



**HAL**  
open science

## Improved potency of pyridin-2(1H)one derivatives for the treatment of mechanical allodynia

Alexia Visseq, Amélie Descheemaeker, Karine Héroult, Francis Giraud, Isabelle Abrunhosa-Thomas, Alain Artola, Fabrice Anizon, Radhouane Dallel, Pascale Moreau

► **To cite this version:**

Alexia Visseq, Amélie Descheemaeker, Karine Héroult, Francis Giraud, Isabelle Abrunhosa-Thomas, et al.. Improved potency of pyridin-2(1H)one derivatives for the treatment of mechanical allodynia. European Journal of Medicinal Chemistry, 2021, 225, pp.113748. 10.1016/j.ejmech.2021.113748 . hal-03334145

**HAL Id: hal-03334145**

**<https://hal.science/hal-03334145v1>**

Submitted on 3 Sep 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Improved potency of pyridin-2(1H)one derivatives for the treatment of mechanical allodynia

Alexia Visseq<sup>a</sup>, Amélie Descheemaeker<sup>b</sup>, Karine Hérault<sup>b</sup>, Francis Giraud<sup>a</sup>, Isabelle Abrunhosa-Thomas<sup>a,\*</sup>, Alain Artola<sup>b,\*</sup>, Fabrice Anizon<sup>a,\*</sup>, Radhouane Dallel<sup>b,\*</sup>, Pascale Moreau<sup>a</sup>

<sup>a</sup> *Université Clermont Auvergne, CNRS, Clermont Auvergne INP, Institut de Chimie de Clermont-Ferrand, F-63000 Clermont-Ferrand, France*

<sup>b</sup> *Université Clermont Auvergne, CHU Clermont-Ferrand, Inserm, Neuro-Dol, F-63000 Clermont-Ferrand, France*

\*Authors to whom correspondence should be addressed:

(FA) Tel: +33 (0) 4 73 40 53 64. E-mail: [fabrice.anizon@uca.fr](mailto:fabrice.anizon@uca.fr)

(RD) Tel: +33 (0) 4 73 17 73 12. E-mail: [radhouane.dallel@uca.fr](mailto:radhouane.dallel@uca.fr)

(IT) Tel: +33 (0) 4 73 40 71 31. E-mail: [isabelle.thomas@sigma-clermont.fr](mailto:isabelle.thomas@sigma-clermont.fr)

(AA) Tel: +33 (0) 4 73 17 73 67. E-mail: [alain.artola@uca.fr](mailto:alain.artola@uca.fr)

## Abstract

Mechanical allodynia, a painful sensation caused by innocuous touch, is a major chronic pain symptom, which often remains without an effective treatment. There is thus a need for new anti-allodynic treatments based on new drug classes. We recently synthesized new 3,5-disubstituted pyridin-2(1*H*)-one derivatives. By substituting the pyridinone at the 3-position by various aryl/heteroaryl moieties and at the 5-position by a phenylamino group, we discovered that some derivatives exhibited a strong anti-allodynic potency in rats. Here, we report that varying the substitution of the pyridinone 5-position, the 3-position being substituted by an indol-4-yl moiety, further improves such anti-allodynic potency. Compared with **2**, one of the two most active compounds of the first series, eleven out of nineteen newly synthesized compounds showed higher anti-allodynic potency, with two of them completely preventing mechanical allodynia. In the first series, hit compounds **1** and **2** appeared to be inhibitors of p38 $\alpha$  MAPK, a protein kinase known to underlie pain hypersensitivity in animal models. Depending on the substitution at the 5-position, some newly synthesized compounds were also stronger p38 $\alpha$  MAPK inhibitors. Surprisingly, though, anti-allodynic effects and p38 $\alpha$  MAPK inhibitory potencies were not correlated, suggesting that other biological target(s) is/are involved in the analgesic activity in this series. Altogether, these results confirm that 3,5-disubstituted pyridine-2(1*H*)-one derivatives are of high interest for the development of new treatment of mechanical allodynia.

**Keywords:** Mechanical allodynia; Pyridin-2(1*H*)-ones; p38 MAPK; Animal model of chronic pain; Inflammatory chronic pain.

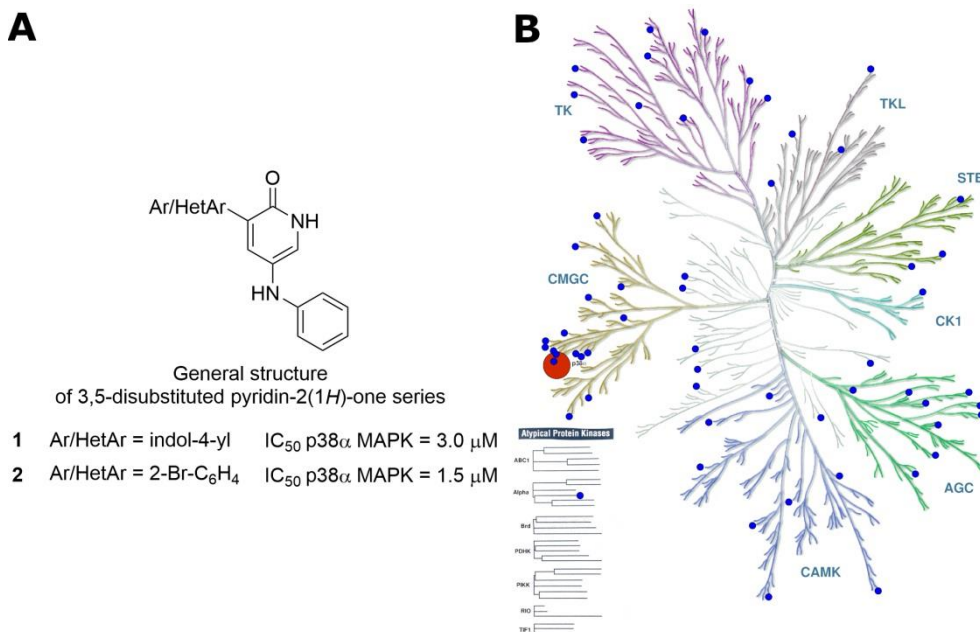
## 1. Introduction

Pain is one of the most common reasons for seeking medical care, and pain management should be considered as a major public health concern [1]. The capacity to experience acute pain has a protective role. By contrast, persistent, chronic pain initiated by tissue damage/inflammation (inflammatory pain) or nervous system lesion (neuropathic pain) offers no biological advantage and causes suffering and distress. Chronic pain affects more than 20% of Europeans and costs several hundred billions each year in medical treatments and societal burden [2]. Currently available therapies are not always effective (some pathologies lack efficacious analgesic solution) and can produce side-effects or have abuse potentials, such as opioid pain relievers. Chronic pain thus constitutes an unmet medical need: it is critical to discover more effective and safer treatments, with novel drug classes and modes of action.

Chronic pain syndromes are characterized by persistent pain hypersensitivity. This includes spontaneous pain, hyperalgesia and allodynia (pain in response to normally innocuous stimuli). It is now well established that each of these pain symptoms relies on different cellular and molecular mechanisms. Peripheral sensitization of nociceptors is obviously involved in acute pain and its transition to chronic pain [3]. However, the role of central sensitization – *i.e.* enhancement in the function of neurons and circuits in central pain pathways – in the manifestation of pain symptoms is increasingly recognized [4].

Protein kinases represent an important class of signaling proteins that are involved in numerous cellular process and act in the coordination of responses to extra- and intracellular signals, such as controlling cell growth and proliferation. Thus, numerous protein kinase inhibitors reached the market as anticancer drugs [5]. However, due to their pleiotropic role, protein kinases can be targeted for other application such as the treatment of pain [6–8]. It appears that some protein kinases are pivotal in the setting of central sensitization. Activation of several protein kinases, including the neuronal extracellular signal-regulated protein kinases (ERK), the  $\gamma$  isoform of protein kinase C (PKC $\gamma$ ) and the microglial p38 mitogen-activating protein kinase (p38), within the superficial spinal dorsal horn or medullary dorsal horn were shown to contribute to pain hypersensitivity. Thus, in animal models (rats, mice), local administration of protein kinase inhibitors produced analgesic effects. For example, targeting p38 [9,10] suppresses spontaneous pain behavior (formalin test). Inhibition of ERK [11], PKC $\gamma$  [12–15], and p38 [16–18] prevents inflammatory mechanical allodynia (MA). Application of p38 inhibitors [18–21] can also reduce neuropathic MA. Thus, protein kinases appear to be relevant biological targets for developing new analgesics.

As part of our ongoing program dedicated to the design and synthesis of small molecules with potent protein kinase inhibitory activities and analgesic properties, we previously reported the identification of a new 3,5-disubstituted pyridin-2(1*H*)-one series with potent *in vivo* activity in rat models of inflammatory and neuropathic MA [18]. The best anti-allodynic agent of the series (compound **2**, Fig. 1A) was screened toward a panel of 62 protein kinases leading to the identification of p38 $\alpha$  as a potential biological target (Fig. 1B). In addition, **2** was selective of p38 $\alpha$  over protein kinases representative of the human kinome or close to p38 $\alpha$  in the kinome phylogenetic tree. IC<sub>50</sub> values toward p38 $\alpha$ , determined for the two best anti-allodynic agents, showed moderate inhibitory potency in the micromolar range (compounds **1** and **2**, Fig. 1A).



**Figure 1. A.** General structure of 3,5-disubstituted pyridin-2(1H)-one series. Structure of most active anti-allodynic agents of the first series (compounds **1** and **2**), and their p38 $\alpha$  MAPK inhibitory activity. **B.** Kinase selectivity of compound **2**. Residual activity at 10  $\mu$ M: Blue disks  $\geq$  65%, red disk: 19% [18]. The tree was generated using the Kinome Render software, and the illustration reproduced courtesy of Cell Signaling Technology, Inc. ([www.cellsignal.com](http://www.cellsignal.com)) [22].

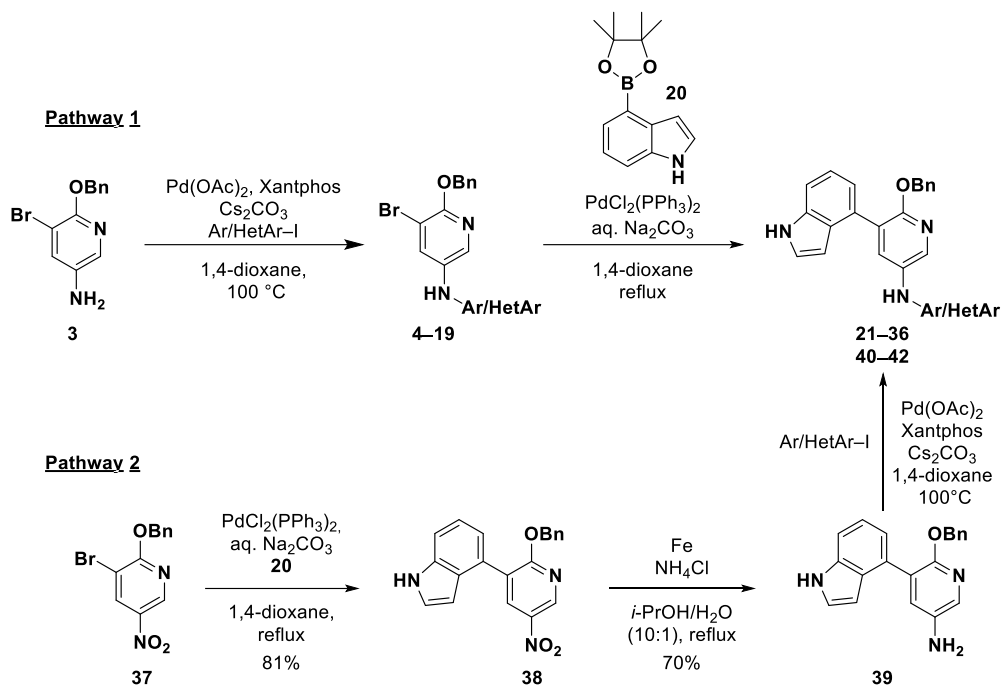
This work describes the enlargement of the structure-activity relationship study (SAR) performed on this series, in order to identify new compounds with improved *in vivo* anti-MA potency. Synthesis of new analogues, *in vivo* assessment of the antiallodynic effect, and evaluation toward p38 $\alpha$  MAPK are described.

## 2. Results and discussion

### 2.1. Synthesis of novel analogues

According to the good results obtained *in vivo* with compounds **1** and **2**, we decided to extend our structure-activity relationship study. In the previous series, position 3 of the pyridinone core was diversely arylated/heteroarylated whereas position 5 was substituted by a phenylamino group. Therefore, in the present work, we synthesized more analogs by varying the substituent at position 5, while the 3-substitution remained unchanged. At this position, indol-4-yl moiety was selected because of the high *in vivo* activity of compound **1** bearing this heterocycle, and for synthetic feasibility. For the majority of new compounds, we used the synthetic pathway described in our previous work (Scheme 1, Table 1, pathway 1). Thus, the amino group of pyridine derivative **3** was substituted in the presence of iodinated aryl/heteroaryl coupling partners in the presence of palladium acetate, Xantphos and cesium carbonate, leading to products **4–19** in yields ranging from 50% to 90%. The next step was a Suzuki cross-coupling using pinacol boronate **20** to give compounds **21–36** in good overall yields. For compounds **40–42** bearing a bromophenylamino group at the 5-position, to prevent regioselectivity issues due to competing bromoaryl moieties, Buchwald-Hartwig and Suzuki-Miyaura coupling steps were reversed, leading to synthetic pathway

2 (Scheme 1, Table 1). Compound **37**, we previously reported [18], was substituted by the indol-4-yl group leading to **38** in 81% yield. Reduction of the nitro group led to **39** and Buchwald-Hartwig coupling produced compounds **40–42** in moderate yields.



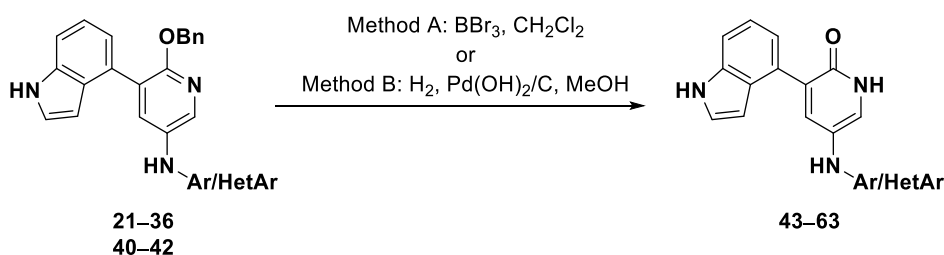
**Scheme 1.** Synthesis of compounds **4–36** and **38–42**.

**Table 1.** Isolated yields for compounds **4–19**, **21–36** and **40–42**.

Compounds <b>4–19</b>			Compounds <b>21–36<sup>a</sup></b> and <b>40–42<sup>b</sup></b>	
Ar/HetAr	Cpd	Yield %	Cpd	Yield %
2-F-C <sub>6</sub> H <sub>4</sub>	<b>4</b>	50	<b>21</b>	94
3-F-C <sub>6</sub> H <sub>4</sub>	<b>5</b>	57	<b>22</b>	99
4-F-C <sub>6</sub> H <sub>4</sub>	<b>6</b>	72	<b>23</b>	93
2-(CO <sub>2</sub> Et)-C <sub>6</sub> H <sub>4</sub>	<b>7</b>	90	<b>24</b>	78
3-(CO <sub>2</sub> Et)-C <sub>6</sub> H <sub>4</sub>	<b>8</b>	83	<b>25</b>	79
4-(CO <sub>2</sub> Et)-C <sub>6</sub> H <sub>4</sub>	<b>9</b>	66	<b>26</b>	88
2-MeO-C <sub>6</sub> H <sub>4</sub>	<b>10</b>	84	<b>27</b>	80
3-MeO-C <sub>6</sub> H <sub>4</sub>	<b>11</b>	60	<b>28</b>	85
4-MeO-C <sub>6</sub> H <sub>4</sub>	<b>12</b>	69	<b>29</b>	93
2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>13</b>	86	<b>30</b>	87
3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>14</b>	76	<b>31</b>	97
4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>15</b>	76	<b>32</b>	93
2-Me-C <sub>6</sub> H <sub>4</sub>	<b>16</b>	74	<b>33</b>	78
Pyridin-2-yl	<b>17</b>	55	<b>34</b>	88
Pyridin-3-yl	<b>18</b>	85	<b>35</b>	94
pyridin-4-yl	<b>19</b>	72	<b>36</b>	64
			<b>40</b>	47
			<b>41</b>	46
			<b>42</b>	46

<sup>a</sup> Pathway 1. <sup>b</sup> Pathway 2.

For the last step, compounds **21–36** and **40–42** were debenzylated using boron tribromide (Method A) or by hydrogenolysis of benzyl group (Method B), leading to compounds **43–63** (Scheme 2, Table 2). For methoxyl derivative **28**, deprotection using boron tribromide led to concomitant cleavage of the methyl ether to give **52** in 52% yield. Hydrogenolysis applied to nitro compound **30** produced aniline derivative **56** in 60% yield.

**Scheme 2.** Synthesis of compounds **43–63**.

**Table 2.** Yields of debenylation of compounds **43–63**.

Starting from	Product	Ar/HetAr	Method	Yield (%)
<b>21</b>	<b>43</b>	2-F-C <sub>6</sub> H <sub>4</sub>	A	81
<b>22</b>	<b>44</b>	3-F-C <sub>6</sub> H <sub>4</sub>	A	57
<b>23</b>	<b>45</b>	4-F-C <sub>6</sub> H <sub>4</sub>	A	70
<b>24</b>	<b>46</b>	2-(CO <sub>2</sub> Et)-C <sub>6</sub> H <sub>4</sub>	B	quant.
<b>25</b>	<b>47</b>	3-(CO <sub>2</sub> Et)-C <sub>6</sub> H <sub>4</sub>	B	53
<b>26</b>	<b>48</b>	4-(CO <sub>2</sub> Et)-C <sub>6</sub> H <sub>4</sub>	B	quant
<b>27</b>	<b>49</b>	2-MeO-C <sub>6</sub> H <sub>4</sub>	B	84
<b>28</b>	<b>50</b>	3-MeO-C <sub>6</sub> H <sub>4</sub>	B	80
<b>29</b>	<b>51</b>	4-MeO-C <sub>6</sub> H <sub>4</sub>	B	99
<b>28</b>	<b>52</b>	3-OH-C <sub>6</sub> H <sub>4</sub>	A	52
<b>30</b>	<b>53</b>	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	A	33
<b>31</b>	<b>54</b>	3-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	A	91
<b>32</b>	<b>55</b>	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	A	31
<b>30</b>	<b>56</b>	2-NH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	B	60
<b>33</b>	<b>57</b>	2-Me-C <sub>6</sub> H <sub>4</sub>	B	77
<b>34</b>	<b>58</b>	pyridin-2-yl	A	61
<b>35</b>	<b>59</b>	pyridin-3-yl	B	48
<b>36</b>	<b>60</b>	pyridin-4-yl	B	55
<b>40</b>	<b>61</b>	2-Br-C <sub>6</sub> H <sub>4</sub>	A	59
<b>41</b>	<b>62</b>	3-Br-C <sub>6</sub> H <sub>4</sub>	A	68
<b>42</b>	<b>63</b>	4-Br-C <sub>6</sub> H <sub>4</sub>	A	52

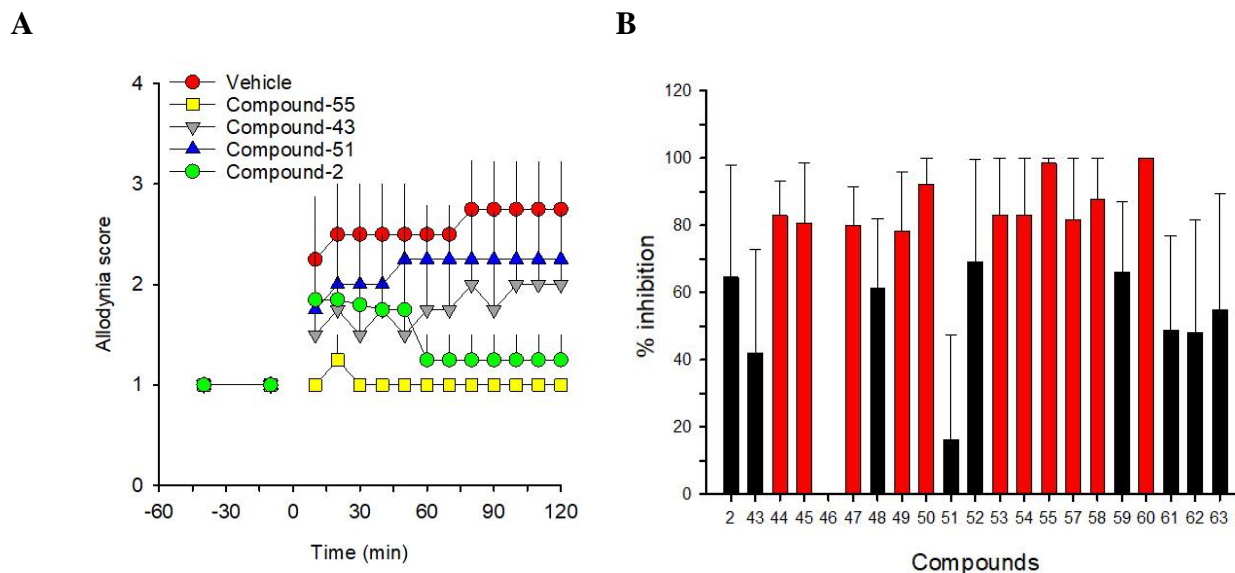
## 2.2. Biological activity of compounds **43–55** and **57–63**.

