sub>2</sub>), 27.6 (CH<sub>2</sub>), 23.5 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>)  $m/z$  calcd for C<sub>34</sub>H<sub>40</sub>N<sub>6</sub>O (M+2H)<sup>2+</sup> 274.1626, found 274.1619.

#### 4.1.64. 3-{1-[3-(Diethylamino)propan-1-yl]-1*H*-Indol-4-yl]-5-(pyridin-4-ylamino)pyridin-2(1*H*)-one **79**

Compound **79** was prepared according to general procedure B, starting from **89** (90 mg, 0.178 mmol). The mixture was stirred at 0 °C for 1 h and then at room temperature for 6 h. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10 + 0.5% Et<sub>3</sub>N to 85:15 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was solubilized in CH<sub>2</sub>Cl<sub>2</sub> and washed with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub>, dried over MgSO<sub>4</sub> and filtered. After evaporation, compound **79** (22 mg, 0.053 mmol, 30%) was obtained as a beige solid.  $R_f = 0.19$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 + 0.5% Et<sub>3</sub>N); Mp > 128 °C (decomposition); IR (ATR) 2965, 2810, 1595, 1513, 1468, 1345, 1209, 997, 817 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.70 (br s, 1H), 8.22 (s, 1H), 8.11 (m, 2H), 7.49 (d,  $J = 2.9$ , 1H), 7.44 (d,  $J = 8.2$ , 1H), 7.37 (d,  $J = 3.1$ , 1H), 7.33 (d,  $J = 2.6$ , 1H), 7.28 (dd,  $J = 7.4$ , 0.9, 1H), 7.15 (dd,  $J = 8.1$ , 7.4, 1H), 6.64 (m, 2H), 6.35 (dd,  $J = 3.2$ , 0.8, 1H), 4.20 (t,  $J = 6.9$ , 2H), 2.43 (q,  $J = 7.1$ , 4H), 2.34 (t,  $J = 7.0$ , 2H), 1.86 (quint,  $J = 6.9$ , 2H), 0.92 (t,  $J = 7.1$ , 6H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 159.9 (C=O), 152.4 (C), 149.9 (2CH), 138.7 (CH), 135.9 (C), 130.6 (C), 129.5 (CH), 128.8 (CH), 128.4 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.3 (CH), 108.1 (2CH), 99.8 (CH), 49.4 (CH<sub>2</sub>), 46.1 (2CH<sub>2</sub>), 43.7 (CH<sub>2</sub>), 27.5

(CH<sub>2</sub>), 11.6 (2CH<sub>3</sub>); HRMS (ESI+) *m/z* calcd for C<sub>25</sub>H<sub>31</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 208.6259, found 208.6254. HPLC purity ≥ 98%, Method A: *t<sub>R</sub>* = 17.78 min, λ = 280 nm.

#### 4.1.65. 3-{1-[4-(Diethylamino)butan-1-yl]-1*H*-Indol-4-yl]-5-(pyridin-4-ylamino)pyridin-2(1*H*)-one 80

Compound **80** was prepared according to general procedure H, starting from **70** (120 mg, 0.231 mmol) in 5 mL of solvent. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10 + 0.5% Et<sub>3</sub>N to 85:15 + 0.5% Et<sub>3</sub>N). The obtained solid was solubilized in CH<sub>2</sub>Cl<sub>2</sub> and washed with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub>, dried over MgSO<sub>4</sub> and filtered. After evaporation compound **80** (55 mg, 0.128 mmol, 55%) was obtained as a beige solid. *R<sub>f</sub>* = 0.32 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 85:15 + 0.5% Et<sub>3</sub>N); Mp > 119 °C; IR (ATR) 2963, 2929, 2800, 1595, 1511, 1345, 1210, 993, 817 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.71 (br s, 1H), 8.22 (s, 1H), 8.12 (d, *J* = 5.7, 2H), 7.49 (d, *J* = 2.6, 1H), 7.46 (d, *J* = 8.2, 1H), 7.38 (d, *J* = 2.9, 1H), 7.33 (d, *J* = 2.5, 1H), 7.28 (d, *J* = 7.2, 1H), 7.15 (t, *J* = 7.8, 1H), 6.64 (d, *J* = 5.8, 2H), 6.35 (d, *J* = 2.8, 1H), 4.19 (t, *J* = 6.8, 2H), 2.38 (q, *J* = 7.1, 4H), 2.33 (t, *J* = 7.2, 2H), 1.75 (quint, *J* = 7.1, 2H), 1.36 (quint, *J* = 7.3, 2H), 0.90 (t, *J* = 7.0, 6H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 160.0 (C=O), 152.4 (C), 149.9 (2CH), 138.6 (CH), 135.9 (C), 130.5 (C), 129.7 (CH), 128.7 (CH), 128.5 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.3 (CH), 108.1 (2CH), 99.8 (CH), 51.8 (CH<sub>2</sub>), 46.2 (2CH<sub>2</sub>), 45.5 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 24.1 (CH<sub>2</sub>), 11.7 (2CH<sub>3</sub>); HRMS (ESI+) *m/z* calcd for C<sub>26</sub>H<sub>33</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 215.6337, found 215.6337. HPLC purity ≥ 99%, Method A: *t<sub>R</sub>* = 18.02 min, λ = 240 nm.

