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

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#### 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 antiallodynic treatments based on new drug classes. We recently synthetized 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 synthetized compounds showed higher anti-allodynic potency, with two of them completely preventing mechanical allodynia. In the first series, hit compounds $\mathbf{1}$ and $\mathbf{2}$ appeared to be inhibitors of p38 MAPK, a protein kinase known to underlie pain hypersensitivity in animal models. Depending on the substitution at the 5-position, some newly synthetized compounds were also stronger p38a MAPK inhibitors. Surprisingly, though, anti-allodynic effects and p38 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(1H)-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 $\mathrm{C}(\mathrm{PKC} \gamma)$ 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 [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- $2(1 \mathrm{H})$-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 $\mathrm{p} 38 \alpha$ as a potential biological target (Fig. 1B). In addition, $\mathbf{2}$ was selective of $\mathrm{p} 38 \alpha$ over protein kinases representative of the human kinome or close to $\mathrm{p} 38 \alpha$ in the kinome phylogenetic tree. $\mathrm{IC}_{50}$ values toward $\mathrm{p} 38 \alpha$, determined for the two best anti-allodynic agents, showed moderate inhibitory potency in the micromolar range (compounds $\mathbf{1}$ 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 $\mathbf{1}$ and 2), and their p38a MAPK inhibitory activity. B. Kinase selectivity of compound 2. Residual activity at $10 \mu \mathrm{M}$ : 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) [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 $\mathbf{1}$ and $\mathbf{2}$, 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 $\mathbf{1}$ 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-4yl group leading to 38 in $81 \%$ yield. Reduction of the nitro group led to 39 and Buchwald-Hartwig coupling produced compounds $\mathbf{4 0 - 4 2}$ 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 4-19 |  | $\begin{gathered} \text { Compounds } \\ \mathbf{2 1 - 3 6} \text { and } \mathbf{4 0}-\mathbf{4 2}^{\mathrm{b}} \end{gathered}$ |  |
| :---: | :---: | :---: | :---: | :---: |
| $\mathrm{Ar} / \mathrm{HetAr}$ | Cpd | Yield <br> \% | Cpd | Yield <br> \% |
| 2-F-C6 $\mathrm{H}_{4}$ | 4 | 50 | 21 | 94 |
| $3-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 5 | 57 | 22 | 99 |
| $4-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 6 | 72 | 23 | 93 |
| 2 -( $\left.\mathrm{CO}_{2} \mathrm{Et}\right)-\mathrm{C}_{6} \mathrm{H}_{4}$ | 7 | 90 | 24 | 78 |
| $3-\left(\mathrm{CO}_{2} \mathrm{Et}\right)-\mathrm{C}_{6} \mathrm{H}_{4}$ | 8 | 83 | 25 | 79 |
| $4-\left(\mathrm{CO}_{2} \mathrm{Et}\right)-\mathrm{C}_{6} \mathrm{H}_{4}$ | 9 | 66 | 26 | 88 |
| $2-\mathrm{MeO}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $10$ | 84 | 27 | 80 |
| $\text { 3-MeO-C }{ }_{6} \mathrm{H}_{4}$ | $11$ | $60$ | $28$ | 85 |
| $4-\mathrm{MeO}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $12$ | $69$ | $29$ | 93 |
| $2-\mathrm{NO}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $13$ | $86$ | $30$ | 87 |
| $3-\mathrm{NO}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $14$ | $76$ | $31$ | 97 |
| $4-\mathrm{NO}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | $15$ | 76 | 32 | 93 |
| $2-\mathrm{Me}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 16 | 74 | 33 | 78 |
| Pyridin-2-yl | 17 | 55 | 34 | 88 |
| Pyridin-3-yl | 18 | 85 | 35 | 94 |
| pyridin-4-yl | 19 | 72 | 36 | 64 |
| $2-\mathrm{Br}-\mathrm{C}_{6} \mathrm{H}_{4}$ |  |  | 40 | 47 |
| $3-\mathrm{Br}-\mathrm{C}_{6} \mathrm{H}_{4}$ |  |  | 41 | 46 |
| $4-\mathrm{Br}-\mathrm{C}_{6} \mathrm{H}_{4}$ |  |  | 42 | 46 |

${ }^{\text {a }}$ Pathway 1. ${ }^{\text {b }}$ Pathway 2.
For the last step, compounds $21-\mathbf{3 6}$ and $\mathbf{4 0 - 4 2}$ 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 $\mathbf{5 2}$ in $52 \%$ yield. Hydrogenolysis applied to nitro compound $\mathbf{3 0}$ produced aniline derivative $\mathbf{5 6}$ in $60 \%$ yield.


Scheme 2. Synthesis of compounds 43-63.