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

We compared the *in vivo* efficacy of new compounds **43–45**, **47–55** and **57–63** with that of compound **2**, one of the most active compounds of the first series [18] (Fig. 1), on the facial Complete Freund's Adjuvant (CFA) model (Fig. 2) [15]. Compound **46** was not tested due to its insufficient solubility. Similarly, compound **56** was not assayed due to an HPLC purity <95%, despite its apparent good <sup>1</sup>H NMR spectra. After receiving a subcutaneous injection of CFA (25 μL; 2.5 mg/kg) into the right vibrissa pad, rats develop a facial MA that lasts days. We found that all intracisternally (i.c.) applied compounds prevented the development of inflammatory MA. However, it is difficult to draw conclusions about the structure-activity relationships. Nevertheless, compared with compound **2**, most of the nineteen newly synthesized compounds produced equal (three compounds: **48**, **52** and **59**) or enhanced MA inhibition (≥ 80% inhibition of allodynic score; eleven compounds: **44**, **45**, **47**, **49**, **50**, **53–55**, **57**, **58** and **60**), including two compounds (**55** and **60**) which completely prevented MA. Notably, there were also two compounds (**43** and **51**) with much less anti-MA efficacy than compound **2**. Therefore, according to these results, the nature of the arylamino group at the pyridinone 5-position appears to greatly impact on the capacity of compounds to prevent MA. The presence of a nitrogen atom (**60**) or highly polar nitro group (**55**) at the aryl 4-position provided compounds with the strongest anti-allodynic effects. On the other hand, bromine atom (**63**), ethoxycarbonyl (**48**) or methoxyl (**51**) groups at the very same position drastically reduced the anti-allodynic activity of the corresponding compounds. This confirms that



the nature of the atom/group at this place is critical for MA inhibition. Various substituents at the phenyl 2-, 3-, or 4-positions are also consistent with strong anti-allodynic activity (> 80%, larger than that of compound **2**) such as 2- and 3-nitro (**53**, **54**), 3-methoxyl (**50**), 2-methyl (**57**) groups, 3-F and 4-F atoms (**44**, **45**) or when the phenyl group was replaced by a pyridin-2-yl moiety (**58**). In summary, compared with **2**, compounds **55** and **60** are the most interesting compounds of the new series, with an enhanced effect and a complete MA inhibition.



**Figure 2.** Intracisternal (i.c.) application of new 3,5-disubstituted pyridin-2(1H)-one derivatives prevent MA in a rat model of facial inflammatory pain (Complete Freund's Adjuvant; CFA). **A.** I.c. application of compounds **2**, **43**, **51** or **55** variably prevents inflammatory MA. Time courses of changes in behavioral responses (allodynic score) evoked by static mechanical stimuli (6-g von Frey filament) applied on the face of rats intracisternally treated with compounds **2**, **43**, **51** or **55** or vehicle. Compound **51** produced a 16% inhibition, compound **43**, a 42% one and compound **55**, an almost complete inhibition (98%), therefore stronger than that of compound **2** (65%) of inflammatory MA. **B.** I.c. application of compounds **2**, **43–45**, **47–55** or **57–63** prevents inflammatory MA. Bar histograms summarizing MA inhibitions by compound **2**, one of the two most active compounds of the first series, and new compounds **43–45**, **47–55** and **57–63**. Compounds **55** and **60** almost completely (98%) or completely (100%) inhibited inflammatory MA, respectively. In **A** and **B**, compounds (5  $\mu$ L at 10  $\mu$ M) or vehicle were intracisternally injected 30 min before CFA subcutaneous injection (at time 0 in **A**). Results are presented as mean + s.e.m.; n = 4 rats (**A**) and n = 4 rats (**B**, except compound **48**: n = 1 rat and compound **59**: n = 2 rats) in each group. Allodynic score (from 0 to 4) according to Vos *et al.* [23]. MA score in each group of treated rats is compared with that in control rats (injected with vehicle) using the unpaired Student *t* test. Red bars: MA score in treated rats vs. MA score in control rats:  $P < 0.05$ . Thus, when using such low doses of compounds (5  $\mu$ L at 10  $\mu$ M), 11 compounds of this second series (**44**, **45**, **47**, **49**, **50**, **53–55**, **57**, **58** and **60** – but not compound **2**, one of the two most potent compounds of the first series), significantly inhibit MA. For the computing of MA inhibition, see 4. Experimental section.

### 2.2.2. p38 $\alpha$ MAPK inhibitory potency.

Compounds **43–55** and **57–63** were evaluated for their p38 $\alpha$  MAPK inhibitory potency (International Center for Kinase Profiling, ICKP, Dundee, Scotland) [24]. First, compounds **43–55** and **57–63** were screened at a concentration of 1  $\mu$ M (Table 3) and IC<sub>50</sub> values were determined when the percentage of p38 $\alpha$  residual activity was found <50% at this concentration. Compared to previous results obtained from compounds **1** and **2**, data showed improved kinase inhibition for

fluorinated derivatives **43** and **45**, *meta*-phenol **52**, *ortho*-tolyl **57** and *meta*-bromophenyl derivative **62**. Conversely, ethyl ester and nitro derivatives (**46–48**, **53–55**) were almost inactive whereas pyridinyl analogues **58–60** showed low potency at 1  $\mu$ M. Thus, best IC<sub>50</sub> values were found in the submicromolar range for compounds **43**, **45** and **62**, with an improved potency compared to compounds **1** and **2**.

**Table 3.** p38 $\alpha$  MAPK inhibitory activity of compounds **43–55** and **57–63**.

Compound	% res. activity (1 $\mu$ M)	IC <sub>50</sub> ( $\mu$ M)
<b>1</b>	59 $\pm$ 10	3.0
<b>2</b>	59 $\pm$ 15	1.5
<b>43</b>	28 $\pm$ 4	0.23 $\pm$ 0.01
<b>44</b>	47 $\pm$ 6	1.4 $\pm$ 0.3
<b>45</b>	39 $\pm$ 10	0.4 $\pm$ 0.1
<b>46</b>	104 $\pm$ 22	nd
<b>47</b>	81 $\pm$ 18	nd
<b>48</b>	86 $\pm$ 7	nd
<b>49</b>	50 $\pm$ 5	5.2 $\pm$ 0.7
<b>50</b>	50 $\pm$ 6	5.5 $\pm$ 2.3
<b>51</b>	59 $\pm$ 9	3.7 $\pm$ 1.4
<b>52</b>	34 $\pm$ 7	1.0 $\pm$ 0.2
<b>53</b>	92.3 $\pm$ 0.3	nd
<b>54</b>	73.9 $\pm$ 0.2	nd
<b>55</b>	93 $\pm$ 8	nd
<b>57</b>	33 $\pm$ 6	1.1 $\pm$ 0.3
<b>58</b>	70 $\pm$ 9	nd
<b>59</b>	64 $\pm$ 11	nd
<b>60</b>	67 $\pm$ 7	nd
<b>61</b>	45 $\pm$ 2	2.7 $\pm$ 0.4
<b>62</b>	31 $\pm$ 11	0.7 $\pm$ 0.2
<b>63</b>	43 $\pm$ 14	2.4 $\pm$ 0.5

The results are expressed as mean kinase residual activity  $\pm$  SD for duplicate assays. nd: not determined.

### 2.2.3. Correlation anti-allodynic potency/p38 $\alpha$ MAPK inhibition.

We next examined whether the *in vivo* antiallodynic potency of compounds was correlated with their inhibitory effects toward p38 $\alpha$  MAPK. Surprisingly, there was no correlation. For example, compound **60**, exhibiting the strongest antiallodynic activity, showed only a modest p38 $\alpha$  MAPK inhibition (33% inhibition at 1  $\mu$ M), lower than that of compound **2** (41% inhibition at 1  $\mu$ M). Conversely, compound **43**, the best p38 $\alpha$  MAPK inhibitor, with an IC<sub>50</sub> value of 0.23  $\mu$ M (72% inhibition at 1  $\mu$ M) only produced 42% inhibition of MA (Fig. 2A). These results cannot be explained only by a cellular localization/penetration difference of the various compounds, but strongly suggest that other(s) biological target(s) is/are involved in the anti-allodynic activity, without ruling out p38 $\alpha$  MAPK inhibition.

### 3. Conclusion

In a work aiming at designing novel anti-allodynic drugs, we synthesized a new series of pyridine-2(1*H*)-one derivatives in three or four steps from precursors **3** and **37**, respectively. The heterocyclic core was substituted at the 3-position by an indol-4-yl moiety whereas the 5-position was substituted by various aryl/heteroaryl amino moieties. Compared with compound **2**, one of the two most active compounds of the previously reported series, most of the new derivatives (eleven out of nineteen) were more potent in preventing MA. Moreover, two of them completely suppressed MA in the conditions used. We also investigated the biological target(s) involved in such anti-allodynic potency. Since previously reported derivatives appeared to be selective p38 $\alpha$  MAPK inhibitors, the new compounds were assessed for their p38 $\alpha$  MAPK inhibitory activity. Some of them exhibited submicromolar p38 $\alpha$  MAPK inhibitory potency. Their *in vitro* efficacy depended on the substitution at the 5-position and could be stronger than that of compound **2**. Surprisingly, though, anti-allodynic effects and p38 $\alpha$  MAPK inhibitory potencies were not correlated, suggesting that other biological target(s) is/are involved in the analgesic activity in this series. Additional *in vivo* and *in vitro* work to identify this/these target(s) as well as to test other routes of administration (*e.g.* systemic) and assess putative adverse effects such as motor impairment or sedation – of note, we used very low doses and animals behaved normally – is under progress. Thus, these results show that, compared with our first series of pyridin-2(1*H*)one derivatives, substitution at the 5-position can improve the anti-allodynic potency. They confirm that, altogether, pyridin-2(1*H*)one derivatives are of high interest for the development of novel analgesics for the treatment of MA.

### 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) 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), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of doublet of doublet of doublet (dddd), doublet of triplets (dt), triplet of doublets (td), multiplet (m), broad signal (br s). Coupling constants are expressed in Hertz. High resolution mass spectra were determined on a high-resolution Waters Micro Q-ToF or 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. 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 **43–63** was established by HPLC analysis using an Agilent infinity 1260 chromatograph with DAD detector and an Agilent Zorbax SB-Phenyl column (4.6 mm x150 mm, 3.5  $\mu\text{m}$ ). Flow rate was 0.8 mL/min and the analysis was performed at 25 °C. Detection wavelength is indicated for each compound. Solvents were (A) water/0.1% formic acid, (B) Acetonitrile. Gradient was 100:0 A/B to 30:70 A/B in 8 min and then 30:70 A/B for 3 min.

#### 4.1.2. General procedures.

**Procedure A:** Buchwald-Hartwig cross-coupling between compound **3** and iodide derivatives.

A 5–9 mL screw-cap tube under argon was charged with compound **20** (1 equiv), Pd(OAc)<sub>2</sub> (0.05 equiv), Xantphos (0.05 equiv) and Cs<sub>2</sub>CO<sub>3</sub> (2 equiv). Then, anhydrous 1,4-dioxane (amount for 0.2 M substrate concentration, unless otherwise indicated) degassed with argon and the iodide derivative (1 equiv) 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 B:** Suzuki cross-coupling, conventional heating.

To a solution under argon of brominated derivative (1 equiv) in 1,4-dioxane (amount for 0.1 M substrate concentration) were added the indole-4-boronic acid pinacol ester **20** (1.5 equiv) and 2 M Na<sub>2</sub>CO<sub>3</sub> aqueous solution (5 equiv). 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 equiv). The solution was refluxed overnight. Ethyl acetate was added and the resulting mixture was washed with water. The organic phase was dried over MgSO<sub>4</sub> and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography.

**Procedure C:** Debenzylation by BBr<sub>3</sub>.

A solution under argon of benzylated compound (1 equiv) in anhydrous dichloromethane (amount for 0.02 M substrate concentration) was cooled to 0 °C (procedure C1) or to –10 °C (procedure C2). A solution of BBr<sub>3</sub> in dichloromethane (1 M, 4 equiv unless otherwise indicated) was added dropwise. The mixture was stirred at room temperature (C1) or at 0 °C (C2) in the dark. The reaction mixture was then quenched by addition of NEt<sub>3</sub> and methanol. After evaporation under reduced pressure, EtOAc was added. The mixture was washed with water and saturated aqueous NaCl solution, dried over MgSO<sub>4</sub> and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography.

**Procedure D:** Debenzylation by catalytic hydrogenolysis.

To a solution under argon of benzylated derivative (1 equiv) in MeOH degassed with argon was added 20% Pd(OH)<sub>2</sub>/C (0.08 equiv, unless otherwise indicated). The mixture was then hydrogenated at room temperature for 6 h in the dark. The mixture was filtered through a pad of Celite and then washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the obtained crude was purified by column chromatography.

#### 4.1.3. 6-(Benzyloxy)-5-bromo-N-(2-fluorophenyl)pyridin-3-amine (**4**)

Compound **4** was prepared according to general procedure A, starting from **3** (199 mg, 0.713 mmol) in 7 mL of anhydrous 1,4-dioxane. The mixture was heated for 20 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 8:92) to give **4** (134 mg, 0.360 mmol, 50%) as a beige solid. *R*<sub>f</sub> = 0.55 (EtOAc/cyclohexane 1:9); Mp 67 °C; IR (ATR) 3306, 1619, 1443, 1356, 1295, 1219, 1181, 1098, 1056, 1012, 733 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 7.96 (s, 1H), 7.94 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 2.5 Hz, 1H), 7.48–7.44 (m, 2H), 7.42–7.37

(m, 2H), 7.35–7.30 (m, 1H), 7.20 (ddd,  $J_1 = 11.9$  Hz,  $J_2 = 8.1$  Hz,  $J_3 = 1.4$  Hz, 1H), 7.14 (td,  $J_1 = 8.3$  Hz,  $J_2 = 1.7$  Hz, 1H), 7.06 (td,  $J_1 = 7.7$  Hz,  $J_2 = 1.3$  Hz, 1H), 6.90 (dddd,  $J_1 = 8.1$  Hz,  $J_2 = 7.3$  Hz,  $J_3 = 4.9$  Hz,  $J_4 = 1.8$  Hz, 1H), 5.37 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 153.5 (C), 152.8 (d,  $J_{\text{CF}} = 242$  Hz, C), 137.1 (C), 135.5 (CH), 135.0 (C), 133.0 (CH), 131.5 (d,  $J_{\text{CF}} = 11$  Hz, C), 128.4 (2CH), 127.7 (CH), 127.5 (2CH), 124.9 (d,  $J_{\text{CF}} = 3$  Hz, CH), 121.0 (d,  $J_{\text{CF}} = 7$  Hz, CH), 117.7 (d,  $J_{\text{CF}} = 3$  Hz, CH), 115.8 (d,  $J_{\text{CF}} = 19$  Hz, CH), 105.8 (C), 67.7 (CH $_2$ ); HRMS (ESI+) calcd for C $_{18}$ H $_{15}$ BrFN $_2$ O (M+H) $^+$  373.0346, found 373.0343.

#### 4.1.4. 6-(Benzyloxy)-5-bromo-N-(3-fluorophenyl)pyridin-3-amine (5)

Compound **5** was prepared according to general procedure A, starting from **3** (202 mg, 0.724 mmol). The mixture was heated for 2 h 30 min. The crude oil was purified by column chromatography (SiO $_2$ , cyclohexane to EtOAc/cyclohexane 5:95) to give **5** (153 mg, 0.410 mmol, 57%) as a brown solid.  $R_f = 0.72$  (EtOAc/cyclohexane 3:7); Mp 43 °C; IR (ATR) 3431, 1619, 1594, 1466, 1450, 1432, 1354, 1293, 1260, 1217, 1136, 1051, 970, 691 cm $^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 8.34 (s, 1H), 8.01 (d,  $J = 2.5$  Hz, 1H), 7.84 (d,  $J = 2.5$  Hz, 1H), 7.49–7.45 (m, 2H), 7.42–7.37 (m, 2H), 7.35–7.30 (m, 1H), 7.22 (td,  $J_1 = 8.2$  Hz,  $J_2 = 7.0$  Hz, 1H), 6.74 (ddd,  $J_1 = 8.2$  Hz,  $J_2 = 2.2$  Hz,  $J_3 = 0.7$  Hz, 1H), 6.67 (dt,  $J_1 = 11.7$  Hz,  $J_2 = 2.3$  Hz, 1H), 6.57 (dddd,  $J_1 = 8.9$  Hz,  $J_2 = 8.1$  Hz,  $J_3 = 2.5$  Hz,  $J_4 = 0.9$  Hz, 1H), 5.39 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 163.2 (d,  $J_{\text{CF}} = 241$  Hz, C), 154.1 (C), 146.3 (d,  $J_{\text{CF}} = 11$  Hz, C), 137.0 (C), 136.8 (CH), 134.3 (CH), 134.2 (C), 130.9 (d,  $J_{\text{CF}} = 10$  Hz, CH), 128.4 (2CH), 127.8 (CH), 127.5 (2CH), 110.9 (d,  $J_{\text{CF}} = 2$  Hz, CH), 106.0 (C), 105.5 (d,  $J_{\text{CF}} = 21$  Hz, CH), 101.4 (d,  $J_{\text{CF}} = 25$  Hz, CH), 67.8 (CH $_2$ ); HRMS (ESI+) calcd for C $_{18}$ H $_{15}$ BrFN $_2$ O (M+H) $^+$  373.0346, found 373.0369.

#### 4.1.5. 6-(Benzyloxy)-5-bromo-N-(4-fluorophenyl)pyridin-3-amine (6)

Compound **6** was prepared according to general procedure A, starting from **3** (202 mg, 0.724 mmol). The mixture was heated for 2 h 45 min. The crude oil was purified by column chromatography (SiO $_2$ , cyclohexane to EtOAc/cyclohexane 5:95) to give **6** (193.6 mg, 0.519 mmol, 72%) as a brown solid.  $R_f = 0.73$  (EtOAc/cyclohexane 3/7); Mp 43 °C; IR (ATR) 3394, 1506, 1444, 1215, 1052, 825, 735 cm $^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 8.06 (s, 1H), 7.92 (d,  $J = 2.5$  Hz, 1H), 7.72 (d,  $J = 2.5$  Hz, 1H), 7.47–7.43 (m, 2H), 7.42–7.36 (m, 2H), 7.35–7.29 (m, 1H), 7.07 (t,  $J = 8.8$  Hz, 2H), 6.99 (dd,  $J_1 = 9.0$  Hz,  $J_2 = 4.7$  Hz, 2H), 5.36 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 156.4 (d,  $J_{\text{CF}} = 236$  Hz, C), 153.1 (C), 140.0 (d,  $J_{\text{CF}} = 2$  Hz, C), 137.2 (C), 135.9 (C), 134.5 (CH), 132.0 (CH), 128.4 (2CH), 127.7 (CH), 127.5 (2CH), 117.8 (d,  $J_{\text{CF}} = 8$  Hz, 2CH), 115.9 (d,  $J_{\text{CF}} = 22$  Hz, 2CH), 106.0 (C), 67.7 (CH $_2$ ); HRMS (ESI+) calcd for C $_{18}$ H $_{15}$ BrFN $_2$ O (M+H) $^+$  373.0346, found 373.0349.