#### 4.1.66. 3-{1-[3-(Pyrrolidin-1-yl)propan-1-yl]-1*H*-Indol-4-yl]-5-(pyridin-4-ylamino)pyridin-2(1*H*)-one 81

Compound **81** was prepared according to general procedure H, starting from **71** (120 mg, 0.238 mmol) in 5 mL of solvent. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N to 90:10 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was solubilized in CH<sub>2</sub>Cl<sub>2</sub> and the solution was washed with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub>, dried over MgSO<sub>4</sub> and filtered. After evaporation, the solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give compound **81** (52 mg, 0.126 mmol, 53%) was obtained as a pale-yellow solid. *R<sub>f</sub>* = 0.31 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 85:15 + 0.5% Et<sub>3</sub>N); Mp > 139 °C; IR (ATR) 2925, 2791, 1591, 1510, 1344, 1213, 994, 814 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.69 (br s, 1H), 8.24 (s, 1H), 8.12 (d, *J* = 5.1, 2H), 7.49 (d, *J* = 2.8, 1H), 7.45 (d, *J* = 8.2, 1H), 7.37 (d, *J* = 3.1, 1H), 7.34 (d, *J* = 2.7, 1H), 7.28 (d, *J* = 7.3, 1H), 7.16 (t, *J* = 7.8, 1H), 6.64 (d, *J* = 5.8, 2H), 6.35 (d, *J* = 3.0, 1H), 4.23

(t,  $J = 6.7$ , 2H), 2.47–2.40 (m, 4H), 2.36 (t,  $J = 6.8$ , 2H), 1.92 (quint,  $J = 6.8$ , 2H), 1.65–1.73 (4H, m);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  159.9 (C=O), 152.5 (C), 149.9 (2CH), 138.7 (CH), 135.9 (C), 130.6 (C), 129.5 (CH), 128.8 (CH), 128.4 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.3 (CH), 108.1 (2CH), 99.9 (CH), 53.5 (2CH<sub>2</sub>), 52.5 (CH<sub>2</sub>), 43.6 (CH<sub>2</sub>), 29.0 (CH<sub>2</sub>), 23.1 (2CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>25</sub>H<sub>29</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 207.6181, found 207.6181. HPLC purity  $\geq$  98%, Method A:  $t_R = 17.70$  min,  $\lambda = 280$  nm.