Table 2. Yields of debenzylation of compounds 43-63.

| Starting from | Product | $\mathrm{Ar} / \mathrm{HetAr}$ | Method | Yield (\%) |
| :---: | :---: | :---: | :---: | :---: |
| 21 | 43 | $2-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 81 |
| 22 | 44 | $3-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 57 |
| 23 | 45 | $4-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 70 |
| 24 | 46 | $2-\left(\mathrm{CO}_{2} \mathrm{Et}\right)-\mathrm{C}_{6} \mathrm{H}_{4}$ | B | quant. |
| 25 | 47 | 3-( $\left.\mathrm{CO}_{2} \mathrm{Et}\right)-\mathrm{C}_{6} \mathrm{H}_{4}$ | B | 53 |
| 26 | 48 | 4-( $\left.\mathrm{CO}_{2} \mathrm{Et}\right)-\mathrm{C}_{6} \mathrm{H}_{4}$ | B | quant |
| 27 | 49 | $2-\mathrm{MeO}-\mathrm{C}_{6} \mathrm{H}_{4}$ | B | 84 |
| 28 | 50 | $3-\mathrm{MeO}-\mathrm{C}_{6} \mathrm{H}_{4}$ | B | 80 |
| 29 | 51 | $4-\mathrm{MeO}-\mathrm{C}_{6} \mathrm{H}_{4}$ | B | 99 |
| 28 | 52 | $3-\mathrm{OH}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 52 |
| 30 | 53 | 2- $\mathrm{NO}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 33 |
| 31 | 54 | $3-\mathrm{NO}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 91 |
| 32 | 55 | $4-\mathrm{NO}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 31 |
| 30 | 56 | 2- $\mathrm{NH}_{2}-\mathrm{C}_{6} \mathrm{H}_{4}$ | B | 60 |
| 33 | 57 | $2-\mathrm{Me}-\mathrm{C}_{6} \mathrm{H}_{4}$ | B | 77 |
| 34 | 58 | pyridin-2-yl | A | 61 |
| 35 | 59 | pyridin-3-yl | B | 48 |
| 36 | 60 | pyridin-4-yl | B | 55 |
| 40 | 61 | $2-\mathrm{Br}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 59 |
| 41 | 62 | $3-\mathrm{Br}-\mathrm{C}_{6} \mathrm{H}_{4}$ | A | 68 |
| 42 | 63 | $4-\mathrm{Br}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 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 ${ }^{1}$ H NMR spectra. After receiving a subcutaneous injection of CFA ( $25 \mu \mathrm{~L}$; $2.5 \mathrm{mg} / \mathrm{kg}$ ) 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 $\mathbf{2}$, most of the nineteen newly synthetized compounds produced equal (three compounds: 48, $\mathbf{5 2}$ and 59) or enhanced MA inhibition ( $\geq 80 \%$ inhibition of allodynic score; eleven compounds: $\mathbf{4 4}, \mathbf{4 5}, \mathbf{4 7}, \mathbf{4 9}, \mathbf{5 0}, \mathbf{5 3 - 5 5}, \mathbf{5 7}, \mathbf{5 8}$ and $\mathbf{6 0}$ ), including two compounds ( $\mathbf{5 5}$ and $\mathbf{6 0}$ ) which completely prevented MA. Notably, there were also two compounds ( $\mathbf{4 3}$ and $\mathbf{5 1}$ ) with much less anti-MA efficacy than compound $\mathbf{2}$. 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 $\mathbf{2}$ ) such as 2 - and 3 -nitro ( $\mathbf{5 3}, \mathbf{5 4}$ ), 3-methoxyl (50), 2-methyl (57) groups, 3F and 4 -F atoms $(\mathbf{4 4}, \mathbf{4 5}$ ) or when the phenyl group was replaced by a pyridin-2-yl moiety (58). In summary, compared with $\mathbf{2}$, compounds $\mathbf{5 5}$ and $\mathbf{6 0}$ are the most interesting compounds of the new series, with an enhanced effect and a complete MA inhibition.

A


B


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 $\mathbf{5 5}$ 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 $\mathbf{2}, \mathbf{4 3}, \mathbf{5 1}$ or 55 or vehicle. Compound $\mathbf{5 1}$ produced a $16 \%$ inhibition, compound $\mathbf{4 3}$, 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, $\mathbf{4 7 - 5 5}$ 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 $\mathbf{A}$ and $\mathbf{B}$, compounds $(5 \mu \mathrm{~L}$ at $10 \mu \mathrm{M})$ 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 ( $\mathbf{A}$ ) and $n=4$ rats ( $\mathbf{B}$, except compound 48: $\mathrm{n}=1$ rat and compound 59: $\mathrm{n}=2$ 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 ( $5 \mu \mathrm{~L}$ at $10 \mu \mathrm{M}$ ), 11 compounds of this second series $(\mathbf{4 4}, \mathbf{4 5}, \mathbf{4 7}, \mathbf{4 9}, \mathbf{5 0}, \mathbf{5 3}-\mathbf{5 5}, \mathbf{5 7}, \mathbf{5 8}$ and $\mathbf{6 0}$ - but not compound $\mathbf{2}$, 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. p38a MAPK inhibitory potency.