#### 4.1.6. Ethyl 2-((6-(benzyloxy)-5-bromopyridin-3-yl)amino)benzoate (7)

Compound **7** was prepared according to general procedure A, starting from **3** (50.1 mg, 0.179 mmol). The mixture was heated for 1 h 30 min. The crude oil was purified by column chromatography (SiO $_2$ , cyclohexane to EtOAc/cyclohexane 3:97) to give **7** (69.0 mg, 0.161 mmol, 90%) as a white solid.  $R_f = 0.68$  (EtOAc/cyclohexane 1:9); Mp 90 °C; IR (ATR) 3281, 1668, 1584, 1517, 1431, 1361, 1243, 1225, 736, 697 cm $^{-1}$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 9.15 (s, 1H), 8.13 (d,  $J = 2.4$  Hz, 1H), 8.04 (d,  $J = 2.4$  Hz, 1H), 7.90 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1H), 7.50–7.46 (m, 2H), 7.43–7.37 (m, 3H), 7.36–7.31 (m, 1H), 6.93 (dd,  $J_1 = 8.5$  Hz,  $J_2 = 1.0$  Hz, 1H), 6.81 (ddd,  $J_1 = 8.1$  Hz,  $J_2 = 7.1$  Hz,  $J_3 = 1.1$  Hz, 1H), 5.43 (s, 2H), 4.32 (q,  $J = 7.1$  Hz, 2H), 1.33 (t,  $J = 7.1$  Hz,

3H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 167.5 (C=O), 155.7 (C), 147.6 (C), 140.9 (CH), 138.3 (CH), 136.9 (C), 134.6 (CH), 132.2 (C), 131.3 (CH), 128.4 (2CH), 127.8 (CH), 127.5 (2CH), 117.7 (CH), 113.6 (CH), 112.0 (C), 106.0 (C), 68.0 (CH<sub>2</sub>), 60.6 (CH<sub>2</sub>), 14.1 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>21</sub>H<sub>20</sub>BrN<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup> 427.0652, found 427.0654.

#### 4.1.7. Ethyl 3-((6-(benzyloxy)-5-bromopyridin-3-yl)amino)benzoate (**8**)

Compound **8** was prepared according to general procedure A, starting from **3** (199 mg, 0.713 mmol). The mixture was heated for 1 h 45 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 1:9) to give **8** (252.6 mg, 0.591 mmol, 83%) as a brown solid.  $R_f$  = 0.19 (EtOAc/cyclohexane 1:9); Mp 99 °C; IR (ATR) 3378, 3336, 1694, 1450, 1358, 1304, 1276, 1052, 739 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 8.38 (s, 1H), 8.02 (d,  $J$  = 2.5 Hz, 1H), 7.84 (d,  $J$  = 2.5 Hz, 1H), 7.52–7.50 (m, 1H), 7.49–7.46 (m, 2H), 7.43–7.31 (m, 5H), 7.21 (ddd,  $J_1$  = 7.6 Hz,  $J_2$  = 2.5 Hz,  $J_3$  = 1.6 Hz, 1H), 5.40 (s, 2H), 4.29 (q,  $J$  = 7.1 Hz, 2H), 1.31 (t,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 165.8 (C=O), 153.9 (C), 144.5 (C), 137.1 (C), 136.3 (CH), 134.5 (C), 133.9 (CH), 130.9 (C), 129.8 (CH), 128.4 (2CH), 127.7 (CH), 127.5 (2CH), 119.9 (CH), 119.3 (CH), 115.4 (CH), 106.0 (C), 67.8 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 14.1 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>21</sub>H<sub>20</sub>BrN<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup> 427.0652, found 427.0652.

#### 4.1.8. Ethyl 4-((6-(benzyloxy)-5-bromopyridin-3-yl)amino)benzoate (**9**)

Compound **9** was prepared according to general procedure A, starting from **3** (200.8 mg, 0.719 mmol). The mixture was heated for 2 h 15 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 1:9) to give **9** (201.9 mg, 0.473 mmol, 66%) as a white solid.  $R_f$  = 0.16 (EtOAc/cyclohexane 1:9); Mp 139 °C; IR (ATR) 3316, 1677, 1595, 1464, 1367, 1285, 1244, 1176, 1054, 1008, 767, 730, 696 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 8.71 (s, 1H), 8.08 (d,  $J$  = 2.5 Hz, 1H), 7.91 (d,  $J$  = 2.5 Hz, 1H), 7.80 (d,  $J$  = 8.8 Hz, 2H), 7.49–7.45 (m, 2H), 7.43–7.38 (m, 2H), 7.36–7.31 (m, 1H), 6.94 (d,  $J$  = 8.9 Hz, 2H), 5.40 (s, 2H), 4.24 (q,  $J$  = 7.1 Hz, 2H), 1.28 (t,  $J$  = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 165.5 (C=O), 154.7 (C), 148.9 (C), 138.0 (CH), 137.0 (C), 135.5 (CH), 133.1 (C), 131.2 (2CH), 128.4 (2CH), 127.8 (CH), 127.6 (2CH), 119.6 (C), 113.4 (2CH), 106.1 (C), 67.9 (CH<sub>2</sub>), 60.0 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>21</sub>H<sub>20</sub>BrN<sub>2</sub>O<sub>3</sub> (M+H)<sup>+</sup> 427.0652, found 427.0662.

#### 4.1.9. 6-(Benzyloxy)-5-bromo-N-(2-methoxyphenyl)pyridin-3-amine (**10**)

Compound **10** was prepared according to general procedure A, starting from **3** (200.2 mg, 0.717 mmol). The mixture was heated for 1 h 30 min. The crude oil was purified by two successive chromatography columns (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 8:92 and SiO<sub>2</sub>, cyclohexane to Et<sub>2</sub>O/cyclohexane 1:9) to give **10** (232 mg, 0.602 mmol, 84%) as a beige oil.  $R_f$  = 0.39 (EtOAc/cyclohexane 1:9); IR (ATR) 3392, 3283, 1594, 1509, 1445, 1237, 733, 695 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 7.93 (d,  $J$  = 2.5 Hz, 1H), 7.72 (d,  $J$  = 2.5 Hz, 1H), 7.48–7.43 (m, 3H), 7.41–7.36 (m, 2H), 7.35–7.29 (m, 1H), 7.03 (dd,  $J_1$  = 7.4 Hz,  $J_2$  = 1.9 Hz, 1H), 7.00 (dd,  $J_1$  = 7.7 Hz,  $J_2$  = 1.4 Hz, 1H), 6.90–6.81 (m, 2H), 5.35 (s, 2H), 3.81 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 152.9 (C), 149.1 (C), 137.2 (C), 135.8 (C), 135.1 (CH), 132.7 (CH), 132.3 (C), 128.4 (2CH), 127.7 (CH), 127.5 (2CH), 120.9 (CH), 120.8 (CH), 115.6 (CH), 111.5 (CH), 105.7 (C), 67.6 (CH<sub>2</sub>), 55.5 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>18</sub>BrN<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup> 385.0546, found 385.0551.

#### 4.1.10. 6-(Benzyloxy)-5-bromo-N-(3-methoxyphenyl)pyridin-3-amine (**11**)

Compound **11** was prepared according to general procedure A, starting from **3** (151.1 mg, 0.541 mmol) in 5 mL of anhydrous 1,4-dioxane. The mixture was heated for 1 h 30 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 1:9) to give **11** (125.4 mg, 0.325 mmol, 60%) as a brown orange solid.  $R_f = 0.45$  (EtOAc/cyclohexane 1:9); Mp 61 °C; IR (ATR) 3375, 1619–1583, 1493, 1438, 1356, 1278 1215, 1158, 1052, 841, 765, 744, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 8.12 (s, 1H), 7.97 (d,  $J = 2.5$  Hz, 1H), 7.79 (d,  $J = 2.5$  Hz, 1H), 7.48–7.44 (m, 2H), 7.42–7.36 (m, 2H), 7.35–7.30 (m, 1H), 7.12 (t,  $J = 8.1$  Hz, 1H), 6.54 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.7$  Hz, 1H), 6.47 (t,  $J = 2.2$  Hz, 1H), 6.40 (dd,  $J_1 = 8.1$  Hz,  $J_2 = 2.2$  Hz, 1H), 5.39 (s, 2H), 3.70 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 160.4 (C), 153.4 (C), 145.1 (C), 137.1 (C), 135.7 (CH), 135.2 (C), 133.2 (CH), 130.2 (CH), 128.4 (2CH), 127.8 (CH), 127.5 (2CH), 108.0 (CH), 105.9 (C), 105.2 (CH), 101.3 (CH), 67.8 (CH<sub>2</sub>), 54.9 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>19</sub>H<sub>18</sub>BrN<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup> 385.0546, found 385.0548.

#### 4.1.11. 6-(Benzyloxy)-5-bromo-N-(4-methoxyphenyl)pyridin-3-amine (**12**)

Compound **12** was prepared according to general procedure A, starting from **3** (200.7 mg, 0.719 mmol). The mixture was heated for 20 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 1:9) to give **12** (190.9 mg, 0.496 mmol, 69%) as a beige solid.  $R_f = 0.20$  (cyclohexane/EtOAc 9:1); Mp 86 °C; IR (ATR) 3390, 1508, 1437, 1360, 1242, 1052, 1020, 727, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 7.84 (br s, 1H), 7.83 (d,  $J = 2.5$  Hz, 1H), 7.60 (d,  $J = 2.5$  Hz, 1H), 7.46–7.43 (m, 2H), 7.41–7.36 (m, 2H), 7.34–7.29 (m, 1H), 6.98 (d,  $J = 9.0$  Hz, 2H), 6.87 (d,  $J = 9.0$  Hz, 2H), 5.33 (s, 2H), 3.71 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 154.0 (C), 152.2 (C), 137.4 (C), 137.3 (C), 136.1 (C), 132.7 (CH), 130.1 (CH), 128.4 (2CH), 127.7 (CH), 127.5 (2CH), 119.5 (2CH), 114.8 (2CH), 106.0 (C), 67.6 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>19</sub>H<sub>18</sub>BrN<sub>2</sub>O<sub>2</sub> (M+H)<sup>+</sup> 385.0546, found 385.0557.

#### 4.1.12. 6-(Benzyloxy)-5-bromo-N-(2-nitrophenyl)pyridin-3-amine (**13**)

Compound **13** was prepared according to general procedure A, starting from **3** (200.9 mg, 0.720 mmol). The mixture was heated for 2 h 30 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 7:97) to give **13** (249.1 mg, 0.622 mmol, 86%) as an orange solid.  $R_f = 0.78$  (cyclohexane/EtOAc 7:3); Mp 106 °C; IR (ATR) 3340, 1616, 1571, 1498, 1471, 1439, 1350, 1256, 1149, 1056, 1023, 732 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 9.32 (s, 1H), 8.18 (d,  $J = 2.4$  Hz, 1H), 8.14–8.10 (m, 2H), 7.53–7.47 (m, 3H), 7.44–7.38 (m, 2H), 7.37–7.32 (m, 1H), 6.99 (dd,  $J_1 = 8.7$  Hz,  $J_2 = 1.1$  Hz, 1H), 6.88 (ddd,  $J_1 = 8.4$  Hz,  $J_2 = 7.0$  Hz,  $J_3 = 1.2$  Hz, 1H), 5.45 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 156.5 (C), 142.8 (C), 142.7 (CH), 140.0 (CH), 136.8 (C), 136.2 (CH), 133.2 (C), 131.0 (C), 128.4 (2CH), 127.9 (CH), 127.6 (2CH), 126.1 (CH), 118.0 (CH), 116.4 (CH), 105.9 (C), 68.1 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>18</sub>H<sub>15</sub>BrN<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup> 400.0291, found 400.0291.

#### 4.1.13. 6-(Benzyloxy)-5-bromo-N-(3-nitrophenyl)pyridin-3-amine (**14**)

Compound **14** was prepared according to general procedure A, starting from **3** (168.7 mg, 0.604 mmol). The mixture was heated for 3 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 17:83) to give **14** (184.2 mg, 0.460 mmol, 76%) as an orange solid.  $R_f = 0.58$  (cyclohexane/EtOAc 7:3); Mp 105 °C; IR (ATR) 3387, 1519, 1448, 1340, 1235, 1052, 976, 845, 743, 730, 691, 667 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 8.65 (s, 1H), 8.08

(d,  $J = 2.5$  Hz, 1H), 7.93 (d,  $J = 2.5$  Hz, 1H), 7.64 (t,  $J = 2.2$  Hz, 1H), 7.59 (ddd,  $J_1 = 8.1$  Hz,  $J_2 = 2.2$  Hz,  $J_3 = 0.9$  Hz, 1H), 7.49–7.38 (m, 5H), 7.36–7.31 (m, 1H) 7.31 (ddd,  $J_1 = 8.3$  Hz,  $J_2 = 2.4$  Hz,  $J_3 = 0.9$  Hz, 1H), 5.41 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 154.7 (C), 148.8 (C), 145.9 (C), 137.8 (CH), 137.0 (C), 135.3 (CH), 133.3 (C), 130.6 (CH), 128.4 (2CH), 127.8 (CH), 127.6 (2CH), 120.6 (CH), 113.2 (CH), 108.1 (CH), 106.2 (C), 67.9 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>18</sub>H<sub>15</sub>BrN<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup> 400.0291, found 400.0295.

#### 4.1.14. 6-(Benzyloxy)-5-bromo-N-(4-nitrophenyl)pyridin-3-amine (**15**)

Compound **15** was prepared according to general procedure A, starting from **3** (200.8 mg, 0.719 mmol). The mixture was heated for 2 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 15/85) to give **15** (217.5 mg, 0.543 mmol, 76%) as an orange solid.  $R_f = 0.17$  (cyclohexane/EtOAc 9:1); Mp 153 °C; IR (ATR) 3304, 1599, 1587, 1464, 1445, 1277, 1183, 1105, 1049, 983, 831, 738, 690 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 9.21 (s, 1H), 8.13 (d,  $J = 2.5$  Hz, 1H), 8.09 (d,  $J = 9.3$  Hz, 2H), 8.01 (d,  $J = 2.5$  Hz, 1H), 7.50–7.46 (m, 2H), 7.43–7.38 (m, 2H), 7.37–7.31 (m, 1H), 6.94 (d,  $J = 9.3$  Hz, 2H), 5.43 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 155.6 (C), 151.3 (C), 139.6 (CH), 138.2 (C), 136.9 (CH), 136.8 (C), 131.8 (C), 128.4 (2CH), 127.8 (CH), 127.6 (2CH), 126.2 (2CH), 113.0 (2CH), 106.2 (C), 68.1 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>18</sub>H<sub>15</sub>BrN<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup> 400.0291, found 400.0291.

#### 4.1.15. 6-(Benzyloxy)-5-bromo-N-(*o*-tolyl)pyridin-3-amine (**16**)

Compound **16** was prepared according to general procedure A, starting from **3** (161.4 mg, 0.578 mmol) in 3 mL of anhydrous 1,4-dioxane. The mixture was heated for 2 h 30 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 5:95) to give **16** (157.1 mg, 0.425 mmol, 74%) as a brown oil.  $R_f = 0.77$  (EtOAc/cyclohexane 3:7); IR (ATR) 3398, 1586, 1498, 1464, 1443, 1358, 1291, 1236, 1051, 736, 696 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 7.84 (d,  $J = 2.5$  Hz, 1H), 7.62 (d,  $J = 2.5$  Hz, 1H), 7.47–7.44 (m, 2H), 7.41–7.36 (m, 2H), 7.35 (s, 1H), 7.34–7.29 (m, 1H), 7.17 (d,  $J = 7.4$  Hz, 1H), 7.09 (td,  $J_1 = 7.7$  Hz,  $J_2 = 1.5$  Hz, 1H), 7.00 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.1$  Hz, 1H), 6.86 (td,  $J_1 = 7.3$  Hz,  $J_2 = 1.3$  Hz, 1H), 5.36 (s, 2H), 2.20 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 152.8 (C), 141.6 (C), 137.2 (C), 136.7 (C), 134.6 (CH), 132.2 (CH), 130.9 (CH), 128.4 (2CH), 127.9 (C), 127.7 (CH), 127.5 (2CH), 126.7 (CH), 121.5 (CH), 117.3 (CH), 105.9 (C), 67.7 (CH<sub>2</sub>), 17.8 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>18</sub>BrN<sub>2</sub>O (M+H)<sup>+</sup> 369.0597, found 369.0607.

#### 4.1.16. N-(6-(Benzyloxy)-5-bromopyridin-3-yl)pyridin-2-amine (**17**)

Compound **17** was prepared according to general procedure A, starting from **3** (250 mg, 0.896 mmol). The mixture was heated for 5 h 30 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 2:8) to give **17** (177 mg, 0.497 mmol, 55%) as a red powder.  $R_f = 0.12$  (EtOAc:cyclohexane 1:9); Mp > 132 °C (decomposition); IR (ATR) 3250–2900, 1600, 1449, 1438, 1354, 1288, 1219, 1048, 992, 764, 736, 695 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 9.14 (s, 1H), 8.55 (d,  $J = 2.4$ , 1H), 8.37 (d,  $J = 2.4$ , 1H), 8.15 (ddd,  $J_1 = 5.0$  Hz,  $J_2 = 1.9$  Hz,  $J_3 = 0.9$  Hz, 1H), 7.58 (ddd,  $J_1 = 8.4$  Hz,  $J_2 = 7.1$  Hz,  $J_3 = 2.0$  Hz, 1H), 7.48–7.44 (m, 2H), 7.42–7.36 (m, 2H), 7.34–7.29 (m, 1H), 6.79–6.75 (m, 2H), 5.38 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 155.4 (C), 152.9 (C), 147.2 (CH), 137.5 (CH), 137.2 (C), 134.9 (CH), 133.9 (C), 132.3 (CH), 128.4 (2CH), 127.7 (CH), 127.5 (2CH), 114.7 (CH), 110.7



(CH), 105.1 (C), 67.6 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>17</sub>H<sub>15</sub>BrN<sub>3</sub>O (M+H)<sup>+</sup> 356.0393, found 356.0394.

#### 4.1.17. 6-(Benzyloxy)-5-bromo-N-(pyridin-3-yl)pyridin-3-amine (**18**)

Compound **18** was prepared according to general procedure A, starting from **3** (201 mg, 0.720 mmol). The mixture was heated for 2 h 45 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 3:7 + 0.5% NEt<sub>3</sub>). CH<sub>2</sub>Cl<sub>2</sub> was added to the product and the solution was washed with aqueous saturated NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub> and filtered. Evaporation gave compound **18** (218.8 mg, 0.614 mmol, 85%) as a red powder. *R*<sub>f</sub> = 0.15 (EtOAc/cyclohexane 3:7); Mp 68 °C; IR (ATR) 3239, 1583, 1448, 1356, 1287, 1048, 992, 792, 732, 691 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 8.31 (s, 1H), 8.25 (d, *J* = 2.8 Hz, 1H), 8.02 (dd, *J*<sub>1</sub> = 4.6 Hz, *J*<sub>2</sub> = 1.4 Hz, 1H), 8.01 (d, *J* = 2.5 Hz, 1H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.48–7.45 (m, 2H), 7.42–7.37 (m, 2H), 7.37–7.30 (m, 2H), 7.21 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 4.6 Hz, 1H), 5.38 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 153.9 (C), 140.5 (CH), 140.4 (C), 138.2 (CH), 137.1 (C), 136.0 (CH), 134.3 (C), 133.4 (CH), 128.4 (2CH), 127.7 (CH), 127.5 (2CH), 123.9 (CH), 121.1 (CH), 106.1 (C), 67.8 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>17</sub>H<sub>15</sub>BrN<sub>3</sub>O (M+H)<sup>+</sup> 356.0393, found 356.0398.