#### 4.1.67. 3-{1-[4-(Pyrrolidin-1-yl)butan-1-yl]-1H-Indol-4-yl}-5-(pyridin-4-ylamino)pyridin-2(1H)-one **82**

Compound **82** was prepared according to general procedure H, starting from **72** (120 mg, 0.232 mmol) in 5 mL of solvent. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10 + 0.5% Et<sub>3</sub>N to 85:15 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **82** (53 mg, 0.124 mmol, 53%) as a yellow solid.  $R_f = 0.08$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 + 0.5% Et<sub>3</sub>N); Mp > 127 °C (decomposition); IR (ATR) 2927, 2788, 1594, 1511, 1345, 1209, 995, 816 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.71 (br-s, 1H), 8.22 (s, 1H), 8.12 (d,  $J = 5.2$ , 2H), 7.49 (d,  $J = 2.6$ , 1H), 7.45 (d,  $J = 8.2$ , 1H), 7.38 (d,  $J = 2.9$ , 1H), 7.33 (d,  $J = 2.5$ , 1H), 7.28 (d,  $J = 7.2$ , 1H), 7.15 (t,  $J = 7.7$ , 1H), 6.64 (d,  $J = 5.7$ , 2H), 6.35 (d,  $J = 2.8$ , 1H), 4.19 (t,  $J = 6.8$ , 2H), 2.43–2.34 (m, 6H), 1.78 (quint,  $J = 7.0$ , 2H), 1.69–1.59 (4H), 1.40 (quint,  $J = 7.3$ , 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  159.9 (C=O), 152.5 (C), 149.9 (2CH), 138.7 (CH), 135.9 (C), 130.7 (C), 129.5 (CH), 128.8 (CH), 128.5 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.6 (C), 109.4 (CH), 108.1 (2CH), 99.8 (CH), 55.0 (CH<sub>2</sub>), 53.5 (2CH<sub>2</sub>), 45.4 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 23.0 (2CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 214.6259, found 214.6258. HPLC purity  $\geq$  99%, Method A:  $t_R = 17.89$  min,  $\lambda = 240$  nm.

#### 4.1.68. 3-{1-[3-(Piperidin-1-yl)propan-1-yl]-1H-indol-4-yl}-5-(pyridin-4-ylamino)pyridin-2(1H)-one **83**

Compound **83** was prepared according to general procedure B, starting from **73** (120 mg, 0.232 mmol). The mixture was stirred at 0 °C for 1 h and then at room temperature for 3 h. The crude was purified by column chromatography (SiO<sub>2</sub>, acetone/MeOH 90:10 + 0.5% Et<sub>3</sub>N to 85:15 + 1% Et<sub>3</sub>N). After evaporation, the solid was washed with cyclohexane to give compound **83** (46 mg, 0.108 mmol, 46%) as an orange solid.  $R_f = 0.19$  (acetone/MeOH 85:15 + 1% Et<sub>3</sub>N); Mp > 142 °C (decomposition); IR (ATR) 2930, 1594, 1511, 1211, 996, 816 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.71 (br s, 1H), 8.22 (s, 1H), 8.11 (d,  $J = 5.5$ , 2H), 7.49 (d,  $J = 2.7$ , 1H), 7.45 (d,

$J = 8.2$ , 1H), 7.36 (d,  $J = 3.0$ , 1H), 7.33 (m, 1H), 7.28 (d,  $J = 7.3$ , 1H), 7.15 (t,  $J = 7.7$ , 1H), 6.64 (d,  $J = 5.7$ , 2H), 6.35 (d,  $J = 2.9$ , 1H), 4.20 (t,  $J = 6.6$ , 2H), 2.32–2.21 (br s, 4H), 2.16 (t,  $J = 6.7$ , 2H), 1.89 (quint,  $J = 6.7$ , 2H), 1.54–1.46 (m, 4H), 1.42–1.33 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  159.9 (C), 152.5 (C), 149.9 (2CH), 138.7 (CH), 135.9 (C), 130.6 (C), 129.5 (CH), 128.8 (CH), 128.4 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.3 (CH), 108.1 (2CH), 99.9 (CH), 55.2 (CH<sub>2</sub>), 53.9 (2CH<sub>2</sub>), 43.5 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 25.6 (2CH<sub>2</sub>), 24.1 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>26</sub>H<sub>31</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 214.6259, found 214.6258. HPLC purity  $\geq$  95%, Method A:  $t_R = 17.49$  min,  $\lambda = 280$  nm.