Compounds 43-55 and 57-63 were evaluated for their p38a 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 $1 \mu \mathrm{M}$ (Table 3) and IC $\mathrm{IC}_{50}$ values were determined when the percentage of $\mathrm{p} 38 \alpha$ 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 ( $\mathbf{4 6}-\mathbf{4 8}, 53-55$ ) were almost inactive whereas pyridinyl analogues $\mathbf{5 8 - 6 0}$ showed low potency at $1 \mu \mathrm{M}$. Thus, best $\mathrm{IC}_{50}$ values were found in the submicromolar range for compounds $\mathbf{4 3}, 45$ and $\mathbf{6 2}$, with an improved potency compared to compounds $\mathbf{1}$ and 2 .

Table 3. p38 MAPK inhibitory activity of compounds 43-55 and 57-63.

| Compound | \% res. activity $(1 \mu \mathrm{M})$ | $\mathrm{IC}_{50}(\mu \mathrm{M})$ |
| :---: | :---: | :---: |
| $\mathbf{1}$ | $59 \pm 10$ | 3.0 |
| $\mathbf{2}$ | $59 \pm 15$ | 1.5 |
| $\mathbf{4 3}$ | $28 \pm 4$ | $0.23 \pm 0.01$ |
| $\mathbf{4 4}$ | $47 \pm 6$ | $1.4 \pm 0.3$ |
| $\mathbf{4 5}$ | $39 \pm 10$ | $0.4 \pm 0.1$ |
| $\mathbf{4 6}$ | $104 \pm 22$ | nd |
| $\mathbf{4 7}$ | $81 \pm 18$ | nd |
| $\mathbf{4 8}$ | $86 \pm 7$ | nd |
| $\mathbf{4 9}$ | $50 \pm 5$ | $5.2 \pm 0.7$ |
| $\mathbf{5 0}$ | $50 \pm 6$ | $5.5 \pm 2.3$ |
| $\mathbf{5 1}$ | $59 \pm 9$ | $3.7 \pm 1.4$ |
| $\mathbf{5 2}$ | $34 \pm 7$ | $1.0 \pm 0.2$ |
| $\mathbf{5 3}$ | $92.3 \pm 0.3$ | nd |
| $\mathbf{5 4}$ | $73.9 \pm 0.2$ | nd |
| $\mathbf{5 5}$ | $93 \pm 8$ | nd |
| $\mathbf{5 7}$ | $33 \pm 6$ | $1.1 \pm 0.3$ |
| $\mathbf{5 8}$ | $70 \pm 9$ | nd |
| $\mathbf{5 9}$ | $64 \pm 11$ | nd |
| $\mathbf{6 0}$ | $67 \pm 7$ | nd |
| $\mathbf{6 1}$ | $45 \pm 2$ | $2.7 \pm 0.4$ |
| $\mathbf{6 2}$ | $31 \pm 11$ | $0.7 \pm 0.2$ |
| $\mathbf{6 3}$ | $43 \pm 14$ | $2.4 \pm 0.5$ |
| $\mathbf{7}$ |  |  |

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 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 p38a MAPK inhibition ( $33 \%$ inhibition at $1 \mu \mathrm{M}$ ), lower than that of compound $2(41 \%$ inhibition at 1 $\mu \mathrm{M})$. Conversely, compound 43, the best $\mathrm{p} 38 \alpha$ MAPK inhibitor, with an $\mathrm{IC}_{50}$ value of $0.23 \mu \mathrm{M}$ ( $72 \%$ inhibition at $1 \mu \mathrm{M}$ ) 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 $\mathrm{p} 38 \alpha$ MAPK inhibition.

## 3. Conclusion

In a work aiming at designing novel anti-allodynic drugs, we synthesized a new series of pyridine-2(1H)-one derivatives in three or four steps from precursors $\mathbf{3}$ 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/heteroarylamino moieties. Compared with compound 2, one 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 M 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 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(1H)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 ( $\bar{v}$ in $\left.\mathrm{cm}^{-1}\right)$. NMR spectra, performed on a Bruker AVANCE 400 III HD $\left({ }^{1} \mathrm{H}: 400 \mathrm{MHz},{ }^{13} \mathrm{C}: 101\right.$ 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 $\mu \mathrm{m}$ 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 ( $4.6 \mathrm{~mm} \times 150 \mathrm{~mm}$, $3.5 \mu \mathrm{~m}$ ). Flow rate was $0.8 \mathrm{~mL} / \mathrm{min}$ and the analysis was performed at $25^{\circ} \mathrm{C}$. 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 $30: 70 \mathrm{~A} / \mathrm{B}$ for 3 min .