#### 4.1.18. 6-(Benzyloxy)-5-bromo-N-(pyridin-4-yl)pyridin-3-amine (**19**)

Compound **19** was prepared according to general procedure A, starting from **3** (150.4 mg, 0.539 mmol). The mixture was heated for 2 h 45 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 9:1 + 0.5% NEt<sub>3</sub> to EtOAc + 0.5% NEt<sub>3</sub>). CH<sub>2</sub>Cl<sub>2</sub> was added to the product and the solution was washed with aqueous saturated NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub> and filtered. Evaporation gave compound **19** (138 mg, 0.387 mmol, 72%) as an orange solid. *R*<sub>f</sub> = 0.23 (EtOAc + 0.5% NEt<sub>3</sub>); Mp 138 °C; IR (ATR) 3500–3000, 1587, 1470, 1436, 1358, 1056, 992, 811, 729, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 8.71 (s, 1H), 8.19–8.16 (m, 2H), 8.08 (d, *J* = 2.5 Hz, 1H), 7.94 (d, *J* = 2.5 Hz, 1H), 7.49–7.45 (m, 2H), 7.43–7.37 (m, 2H), 7.36–7.31 (m, 1H), 6.78–6.75 (m, 2H), 5.41 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 155.1 (C), 150.7 (C), 150.1 (2CH), 138.9 (CH), 136.9 (C), 136.3 (CH), 132.2 (C), 128.4 (2CH), 127.8 (CH), 127.6 (2CH), 108.7 (2CH), 106.1 (C), 68.0 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>17</sub>H<sub>15</sub>BrN<sub>3</sub>O (M+H)<sup>+</sup> 356.0393, found 356.0398.

#### 4.1.19. 6-(Benzyloxy)-N-(2-fluorophenyl)-5-(1H-indol-4-yl)pyridin-3-amine (**21**)

Compound **21** was prepared according to general procedure B, starting from **4** (191 mg, 0.512 mmol). The mixture was refluxed for 17 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 5:95 to 1:9) to give **21** (198 mg, 0.484 mmol, 94%) as a beige solid. *R*<sub>f</sub> = 0.36 (EtOAc/cyclohexane 2:8); Mp 56 °C; IR (ATR) 3406, 1619, 1507, 1443, 1231, 987, 742, 695 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.19 (s, 1H), 7.99 (d, *J* = 2.8 Hz, 1H), 7.89 (d, *J* = 1.4 Hz, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 7.42–7.10 (m, 11H), 7.04 (td, *J*<sub>1</sub> = 7.6 Hz, *J*<sub>2</sub> = 1.4 Hz, 1H), 6.83 (dddd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 7.5 Hz, *J*<sub>3</sub> = 4.8 Hz, *J*<sub>4</sub> = 1.7 Hz, 1H), 6.32 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 2.0 Hz, *J*<sub>3</sub> = 0.9 Hz, 1H), 5.35 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 155.0 (C), 152.6 (d, *J*<sub>CF</sub> = 241 Hz, C), 137.7 (C), 136.0 (C), 135.7 (CH), 133.6 (C), 132.4 (d, *J*<sub>CF</sub> = 11 Hz, C), 131.6 (CH), 128.1 (2CH), 127.8 (C), 127.4 (2CH), 127.3 (CH), 126.5 (C), 125.5 (CH), 124.8 (d, *J*<sub>CF</sub> = 3 Hz, CH), 123.6 (C), 120.7 (CH), 120.05 (CH), 120.04 (d, *J*<sub>CF</sub> = 7 Hz, CH), 116.9 (d, *J*<sub>CF</sub> = 3 Hz,

CH), 115.7 (d,  $J_{CF} = 19$  Hz, CH), 111.1 (CH), 100.5 (CH), 66.9 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>26</sub>H<sub>21</sub>FN<sub>3</sub>O (M+H)<sup>+</sup> 410.1663, found 410.1656.

#### 4.1.20. 6-(Benzyloxy)-N-(3-fluorophenyl)-5-(1H-indol-4-yl)pyridin-3-amine (**22**)

Compound **22** was prepared according to general procedure B, starting from **5** (112 mg, 0.300 mmol). The mixture was refluxed for 16 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 2:8) to give **22** (122 mg, 0.298 mmol, 99%) as a light green powder.  $R_f = 0.31$  (EtOAc/cyclohexane 2:8); Mp 62 °C; IR (ATR) 3391, 1615, 1592, 1443, 1228, 1140, 750 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 11.20 (s, 1H), 8.30 (s, 1H), 8.05 (d,  $J = 2.7$  Hz, 1H), 7.60 (d,  $J = 2.7$  Hz, 1H), 7.43–7.11 (m, 10H), 6.77 (dd,  $J_1 = 8.1$  Hz,  $J_2 = 2.1$  Hz, 1H), 6.68 (dt,  $J_1 = 11.9$  Hz,  $J_2 = 2.3$  Hz, 1H), 6.52 (td,  $J_1 = 8.5$  Hz,  $J_2 = 2.5$  Hz, 1H), 6.32–6.30 (m, 1H), 5.36 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 163.3 (d,  $J_{CF} = 241$  Hz, C), 155.4 (C), 147.1 (d,  $J_{CF} = 11$  Hz, C), 137.6 (C), 136.6 (CH), 136.0 (C), 133.0 (C), 132.5 (CH), 130.9 (d,  $J_{CF} = 10$  Hz, CH), 128.1 (2CH), 127.7 (C), 127.5 (2CH), 127.4 (CH), 126.5 (C), 125.6 (CH), 123.9 (C), 120.7 (CH), 120.1 (CH), 111.2 (CH), 110.6 (d,  $J_{CF} = 2$  Hz, CH), 104.9 (d,  $J_{CF} = 21$  Hz, CH), 101.0 (d,  $J_{CF} = 25$  Hz, CH), 100.5 (CH), 67.0 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>26</sub>H<sub>21</sub>FN<sub>3</sub>O (M+H)<sup>+</sup> 410.1663, found 410.1641.

#### 4.1.21. 6-(Benzyloxy)-N-(4-fluorophenyl)-5-(1H-indol-4-yl)pyridin-3-amine (**23**)

Compound **23** was prepared according to general procedure B, starting from **6** (166.2 mg, 0.445 mmol). The mixture was refluxed for 16 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to EtOAc/cyclohexane 2:8) to give **23** (170.2 mg, 0.416 mmol, 93%) as a grey-green solid.  $R_f = 0.21$  (EtOAc/cyclohexane 2:8); Mp > 82 °C (decomposition); IR (ATR) 3395, 1505, 1213, 751 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 11.18 (s, 1H), 8.00 (s, 1H), 7.98 (d,  $J = 2.8$  Hz, 1H), 7.53 (d,  $J = 2.8$  Hz, 1H), 7.42–7.10 (m, 9H), 7.05 (t,  $J = 8.8$  Hz, 2H), 7.01 (dd,  $J_1 = 9.2$  Hz,  $J_2 = 4.9$  Hz, 2H), 6.30 (ddd,  $J_1 = 3.0$  Hz,  $J_2 = 2.0$  Hz,  $J_3 = 0.9$  Hz, 1H), 5.34 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 156.0 (d,  $J_{CF} = 235$  Hz, C), 154.6 (C), 140.9 (d,  $J_{CF} = 2$  Hz, C), 137.7 (C), 136.0 (C), 134.7 (C), 134.6 (CH), 130.7 (CH), 128.1 (2CH), 127.9 (C), 127.4 (2CH), 127.3 (CH), 126.5 (C), 125.5 (CH), 123.8 (C), 120.7 (CH), 120.0 (CH), 117.1 (d,  $J_{CF} = 8$  Hz, 2CH), 115.8 (d,  $J_{CF} = 22$  Hz, 2CH), 111.1 (CH), 100.6 (CH), 66.9 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>26</sub>H<sub>21</sub>FN<sub>3</sub>O (M+H)<sup>+</sup> 410.1663, found 410.1670.

#### 4.1.22. Ethyl 2-((6-(benzyloxy)-5-(1H-indol-4-yl)pyridin-3-yl)amino)benzoate (**24**)

Compound **24** was prepared according to general procedure B, starting from **7** (115 mg, 0.269 mmol). The mixture was refluxed for 14 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 12:88) to give **24** (97.6 mg, 0.211 mmol, 78%) as a beige solid.  $R_f = 0.13$  (EtOAc/cyclohexane 1:9); Mp 63 °C; IR (ATR) 3411, 3311, 1677, 1582, 1500, 1444, 1227, 1079, 746, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 11.19 (br s, 1H), 9.23 (s, 1H), 8.15 (d,  $J = 2.7$ , 1H), 7.90 (dd,  $J_1 = 8.0$  Hz,  $J_2 = 1.6$  Hz, 1H), 7.70 (d,  $J = 2.7$  Hz, 1H), 7.43–7.22 (m, 8H), 7.17–7.11 (m, 2H), 7.01 (dd,  $J_1 = 8.6$  Hz,  $J_2 = 0.8$  Hz, 1H), 6.77 (ddd,  $J_1 = 8.1$  Hz,  $J_2 = 7.1$  Hz,  $J_3 = 1.1$  Hz, 1H), 6.33 (ddd,  $J_1 = 3.0$  Hz,  $J_2 = 2.0$  Hz,  $J_3 = 0.9$  Hz, 1H), 5.40 (s, 2H), 4.33 (q,  $J = 7.1$  Hz, 2H), 1.34 (t,  $J = 7.1$  Hz, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  (ppm) 167.6 (C=O), 157.0 (C), 148.3 (C), 140.7 (CH), 137.4 (C), 136.04 (CH), 136.02 (C), 134.6 (CH), 131.3 (CH), 131.1 (C), 128.2 (2CH), 127.5 (2CH), 127.4 (C+CH), 126.5 (C), 125.6 (CH), 124.1 (C), 120.7

(CH), 120.1 (CH), 117.1 (CH), 113.3 (CH), 111.5 (C), 111.2 (CH), 100.6 (CH), 67.2 (CH<sub>2</sub>), 60.5 (CH<sub>2</sub>), 14.1 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>29</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup> 464.1969, found 464.1970.

#### 4.1.23. Ethyl 3-((6-(benzyloxy)-5-(1H-indol-4-yl)pyridin-3-yl)amino)benzoate (**25**)

Compound **25** was prepared according to general procedure B, starting from **8** (250 mg, 0.585 mmol). The mixture was refluxed for 14 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 15:85) to give **25** (212.9 mg, 0.459 mmol, 79%) as a beige solid. *R*<sub>f</sub> = 0.16 (EtOAc/cyclohexane 2:8); Mp > 186 °C (decomposition); IR (ATR) 3345, 3177, 1697, 1436, 1300, 1223, 746 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.20 (s, 1H), 8.33 (s, 1H), 8.05 (d, *J* = 2.8 Hz, 1H), 7.61 (d, *J* = 2.8 Hz, 1H), 7.58–7.56 (m, 1H), 7.43–7.19 (m, 10H), 7.16–7.11 (m, 2H), 6.34 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 2.0 Hz, *J*<sub>3</sub> = 1.0 Hz, 1H), 5.37 (s, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 165.9 (C=O), 155.3 (C), 145.3 (C), 137.6 (C), 136.4 (CH), 136.1 (C), 133.2 (C), 132.3 (CH), 130.9 (C), 129.7 (CH), 128.1 (2CH), 127.7 (C), 127.5 (2CH), 127.4 (CH), 126.5 (C), 125.6 (CH), 123.9 (C), 120.7 (CH), 120.1 (CH), 119.3 (CH), 119.2 (CH), 114.7 (CH), 111.2 (CH), 100.5 (CH), 67.0 (CH<sub>2</sub>), 60.7 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>29</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup> 464.1969, found 464.1974.

#### 4.1.24. Ethyl 4-((6-(benzyloxy)-5-(1H-indol-4-yl)pyridin-3-yl)amino)benzoate (**26**)

Compound **26** was prepared according to general procedure B, starting from **9** (152 mg, 0.356 mmol). The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 2:8) to give **26** (144.5 mg, 0.312 mmol, 88%) as a light yellow solid. *R*<sub>f</sub> = 0.3 (EtOAc/cyclohexane 3:7); Mp > 188 °C (decomposition); IR (ATR) 3390, 3314, 1683, 1597, 1456, 1283, 1229, 1174, 1120, 980, 746, 697 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.20 (s, 1H), 8.69 (s, 1H), 8.11 (d, *J* = 2.7 Hz, 1H), 7.79 (d, *J* = 8.9 Hz, 2H), 7.64 (d, *J* = 2.7 Hz, 1H), 7.43–7.22 (m, 6H), 7.38 (t, *J* = 2.8 Hz, 1H), 7.17–7.11 (m, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.32 (ddd, *J*<sub>1</sub> = 2.9 Hz, *J*<sub>2</sub> = 1.9 Hz, *J*<sub>3</sub> = 0.8 Hz, 1H), 5.38 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 165.6 (C=O), 156.0 (C), 149.5 (C), 137.7 (CH), 137.5 (C), 136.0 (C), 133.5 (CH), 132.0 (C), 131.2 (2CH), 128.2 (2CH), 127.53 (C), 127.50 (2CH), 127.4 (CH), 126.5 (C), 125.6 (CH), 124.0 (C), 120.7 (CH), 120.1 (CH), 119.0 (C), 113.1 (2CH), 111.2 (CH), 100.5 (CH), 67.1 (CH<sub>2</sub>), 59.9 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>29</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup> 464.1969, found 464.1966.

#### 4.1.25. 6-(Benzyloxy)-5-(1H-indol-4-yl)-N-(2-methoxyphenyl)pyridin-3-amine (**27**)

Compound **27** was prepared according to general procedure B, starting from **10** (200 mg, 0.519 mmol). The mixture was refluxed for 3 h. The crude oil was purified by two successive chromatography columns (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 2:8 and SiO<sub>2</sub>, Et<sub>2</sub>O/pentane 1:9 to 7:3) to give **27** (175.5 mg, 0.416 mmol, 80%) as a white powder. *R*<sub>f</sub> = 0.20 (EtOAc/cyclohexane 2:8); Mp 73 °C; IR (ATR) 3402, 1595, 1507, 1446, 1228, 1114, 1022, 736, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.18 (s, 1H), 8.00 (d, *J* = 2.7 Hz, 1H), 7.56 (d, *J* = 2.8 Hz, 1H), 7.41–7.21 (m, 8H), 7.15–7.10 (m, 2H), 7.07–7.03 (m, 1H), 6.99–6.95 (m, 1H), 6.83–6.77 (m, 2H), 6.32 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 2.0 Hz, *J*<sub>3</sub> = 0.9 Hz, 1H), 5.34 (s, 2H), 3.84 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 154.7 (C), 148.6 (C), 137.8 (C), 136.0 (C), 135.8 (CH), 134.3 (C), 133.5 (C), 131.7 (CH), 128.2 (2CH), 128.0 (C), 127.5 (2CH), 127.3 (CH), 126.6 (C), 125.5 (CH), 123.5 (C), 120.8 (CH), 120.7 (CH), 120.1 (CH), 119.8 (CH), 114.3 (CH), 111.3 (CH), 111.0 (CH), 100.7 (CH), 66.9 (CH<sub>2</sub>), 55.5 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>27</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> 422.1863, found 422.1865.

#### 4.1.26. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)-*N*-(3-methoxyphenyl)pyridin-3-amine (**28**)

Compound **28** was prepared according to general procedure B, starting from **11** (125.4 mg, 0.325 mmol). The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, pentane/Et<sub>2</sub>O 9:1 to 45:55) to give **28** (116 mg, 0.275 mmol, 85%) as a pink powder. *R*<sub>f</sub> = 0.14 (EtOAc/cyclohexane 2:8); Mp > 53 °C (decomposition); IR (ATR) 3390, 1594, 1494, 1445, 1226, 1154, 750, 692 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.19 (s, 1H), 8.07 (s, 1H), 8.01 (d, *J* = 2.8 Hz, 1H), 7.58 (d, *J* = 2.8 Hz, 1H), 7.42–7.21 (m, 6H), 7.36 (t, *J* = 2.8 Hz, 1H), 7.16–7.11 (m, 2H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.56 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 1.9 Hz, 1H), 6.51 (t, *J* = 2.2 Hz, 1H), 6.35 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 2.3 Hz, 1H), 6.32–6.30 (m, 1H), 5.35 (s, 2H), 3.70 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 160.4 (C), 154.9 (C), 145.9 (C), 137.7 (C), 136.0 (C), 135.7 (CH), 133.9 (C), 131.6 (CH), 130.1 (CH), 128.1 (2CH), 127.8 (C), 127.4 (2CH), 127.3 (CH), 126.5 (C), 125.5 (CH), 123.7 (C), 120.7 (CH), 120.0 (CH), 111.1 (CH), 107.6 (CH), 104.5 (CH), 100.8 (CH), 100.5 (CH), 66.9 (CH<sub>2</sub>), 54.8 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>27</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> 422.1863, found 422.1862.

#### 4.1.27. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)-*N*-(4-methoxyphenyl)pyridin-3-amine (**29**)

Compound **29** was prepared according to general procedure B, starting from **12** (192 mg, 0.498 mmol). The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 9:1 to 15:85) to give **29** (196 mg, 0.465 mmol, 93%) as a grey solid. *R*<sub>f</sub> = 0.16 (EtOAc/cyclohexane 2:8); Mp > 61 °C (decomposition); IR (ATR) 3391, 1508, 1446, 1224, 1022, 751, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.17 (s, 1H), 7.90 (d, *J* = 2.8 Hz, 1H), 7.75 (s, 1H), 7.45 (d, *J* = 2.8 Hz, 1H), 7.38 (ddd, *J*<sub>1</sub> = 7.1 Hz, *J*<sub>2</sub> = 2.0 Hz, *J*<sub>3</sub> = 0.9 Hz, 1H), 7.35 (dd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 2.5 Hz, 1H), 7.33–7.20 (m, 5H), 7.15–7.08 (m, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.29 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 2.0 Hz, *J*<sub>3</sub> = 1.0 Hz, 1H), 5.32 (s, 2H), 3.68 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 153.8 (C), 153.4 (C), 137.9 (C), 137.2 (C), 136.0 (2C), 132.9 (CH), 129.1 (CH), 128.14 (C), 128.11 (2CH), 127.4 (2CH), 127.3 (CH), 126.5 (C), 125.5 (CH), 123.6 (C), 120.7 (CH), 120.0 (CH), 118.7 (2CH), 114.7 (2CH), 111.0 (CH), 100.6 (CH), 66.8 (CH<sub>2</sub>), 55.2 (CH<sub>3</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>27</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> 422.1863, found 422.1867.

#### 4.1.28. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)-*N*-(2-nitrophenyl)pyridin-3-amine (**30**)

Compound **30** was prepared according to general procedure B, starting from **13** (248 mg, 0.620 mmol). The mixture was refluxed for 14 h 20 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 2:8) to give **30** (234 mg, 0.536 mmol, 87%) as an orange solid. *R*<sub>f</sub> = 0.24 (cyclohexane/EtOAc 8:2); Mp 87 °C; IR (ATR) 3414, 3347, 3177, 1615, 1571, 1495, 1345, 1260, 1218, 735, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.20 (s, 1H), 9.43 (s, 1H), 8.20 (d, *J* = 2.7 Hz, 1H), 8.12 (dd, *J*<sub>1</sub> = 8.6 Hz, *J*<sub>2</sub> = 1.6 Hz, 1H), 7.76 (d, *J* = 2.7 Hz, 1H), 7.51 (ddd, *J*<sub>1</sub> = 8.6 Hz, *J*<sub>2</sub> = 6.7 Hz, *J*<sub>3</sub> = 1.6 Hz, 1H), 7.41 (ddd, *J*<sub>1</sub> = 7.3 Hz, *J*<sub>2</sub> = 1.7 Hz, *J*<sub>3</sub> = 1.0 Hz, 1H), 7.38–7.23 (m, 6H), 7.19–7.12 (m, 2H), 7.08 (dd, *J*<sub>1</sub> = 8.7 Hz, *J*<sub>2</sub> = 1.2 Hz, 1H), 6.84 (ddd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 6.9 Hz, *J*<sub>3</sub> = 1.2 Hz, 1H), 6.37 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 1.9 Hz, *J*<sub>3</sub> = 0.8 Hz, 1H), 5.42 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 157.7 (C), 143.4 (C), 142.3 (CH), 137.6 (CH), 137.3 (C), 136.2 (CH), 136.0 (C), 132.9 (C), 130.0 (C), 128.2 (2CH), 127.53 (2CH), 127.49 (CH), 127.2 (C), 126.5 (C), 126.2 (CH), 125.6 (CH), 124.2 (C), 120.7 (CH), 120.1 (CH), 117.5 (CH), 116.2 (CH), 111.3 (CH), 100.6 (CH), 67.3 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>26</sub>H<sub>21</sub>N<sub>4</sub>O<sub>3</sub> (M+H)<sup>+</sup> 437.1608, found 437.1617.