#### 4.1.69. 3-{1-[4-(Piperidin-1-yl)butan-1-yl]-1H-indol-4-yl]-5-(pyridin-4-ylamino)pyridin-2(1H)-one 84

Compound **84** was prepared according to general procedure H, starting from **74** (75 mg, 0.141 mmol) in 4 mL of solvent. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N to 90:10 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was solubilized in CH<sub>2</sub>Cl<sub>2</sub> and the solution was washed with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub>, dried over MgSO<sub>4</sub> and filtered. After evaporation, compound **84** (31 mg, 0.070 mmol, 50%) was obtained as a pale-yellow solid.  $R_f = 0.33$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 + 0.5% Et<sub>3</sub>N); Mp > 128 °C (decomposition); IR (ATR) 2930, 1598, 1512, 1347, 1210, 997, 817 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.68 (br s, 1H), 8.21 (s, 1H), 8.11 (m, 2H), 7.48 (d,  $J = 2.9$ , 1H), 7.45 (d,  $J = 8.2$ , 1H), 7.37 (d,  $J = 3.1$ , 1H), 7.34 (d,  $J = 2.8$ , 1H), 7.28 (dd,  $J = 7.3$ , 0.9, 1H), 7.15 (dd,  $J = 8.1$ , 7.4, 1H), 6.63 (m, 2H), 6.34 (dd,  $J = 3.1$ , 0.8, 1H), 4.18 (t,  $J = 7.0$ , 2H), 2.28–2.18 (br s, 4H), 2.20 (t,  $J = 7.3$ , 2H), 1.75 (quint,  $J = 7.3$ , 2H), 1.48–1.30 (m, 8H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  160.1 (C=O), 152.5 (C), 149.9 (2CH), 138.6 (CH), 135.8 (C), 130.4 (C), 129.9 (CH), 128.7 (CH), 128.6 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.3 (CH), 108.1 (2CH), 99.8 (CH), 55.9 (CH<sub>2</sub>), 54.0 (2CH<sub>2</sub>), 45.5 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 25.6 (2CH<sub>2</sub>), 24.2 (CH<sub>2</sub>), 23.6 (CH<sub>2</sub>); HRMS (ESI+)  $m/z$  calcd for C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O (M+2H)<sup>2+</sup> 221.6337, found 221.6332. HPLC purity  $\geq$  96%, Method A:  $t_R = 17.99$  min,  $\lambda = 240$  nm.

#### 4.1.70. 3-{1-[3-(Morpholin-4-yl)propan-1-yl]-1H-Indol-4-yl]-5-(pyridin-4-ylamino)pyridin-2(1H)-one 85

Compound **85** was prepared according to general procedure B, starting from **75** (100 mg, 0.192 mmol). The mixture was stirred at 0 °C for 1 h and then at room temperature for 5 h. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N to 90:10 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give compound **85** (20

mg, 0.047 mmol, 24%) as a pale-yellow solid.  $R_f = 0.40$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9:1 + 0.5%  $\text{Et}_3\text{N}$ ); Mp > 132 °C; IR (ATR) 2923, 2853, 2807, 1593, 1511, 1210, 1114, 995, 816  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.71 (br s, 1H), 8.23 (s, 1H), 8.12 (d,  $J = 5.1$ , 2H), 7.49 (d,  $J = 2.6$ , 1H), 7.46 (d,  $J = 8.2$ , 1H), 7.38 (d,  $J = 3.0$ , 1H), 7.34 (br s, 1H), 7.28 (d,  $J = 7.2$ , 1H), 7.15 (t,  $J = 7.7$ , 1H), 6.64 (d,  $J = 5.4$ , 2H), 6.35 (d,  $J = 2.8$ , 1H), 4.22 (t,  $J = 6.6$ , 2H), 3.60–3.55 (m, 4H), 2.34–2.25 (br s, 4H), 2.20 (t,  $J = 6.8$ , 2H), 1.91 (quint,  $J = 6.6$ , 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  159.9 (C=O), 152.5 (C), 149.9 (2CH), 138.7 (CH), 135.9 (C), 130.6 (C), 129.5 (CH), 128.8 (CH), 128.4 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.3 (CH), 108.1 (2CH), 99.9 (CH), 66.2 (2 $\text{CH}_2$ ), 55.0 ( $\text{CH}_2$ ), 53.2 (2 $\text{CH}_2$ ), 43.4 ( $\text{CH}_2$ ), 26.7 ( $\text{CH}_2$ ); HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{25}\text{H}_{29}\text{N}_5\text{O}_2$  ( $\text{M}+2\text{H}$ ) $^{2+}$  215.6155, found 215.6151. HPLC purity  $\geq$  98%, Method A:  $t_R = 17.49$  min,  $\lambda = 280$  nm.