### 4.1.2. General procedures.

Procedure A: Buchwald-Hartwig cross-coupling between compound $\mathbf{3}$ and iodide derivatives. A 5-9 mL screw-cap tube under argon was charged with compound 20 ( 1 equiv), $\mathrm{Pd}(\mathrm{OAc})_{2}(0.05$ equiv), Xantphos ( 0.05 equiv) and $\mathrm{Cs}_{2} \mathrm{CO}_{3}$ (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 $100{ }^{\circ} \mathrm{C}$ 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 $\mathrm{Na}_{2} \mathrm{CO}_{3}$ aqueous solution (5 equiv). The mixture was degassed with argon for 10 min before the addition of $\mathrm{PdCl}_{2}\left(\mathrm{PPh}_{3}\right)_{2}$ ( 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 $\mathrm{MgSO}_{4}$ and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography.

## Procedure C: Debenzylation by $\mathrm{BBr}_{3}$.

A solution under argon of benzylated compound (1 equiv) in anhydrous dichloromethane (amount for 0.02 M substrate concentration) was cooled to $0^{\circ} \mathrm{C}$ (procedure C 1 ) or to $-10^{\circ} \mathrm{C}$ (procedure C 2 ). A solution of $\mathrm{BBr}_{3}$ in dichloromethane ( $1 \mathrm{M}, 4$ equiv unless otherwise indicated) was added dropwise. The mixture was stirred at room temperature $(\mathrm{C} 1)$ or at $0{ }^{\circ} \mathrm{C}(\mathrm{C} 2)$ in the dark. The reaction mixture was then quenched by addition of $\mathrm{NEt}_{3}$ and methanol. After evaporation under reduced pressure, EtOAc was added. The mixture was washed with water and saturated aqueous NaCl solution, dried over $\mathrm{MgSO}_{4}$ 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 $20 \% \mathrm{Pd}(\mathrm{OH})_{2} / \mathrm{C}(0.08$ 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 $\mathbf{4}$ was prepared according to general procedure A, starting from $\mathbf{3}$ ( $199 \mathrm{mg}, 0.713 \mathrm{mmol}$ ) in 7 mL of anhydrous 1,4 -dioxane. The mixture was heated for 20 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, cyclohexane to EtOAc/cyclohexane 8:92) to give 4 ( $134 \mathrm{mg}, 0.360$ $\mathrm{mmol}, 50 \%$ ) as a beige solid. $R_{\mathrm{f}}=0.55$ (EtOAc/cyclohexane 1:9); Mp $67^{\circ} \mathrm{C}$; IR (ATR) 3306, 1619, 1443, 1356, 1295, 1219, 1181, 1098, 1056, 1012, $733 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta$ (ppm) 7.96 (s, 1H), 7.94 (d, $J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.73(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.48-7.44(\mathrm{~m}, 2 \mathrm{H}), 7.42-7.37$
$(\mathrm{m}, 2 \mathrm{H}), 7.35-7.30(\mathrm{~m}, 1 \mathrm{H}), 7.20\left(\mathrm{ddd}, J_{1}=11.9 \mathrm{~Hz}, J_{2}=8.1 \mathrm{~Hz}, J_{3}=1.4 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.14\left(\mathrm{td}, J_{1}=\right.$ $\left.8.3 \mathrm{~Hz}, J_{2}=1.7 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.06\left(\mathrm{td}, J_{1}=7.7 \mathrm{~Hz}, J_{2}=1.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.90\left(\mathrm{dddd}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=7.3\right.$ $\left.\mathrm{Hz}, J_{3}=4.9 \mathrm{~Hz}, J_{4}=1.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.37(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 153.5(\mathrm{C})$, $152.8\left(\mathrm{~d}, J_{\mathrm{CF}}=242 \mathrm{~Hz}, \mathrm{C}\right), 137.1(\mathrm{C}), 135.5(\mathrm{CH}), 135.0(\mathrm{C}), 133.0(\mathrm{CH}), 131.5\left(\mathrm{~d}, J_{\mathrm{CF}}=11 \mathrm{~Hz}\right.$, C), $128.4(2 \mathrm{CH}), 127.7(\mathrm{CH}), 127.5(2 \mathrm{CH}), 124.9\left(\mathrm{~d}, J_{\mathrm{CF}}=3 \mathrm{~Hz}, \mathrm{CH}\right), 121.0\left(\mathrm{~d}, J_{\mathrm{CF}}=7 \mathrm{~Hz}, \mathrm{CH}\right)$, $117.7\left(\mathrm{~d}, J_{\mathrm{CF}}=3 \mathrm{~Hz}, \mathrm{CH}\right), 115.8\left(\mathrm{~d}, J_{\mathrm{CF}}=19 \mathrm{~Hz}, \mathrm{CH}\right), 105.8(\mathrm{C}), 67.7\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{BrFN}_{2} \mathrm{O}(\mathrm{M}+\mathrm{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 ( $202 \mathrm{mg}, 0.724$ mmol ). The mixture was heated for 2 h 30 min . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, cyclohexane to EtOAc/cyclohexane 5:95) to give 5 ( $153 \mathrm{mg}, 0.410 \mathrm{mmol}$, $57 \%$ ) as a brown solid. $R_{\mathrm{f}}=0.72$ (EtOAc/cyclohexane 3:7); Mp $43^{\circ} \mathrm{C}$; IR (ATR) 3431, 1619, 1594, 1466, 1450, 1432, 1354, 1293, 1260, 1217, 1136, 1051, $970,691 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 8.34(\mathrm{~s}, 1 \mathrm{H}), 8.01(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.84(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.49-7.45(\mathrm{~m}$, 2H), 7.42-7.37 (m, 2H), 7.35-7.30 (m, 1H), $7.22\left(\mathrm{td}, J_{1}=8.2 \mathrm{~Hz}, J_{2}=7.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.74\left(\mathrm{ddd}, J_{1}=\right.$ $\left.8.2 \mathrm{~Hz}, J_{2}=2.2 \mathrm{~Hz}, J_{3}=0.7 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.67\left(\mathrm{dt}, J_{1}=11.7 \mathrm{~Hz}, J_{2}=2.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.57\left(\mathrm{dddd}, J_{1}=8.9\right.$ $\left.\mathrm{Hz}, J_{2}=8.1 \mathrm{~Hz}, J_{3}=2.5 \mathrm{~Hz}, J_{4}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.39(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}\right.$, DMSO- $\left.d_{6}\right) \delta$ $(\mathrm{ppm}) 163.2\left(\mathrm{~d}, J_{\mathrm{CF}}=241 \mathrm{~Hz}, \mathrm{C}\right), 154.1(\mathrm{C}), 146.3\left(\mathrm{~d}, J_{\mathrm{CF}}=11 \mathrm{~Hz}, \mathrm{C}\right), 137.0(\mathrm{C}), 136.8(\mathrm{CH})$, $134.3(\mathrm{CH}), 134.2(\mathrm{C}), 130.9\left(\mathrm{~d}, J_{\mathrm{CF}}=10 \mathrm{~Hz}, \mathrm{CH}\right), 128.4(2 \mathrm{CH}), 127.8(\mathrm{CH}), 127.5(2 \mathrm{CH}), 110.9$ $\left(\mathrm{d}, J_{\mathrm{CF}}=2 \mathrm{~Hz}, \mathrm{CH}\right), 106.0(\mathrm{C}), 105.5\left(\mathrm{~d}, J_{\mathrm{CF}}=21 \mathrm{~Hz}, \mathrm{CH}\right), 101.4\left(\mathrm{~d}, J_{\mathrm{CF}}=25 \mathrm{~Hz}, \mathrm{CH}\right), 67.8\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{BrFN}_{2} \mathrm{O}(\mathrm{M}+\mathrm{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 ( $202 \mathrm{mg}, 0.724$ $\mathrm{mmol})$. The mixture was heated for 2 h 45 min . The crude oil was purified by column chromatography $\left(\mathrm{SiO}_{2}\right.$, cyclohexane to $\mathrm{EtOAc} /$ cyclohexane $\left.5: 95\right)$ to give $\mathbf{6}$ ( $193.6 \mathrm{mg}, 0.519 \mathrm{mmol}$, $72 \%$ ) as a brown solid. $R_{\mathrm{f}}=0.73$ (EtOAc/cyclohexane 3/7); Mp $43^{\circ} \mathrm{C}$; IR (ATR) 3394, 1506, 1444, $1215,1052,825,735 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 8.06(\mathrm{~s}, 1 \mathrm{H}), 7.92(\mathrm{~d}, J=2.5$ $\mathrm{Hz}, 1 \mathrm{H}), 7.72(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.47-7.43(\mathrm{~m}, 2 \mathrm{H}), 7.42-7.36(\mathrm{~m}, 2 \mathrm{H}), 7.35-7.29(\mathrm{~m}, 1 \mathrm{H}), 7.07$ $(\mathrm{t}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H}), 6.99\left(\mathrm{dd}, J_{1}=9.0 \mathrm{~Hz}, J_{2}=4.7 \mathrm{~Hz}, 2 \mathrm{H}\right), 5.36(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 156.4\left(\mathrm{~d}, J_{\mathrm{CF}}=236 \mathrm{~Hz}, \mathrm{C}\right), 153.1(\mathrm{C}), 140.0\left(\mathrm{~d}, J_{\mathrm{CF}}=2 \mathrm{~Hz}, \mathrm{C}\right), 137.2(\mathrm{C}), 135.9$ (C), $134.5(\mathrm{CH}), 132.0(\mathrm{CH}), 128.4(2 \mathrm{CH}), 127.7(\mathrm{CH}), 127.5(2 \mathrm{CH}), 117.8\left(\mathrm{~d}, J_{\mathrm{CF}}=8 \mathrm{~Hz}, 2 \mathrm{CH}\right)$, $115.9\left(\mathrm{~d}, J_{\mathrm{CF}}=22 \mathrm{~Hz}, 2 \mathrm{CH}\right), 106.0(\mathrm{C}), 67.7\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{BrFN}_{2} \mathrm{O}$ $(\mathrm{M}+\mathrm{H})^{+} 373.0346$, 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 ( $50.1 \mathrm{mg}, 0.179$ mmol ). The mixture was heated for 1 h 30 min . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, cyclohexane to EtOAc/cyclohexane 3:97) to give 7 ( $69.0 \mathrm{mg}, 0.161 \mathrm{mmol}$, $90 \%$ ) as a white solid. $R_{\mathrm{f}}=0.68$ (EtOAc/cyclohexane 1:9); Mp $90^{\circ} \mathrm{C}$; IR (ATR) 3281, 1668, 1584, $1517,1431,1361,1243,1225,736,697 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 9.15(\mathrm{~s}, 1 \mathrm{H})$, $8.13(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 1 \mathrm{H}), 8.04(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.90\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.50-7.46$ $(\mathrm{m}, 2 \mathrm{H}), 7.43-7.37(\mathrm{~m}, 3 \mathrm{H}), 7.36-7.31(\mathrm{~m}, 1 \mathrm{H}), 6.93\left(\mathrm{dd}, J_{1}=8.5 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.81$ (ddd, $\left.J_{1}=8.1 \mathrm{~Hz}, J_{2}=7.1 \mathrm{~Hz}, J_{3}=1.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.43(\mathrm{~s}, 2 \mathrm{H}), 4.32(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.33(\mathrm{t}, J=7.1 \mathrm{~Hz}$,