#### 4.1.29. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)-*N*-(3-nitrophenyl)pyridin-3-amine (**31**)

Compound **31** was prepared according to general procedure B, starting from **14** (170 mg, 0.425 mmol). The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 25:75) to give **31** (180.7 mg, 0.414 mmol, 97%) as an orange solid. *R<sub>f</sub>* = 0.35 (cyclohexane/EtOAc 7:3); Mp > 189 °C (decomposition); IR (ATR) 3364, 1532, 1341, 983, 747, 735, 689 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.21 (s, 1H), 8.64 (s, 1H), 8.12 (d, *J* = 2.7 Hz, 1H), 7.70 (t, *J* = 2.2 Hz, 1H), 7.66 (d, *J* = 2.7 Hz, 1H), 7.55 (ddd, *J*<sub>1</sub> = 7.9 Hz, *J*<sub>2</sub> = 2.3 Hz, *J*<sub>3</sub> = 0.8 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.40 (ddd, *J*<sub>1</sub> = 6.7 Hz, *J*<sub>2</sub> = 2.3 Hz, *J*<sub>3</sub> = 0.8 Hz, 1H), 7.37 (t, *J* = 2.8 Hz, 1H), 7.36–7.22 (m, 6H), 7.18–7.11 (m, 2H), 6.36–6.34 (m, 1H), 5.39 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 156.0 (C), 148.8 (C), 146.6 (C), 137.5 (C+CH), 136.1 (C), 133.2 (CH), 132.2 (C), 130.6 (CH), 128.2 (2CH), 127.5 (2CH+C), 127.4 (CH), 126.5 (C), 125.6 (CH), 124.1 (C), 120.7 (CH), 120.4 (CH), 120.1 (CH), 112.6 (CH), 111.2 (CH), 107.5 (CH), 100.5 (CH), 67.1 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>26</sub>H<sub>21</sub>N<sub>4</sub>O<sub>3</sub> (M+H)<sup>+</sup> 437.1608, found 437.1614.

#### 4.1.30. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)-*N*-(4-nitrophenyl)pyridin-3-amine (**32**)

Compound **32** was prepared according to general procedure B, starting from **15** (188.9 mg, 0.472 mmol). The mixture was refluxed for 14 h 30 min. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 2:8 to 7:3) to give **32** (192.2 mg, 0.440 mmol, 93%) as a brown solid. *R<sub>f</sub>* = 0.25 (cyclohexane/EtOAc 7:3); Mp 238 °C; IR (ATR) 3375, 1590, 1498, 1455, 1419, 1296, 1110, 1080, 1007, 837, 750, 735 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.21 (s, 1H), 9.24 (s, 1H), 8.17 (d, *J* = 2.7 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 2H), 7.69 (d, *J* = 2.7 Hz, 1H), 7.41 (ddd, *J*<sub>1</sub> = 7.0 Hz, *J*<sub>2</sub> = 2.1 Hz, *J*<sub>3</sub> = 0.9 Hz, 1H), 7.38 (t, *J* = 2.8 Hz, 1H), 7.36–7.22 (m, 5H), 7.18–7.12 (m, 2H), 6.99 (d, *J* = 9.3 Hz, 2H), 6.34–6.32 (m, 1H), 5.40 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 156.8 (C), 151.8 (C), 139.1 (CH), 137.8 (C), 137.4 (C), 136.0 (C), 134.5 (CH), 130.9 (C), 128.2 (2CH), 127.53 (2CH), 127.47 (CH), 127.3 (C), 126.5 (C), 126.3 (2CH), 125.7 (CH), 124.3 (C), 120.7 (CH), 120.2 (CH), 112.7 (2CH), 111.3 (CH), 100.5 (CH), 67.2 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>26</sub>H<sub>21</sub>N<sub>4</sub>O<sub>3</sub> (M+H)<sup>+</sup> 437.1608, found 437.1614.

#### 4.1.31. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)-*N*-(*o*-tolyl)pyridin-3-amine (**33**)

Compound **33** was prepared according to general procedure B, starting from **16** (120 mg, 0.325 mmol). The mixture was refluxed for 16 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 15:85) to give **33** (103 mg, 0.254 mmol, 78%) as a brown solid. *R<sub>f</sub>* = 0.45 (EtOAc/cyclohexane 2:8); Mp > 58 °C (decomposition); IR (ATR) 3406, 1585, 1498, 1443, 1350, 1229, 746, 695 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.17 (s, 1H), 7.91 (d, *J* = 2.8 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.40–7.21 (m, 7H), 7.35 (dd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 2.6 Hz, 1H), 7.16–7.10 (m, 3H), 7.09–7.03 (m, 2H), 6.81–6.76 (m, 1H), 6.30 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 1.9 Hz, *J*<sub>3</sub> = 0.9 Hz, 1H), 5.34 (s, 2H), 2.24 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 154.5 (C), 142.7 (C), 137.8 (C), 136.0 (C), 135.3 (C), 135.2 (CH), 131.2 (CH), 130.8 (CH), 128.1 (2CH), 128.0 (C), 127.4 (2CH), 127.3 (CH), 127.1 (C), 126.6 (CH), 126.5 (C), 125.5 (CH), 123.6 (C), 120.7 (CH), 120.5 (CH), 120.0 (CH), 116.2 (CH), 111.0 (CH), 100.6 (CH), 66.9 (CH<sub>2</sub>), 18.0 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>27</sub>H<sub>24</sub>N<sub>3</sub>O (M+H)<sup>+</sup> 406.1914, found 406.1916.

#### 4.1.32. *N*-(6-(Benzyloxy)-5-(1*H*-indol-4-yl)pyridin-3-yl)pyridin-2-amine (**34**)

Compound **34** was prepared according to general procedure B, starting from **17** (139 mg, 0.390 mmol). The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 3:7). CH<sub>2</sub>Cl<sub>2</sub> was added to the product and the solution was washed with aqueous saturated NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub> and filtered. Evaporation gave compound **34** (135 mg, 0.344 mmol, 88%) as a light green solid. *R*<sub>f</sub> = 0.17 (EtOAc/cyclohexane 3:7); Mp 98 °C; IR (ATR) 3396, 1599, 1439, 1423, 1352, 1227, 987, 751, 732, 695 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.18 (s, 1H), 9.03 (s, 1H), 8.45 (d, *J* = 2.7 Hz, 1H), 8.21 (d, *J* = 2.7 Hz, 1H), 8.08 (ddd, *J*<sub>1</sub> = 5.0 Hz, *J*<sub>2</sub> = 1.9 Hz, *J*<sub>3</sub> = 0.8 Hz, 1H), 7.55 (ddd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 7.1 Hz, *J*<sub>3</sub> = 2.0 Hz, 1H), 7.43–7.21 (m, 6H), 7.37 (dd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 2.5 Hz, 1H), 7.17–7.12 (m, 2H), 6.78 (dt, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 6.70 (ddd, *J*<sub>1</sub> = 7.1 Hz, *J*<sub>2</sub> = 5.0 Hz, *J*<sub>3</sub> = 1.0 Hz, 1H), 6.40 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 1.9 Hz, *J*<sub>3</sub> = 0.9 Hz, 1H), 5.36 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 155.9 (C), 154.4 (C), 147.2 (CH), 137.9 (C), 137.3 (CH), 136.1 (C), 134.9 (CH), 132.9 (C), 131.3 (CH), 128.13 (C), 128.12 (2CH), 127.4 (2CH), 127.3 (CH), 126.7 (C), 125.5 (CH), 122.8 (C), 120.7 (CH), 120.1 (CH), 114.1 (CH), 111.0 (CH), 110.3 (CH), 100.7 (CH), 66.8 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>25</sub>H<sub>21</sub>N<sub>4</sub>O (M+H)<sup>+</sup> 393.1710, found 393.1722.

#### 4.1.33. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)-*N*-(pyridin-3-yl)pyridin-3-amine (**35**)

Compound **35** was prepared according to general procedure B, starting from **18** (150 mg, 0.421 mmol). The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 6:4). CH<sub>2</sub>Cl<sub>2</sub> was added to the product and the solution was washed with aqueous saturated NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub> and filtered. Evaporation gave compound **35** (156 mg, 0.397 mmol, 94%) as a green solid. *R*<sub>f</sub> = 0.21 (EtOAc/cyclohexane 6:4); Mp > 79 °C (decomposition); IR (ATR) 3374, 1579, 1447, 1423, 1229, 751, 694 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.20 (br s, 1H), 8.29 (d, *J* = 2.7 Hz, 1H), 8.26 (s, 1H), 8.06 (d, *J* = 2.8 Hz, 1H), 7.97 (dd, *J*<sub>1</sub> = 4.6 Hz, *J*<sub>2</sub> = 1.3 Hz, 1H), 7.68–7.51 (m, 1H), 7.59 (d, *J* = 2.8 Hz, 1H), 7.44–7.09 (m, 10H), 6.31 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 1.9 Hz, *J*<sub>3</sub> = 0.8 Hz, 1H), 5.36 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 155.3 (C), 141.1 (C), 139.9 (CH), 138.0 (CH), 137.6 (C), 136.0 (C), 135.8 (CH), 133.1 (C), 131.7 (CH), 128.1 (2CH), 127.7 (C), 127.5 (2CH), 127.4 (CH), 126.5 (C), 125.6 (CH), 124.0 (C), 123.9 (CH), 120.7 (CH), 120.6 (CH), 120.1 (CH), 111.2 (CH), 100.5 (CH), 67.0 (CH<sub>2</sub>); HRMS (ESI<sup>+</sup>) calcd for C<sub>25</sub>H<sub>21</sub>N<sub>4</sub>O (M+H)<sup>+</sup> 393.1710, found 393.1708.

#### 4.1.34. 6-(Benzyloxy)-5-(1*H*-indol-4-yl)-*N*-(pyridin-4-yl)pyridin-3-amine (**36**)

Compound **36** was prepared according to general procedure B, starting from **19** (117 mg, 0.328 mmol). The mixture was refluxed for 16 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, acetone/cyclohexane + 0.1% NEt<sub>3</sub> 5:5 to 7:3). CH<sub>2</sub>Cl<sub>2</sub> was added to the product and the solution was washed with aqueous saturated NaHCO<sub>3</sub> solution, dried over MgSO<sub>4</sub> and filtered. Evaporation gave compound **36** (82.9 mg, 0.211 mmol, 64%) as an orange solid. *R*<sub>f</sub> = 0.34 (EtOAc/cyclohexane 7:3 + 0.1% NEt<sub>3</sub>); Mp 90 °C; IR (ATR) 3500–3000, 1593, 1512, 1445, 1353, 1214, 995, 816, 752, 733 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.21 (s, 1H), 8.69 (s, 1H), 8.17–8.14 (m, 2H), 8.11 (d, *J* = 2.7 Hz, 1H), 7.64 (d, *J* = 2.7 Hz, 1H), 7.43–7.22 (m, 6H), 7.37 (dd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 2.6 Hz, 1H), 7.17–7.12 (m, 2H), 6.82–6.79 (m, 2H), 6.32 (ddd, *J*<sub>1</sub> = 2.9 Hz, *J*<sub>2</sub> = 1.9 Hz, *J*<sub>3</sub> = 0.9 Hz, 1H), 5.39 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 156.3 (C), 151.1 (C), 150.1 (2CH), 138.4 (CH), 137.5 (C), 136.0 (C), 134.0 (CH), 131.2 (C), 128.2 (2CH), 127.5 (2CH), 127.46 (C), 127.44 (CH), 126.5 (C), 125.7 (CH), 124.1 (C), 120.7 (CH), 120.1 (CH), 111.3

(CH), 108.5 (2CH), 100.5 (CH), 67.1 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>25</sub>H<sub>21</sub>N<sub>4</sub>O (M+H)<sup>+</sup> 393.1710, found 393.1710.

#### 4.1.35. 4-(2-(Benzyloxy)-5-nitropyridin-3-yl)-1H-indole (**38**)

Compound **38** was prepared according to general procedure B, starting from **37** (1 g, 3.24 mmol). The mixture was refluxed for 14 h 30 min. The crude oil was purified by three column chromatographies (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 15:85; SiO<sub>2</sub>, cyclohexane/Et<sub>2</sub>O 9:1 to 75:25; SiO<sub>2</sub>; cyclohexane/acetone 75:25) to give **38** (899.9 mg, 2.61 mmol, 81%) as an orange solid. *R*<sub>f</sub> = 0.25 (EtOAc/cyclohexane 2:8); Mp 161 °C; IR (ATR) 3277, 1584, 1506, 1332, 1303, 1215, 998, 758, 719 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.30 (s, 1H), 9.13 (d, *J* = 2.8 Hz, 1H), 8.47 (d, *J* = 2.8 Hz, 1H), 7.47 (dd, *J*<sub>1</sub> = 6.8 Hz, *J*<sub>2</sub> = 2.1 Hz, 1H), 7.41 (t, *J* = 2.8 Hz, 1H), 7.37–7.24 (m, 5H), 7.21–7.15 (m, 2H), 6.35–6.33 (m, 1H), 5.55 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 163.4 (C), 142.5 (CH), 139.6 (C), 136.2 (C), 136.1 (C), 134.1 (CH), 128.3 (2CH), 127.9 (CH), 127.8 (2CH), 126.4 (C), 126.1 (CH), 125.5 (C), 124.2 (C), 120.8 (CH), 120.2 (CH), 112.1 (CH), 100.2 (CH), 68.8 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>20</sub>H<sub>16</sub>N<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup> 346.1186, found 346.1195.

#### 4.1.36. 6-(Benzyloxy)-5-(1H-indol-4-yl)pyridin-3-amine (**39**)

To a solution of compound **38** (72 mg, 0.208 mmol, 1 equiv) in a 10:1 propan-2-ol/water mixture (4.4 mL) were added Fe powder (70.5 mg, 1.26 mmol, 6.1 equiv) and NH<sub>4</sub>Cl (4.5 mg, 0.084 mmol, 0.4 equiv). The mixture was refluxed for 1 h 30 min. Then, the mixture was filtered through a Celite pad and the solid was washed with EtOAc. The filtrate was washed with water, and the aqueous phase was extracted with EtOAc. The organic phase was dried over MgSO<sub>4</sub>, filtered and then evaporated. The obtained orange oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 3:7 to 5:5) to give **39** (46 mg, 0.146 mmol, 70%) as a brown solid. *R*<sub>f</sub> = 0.13 (EtOAc/cyclohexane 3:7); Mp 68 °C; IR (ATR) 3404, 1608, 1582, 1455, 1423, 1407, 1355, 1220, 751, 731, 695 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.13 (s, 1H), 7.54 (d, *J* = 2.8 Hz, 1H), 7.36 (dt, *J*<sub>1</sub> = 8.1 Hz, *J*<sub>2</sub> = 1.0 Hz, 1H), 7.33 (t, *J* = 2.8 Hz, 1H), 7.29–7.18 (m, 5H), 7.15 (d, *J* = 2.8 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.05 (dd, *J*<sub>1</sub> = 7.3 Hz, *J*<sub>2</sub> = 1.1 Hz, 1H), 6.27 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 1.9 Hz, *J*<sub>3</sub> = 1.0 Hz, 1H), 5.24 (s, 2H), 4.85 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 152.0 (C), 139.7 (C), 138.2 (C), 136.0 (C), 129.8 (CH), 128.7 (C), 128.0 (2CH), 127.3 (2CH), 127.1 (CH), 126.9 (CH), 126.6 (C), 125.2 (CH), 123.3 (C), 120.6 (CH), 119.9 (CH), 110.7 (CH), 100.8 (CH), 66.5 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O (M+H)<sup>+</sup> 316.1444, found 316.1446.

#### 4.1.37. 6-(Benzyloxy)-N-(2-bromophenyl)-5-(1H-indol-4-yl)pyridin-3-amine (**40**)

Compound **40** was prepared according to general procedure A, starting from **39** (149.5 mg, 0.474 mmol). The mixture was heated for 24 h. Pd(OAc)<sub>2</sub> (0.05 equiv) was added and the mixture was heated for 48 h. PdOAc (0.05 equiv) and Xantphos (0.05 equiv) were added and the mixture was heated for 72 h. The crude oil was purified by two successive chromatography columns (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 15:85 and SiO<sub>2</sub>, pentane/Et<sub>2</sub>O 9:1 to 8:2) to give **40** (105.8 mg, 0.225 mmol, 47%) as a white solid. *R*<sub>f</sub> = 0.42 (EtOAc/cyclohexane 3:7); Mp 74 °C; IR (ATR) 3384, 3500–3100, 1593, 1494, 1441, 1353, 1021, 744, 728, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.18 (s, 1H), 8.03 (d, *J* = 2.8 Hz, 1H), 7.57 (d, *J* = 2.7 Hz, 1H), 7.55 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 1.5 Hz, 1H), 7.46 (s, 1H), 7.41–7.18 (m, 7H), 7.36 (dd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 2.5 Hz, 1H), 7.15–7.10 (m, 2H), 7.06 (dd, *J*<sub>1</sub> = 8.2 Hz, *J*<sub>2</sub> = 1.6 Hz, 1H), 6.79–6.74 (m, 1H), 6.33 (ddd, *J*<sub>1</sub> = 3.0 Hz, *J*<sub>2</sub> = 2.0 Hz,

$J_3 = 0.9$  Hz, 1H), 5.37 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 155.6 (C), 142.9 (C), 137.8 (CH), 137.6 (C), 136.0 (C), 133.5 (CH), 133.3 (C), 133.2 (CH), 128.6 (CH), 128.1 (2CH), 127.7 (C), 127.5 (2CH), 127.4 (CH), 126.5 (C), 125.5 (CH), 123.8 (C), 121.1 (CH), 120.7 (CH), 120.1 (CH), 116.5 (CH), 111.9 (C), 111.1 (CH), 100.6 (CH), 67.0 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>26</sub>H<sub>21</sub>BrN<sub>3</sub>O (M+H)<sup>+</sup> 470.0863, found 470.0864.

#### 4.1.38. 6-(Benzyloxy)-N-(3-bromophenyl)-5-(1H-indol-4-yl)pyridin-3-amine (**41**)

Compound **41** was prepared according to general procedure A, starting from **39** (150.2 mg, 0.476 mmol). The mixture was heated for 5 h. The crude oil was purified by column chromatography (SiO<sub>2</sub>, EtOAc/cyclohexane 1:9 to 15:85) to give **41** (104.1 mg, 0.221 mmol, 46%) as an orange solid.  $R_f = 0.52$  (EtOAc/cyclohexane 3:7); Mp > 155 °C (decomposition); IR (ATR) 3383, 1589, 1446, 1421, 1406, 1229, 989, 751, 695 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 11.21 (s, 1H), 8.28 (s, 1H), 8.04 (d,  $J = 2.8$  Hz, 1H), 7.60 (d,  $J = 2.8$  Hz, 1H), 7.42–7.37 (m, 1H), 7.37 (t,  $J = 2.8$  Hz, 1H), 7.35–7.21 (m, 5H), 7.16–7.11 (m, 3H), 7.08 (t,  $J = 2.1$  Hz, 1H), 6.93 (ddd,  $J_1 = 8.3$  Hz,  $J_2 = 2.3$  Hz,  $J_3 = 0.9$  Hz, 1H), 6.89 (ddd,  $J_1 = 7.9$  Hz,  $J_2 = 1.9$  Hz,  $J_3 = 0.9$  Hz, 1H), 6.32 (ddd,  $J_1 = 3.0$  Hz,  $J_2 = 2.0$  Hz,  $J_3 = 1.0$  Hz, 1H), 5.37 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 155.5 (C), 146.8 (C), 137.6 (C), 136.8 (CH), 136.1 (C), 132.8 (C), 132.6 (CH), 131.2 (CH), 128.2 (2CH), 127.6 (C), 127.5 (2CH), 127.4 (CH), 126.5 (C), 125.6 (CH), 123.9 (C), 122.4 (C), 121.0 (CH), 120.7 (CH), 120.1 (CH), 116.7 (CH), 113.4 (CH), 111.2 (CH), 100.4 (CH), 67.0 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>26</sub>H<sub>21</sub>BrN<sub>3</sub>O (M+H)<sup>+</sup> 470.0863, found 470.0865.