#### 4.1.71. 3-{1-[4-(Morpholin-4-yl)butan-1-yl]-1H-Indol-4-yl}-5-(pyridin-4-ylamino)pyridin-2(1H)-one **86**

Compound **86** was prepared according to general procedure H, starting from **76** (100 mg, 0.187 mmol) in 5 mL of solvent. The crude was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5 + 0.5%  $\text{Et}_3\text{N}$  to 90:10 + 0.5%  $\text{Et}_3\text{N}$ ). After evaporation, the solid was solubilized in  $\text{CH}_2\text{Cl}_2$  and washed with a saturated aqueous solution of  $\text{Na}_2\text{CO}_3$ , dried over  $\text{MgSO}_4$  and filtered. After evaporation, compound **86** (46 mg, 0.104 mmol, 55%) was obtained as a pale-yellow solid.  $R_f = 0.45$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  9:1 + 0.5%  $\text{Et}_3\text{N}$ ); Mp > 128°C (decomposition); IR (ATR) 2927, 2860, 2807, 1591, 1510, 1211, 1114, 994, 863, 815  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.70 (br s, 1H), 8.21 (s, 1H), 8.11 (m, 2H), 7.48 (d,  $J = 2.9$ , 1H), 7.46 (d,  $J = 8.2$ , 1H), 7.38 (d,  $J = 3.2$ , 1H), 7.33 (d,  $J = 2.6$ , 1H), 7.28 (d,  $J = 7.2$ , 1H), 7.15 (t,  $J = 7.8$ , 1H), 6.63 (m, 2H), 6.34 (d,  $J = 3.0$ , 1H), 4.19 (t,  $J = 6.9$ , 2H), 3.55–3.48 (m, 4H), 2.31–2.22 (br s, 4H), 2.25 (t,  $J = 7.3$ , 2H), 1.77 (quint,  $J = 7.2$ , 2H), 1.39 (quint,  $J = 7.4$ , 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO}-d_6$ )  $\delta$  160.1 (C=O), 152.5 (C), 149.9 (2CH), 138.6 (CH), 135.8 (C), 130.5 (C), 129.8 (CH), 128.7 (CH), 128.6 (C), 126.6 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.3 (CH), 108.1 (2CH), 99.8 (CH), 66.2 (2 $\text{CH}_2$ ), 57.5 ( $\text{CH}_2$ ), 53.2 (2 $\text{CH}_2$ ), 45.4 ( $\text{CH}_2$ ), 27.6 ( $\text{CH}_2$ ), 23.2 ( $\text{CH}_2$ ); HRMS (ESI+)  $m/z$  calcd for  $\text{C}_{26}\text{H}_{31}\text{N}_5\text{O}_2$  ( $\text{M}+2\text{H}$ ) $^{2+}$  222.6233, found 222.6230. HPLC purity  $\geq$  98%, Method A:  $t_R = 17.63$  min,  $\lambda = 240$  nm.



**4.1.72. 3-{1-[3-(4-Methylpiperazin-1-yl)propan-1-yl]-1H-indol-4-yl]-5-(pyridin-4-ylamino)pyridin-2(1H)-one 87**

Compound **87** was prepared according to general procedure H, starting from **77** (120 mg, 0.225 mmol) in 5 mL of solvent. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% Et<sub>3</sub>N to 85:15 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to **87** (67 mg, 0.151 mmol, 67%) as a white solid. *R*<sub>f</sub> = 0.40 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 85:15 + 0.5% Et<sub>3</sub>N); Mp > 150 °C (decomposition); IR (ATR) 2934, 2792, 1602, 1517, 1275, 1214, 998, 818 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.71 (br s, 1H), 8.22 (s, 1H), 8.11 (d, *J* = 5.9, 2H), 7.49 (d, *J* = 2.8, 1H), 7.45 (d, *J* = 8.2, 1H), 7.36 (d, *J* = 3.0, 1H), 7.33 (d, *J* = 2.4, 1H), 7.28 (d, *J* = 7.3, 1H), 7.15 (t, *J* = 7.8, 1H), 6.63 (d, *J* = 6.1, 2H), 6.35 (d, *J* = 2.9, 1H), 4.20 (t, *J* = 6.5, 2H), 2.40–2.22 (br s, 8H), 2.18 (t, *J* = 6.8, 2H), 2.14 (s, 3H), 1.89 (quint, *J* = 6.7, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 159.9 (C=O), 152.4 (C), 149.9 (2CH), 138.7 (CH), 135.9 (C), 130.6 (C), 129.5 (CH), 128.8 (CH), 128.4 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.3 (CH), 108.1 (2CH), 99.9 (CH), 54.8 (2CH<sub>2</sub>), 54.5 (CH<sub>2</sub>), 52.6 (2CH<sub>2</sub>), 45.7 (CH<sub>3</sub>), 43.4 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>); HRMS (ESI+) *m/z* calcd for C<sub>26</sub>H<sub>32</sub>N<sub>6</sub>O (M+2H)<sup>2+</sup> 222.1313, found 222.1308. HPLC purity ≥ 99%, Method A: *t*<sub>R</sub> = 17.74 min, λ = 240 nm.