$3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 167.5$ (C=O), 155.7 (C), 147.6 (C), 140.9 (CH), $138.3(\mathrm{CH}), 136.9(\mathrm{C}), 134.6(\mathrm{CH}), 132.2(\mathrm{C}), 131.3(\mathrm{CH}), 128.4(2 \mathrm{CH}), 127.8(\mathrm{CH}), 127.5(2 \mathrm{CH})$, $117.7(\mathrm{CH}), 113.6(\mathrm{CH}), 112.0(\mathrm{C}), 106.0(\mathrm{C}), 68.0\left(\mathrm{CH}_{2}\right), 60.6\left(\mathrm{CH}_{2}\right), 14.1\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{21} \mathrm{H}_{20} \mathrm{BrN}_{2} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 427.0652$, 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 ( $199 \mathrm{mg}, 0.713$ $\mathrm{mmol})$. The mixture was heated for 1 h 45 min . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, cyclohexane to EtOAc/cyclohexane 1:9) to give $\mathbf{8}$ ( $252.6 \mathrm{mg}, 0.591 \mathrm{mmol}$, $83 \%$ ) as a brown solid. $R_{\mathrm{f}}=0.19$ (EtOAc/cyclohexane 1:9); Mp $99^{\circ} \mathrm{C}$; IR (ATR) 3378, 3336, 1694, $1450,1358,1304,1276,1052,739 \mathrm{~cm}^{-1}$; ${ }^{1}$ H NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 8.38(\mathrm{~s}, 1 \mathrm{H}), 8.02$ $(\mathrm{d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.84(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.52-7.50(\mathrm{~m}, 1 \mathrm{H}), 7.49-7.46(\mathrm{~m}, 2 \mathrm{H}), 7.43-7.31(\mathrm{~m}$, $5 \mathrm{H}), 7.21\left(\mathrm{ddd}, J_{1}=7.6 \mathrm{~Hz}, J_{2}=2.5 \mathrm{~Hz}, J_{3}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.40(\mathrm{~s}, 2 \mathrm{H}), 4.29(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H})$, $1.31(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 165.8(\mathrm{C}=\mathrm{O}), 153.9(\mathrm{C}), 144.5$ (C), 137.1 (C), $136.3(\mathrm{CH}), 134.5(\mathrm{C}), 133.9(\mathrm{CH}), 130.9(\mathrm{C}), 129.8(\mathrm{CH}), 128.4(2 \mathrm{CH}), 127.7$ $(\mathrm{CH}), 127.5(2 \mathrm{CH}), 119.9(\mathrm{CH}), 119.3(\mathrm{CH}), 115.4(\mathrm{CH}), 106.0(\mathrm{C}), 67.8\left(\mathrm{CH}_{2}\right), 60.7\left(\mathrm{CH}_{2}\right), 14.1$ $\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{21} \mathrm{H}_{20} \mathrm{BrN}_{2} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 427.0652$, 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 ( $200.8 \mathrm{mg}, 0.719$ $\mathrm{mmol})$. The mixture was heated for 2 h 15 min . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, cyclohexane to EtOAc/cyclohexane 1:9) to give 9 ( $201.9 \mathrm{mg}, 0.473 \mathrm{mmol}$, $66 \%$ ) as a white solid. $R_{\mathrm{f}}=0.16$ (EtOAc/cyclohexane 1:9); Mp $139{ }^{\circ} \mathrm{C}$; IR (ATR) 3316, 1677, 1595, 1464, 1367, 1285, 1244, 1176, 1054, 1008, 767, 730, $696 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO$\left.d_{6}\right) \delta(\mathrm{ppm}) 8.71(\mathrm{~s}, 1 \mathrm{H}), 8.08(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.91(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.80(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H})$, 7.49-7.45 (m, 2H), 7.43-7.38 (m, 2H), 7.36-7.31 (m, 1H), 6.94 (d, J = $8.9 \mathrm{~Hz}, 2 \mathrm{H}), 5.40(\mathrm{~s}, 2 \mathrm{H})$, $4.24(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.28(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $101 \mathrm{MHz}, \mathrm{DMSO}-d_{6}$ ) $\delta(\mathrm{ppm}) 165.5$ (C=O), 154.7 (C), 148.9 (C), $138.0(\mathrm{CH}), 137.0(\mathrm{C}), 135.5(\mathrm{CH}), 133.1(\mathrm{C}), 131.2$ (2CH), 128.4 $(2 \mathrm{CH}), 127.8(\mathrm{CH}), 127.6(2 \mathrm{CH}), 119.6(\mathrm{C}), 113.4(2 \mathrm{CH}), 106.1(\mathrm{C}), 67.9\left(\mathrm{CH}_{2}\right), 60.0\left(\mathrm{CH}_{2}\right), 14.3$ $\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{21} \mathrm{H}_{20} \mathrm{BrN}_{2} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 427.0652$, found 427.0662.