#### 4.1.39. 6-(Benzyloxy)-N-(4-bromophenyl)-5-(1H-indol-4-yl)pyridin-3-amine (**42**)

Compound **42** was prepared according to general procedure A, starting from **39** (150.8 mg, 0.478 mmol). The mixture was heated for 5 h. The crude oil was purified by two successive chromatography columns (SiO<sub>2</sub>, cyclohexane to EtOAc/cyclohexane 2:8 and SiO<sub>2</sub>, pentane/Et<sub>2</sub>O 9:1 to 8:2) to give **42** (103.8 mg, 0.221 mmol, 46%) as a beige solid.  $R_f = 0.35$  (EtOAc/cyclohexane 3:7); Mp 161 °C; IR (ATR) 3398, 3171, 1586, 1496, 1447, 1353, 1225, 1007, 748, 724, 688 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 11.19 (s, 1H), 8.21 (s, 1H), 8.03 (d,  $J = 2.8$  Hz, 1H), 7.57 (d,  $J = 2.8$  Hz, 1H), 7.42–7.21 (m, 8H), 7.36 (dd,  $J_1 = 3.1$  Hz,  $J_2 = 2.5$  Hz, 1H), 7.16–7.11 (m, 2H), 6.92 (d,  $J = 8.9$  Hz, 2H), 6.30 (ddd,  $J_1 = 3.0$  Hz,  $J_2 = 2.0$  Hz,  $J_3 = 1.0$  Hz, 1H), 5.36 (s, 2H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 155.2 (C), 144.2 (C), 137.6 (C), 136.1 (CH), 136.0 (C), 133.4 (C), 132.0 (CH), 131.9 (2CH), 128.1 (2CH), 127.7 (C), 127.5 (2CH), 127.4 (CH), 126.5 (C), 125.6 (CH), 123.9 (C), 120.7 (CH), 120.1 (CH), 116.8 (2CH), 111.1 (CH), 109.4 (C), 100.5 (CH), 67.0 (CH<sub>2</sub>); HRMS (ESI+) calcd for C<sub>26</sub>H<sub>21</sub>BrN<sub>3</sub>O (M+H)<sup>+</sup> 470.0863, found 470.0869.

#### 4.1.40. 5-((2-Fluorophenyl)amino)-3-(1H-indol-4-yl)pyridin-2(1H)-one (**43**)

Compound **43** was prepared according to general procedure C1, starting from **21** (65.0 mg, 0.159 mmol) and with 3.2 equiv of BBr<sub>3</sub>. The mixture was stirred for 1 h and was quenched with NEt<sub>3</sub> (12 equiv) and MeOH (4 equiv). The crude was purified by column chromatography (SiO<sub>2</sub>, EtOAc + 0.5% NEt<sub>3</sub>) to give **43** (41 mg, 0.128 mmol, 81%) as a beige solid.  $R_f = 0.22$  (EtOAc); Mp > 141 °C (decomposition); IR (ATR) 3353, 1649, 1609, 1505, 1337, 881, 739 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 11.61 (br s, 1H), 11.13 (s, 1H), 7.54 (d,  $J = 2.9$  Hz, 1H), 7.39 (d,  $J = 1.6$  Hz, 1H), 7.36 (dt,  $J_1 = 8.1$  Hz,  $J_2 = 0.9$  Hz, 1H), 7.34 (t,  $J = 2.8$  Hz, 1H), 7.28 (dd,  $J_1 = 7.3$  Hz,  $J_2 = 1.0$  Hz, 1H), 7.23 (d,  $J = 2.9$  Hz, 1H), 7.12 (ddd,  $J_1 = 12.2$  Hz,  $J_2 = 8.1$  Hz,  $J_3 = 1.4$  Hz, 1H), 7.10 (t,  $J = 7.7$  Hz, 1H), 7.00 (td,  $J_1 = 7.7$  Hz,  $J_2 = 1.4$  Hz, 1H), 6.89 (td,  $J_1 = 8.5$  Hz,  $J_2 = 1.6$  Hz, 1H), 6.74–



6.67 (m, 1H), 6.40–6.38 (m, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 159.7 (C), 151.5 (d, *J*<sub>CF</sub> = 240 Hz, C), 138.4 (CH), 136.1 (C), 134.7 (d, *J*<sub>CF</sub> = 11 Hz, C), 130.5 (C), 128.3 (C), 127.6 (CH), 126.1 (C), 125.3 (CH), 124.8 (d, *J*<sub>CF</sub> = 3 Hz, CH), 121.7 (C), 120.4 (CH), 119.9 (CH), 118.2 (d, *J*<sub>CF</sub> = 7 Hz, CH), 115.3 (d, *J*<sub>CF</sub> = 18 Hz, CH), 114.6 (d, *J*<sub>CF</sub> = 3 Hz, CH), 110.9 (CH), 100.6 (CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>15</sub>FN<sub>3</sub>O (M+H)<sup>+</sup> 320.1194, found 320.1195; HPLC purity ≥ 96%, *t*<sub>R</sub> = 7.93 min, λ = 272 nm.

#### 4.1.41. 5-((3-Fluorophenyl)amino)-3-(1*H*-indol-4-yl)pyridin-2(1*H*)-one (**44**)

Compound **44** was prepared according to general procedure C1, starting from **22** (91.0 mg, 0.222 mmol) and with 3 equiv of BBr<sub>3</sub>. The mixture was stirred for 3 h and was quenched with NEt<sub>3</sub> (10 equiv) and MeOH (6 equiv). The crude was filtered and washed with water, acetone and a mixture of CH<sub>2</sub>Cl<sub>2</sub> and cyclohexane to give **44** as a dark green solid (40.8 mg, 0.128 mmol, 57%). *R*<sub>f</sub> = 0.20 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); Mp > 166 °C; IR (ATR) 3181, 1651, 1602, 1139, 751 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.63 (br s, 1H), 11.14 (s, 1H), 7.78 (s, 1H), 7.50 (d, *J* = 3.0 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.34 (t, *J* = 2.8 Hz, 1H), 7.27 (dd, *J*<sub>1</sub> = 7.3 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.26 (br s, 1H), 7.16 (td, *J*<sub>1</sub> = 8.2 Hz, *J*<sub>2</sub> = 7.0 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.57 (dd, *J*<sub>1</sub> = 8.3 Hz, *J*<sub>2</sub> = 2.2 Hz, *J*<sub>3</sub> = 0.8 Hz, 1H), 6.48 (dt, *J*<sub>1</sub> = 11.9 Hz, *J*<sub>2</sub> = 2.3 Hz, 1H), 6.47–6.41 (m, 1H), 6.37–6.34 (m, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 163.3 (d, *J*<sub>CF</sub> = 240 Hz, C), 159.8 (C), 149.0 (d, *J*<sub>CF</sub> = 11 Hz, C), 138.6 (CH), 136.1 (C), 130.78 (C), 130.76 (d, *J*<sub>CF</sub> = 10 Hz, CH), 128.2 (C), 128.1 (CH), 126.1 (C), 125.4 (CH), 121.4 (C), 120.5 (CH), 119.9 (CH), 111.0 (CH), 109.6 (CH), 103.8 (d, *J*<sub>CF</sub> = 21 Hz, CH), 100.4 (CH), 99.9 (d, *J*<sub>CF</sub> = 25 Hz, CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>15</sub>FN<sub>3</sub>O (M+H)<sup>+</sup> 320.1194, found 320.1211; HPLC purity ≥ 95%, *t*<sub>R</sub> = 7.93 min, λ = 288 nm.

#### 4.1.42. 5-((4-Fluorophenyl)amino)-3-(1*H*-indol-4-yl)pyridin-2(1*H*)-one (**45**)

Compound **45** was prepared according to general procedure C2, starting from **23** (119 mg, 0.291 mmol) and 4.1 equiv of BBr<sub>3</sub>. The mixture was stirred for 15 h. The reaction mixture was then quenched by addition of NEt<sub>3</sub> (12 equiv) and MeOH (9 equiv). The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 to 95:5) to give **45** (64.9 mg, 0.203 mmol, 70%) as a beige solid. *R*<sub>f</sub> = 0.28 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); Mp > 146 °C (decomposition); IR (ATR) 3242, 1651, 1599, 1504, 1210, 754 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.55 (br s, 1H), 11.13 (s, 1H), 7.49 (d, *J* = 3.0 Hz, 1H), 7.45 (s, 1H), 7.36 (dt, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.34 (dd, *J*<sub>1</sub> = 3.2 Hz, *J*<sub>2</sub> = 2.5 Hz, 1H), 7.26 (dd, *J*<sub>1</sub> = 7.3 Hz, *J*<sub>2</sub> = 1.0 Hz, 1H), 7.18 (br s, 1H), 7.09 (dd, *J*<sub>1</sub> = 8.1 Hz, *J*<sub>2</sub> = 7.4 Hz, 1H), 7.00 (t, *J* = 8.9 Hz, 2H), 6.77 (dd, *J*<sub>1</sub> = 9.1 Hz, *J*<sub>2</sub> = 4.6 Hz, 2H), 6.35 (ddd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 2.0 Hz, *J*<sub>3</sub> = 0.9 Hz, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 159.5 (C=O), 155.4 (d, *J*<sub>CF</sub> = 234 Hz, C), 143.1 (d, *J*<sub>CF</sub> = 2 Hz, C), 138.0 (CH), 136.1 (C), 130.7 (C), 128.3 (C), 126.3 (CH), 126.1 (C), 125.3 (CH), 123.0 (C), 120.4 (CH), 119.9 (CH), 115.7 (d, *J*<sub>CF</sub> = 22 Hz, 2CH), 115.2 (d, *J*<sub>CF</sub> = 7.5 Hz, 2CH), 110.9 (CH), 100.5 (CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>15</sub>FN<sub>3</sub>O (M+H)<sup>+</sup> 320.1194, found 320.1176; HPLC purity ≥ 98%, *t*<sub>R</sub> = 7.89 min, λ = 276 nm.

#### 4.1.43. Ethyl 2-((5-(1*H*-indol-4-yl)-6-oxo-1,6-dihydropyridin-3-yl)amino)benzoate (**46**)

Compound **46** was prepared according to general procedure D, starting from **24** (104.6 mg, 0.226 mmol) in 2 mL of MeOH. The mixture was stirred for 6 h in the dark. The mixture was filtered through a Celite pad and the solid was washed with EtOAc and MeOH. After evaporation under reduced pressure, compound **46** (84 mg, 0.225 mmol, quant.) was obtained as an orange solid. *R*<sub>f</sub> = 0.35 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 + 0.5% NEt<sub>3</sub>); Mp > 263 °C (decomposition); IR (ATR) 3285, 1680,

1654, 1627, 1452, 1238, 750  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 11.79 (br s, 1H), 11.13 (s, 1H), 8.88 (s, 1H), 7.87 (dd,  $J_1 = 8.1$  Hz,  $J_2 = 1.7$  Hz, 1H), 7.51 (d,  $J = 3.0$  Hz, 1H), 7.43–7.37 (m, 2H), 7.36 (dt,  $J = 8.1$  Hz,  $J_2 = 0.9$  Hz, 1H), 7.33 (t,  $J = 2.8$  Hz, 1H), 7.26 (dd,  $J_1 = 7.4$  Hz,  $J_2 = 0.9$  Hz, 1H), 7.09 (t,  $J = 7.7$  Hz, 1H), 6.82 (dd,  $J_1 = 8.6$  Hz,  $J_2 = 0.9$  Hz, 1H), 6.72 (ddd,  $J_1 = 8.2$  Hz,  $J_2 = 7.2$  Hz,  $J_3 = 1.2$  Hz, 1H), 6.38–6.35 (m, 1H), 4.31 (q,  $J = 7.1$  Hz, 2H), 1.33 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 167.5 (C=O), 160.3 (C=O), 149.8 (C), 140.0 (CH), 136.1 (C), 134.6 (CH), 131.5 (CH), 131.2 (CH), 130.9 (C), 128.2 (C), 126.1 (C), 125.3 (CH), 120.4 (CH), 119.9 (CH), 119.3 (C), 116.4 (CH), 113.2 (CH), 110.9 (CH), 110.7 (C), 100.5 (CH), 60.4 ( $\text{CH}_2$ ), 14.2 ( $\text{CH}_3$ ); HRMS (ESI+) calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_3$  ( $\text{M}+\text{H}$ ) $^+$  374.1499, found 374.1490; HPLC purity  $\geq 96\%$ ,  $t_{\text{R}} = 8.65$  min,  $\lambda = 270$  nm.

#### 4.1.44. Ethyl 3-((5-(1H-indol-4-yl)-6-oxo-1,6-dihydropyridin-3-yl)amino)benzoate (**47**)

Compound **47** was prepared according to general procedure D, starting from **25** (169.3 mg, 0.365 mmol) in 4 mL of MeOH. The mixture was stirred for 20 h in the dark. The mixture was filtered through a pad of Celite and the solid was washed with EtOAc and MeOH. The obtained crude was purified by column chromatography ( $\text{NEt}_3$ -treated  $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5) to give **47** containing  $\text{NEt}_3$  salts. The product was washed with  $\text{CH}_2\text{Cl}_2$  to give **47** (72.1 mg, 0.193 mmol, 53%) as a beige solid.  $R_{\text{f}} = 0.35$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5 + 0.5%  $\text{NEt}_3$ ); Mp  $> 244$  °C (decomposition); IR (ATR) 3365, 3207, 1691, 1660, 1601, 1539, 1465, 1285, 846, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 11.61 (s, 1H), 11.15 (s, 1H), 7.82 (s, 1H), 7.50 (d,  $J = 2.9$  Hz, 1H), 7.38–7.25 (m, 7H), 7.10 (t,  $J = 7.7$  Hz, 1H), 7.02 (dt,  $J_1 = 6.6$  Hz,  $J_2 = 2.5$  Hz, 1H), 6.39 (ddd,  $J_1 = 3.0$  Hz,  $J_2 = 2.0$  Hz,  $J_3 = 1.0$  Hz, 1H), 4.28 (q,  $J = 7.1$  Hz, 2H), 1.29 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 166.0 (C=O), 159.8 (C=O), 147.2 (C), 138.5 (CH), 136.1 (C), 130.83 (C), 130.76 (C), 129.6 (CH), 128.2 (C), 127.8 (CH), 126.1 (C), 125.4 (CH), 121.6 (C), 120.4 (CH), 119.9 (CH), 118.4 (CH), 118.2 (CH), 113.5 (CH), 111.0 (CH), 100.4 (CH), 60.6 ( $\text{CH}_2$ ), 14.2 ( $\text{CH}_3$ ); HRMS (ESI+) calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_3$  ( $\text{M}+\text{H}$ ) $^+$  374.1499, found 374.1499; HPLC purity  $\geq 96\%$ ,  $t_{\text{R}} = 8.03$  min,  $\lambda = 278$  nm.

#### 4.1.45. Ethyl 4-((5-(1H-indol-4-yl)-6-oxo-1,6-dihydropyridin-3-yl)amino)benzoate (**48**)

Compound **48** was prepared according to general procedure D, starting from **26** (145.4 mg, 0.314 mmol) in 3 mL of MeOH. The mixture was stirred for 6 h 30 min in the dark. The mixture was filtered through a pad of Celite and the solid was washed with EtOAc and MeOH. The filtrate was evaporated under reduced pressure to give **48** (116.6 mg, 0.312 mmol, quant.) as a yellow-brown solid.  $R_{\text{f}} = 0.30$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5 + 0.5%  $\text{NEt}_3$ ); Mp  $> 255$  °C (decomposition); IR (ATR) 3500–3200, 3280, 1687, 1656, 1595, 1454, 1257, 1168, 1098, 756  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 11.57 (br s, 1H), 11.14 (s, 1H), 8.21 (s, 1H), 7.76 (d,  $J = 8.8$  Hz, 2H), 7.50 (d,  $J = 2.9$  Hz, 1H), 7.37–7.33 (m, 2H), 7.33 (br s, 1H), 7.28 (dd,  $J_1 = 7.3$  Hz,  $J_2 = 0.9$  Hz, 1H), 7.09 (t,  $J = 7.7$  Hz, 1H), 6.78 (d,  $J = 8.9$  Hz, 2H), 6.37–6.35 (m, 1H), 4.22 (q,  $J = 7.1$  Hz, 2H), 1.27 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 165.7 (C=O), 160.2 (C=O), 151.3 (C), 138.5 (CH), 136.1 (C), 131.2 (2CH), 130.6 (C), 129.4 (CH), 128.3 (C), 126.1 (C), 125.4 (CH), 120.44 (CH), 120.36 (C), 119.9 (CH), 118.1 (C), 112.3 (2CH), 110.9 (CH), 100.5 (CH), 59.8 ( $\text{CH}_2$ ), 14.3 ( $\text{CH}_3$ ); HRMS (ESI+) calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_3$  ( $\text{M}+\text{H}$ ) $^+$  374.1499, found 374.1486; HPLC purity  $\geq 98\%$ ,  $t_{\text{R}} = 7.95$  min,  $\lambda = 310$  nm.

#### 4.1.46. 3-(1H-Indol-4-yl)-5-((2-methoxyphenyl)amino)pyridin-2(1H)-one (**49**)

Compound **49** was prepared according to general procedure D, starting from **27** (148 mg, 0.351 mmol) in 3.6 mL of MeOH. The mixture was stirred for 6 h in the dark. The mixture was filtered through a pad of Celite and the solid was washed with EtOAc and MeOH. After evaporation under reduced pressure, the solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **49** (97.8 mg, 0.295 mmol, 84%) as a beige solid. *R*<sub>f</sub> = 0.51 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 240 °C (decomposition); IR (ATR) 3395, 3351, 3314, 1653, 1619, 1595, 1556, 1503, 1454, 1342, 1251, 1116, 1021, 738 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.51 (br s, 1H), 11.13 (s, 1H), 7.53 (d, *J* = 3.0 Hz, 1H), 7.35 (dt, *J*<sub>1</sub> = 8.1 Hz, *J*<sub>2</sub> = 1.0 Hz, 1H), 7.33 (t, *J* = 2.8 Hz, 1H), 7.27 (dd, *J*<sub>1</sub> = 7.4 Hz, *J*<sub>2</sub> = 1.0 Hz, 1H), 7.20 (br d, *J* = 2.8 Hz, 1H), 7.09 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 7.4 Hz, 1H), 6.91 (dd, *J*<sub>1</sub> = 8.0 Hz, *J*<sub>2</sub> = 1.4 Hz, 1H), 6.85 (s, 1H), 6.80–6.66 (m, 3H), 6.39–6.37 (m, 1H), 3.82 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 159.7 (C=O), 147.3 (C), 138.8 (CH), 136.1 (C), 136.0 (C), 130.3 (C), 128.4 (C), 127.5 (CH), 126.1 (C), 125.3 (CH), 122.2 (C), 120.8 (CH), 120.4 (CH), 119.9 (CH), 118.0 (CH), 111.9 (CH), 110.83 (CH), 110.82 (CH), 100.6 (CH), 55.4 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> 332.1394, found 332.1393; HPLC purity ≥ 97%, t<sub>R</sub> = 8.00 min, λ = 276 nm.

#### 4.1.47. 3-(1*H*-Indol-4-yl)-5-((3-methoxyphenyl)amino)pyridin-2(1*H*)-one (**50**)

Compound **50** was prepared according to general procedure D, starting from **28** (204.5 mg, 0.485 mmol) in 2 mL of MeOH. The mixture was stirred for 6 h in the dark. The mixture was filtered through a pad of Celite and the solid was washed with EtOAc and MeOH. After evaporation under reduced pressure, the solid was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **50** (129.3 mg, 0.390 mmol, 80%) as a brown solid. *R*<sub>f</sub> = 0.45 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 141 °C (decomposition); IR (ATR) 3500–3000, 1650, 1591, 1153, 752, 688 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.52 (br s, 1H), 11.14 (s, 1H), 7.52 (s, 1H), 7.51 (d, *J* = 3.0 Hz, 1H), 7.36 (dt, *J*<sub>1</sub> = 8.1 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.34 (t, *J* = 2.8 Hz, 1H), 7.26 (dd, *J*<sub>1</sub> = 7.3 Hz, *J*<sub>2</sub> = 1.0 Hz, 1H), 7.20 (br d, *J* = 2.6 Hz, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 8.1 Hz, 1H), 6.37–6.33 (m, 2H), 6.30 (t, *J* = 2.2 Hz, 1H), 6.27 (ddd, *J*<sub>1</sub> = 8.1 Hz, *J*<sub>2</sub> = 2.5 Hz, *J*<sub>3</sub> = 0.8 Hz, 1H), 3.68 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 160.4 (C=O), 159.6 (C), 148.0 (C), 138.5 (CH), 136.1 (C), 130.5 (C), 130.0 (CH), 128.3 (C), 127.0 (CH), 126.1 (C), 125.3 (CH), 122.3 (C), 120.5 (CH), 119.9 (CH), 110.9 (CH), 106.6 (CH), 103.4 (CH), 100.5 (CH), 99.7 (CH), 54.8 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> 332.1394, found 332.1392; HPLC purity ≥ 97%, t<sub>R</sub> = 7.81 min, λ = 278 nm.