**4.1.73. 3-{1-[4-(4-Methylpiperazin-1-yl)butan-1-yl]-1H-indol-4-yl]-5-(pyridin-4-ylamino)pyridin-2(1H)-one 88**

Compound **88** was prepared according to general procedure H, starting from **78** (120 mg, 0.219 mmol) in 5 mL of solvent. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 90:10 + 0.5% Et<sub>3</sub>N to 85:15 + 0.5% Et<sub>3</sub>N). After evaporation, the solid was solubilized in CH<sub>2</sub>Cl<sub>2</sub> and the solution was washed with a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub>, dried over MgSO<sub>4</sub> and filtered. After evaporation, compound **88** (79 mg, 0.173 mmol, 79%) was obtained as a pale-yellow solid. *R*<sub>f</sub> = 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 85:15 + 0.5% Et<sub>3</sub>N); Mp > 135 °C (decomposition); IR (ATR) 2934, 2794, 1596, 1512, 1461, 1281, 1211, 995, 817 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.67 (br s, 1H), 8.21 (s, 1H), 8.11 (d, *J* = 5.9, 2H), 7.47 (d, *J* = 2.8, 1H), 7.45 (d, *J* = 8.6, 1H), 7.37 (d, *J* = 3.0, 1H), 7.34 (d, *J* = 2.4, 1H), 7.28 (d, *J* = 7.2, 1H), 7.14 (t, *J* = 7.7, 1H), 6.63 (d, *J* = 6.0, 2H), 6.34 (d, *J* = 2.9, 1H), 4.18 (t, *J* = 7.0, 2H), 2.38–2.16 (br s, 8H), 2.24 (t, *J* = 7.1, 2H), 2.11 (s, 3H), 1.75 (quint, *J* = 7.0, 2H), 1.38 (quint, *J* = 7.3, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ 160.0 (C=O), 152.5 (C), 149.9 (2CH), 138.6 (CH), 135.8 (C), 130.5 (C), 129.8 (CH), 128.7 (CH), 128.6 (C), 126.5 (C), 120.5 (CH), 120.0 (CH), 119.5 (C), 109.4 (CH), 108.1 (2CH), 99.8 (CH), 57.1 (CH<sub>2</sub>), 54.8 (2CH<sub>2</sub>), 52.6 (2CH<sub>2</sub>),

45.7 (CH<sub>3</sub>), 45.4 (CH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 23.5 (CH<sub>2</sub>); HRMS (ESI+) *m/z* calcd for C<sub>27</sub>H<sub>34</sub>N<sub>6</sub>O (M+2H)<sup>2+</sup> 229.1392, found 229.1391. HPLC purity ≥ 99%, Method A: t<sub>R</sub> = 17.41 min, λ = 240 nm.

## 4.2 *In vivo* assessment of anti-allodynic effect

### Behavioral study in rat

#### *Study Approval*

Animal protocols were approved by the Committee of Animal Research at the University of Clermont Auvergne, France, and authorized by the French Superior Education and Research Ministry (#41113). They were in accordance with the International Association for the Study of Pain (<https://www.iasp-pain.org/resources/guidelines/iasp-guidelines-for-the-use-of-animals-in-research/>) and the European Directive 2010/ 63/EU and ARRIVE guidelines.