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

Compound $\mathbf{1 0}$ was prepared according to general procedure A, starting from $\mathbf{3}$ ( $200.2 \mathrm{mg}, 0.717$ mmol ). The mixture was heated for 1 h 30 min . The crude oil was purified by two successive chromatography columns $\left(\mathrm{SiO}_{2}\right.$, cyclohexane to $\mathrm{EtOAc} /$ cyclohexane $8: 92$ and $\mathrm{SiO}_{2}$, cyclohexane to $\mathrm{Et}_{2} \mathrm{O} /$ cyclohexane $1: 9$ ) to give $\mathbf{1 0}$ ( $232 \mathrm{mg}, 0.602 \mathrm{mmol}, 84 \%$ ) as a beige oil. $R_{\mathrm{f}}=0.39$ (EtOAc/cyclohexane 1:9); IR (ATR) 3392, 3283, 1594, 1509, 1445, 1237, 733, $695 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO $-d_{6}$ ) $\delta(\mathrm{ppm}) 7.93(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.72(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.48-7.43(\mathrm{~m}$, $3 \mathrm{H}), 7.41-7.36(\mathrm{~m}, 2 \mathrm{H}), 7.35-7.29(\mathrm{~m}, 1 \mathrm{H}), 7.03\left(\mathrm{dd}, J_{1}=7.4 \mathrm{~Hz}, J_{2}=1.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.00\left(\mathrm{dd}, J_{1}=\right.$ $\left.7.7 \mathrm{~Hz}, J_{2}=1.4 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.90-6.81(\mathrm{~m}, 2 \mathrm{H}), 5.35(\mathrm{~s}, 2 \mathrm{H}), 3.81(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 152.9(\mathrm{C}), 149.1(\mathrm{C}), 137.2(\mathrm{C}), 135.8(\mathrm{C}), 135.1(\mathrm{CH}), 132.7(\mathrm{CH}), 132.3$ (C), $128.4(2 \mathrm{CH}), 127.7(\mathrm{CH}), 127.5(2 \mathrm{CH}), 120.9(\mathrm{CH}), 120.8(\mathrm{CH}), 115.6(\mathrm{CH}), 111.5(\mathrm{CH}), 105.7$ (C), $67.6\left(\mathrm{CH}_{2}\right)$, $55.5\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{18} \mathrm{BrN}_{2} \mathrm{O}_{2}(\mathrm{M}+\mathrm{H})^{+} 385.0546$, found 385.0551.