#### 4.1.48. 3-(1*H*-Indol-4-yl)-5-((4-methoxyphenyl)amino)pyridin-2(1*H*)-one (**51**)

Compound **51** was prepared according to general procedure D, starting from **29** (100.6 mg, 0.239 mmol) in 1 mL of MeOH. The mixture was stirred for 6 h in the dark. The mixture was filtered through a pad of Celite and the solid was washed with EtOAc and MeOH. After evaporation under reduced pressure, compound **51** (78.4 mg, 0.237 mmol, 99%) was obtained as a red solid. *R*<sub>f</sub> = 0.39 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 132 °C (decomposition); IR (ATR) 3500–3000, 1651, 1605, 1506, 1233, 1036, 820, 756 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.44 (br s, 1H), 11.13 (s, 1H), 7.49 (d, *J* = 3.0 Hz, 1H), 7.37–7.33 (m, 2H), 7.25 (d, *J* = 7.3 Hz, 1H), 7.19 (s, 1H), 7.09 (br s, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.83–6.76 (m, 4H), 6.36–6.34 (m, 1H), 3.66 (s, 3H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 159.3 (C=O), 152.5 (C), 139.7 (C), 137.2 (CH), 136.1 (C), 130.5 (C), 128.5 (C), 126.1 (C), 125.3 (CH), 124.6 (C), 124.0 (CH), 120.4 (CH), 119.9 (CH), 116.5 (2CH), 114.7 (2CH), 110.8 (CH), 100.6 (CH), 55.3 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> 332.1394, found 332.1398; HPLC purity ≥ 96%, t<sub>R</sub> = 7.71 min, λ = 280 nm.

#### 4.1.49. 5-((3-hydroxyphenyl)amino)-3-(1H-indol-4-yl)pyridin-2(1H)-one (**52**)

Compound **52** was prepared according to general procedure C2, starting from **28** (103 mg, 0.244 mmol) and 4.1 equiv of BBr<sub>3</sub>. The mixture was stirred for 15 h. The reaction mixture was then quenched by addition of NEt<sub>3</sub> (13 equiv) and MeOH (10 equiv). The crude was purified by two successive chromatography columns (SiO<sub>2</sub>, EtOAc/MeOH 98:2 to 97:3 and SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 99:1 to 92:8) to give **52** (40 mg, 0.126 mmol, 52%) as a beige solid. *R*<sub>f</sub> = 0.12 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); Mp > 248 °C (decomposition); IR (ATR) 3500–3000, 1647, 1595, 1155, 751, 738, 684 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.51 (s, 1H), 11.13 (s, 1H), 9.09 (s, 1H), 7.52 (d, *J* = 2.9 Hz, 1H), 7.39 (s, 1H), 7.36 (dt, *J*<sub>1</sub> = 8.2 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.34 (t, *J* = 2.8 Hz, 1H), 7.27 (dd, *J*<sub>1</sub> = 7.3 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.17 (d, *J* = 3.0, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.92 (t, *J* = 8.3 Hz, 1H), 6.38–6.36 (m, 1H), 6.23–6.20 (m, 2H), 6.11–6.08 (m, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 159.6 (C=O), 158.3 (C), 147.9 (C), 138.6 (CH), 136.1 (C), 130.5 (C), 129.9 (CH), 128.3 (C), 126.7 (CH), 126.1 (C), 125.3 (CH), 122.6 (C), 120.4 (CH), 119.9 (CH), 110.9 (CH), 105.33 (CH), 105.27 (CH), 100.7 (CH), 100.6 (CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>16</sub>N<sub>3</sub>O<sub>2</sub> (M+H)<sup>+</sup> 318.1237, found 318.1233; HPLC purity ≥ 99%, *t*<sub>R</sub> = 7.06 min, λ = 280 nm.

#### 4.1.50. 3-(1H-Indol-4-yl)-5-((2-nitrophenyl)amino)pyridin-2(1H)-one (**53**)

Compound **53** was prepared according to general procedure C2, starting from **30** (119 mg, 0.273 mmol) and 3.7 equiv of BBr<sub>3</sub>. The mixture was stirred for 3 h 15 min. The reaction mixture was then quenched by addition of NEt<sub>3</sub> (13 equiv) and MeOH (5 equiv). The crude was purified by column chromatography (NEt<sub>3</sub>-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 to 95:5). To eliminate traces of NEt<sub>3</sub> salts, the product was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **53** (31 mg, 0.090 mmol, 33%) as an orange solid. *R*<sub>f</sub> = 0.33 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 268 °C (decomposition); IR (ATR) 3350, 3232, 1653, 1606, 1498, 1470, 1257, 744, 726, 696 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.87 (s, 1H), 11.13 (s, 1H), 9.18 (s, 1H), 8.10 (dd, *J*<sub>1</sub> = 8.5 Hz, *J*<sub>2</sub> = 1.6 Hz, 1H), 7.55 (d, *J* = 2.9 Hz, 1H), 7.53 (ddd, *J*<sub>1</sub> = 8.5 Hz, *J*<sub>2</sub> = 7.0 Hz, *J*<sub>3</sub> = 1.5 Hz, 1H), 7.48 (br s, 1H), 7.36 (dt, *J*<sub>1</sub> = 8.1 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.33 (dd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 2.5 Hz, 1H), 7.28 (dd, *J*<sub>1</sub> = 7.4 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.01 (dd, *J*<sub>1</sub> = 8.7 Hz, *J*<sub>2</sub> = 1.2 Hz, 1H), 6.81 (ddd, *J*<sub>1</sub> = 8.4 Hz, *J*<sub>2</sub> = 6.9 Hz, *J*<sub>3</sub> = 1.2 Hz, 1H), 6.42–6.40 (m, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 160.3 (C=O), 144.5 (C), 140.1 (CH), 136.3 (CH), 136.1 (C), 132.4 (C), 132.3 (CH), 131.0 (C), 128.0 (C), 126.2 (CH+C), 125.4 (CH), 120.4 (CH), 119.9 (CH), 118.4 (C), 117.0 (CH), 116.2 (CH), 111.0 (CH), 100.7 (CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>15</sub>N<sub>4</sub>O<sub>3</sub> (M+H)<sup>+</sup> 347.1139, found 347.1150; HPLC purity ≥ 96%, *t*<sub>R</sub> = 8.11 min, λ = 276 nm.

#### 4.1.51. 3-(1H-Indol-4-yl)-5-((3-nitrophenyl)amino)pyridin-2(1H)-one (**54**)

Compound **54** was prepared according to general procedure C2, starting from **31** (90 mg, 0.206 mmol). The mixture was stirred for 5 h. The reaction mixture was then quenched by addition of NEt<sub>3</sub> (17 equiv) and MeOH (6 equiv). The crude was purified by column chromatography (NEt<sub>3</sub>-treated SiO<sub>2</sub>, 98:2 CH<sub>2</sub>Cl<sub>2</sub>/MeOH to 9:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to give **54** (65.1 mg, 0.188 mmol, 91%) as an orange brown solid. *R*<sub>f</sub> = 0.25 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 295 °C (decomposition); IR (ATR) 3396, 3283, 1604, 1655, 1604, 1509, 1455, 1337, 761, 724 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.74 (br s, 1H), 11.15 (s, 1H), 8.15 (s, 1H), 7.53 (d, *J* = 3.0 Hz, 1H), 7.51–7.47 (m, 2H), 7.42 (t, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.37–7.32 (br s, 1H), 7.33 (t, *J* = 2.7 Hz, 1H), 7.27 (d, *J* = 7.1 Hz, 1H), 7.18–7.14 (m, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.38–6.36 (m, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 159.9 (C=O), 148.9 (C), 148.4 (C), 138.6

(CH), 136.1 (C), 131.1 (C), 130.5 (CH), 129.1 (CH), 128.1 (C), 126.1 (C), 125.4 (CH), 120.5 (C), 120.4 (CH), 120.0 (CH), 119.7 (CH), 111.8 (CH), 111.0 (CH), 106.6 (CH), 100.4 (CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>15</sub>N<sub>4</sub>O<sub>3</sub> (M+H)<sup>+</sup> 347.1139, found 347.1140; HPLC purity ≥ 95%, t<sub>R</sub> = 7.92 min, λ = 260 nm.

#### 4.1.52. 3-(1*H*-Indol-4-yl)-5-((4-nitrophenyl)amino)pyridin-2(1*H*)-one (**55**)

Compound **55** was prepared according to general procedure C2, starting from **32** (125 mg, 0.286 mmol). The mixture was stirred at 0 °C for 5 h, then 2 h 30 min at 10 °C. The reaction mixture was then quenched by addition of NEt<sub>3</sub> (12 equiv) and MeOH (5 equiv). The crude was purified by column chromatography (NEt<sub>3</sub>-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 98:2 to 92:8) to give **55** (30.3 mg, 0.087 mmol, 31%) as a red brown solid. R<sub>f</sub> = 0.22 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 295 °C (decomposition); IR (ATR) 3362, 3280, 1655, 1633, 1588, 1467, 1299, 1111, 747 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.82 (s, 1H), 11.15 (s, 1H), 8.82 (s, 1H), 8.07 (d, *J* = 9.3 Hz, 2H), 7.53 (d, *J* = 2.9 Hz, 1H), 7.41 (br s, 1H), 7.37 (dt, *J*<sub>1</sub> = 8.1 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.35 (t, *J* = 2.8 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 9.3 Hz, 2H), 6.38–6.36 (m, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 160.0 (C=O), 153.2 (C), 138.5 (CH), 137.3 (C), 136.1 (C), 131.1 (C), 130.0 (CH), 128.0 (C), 126.3 (2CH), 126.1 (C), 125.4 (CH), 120.4 (CH), 119.9 (CH), 119.3 (C), 112.2 (2CH), 111.1 (CH), 100.5 (CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>15</sub>N<sub>4</sub>O<sub>3</sub> (M+H)<sup>+</sup> 347.1139, found 347.1140; HPLC purity ≥ 97%, t<sub>R</sub> = 7.80 min, λ = 378 nm.

#### 4.1.53. 5-((2-Aminophenyl)amino)-3-(1*H*-indol-4-yl)pyridin-2(1*H*)-one (**56**)

Compound **56** was prepared according to general procedure D, starting from **30** (50.4 mg, 0.115 mmol) in 3 mL of MeOH. The mixture was stirred under H<sub>2</sub> for 4 h 30 min in the dark. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5) to give **56** (22.1 mg, 0.070 mmol, 60%) as a brown solid. R<sub>f</sub> = 0.20 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 208 °C (decomposition); IR (ATR) 3500–3000, 1649, 1597, 1556, 1500, 1452, 747 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.34 (s, 1H), 11.11 (s, 1H), 7.45 (d, *J* = 2.7 Hz, 1H), 7.36–7.31 (m, 2H), 7.26 (d, *J* = 7.0 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.83 (br s, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.72–6.65 (m, 2H), 6.54 (s, 1H), 6.53–6.48 (m, 1H), 6.40–6.37 (m, 1H), 4.73 (s, 2H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 159.0 (C=O), 139.7 (C), 136.2 (CH), 136.1 (C), 130.9 (C), 130.0 (C), 128.6 (C), 126.2 (C), 125.5 (C), 125.2 (CH), 121.9 (CH), 121.8 (CH), 120.4 (CH), 119.9 (CH), 118.3 (CH), 116.8 (CH), 115.0 (CH), 110.7 (CH), 100.6 (CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>17</sub>N<sub>4</sub>O (M+H)<sup>+</sup> 317.1397, found 317.1394.

#### 4.1.54. 3-(1*H*-Indol-4-yl)-5-(*o*-tolylamino)pyridin-2(1*H*)-one (**57**)

Compound **57** was prepared according to general procedure D, starting from **33** (69.4 mg, 0.171 mmol) in 1 mL of MeOH. The mixture was stirred for 6 h at room temperature in the dark. The crude was purified by column chromatography (NEt<sub>3</sub>-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5) to give **57** containing NEt<sub>3</sub> salts. CH<sub>2</sub>Cl<sub>2</sub> was added and the solution was washed with saturated NaHCO<sub>3</sub> solution and water. The organic phase was dried over MgSO<sub>4</sub> and filtered. After evaporation under reduced pressure, product **57** (41.8 mg, 0.133 mmol, 77%) was obtained as a red powder. R<sub>f</sub> = 0.18 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 199 °C; IR (ATR) 3500–3000, 1650, 1599, 1557, 1498, 1113, 747, 614 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.53 (br s, 1H), 11.13 (s, 1H), 7.51 (d, *J* = 3.0 Hz, 1H), 7.35 (dt, *J*<sub>1</sub> = 8.1 Hz, *J*<sub>2</sub> = 1.0 Hz, 1H), 7.33 (t, *J* = 2.8 Hz, 1H), 7.27 (dd, *J*<sub>1</sub> = 7.3 Hz, *J*<sub>2</sub> = 0.9 Hz, 1H), 7.13 (br s, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.02 (t,

$J = 7.7$  Hz, 1H), 6.75 (s, 1H), 6.72 (d,  $J = 8.2$  Hz, 1H), 6.67 (td,  $J_1 = 7.2$  Hz,  $J_2 = 1.1$  Hz, 1H), 6.36 (ddd,  $J_1 = 3.1$  Hz,  $J_2 = 2.0$  Hz,  $J_3 = 0.9$  Hz, 1H), 2.20 (s, 3H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 159.6 (C=O), 144.8 (C), 138.7 (CH), 136.1 (C), 130.5 (CH), 130.4 (C), 128.3 (C), 126.9 (CH), 126.6 (CH), 126.1 (C), 125.3 (CH), 124.3 (C), 123.1 (C), 120.4 (CH), 119.9 (CH), 118.5 (CH), 113.1 (CH), 110.8 (CH), 100.5 (CH), 17.8 (CH<sub>3</sub>); HRMS (ESI+) calcd for C<sub>20</sub>H<sub>18</sub>N<sub>3</sub>O (M+H)<sup>+</sup> 316.1444, found 316.1449; HPLC purity  $\geq$  96%,  $t_{\text{R}} = 8.09$  min,  $\lambda = 278$  nm.

#### 4.1.55. 3-(1H-Indol-4-yl)-5-(pyridin-2-ylamino)pyridin-2(1H)-one (**58**)

Compound **58** was prepared according to general procedure C1, starting from **34** (102.6 mg, 0.261 mmol). The mixture was stirred for 4 h 40 min and was quenched with NEt<sub>3</sub> (14 equiv) and MeOH (9 equiv). The crude was purified by column chromatography (SiO<sub>2</sub>, acetone/cyclohexane 5:5 + 0.5% NEt<sub>3</sub> to 6:4 + 0.5% NEt<sub>3</sub>) to give **58** (48.5 mg, 0.160 mmol, 61%) as a light orange solid.  $R_{\text{f}} = 0.38$  (acetone/cyclohexane 7:3); Mp  $> 171$  °C (decomposition); IR (ATR) 3500–3000, 1652, 1596, 1338, 754 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 11.44 (br s, 1H), 11.13 (s, 1H), 8.67 (s, 1H), 8.10 (dd,  $J_1 = 5.0$  Hz,  $J_2 = 1.5$  Hz, 1H), 7.97 (d,  $J = 2.8$  Hz, 1H), 7.78 (d,  $J = 2.8$  Hz, 1H), 7.51 (ddd,  $J_1 = 8.7$  Hz,  $J_2 = 7.1$  Hz,  $J_3 = 2.0$  Hz, 1H), 7.38–7.35 (m, 2H), 7.31 (dd,  $J_1 = 7.4$  Hz,  $J_2 = 0.9$  Hz, 1H), 7.10 (t,  $J = 7.7$  Hz, 1H), 6.71–6.68 (m, 1H), 6.67 (ddd,  $J_1 = 7.1$  Hz,  $J_2 = 5.1$  Hz,  $J_3 = 0.9$  Hz, 1H), 6.51–6.49 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 159.1 (C=O), 158.5 (CH), 156.3 (C), 147.2 (CH), 137.1 (CH), 136.1 (C), 136.0 (CH), 129.8 (C), 128.5 (C), 126.2 (C), 125.2 (CH), 122.1 (C), 120.4 (CH), 120.0 (CH), 113.5 (CH), 110.8 (CH), 110.0 (CH), 100.8 (CH); HRMS (ESI+) calcd for C<sub>18</sub>H<sub>15</sub>N<sub>4</sub>O (M+H)<sup>+</sup> 303.1240, found 303.1247; HPLC purity  $\geq$  98%,  $t_{\text{R}} = 5.82$  min,  $\lambda = 320$  nm.

#### 4.1.56. 3-(1H-Indol-4-yl)-5-(pyridin-3-ylamino)pyridin-2(1H)-one (**59**)

Compound **59** was prepared according to general procedure D, starting from **35** (114.6 mg, 0.292 mmol) in 2 mL of MeOH and with 0.14 equiv of Pd(OH)<sub>2</sub>/C. The mixture was stirred under H<sub>2</sub> for 3 days in the dark. The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 to 9:1) to give **59** (42 mg, 0.139 mmol, 48%) as a light orange solid.  $R_{\text{f}} = 0.35$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 9:1 + 0.5% NEt<sub>3</sub>); Mp  $> 179$  °C (decomposition); IR (ATR) 3500–3000, 1651, 1579, 1336, 752, 706 cm<sup>-1</sup>;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 11.63 (s, 1H), 11.14 (s, 1H), 8.13 (dd,  $J_1 = 2.6$  Hz,  $J_2 = 0.8$  Hz, 1H), 7.90 (dd,  $J_1 = 4.4$  Hz,  $J_2 = 1.6$  Hz, 1H), 7.73 (s, 1H), 7.51 (d,  $J = 3.0$  Hz, 1H), 7.36 (dt,  $J_1 = 8.0$  Hz,  $J_2 = 1.0$  Hz, 1H), 7.34 (t,  $J = 2.8$  Hz, 1H), 7.28 (br s, 1H), 7.26 (dd,  $J_1 = 7.4$  Hz,  $J_2 = 1.0$  Hz, 1H), 7.18–7.09 (m, 2H), 7.10 (t,  $J = 7.8$  Hz, 1H), 6.37–6.35 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz, DMSO- $d_6$ )  $\delta$  (ppm) 159.7 (C=O), 143.0 (C), 138.9 (CH), 138.1 (CH), 136.7 (CH), 136.1 (C), 130.9 (C), 128.2 (C), 127.6 (CH), 126.1 (C), 125.4 (CH), 123.9 (CH), 121.4 (C), 120.5 (CH), 119.9 (CH), 119.4 (CH), 111.0 (CH), 100.5 (CH); HRMS (ESI+) calcd for C<sub>18</sub>H<sub>15</sub>N<sub>4</sub>O (M+H)<sup>+</sup> 303.1240, found 303.1246; HPLC purity  $\geq$  96%,  $t_{\text{R}} = 5.71$  min,  $\lambda = 268$  nm.