#### *Rat capsaicin model*

Capsaicin (Sigma-Aldrich) was dissolved in an endolipid solution and conserved at 4 °C. For behavioral testing, animals received a subcutaneous injection of capsaicin (25 µg in 25 µL) solution into the right hindpaw using a 27-gauge needle coupled to a 100 µL Hamilton syringe, as described previously.<sup>13</sup>

#### *Intrathecal injection*

For investigation of the effects of newly synthesized compounds upon capsaicin-induced cutaneous mechanical allodynia, animals were briefly (about 3 min) anesthetized using a mask with 2% isoflurane and received an intrathecal injection of either compound (5 µM in 10 µL saline) or vehicle alone (saline + 0.01% DMSO) using a 10 µL Hamilton syringe. After recovery (about 2 min), rats were placed in an observation field (0.6 x 0.6 m<sup>2</sup>) under red light for a 30 min habituation session. During this period, rats were adapted to the observation field and red light. Immediately after the 30 min habituation period, animals received the subcutaneous injection of capsaicin.

#### *Behavioral responses*

Behavioral sensory testing was performed as previously described.<sup>14</sup> Briefly, rats were first allowed to acclimatize to the 0.6×0.6 m<sup>2</sup> glass chambers used for behavioral testing as well as to innocuous mechanical stimulation for 3 days before the start of the behavioral sensory

testing. The mechanical withdrawal threshold was determined using von Frey (VF) filaments (Bioseb, France) applied to the plantar surface of the right hindpaw via the descending-ascending method. Each filament was applied to the skin for 5 times for 3 s (at 10 s intervals). The VF filament threshold (VFT, in grams) was equal to the filament evoking a hindpaw withdrawal response in three out of five trials. After the injection of capsaicin, the VFT was recorded at 10-minutes intervals for 65-minutes. The level of mechanical allodynia inhibition of a given compound was computed as follows:  $[(AUC \text{ vehicle} - AUC \text{ compound})/AUC \text{ vehicle}] \times 100$  (AUC is the area under the curve).

### **Conflict of interest**

The authors declare no conflict of interest.

### **Data availability**

The data supporting this article ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS spectra of all new compounds) have been included as part of the Supplementary Information.

### **Acknowledgments**

This research was financed by the French government IDEX-ISITE initiative 16-IDEX-0001 (CAP 20-25), région Auvergne-Rhône-Alpes (Pack Ambition Recherche), Université Clermont Auvergne, Inserm and CNRS. The authors (TF, AB, FG, FA, PM) also thank WeylChem InnoTec (Frankfurt, Germany) for financial support and Aurélie Job for HPLC analysis.

### **References**

- 1 S. Lolignier, N. Eijkelkamp, J. N. Wood. Mechanical allodynia. *Pflugers Arch. – Eur. J. Physiol.* **2015**, *467*, 133–139.  
DOI: [10.1007/s00424-014-1532-0](https://doi.org/10.1007/s00424-014-1532-0)
- 2 A. Visseq, A. Descheemaeker, N. Pinto-Pardo, L. Nauton, V. Théry, F. Giraud, I. Abrunhosa-Thomas, A. Artola, F. Anizon, R. Dallel, P. Moreau. Pyridin-2(1H)one derivatives: a possible new class of therapeutics for mechanical allodynia. *Eur J. Med. Chem.* **2020**, *187*, 111917.  
DOI: [10.1016/j.ejmech.2019.111917](https://doi.org/10.1016/j.ejmech.2019.111917)