#### 4.1.57. 3-(1H-Indol-4-yl)-5-(pyridin-4-ylamino)pyridin-2(1H)-one (**60**)

Compound **60** was prepared by a catalytic hydrogenation performed in an H-cube reactor (H-cube Mini - Thales Nano). A solution of **36** (61 mg, 0.155 mmol) in MeOH (6 mL) was engaged in reaction (Pd(OH)<sub>2</sub>/C cartridge, room temperature, 1 mL/min, 3 cycles). The crude was purified by column chromatography (NEt<sub>3</sub>-treated SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 to 8:2) to give **60** after evaporation a ~1:1 solvate with MeOH (29 mg, containing 10.4% w/w of MeOH as measured by NMR, 0.086 mmol, 55%) as a light brown solid.  $R_{\text{f}} = 0.03$  (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5); Mp  $> 200$  °C

(decomposition); IR (ATR) 3400–2900, 1655, 1587, 1357, 1332, 1215, 1027, 1000, 808, 755, 638  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 11.71 (br s, 1H), 11.15 (s, 1H), 8.22 (s, 1H), 8.13–8.10 (m, 2H), 7.50 (d,  $J = 3.0$  Hz, 1H), 7.37 (dt,  $J_1 = 8.0$  Hz,  $J_2 = 1.0$  Hz, 1H), 7.35 (t,  $J = 2.7$  Hz, 1H), 7.33 (br s, 1H), 7.27 (dd,  $J_1 = 7.4$  Hz,  $J_2 = 1.0$  Hz, 1H), 7.10 (t,  $J = 7.7$  Hz, 1H), 6.65–6.63 (m, 2H), 6.36 (ddd,  $J_1 = 3.0$  Hz,  $J_2 = 2.0$  Hz,  $J_3 = 0.8$  Hz, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 159.9 (C=O), 152.6 (C), 149.8 (2CH), 138.6 (CH), 136.1 (C), 130.9 (C), 129.4 (CH), 128.1 (C), 126.1 (C), 125.4 (CH), 120.5 (CH), 119.9 (CH), 119.5 (C), 111.0 (CH), 108.1 (2CH), 100.5 (CH); HRMS (ESI+) calcd for  $\text{C}_{18}\text{H}_{15}\text{N}_4\text{O}$  ( $\text{M}+\text{H}$ ) $^+$  303.1240, found 303.1236; HPLC purity  $\geq 95\%$ ,  $t_{\text{R}} = 5.66$  min,  $\lambda = 270$  nm.

#### 4.1.58. 5-((2-Bromophenyl)amino)-3-(1H-indol-4-yl)pyridin-2(1H)-one (**61**)

Compound **61** was prepared according to general procedure C2, starting from **40** (105 mg, 0.223 mmol). The mixture was stirred for 3 h 30 min. The reaction mixture was then quenched by addition of  $\text{NEt}_3$  (16 equiv) and MeOH (6 equiv). The crude was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  98:2 to 94:6). After evaporation,  $\text{CH}_2\text{Cl}_2$  was added and the solution was washed with saturated aqueous NaCl solution. The organic phase was dried over  $\text{MgSO}_4$ , filtered and evaporated to give **61** (49.8 mg, 0.131 mmol, 59%) as a beige powder.  $R_f = 0.39$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5 + 0.5%  $\text{NEt}_3$ ); Mp  $> 227$  °C (decomposition); IR (ATR) 3500–3000, 1650, 1611, 1589, 1555, 1491, 1449, 1020, 743  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 11.68 (s, 1H), 11.13 (s, 1H), 7.49 (dd,  $J_1 = 7.9$  Hz,  $J_2 = 1.5$  Hz, 1H), 7.49 (d,  $J = 3.0$  Hz, 1H), 7.36 (dt,  $J_1 = 8.0$  Hz,  $J_2 = 0.9$  Hz, 1H), 7.33 (t,  $J = 2.7$  Hz, 1H), 7.29 (br s, 1H), 7.28 (d,  $J = 7.2$  Hz, 1H), 7.18 (ddd,  $J_1 = 8.8$  Hz,  $J_2 = 7.4$  Hz,  $J_3 = 1.5$  Hz, 1H), 7.09 (t,  $J = 7.7$  Hz, 1H), 7.01 (s, 1H), 6.78 (dd,  $J_1 = 8.1$  Hz,  $J_2 = 1.4$  Hz, 1H), 6.66 (ddd,  $J_1 = 7.9$  Hz,  $J_2 = 7.3$  Hz,  $J_3 = 1.6$  Hz, 1H), 6.40–6.38 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 159.9 (C=O), 144.4 (C), 139.4 (CH), 136.1 (C), 132.9 (CH), 130.6 (C), 129.6 (CH), 128.5 (CH), 128.2 (C), 126.1 (C), 125.3 (CH), 121.1 (C), 120.4 (CH), 119.9 (CH), 119.4 (CH), 114.3 (CH), 110.9 (CH), 109.6 (C), 100.5 (CH); HRMS (ESI+) calcd for  $\text{C}_{19}\text{H}_{15}\text{BrN}_3\text{O}$  ( $\text{M}+\text{H}$ ) $^+$  380.0393, found 380.0388; HPLC purity  $\geq 98\%$ ,  $t_{\text{R}} = 8.35$  min,  $\lambda = 274$  nm.

#### 4.1.59. 5-((3-Bromophenyl)amino)-3-(1H-indol-4-yl)pyridin-2(1H)-one (**62**)

Compound **62** was prepared according to general procedure C2, starting from **41** (81 mg, 0.172 mmol). The mixture was stirred for 3 h 30 min. The reaction mixture was then quenched by addition of  $\text{NEt}_3$  (21 equiv) and MeOH (7 equiv). The crude was purified by column chromatography ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  97:3 to 94:6). After evaporation, the product was washed with  $\text{CH}_2\text{Cl}_2$  to give **62** (44.7 mg, 0.118 mmol, 68%) as light green powder.  $R_f = 0.31$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  95:5 + 0.5%  $\text{NEt}_3$ ); Mp  $> 155$  °C (decomposition); IR (ATR) 3500–3000, 1649, 1614, 1588, 1556, 1333, 892, 755  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 11.64 (br s, 1H), 11.15 (s, 1H), 7.77 (s, 1H), 7.50 (d,  $J = 2.9$  Hz, 1H), 7.36 (dt,  $J_1 = 8.0$  Hz,  $J_2 = 0.9$  Hz, 1H), 7.35 (t,  $J = 2.8$  Hz, 1H), 7.27 (d,  $J = 7.2$  Hz, 1H), 7.26 (br s, 1H), 7.12–7.07 (m, 2H), 6.89 (t,  $J = 2.1$  Hz, 1H), 6.82 (ddd,  $J_1 = 7.9$  Hz,  $J_2 = 2.1$  Hz,  $J_3 = 1.0$  Hz, 1H), 6.73 (dd,  $J_1 = 8.3$  Hz,  $J_2 = 2.2$  Hz, 1H), 6.37–6.35 (m, 1H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{DMSO-}d_6$ )  $\delta$  (ppm) 159.8 (C=O), 148.7 (C), 138.6 (CH), 136.1 (C), 131.1 (CH), 130.8 (C), 128.3 (CH), 128.1 (C), 126.1 (C), 125.4 (CH), 122.4 (C), 121.1 (C), 120.4 (CH), 120.0 (CH), 119.9 (CH), 115.6 (CH), 112.5 (CH), 111.0 (CH), 100.4 (CH); HRMS (ESI+) calcd for  $\text{C}_{19}\text{H}_{15}\text{BrN}_3\text{O}$  ( $\text{M}+\text{H}$ ) $^+$  380.0393, found 380.0396; HPLC purity  $\geq 99\%$ ,  $t_{\text{R}} = 8.26$  min,  $\lambda = 278$  nm.

#### 4.1.60. 5-((4-Bromophenyl)amino)-3-(1H-indol-4-yl)pyridin-2(1H)-one (**63**)

Compound **63** was prepared according to general procedure C2, starting from **42** (74.8 mg, 0.159 mmol). The mixture was stirred for 3 h 30 min. The reaction mixture was then quenched by addition of NEt<sub>3</sub> (23 equiv) and MeOH (8 equiv). The crude was purified by column chromatography (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/MeOH 97:3 to 95:5). After evaporation, the product was washed with CH<sub>2</sub>Cl<sub>2</sub> to give **63** (31.4 mg, 0.083 mmol, 52%) as yellow solid. *R*<sub>f</sub> = 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 95:5 + 0.5% NEt<sub>3</sub>); Mp > 167 °C (decomposition); IR (ATR) 3500–3000, 1651, 1610, 1586, 1556, 1487, 1333, 752 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 11.61 (s, 1H), 11.14 (s, 1H), 7.68 (s, 1H), 7.49 (d, *J* = 3.0 Hz, 1H), 7.38–7.33 (m, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 7.26 (d, *J* = 7.2 Hz, 1H), 7.23 (br s, 1H), 7.09 (t, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.36–6.34 (m, 1H); <sup>13</sup>C NMR (101 MHz, DMSO-*d*<sub>6</sub>) δ (ppm) 159.7 (C=O), 146.2 (C), 138.3 (CH), 136.1 (C), 131.8 (2CH), 130.8 (C), 128.2 (C), 127.6 (CH), 126.1 (C), 125.4 (CH), 121.7 (C), 120.4 (CH), 119.9 (CH), 115.6 (2CH), 110.9 (CH), 108.4 (C), 100.5 (CH); HRMS (ESI+) calcd for C<sub>19</sub>H<sub>15</sub>BrN<sub>3</sub>O (M+H)<sup>+</sup> 380.0393, found 380.0396; HPLC purity ≥ 97%, *t*<sub>R</sub> = 8.27 min, λ = 278 nm.

## 4.2. Assessment of anti-allodynic activity

### 4.2.1. Facial Complete Freund's Adjuvant (CFA) model.

CFA (Becton Dickinson) was dissolved in saline solution containing Tween 80 and paraffin oil and conserved at 4 °C. For behavioral testing, animals were briefly (< 2 min) anesthetized using a mask with 2% isoflurane and received a subcutaneous injection of 25 μL of CFA (2.5 mg/kg) solution into the right vibrissa pad using a 27 Ga needle coupled to a 25 μL Hamilton syringe, as described previously [15]. After recovery from anesthesia (< 2 min), rats were placed into an observation field (0.6 x 0.6 m square) under red light for mechanical testing. 6-g von Frey filament – a normally innocuous static mechanical stimulation – was gently applied every 10 min onto the orofacial region by a first experimenter for a 120 min mechanical testing period. Behavioral responses were observed and quantified by a second, blinded, experimenter (see below).

### 4.2.2. Intracisternal injection.

For investigating the effects of synthesized compounds upon CFA-induced MA, animals were briefly (≈ 3 min) anesthetized using a mask with 2% isoflurane and received an intracisternal injection of either compound (10 μM in 5 μL aCSF) or vehicle alone (aCSF + 1% DMSO) using a 10 μL Hamilton syringe [25]. aCSF consisted of 150 mM Na<sup>+</sup>, 3 mM K<sup>+</sup>, 0.8 mM Mg<sup>2+</sup>, 1.4 mM Ca<sup>2+</sup>, 155 mM Cl<sup>-</sup>, pH 7.4, 295 mosmol.kg<sup>-1</sup>. After recovery (≈ 2 min), rats were placed in an observation field (0.6 x 0.6 msquare) under red light for a 30-min habituation session. During this period, rats were adapted to the observation field and red light. The experimenter also reached into the cage to apply innocuous mechanical (6-g von Frey filament) stimulation on the face of the animal, to which animals responded with only a simple detection, showing a non-aversive response. Immediately after the 30 min habituation period, animals were again briefly (≈ 3 min) anesthetized using a mask with 2% isoflurane and received intradermal injection of CFA. Behavioral responses to the very same 6-g von Frey filament as during the habituation session were then evaluated as described in the Behavioral Testing section (see below).

### 4.2.3. Behavioral responses to normally innocuous static (6-g von Frey filament) mechanical stimulation.



The behavioral responses procedure was previously developed by Vos *et al.* [23]. A rat's response to mechanical stimulation consisted of one or more of the following elements: (1) detection, rat turn head toward stimulus; (2) withdrawal reaction, rat pull paw away or turn head away or pull it briskly backward when stimulation is applied (a withdrawal reaction is assumed to include a detection element preceding the head withdrawal and therefore consists of two responses elements); (3) escape/attack, rats avoid further contact with the stimulus, either passively by moving their bodies away from the stimulus, or actively by attacking the tip of the pump; (4) asymmetric grooming, rats display an uninterrupted series of at least three wash strokes directed to the stimulated area.

The level of MA inhibition of a given compound was computed as following:  $[(AUC \text{ vehicle} - AUC \text{ compound})/AUC \text{ vehicle}] \times 100$  (AUC being the area under the curve; see Figure 2A)

## Acknowledgments

We acknowledge CNRS and Université Clermont Auvergne (PEPS de site Clermont-Ferrand 2015), the Ministère de l'Enseignement Supérieur et de la Recherche (A.V., PhD thesis scholarship), and INSERM Tranfert for providing research facilities and financial support. This research was also financed by the French government IDEX-ISITE initiative 16-IDEX-0001 (CAP 20-25).

## Abbreviations

CFA, complete Freund's adjuvant; ERK, Extracellular signal-regulated kinases; MA, Mechanical Allodynia; p38 MAPK, p38 mitogen-activated protein kinases; PKC, protein kinase C.

## References

- [1] D. Borsook, R. Hargreaves, C. Bountra, F. Porreca. Lost but making progress—Where will new analgesic drugs come from? *Sci. Transl. Med.* 6 (2014) 249sr3, doi: 10.1126/scitranslmed.3008320.
- [2] H. Breivik, E. Eisenberg, T. O'Brien. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health* 24 (2013) 1229, doi: 10.1186/1471-2458-13-1229.
- [3] M.S. Gold, G. F. Gebhart. Nociceptor sensitization in pain pathogenesis. *Nat. Med.* 16 (2010) 1248-1257, doi: 10.1038/nm.2235.
- [4] A. Latremoliere, C.J. Woolf. *J. Pain* 10 (2009) 895–926, doi: 10.1016/j.jpain.2009.06.012.
- [5] R. Kannaiyan, D. Mahadevan. A comprehensive review of protein kinase inhibitors for cancer therapy. *Expert Rev. Anticancer Ther.* 18 (2018) 1249–1270, doi: 10.1080/14737140.2018.1527688.
- [6] M.I. Funez, F.H. Veiga de Souza, J.E. Pandossio, P.G.B.D. Nascimento. Protein kinases and pain. In *Protein kinases*, Da Silva Xavier, G., IntechOpen, 2012, doi: 10.5772/38139.
- [7] F. Giraud, E. Pereira, F. Anizon, P. Moreau. Recent advances in pain management: relevant protein kinases and their inhibitors. *Molecules* 26 (2021) 2696, doi: 10.3390/molecules26092696.
- [8] Z. Xie, X. Yang, Y. Duan, J. Han, C. Liao. Small-molecule kinase inhibitors for the treatment of nononcologic diseases. *J. Med. Chem.* 64 (2021) 1283–1345, doi: 10.1021/acs.jmedchem.0c01511.

- [9] K. Li, T. Lin, Y. Cao, A.R. Light, K.Y. Fu. Peripheral formalin injury induces 2 stages of microglial activation in the spinal cord. *J. Pain* 22 (2010) 1056–1065, doi: 10.1016/j.jpain.2010.01.268.
- [10] S. Taves, T. Berta, D.L. Liu, S. Gan, G. Chen, Y.H. Kim, T. Van de Ven, S. Laufer, R.R. Ji. Spinal inhibition of p38 MAP kinase reduces inflammatory and neuropathic pain in male but not female mice: Sex-dependent microglial signaling in the spinal cord. *Brain Behav. Immun.* 55 (2016) 70–81, doi: 10.1016/j.bbi.2015.10.006.
- [11] R.R. Ji, H. Baba, G.J. Brenner, C.J. Woolf. Nociceptive-specific activation of ERK in spinal neurons contributes to pain hypersensitivity. *Nat. Neurosci.* 2 (1999) 1114–1119, doi: 10.1038/16040.
- [12] 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* 124 (2016) 1136–1152, doi: 10.1097/ALN.0000000000001000.
- [13] A. Artola, D. Voisin, R. Dallel. PKC $\gamma$  interneurons, a gateway to pathological pain in the dorsal horn. *J. Neural Transm. (Vienna)* 127 (2020) 527–540, doi: 10.1007/s00702-020-02162-6.
- [14] L.S. Mirauccourt, R. Dallel, D.L. Voisin, D.L. Glycine Inhibitory Dysfunction Turns Touch into Pain through PKC $\gamma$  Interneurons. *PLoS One* 2 (2007) e1116, doi: 10.1371/journal.pone.0001116.
- [15] C. Alba-Delgado, S. Mountadem, N. Mermat-Joret, L. Monconduit, R. Dallel, A. Artola, M. Antri. 5-HT $_2A$  receptor-induced morphological reorganization of PKC $\gamma$ -expressing interneurons gates inflammatory mechanical allodynia in rat. *J. Neurosci.* 38 (2018) 10489–10504, doi: 10.1523/JNEUROSCI.1294-18.2018.
- [16] N.F. Chen, W.F. Chen, C.S. Sung, C.H. Lu, C.L. Chen, H.C. Hung, C.W. Feng, C.H. Chen, K.H. Tsui, H.M. Kuo, H.M. Wang, Z.H. Wen, S.Y. Huang. Contributions of p38 and ERK to the antinociceptive effects of TGF- $\beta$ 1 in chronic constriction injury-induced neuropathic rats. *J. Headache Pain* 17 (2016) 72, doi: 10.1186/s10194-016-0665-2.
- [17] T. Zhang, N. Zhang, R. Zhang, W. Zhao, Y. Chen, Z. Wang, B. Xu, M. Zhang, X. Shi, Q. Zhang, Y. Guo, J. Xiao, D. Chen, Q. Fang. Preemptive intrathecal administration of endomorphins relieves inflammatory pain in male mice via inhibition of p38 MAPK signaling and regulation of inflammatory cytokines. *J. Neuroinflammation* 15 (2018) 320, doi: 10.1186/s12974-018-1358-3.
- [18] 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(1*H*)one derivatives: a possible new class of therapeutics for mechanical allodynia. *Eur. J. Med. Chem.* 187 (2020) 111917. doi: 10.1016/j.ejmech.2019.111917.
- [19] S.X. Jin, Z.Y. Zhuang, C.J. Woolf, R.R. Ji. p38 Mitogen-Activated Protein Kinase Is Activated after a Spinal Nerve Ligation in Spinal Cord Microglia and Dorsal Root Ganglion Neurons and Contributes to the Generation of Neuropathic Pain. *J. Neurosci.* 23 (2003) 4017–4022, doi: 10.1523/JNEUROSCI.23-10-04017.2003.
- [20] M. Tsuda, A. Mizokoshi, Y. Shigemoto-Mogami, S. Koizumi, K. Inoue. Activation of p38 mitogen-activated protein kinase in spinal hyperactive microglia contributes to pain hypersensitivity following peripheral nerve injury. *Glia* 45 (2004) 89–95, doi: 10.1002/glia.10308.

- [21] Y. Cui, Y. Chen, J.L. Zhi, R.X. Guo, J.Q. Feng, P.X. Chen. Activation of p38 mitogen-activated protein kinase in spinal microglia mediates morphine antinociceptive tolerance. *Brain Res.* 1069 (2006) 235–243, doi: 10.1016/j.brainres.2005.11.066.
- [22] M. Chartier, T. Chenard, J. Barker, R. Najmanovich. Kinome Render: a stand-alone and web-accessible tool to annotate the human protein kinome tree. *PeerJ* 1 (2013) e126, doi: 10.7717/peerj.126.
- [23] B.P. Vos, A.M. Strassman, R.J. Maciewicz. Behavioral evidence of trigeminal neuropathic pain following chronic constriction injury to the rat's infraorbital nerve. *J. Neurosci.* 14 (1994) 2708–2723, doi: 10.1523/JNEUROSCI.14-05-02708.1994.
- [24] J. Bain, L. Plater, M. Elliott, N. Shpiro, J. Hastie, H. McLauchlan, I. Klervernic, S.C. Arthur, D.R. Alessi, P. Cohen. The selectivity of protein kinase inhibitors: a further update. *Biochem. J.* 408 (2007) 297–315, doi: 10.1042/BJ20070797.
- [25] L.S. Miraucourt, X. Moisset, R. Dallel, D.L. Voisin. Glycine Inhibitory Dysfunction Induces a Selectively Dynamic, Morphine-Resistant, and Neurokinin 1 Receptor- Independent Mechanical Allodynia. *J. Neurosci.* 29 (2009) 2519–2527, doi: 10.1523/JNEUROSCI.3923-08.2009.