- 3 A. Visseq, A. Descheemaeker, K. Hérault, F. Giraud, I. Abrunhosa-Thomas, A. Artola, F. Anizon, R. Dallel, P. Moreau. Improved potency of pyridin-2(1*H*)one derivatives for the treatment of mechanical allodynia. *Eur. J. Med. Chem.* **2021**, 225, 113748.  
DOI: [10.1016/j.ejmech.2021.113748](https://doi.org/10.1016/j.ejmech.2021.113748)
- 4 C. Cheng, J. Xu, R. Zhu, L. Xing, X. Wang, Y. Hu. A highly efficient Pd–C catalytic hydrogenation of pyridine nucleus under mild conditions. *Tetrahedron* **2009**, 65, 8538-8541.  
DOI: [10.1016/j.tet.2009.08.011](https://doi.org/10.1016/j.tet.2009.08.011)
- 5 F. Ye, C. Wang, Y. Zhang, J. Wang. Synthesis of aryldiazoacetates through palladium(0)-catalyzed deacylative cross-coupling of aryl iodides with acyldiazoacetates. *Angew. Chem. Int. Ed.* **2014**, 53, 11625-11628.  
DOI: [10.1002/anie.201407653](https://doi.org/10.1002/anie.201407653)
- 6 M. Dibakar, A. Prakash, K. Selvakumar, K. Ruckmani, M. Sivakumar. 2-(Trimethylsilyl)ethanol as a new alcohol equivalent for copper-catalyzed coupling of aryl iodides. *Tetrahedron Lett.* **2011**, 52, 5338-5341.  
DOI: [10.1016/j.tetlet.2011.08.023](https://doi.org/10.1016/j.tetlet.2011.08.023)
- 7 F-F. Yong, Y-C. Teo, Y-K. Yan, G-L. Chua. Low catalyst loadings for copper-catalyzed O-arylation of phenols with aryl and heteroaryl halides under mild conditions. *Synlett* **2012**, 23, 101-106.  
DOI: [10.1055/s-0031-1290110](https://doi.org/10.1055/s-0031-1290110)
- 8 T. Frazier, P. Murail, Francis Giraud, Alain Artola, R. Dallel, F. Anizon, P. Moreau. Improved synthesis and preparation of analogues of a pain-relieving pyridin-2(1*H*)-one. *Synthesis*, **2024**, 56, 2093–2099.  
DOI: [10.1055/s-0043-1763758](https://doi.org/10.1055/s-0043-1763758)
- 9 T. Kuramochi, A. Kakefuda, H. Yamada, I. Sato, T. Taguchi, S. Sakamoto. Synthesis and structure–activity relationships of phenoxy pyridine derivatives as novel inhibitors of the sodium–calcium exchanger. *Bioorg. Med. Chem.* **2004**, 12, 5039-5056.  
DOI: [10.1016/j.bmc.2004.07.038](https://doi.org/10.1016/j.bmc.2004.07.038)
- 10 L. Đorđević, H. Sai, Y. Yang, N. A. Sather, L. C. Palmer, S. I. Stupp. Heterocyclic chromophore amphiphiles and their supramolecular polymerization. *Angew. Chem. Int. Ed.* **2023**, 62, e202214997.  
DOI: [10.1002/anie.202214997](https://doi.org/10.1002/anie.202214997)

- 11 W. Tang, H. Zhou, J. Wang, C. Pan, J. Shi, Q. Song. Substituent effects on photosensitized splitting of thymine cyclobutane dimer by an attached indole. *ChemPhysChem* **2012**, *13*, 4180-4185.  
DOI: [10.1002/cphc.201200652](https://doi.org/10.1002/cphc.201200652)
- 12 J. Tu, Z. Li, Y. Jiang, C. Ji, G. Han, Y. Wang, Na. Liu. Discovery of carboline derivatives as potent antifungal agents for the treatment of cryptococcal meningitis. *J. Med. Chem.* **2019**, *62*, 2376-2389.  
DOI: [10.1021/acs.jmedchem.8b01598](https://doi.org/10.1021/acs.jmedchem.8b01598)
- 13 R. Dallel, A. Descheemaeker, P. Luccarini. Recurrent administration of the nitric oxide donor, isosorbide dinitrate, induces a persistent cephalic cutaneous hypersensitivity: A model for migraine progression. *Cephalalgia* **2018**, *38*, 776–785.  
DOI: [10.1177/0333102417714032](https://doi.org/10.1177/0333102417714032)
- 14 C. Peirs N. Bourgois, A. Artola, R. Dallel. Protein Kinase C  $\gamma$  Interneurons Mediate C-fiber-induced Orofacial Secondary Static Mechanical Allodynia, but Not C-fiber-induced Nociceptive Behavior. *Anesthesiology* **2016**, *124*, 1136–1152.  
DOI: [10.1097/ALN.0000000000001000](https://doi.org/10.1097/ALN.0000000000001000)