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

Compound $\mathbf{1 1}$ was prepared according to general procedure A, starting from $\mathbf{3}(151.1 \mathrm{mg}, 0.541$ 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 $\left(\mathrm{SiO}_{2}\right.$, cyclohexane to $\mathrm{EtOAc} /$ cyclohexane $\left.1: 9\right)$ to give $\mathbf{1 1}$ $(125.4 \mathrm{mg}, 0.325 \mathrm{mmol}, 60 \%)$ as a brown orange solid. $R_{\mathrm{f}}=0.45$ (EtOAc/cyclohexane 1:9); Mp 61 ${ }^{\circ} \mathrm{C}$; IR (ATR) 3375, 1619-1583, 1493, 1438, 1356, 1278 1215, 1158, 1052, 841, 765, 744, 692 $\mathrm{cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 8.12(\mathrm{~s}, 1 \mathrm{H}), 7.97(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.79(\mathrm{~d}, J=$ $2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.48-7.44(\mathrm{~m}, 2 \mathrm{H}), 7.42-7.36(\mathrm{~m}, 2 \mathrm{H}), 7.35-7.30(\mathrm{~m}, 1 \mathrm{H}), 7.12(\mathrm{t}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H})$, $6.54\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=1.7 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.47(\mathrm{t}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.40\left(\mathrm{dd}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=2.2 \mathrm{~Hz}\right.$, $1 \mathrm{H}), 5.39(\mathrm{~s}, 2 \mathrm{H}), 3.70(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 160.4$ (C), 153.4 (C), 145.1 (C), $137.1(\mathrm{C}), 135.7(\mathrm{CH}), 135.2(\mathrm{C}), 133.2(\mathrm{CH}), 130.2(\mathrm{CH}), 128.4(2 \mathrm{CH}), 127.8(\mathrm{CH})$, $127.5(2 \mathrm{CH}), 108.0(\mathrm{CH}), 105.9(\mathrm{C}), 105.2(\mathrm{CH}), 101.3(\mathrm{CH}), 67.8\left(\mathrm{CH}_{2}\right), 54.9\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{18} \mathrm{BrN}_{2} \mathrm{O}_{2}(\mathrm{M}+\mathrm{H})^{+} 385.0546$, found 385.0548.

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

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

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

Compound $\mathbf{1 3}$ was prepared according to general procedure A, starting from $\mathbf{3}$ ( $200.9 \mathrm{mg}, 0.720$ $\mathrm{mmol})$. The mixture was heated for 2 h 30 min . The crude oil was purified by column chromatography $\left(\mathrm{SiO}_{2}\right.$, cyclohexane to EtOAc/cyclohexane 7:97) to give $\mathbf{1 3}$ ( $249.1 \mathrm{mg}, 0.622$ $\mathrm{mmol}, 86 \%$ ) as an orange solid. $R_{\mathrm{f}}=0.78$ (cyclohexane/EtOAc 7:3); Mp $106{ }^{\circ} \mathrm{C}$; IR (ATR) 3340, 1616, 1571, 1498, 1471, 1439, 1350, 1256, 1149, 1056, 1023, $732 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 9.32(\mathrm{~s}, 1 \mathrm{H}), 8.18(\mathrm{~d}, J=2.4 \mathrm{~Hz}, 1 \mathrm{H}), 8.14-8.10(\mathrm{~m}, 2 \mathrm{H}), 7.53-7.47(\mathrm{~m}, 3 \mathrm{H})$, $7.44-7.38(\mathrm{~m}, 2 \mathrm{H}), 7.37-7.32(\mathrm{~m}, 1 \mathrm{H}), 6.99\left(\mathrm{dd}, J_{1}=8.7 \mathrm{~Hz}, J_{2}=1.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.88\left(\mathrm{ddd}, J_{1}=8.4\right.$ $\left.\mathrm{Hz}, J_{2}=7.0 \mathrm{~Hz}, J_{3}=1.2 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.45(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 156.5(\mathrm{C})$, 142.8 (C), $142.7(\mathrm{CH}), 140.0(\mathrm{CH}), 136.8(\mathrm{C}), 136.2(\mathrm{CH}), 133.2(\mathrm{C}), 131.0(\mathrm{C}), 128.4(2 \mathrm{CH})$, $127.9(\mathrm{CH}), 127.6(2 \mathrm{CH}), 126.1(\mathrm{CH}), 118.0(\mathrm{CH}), 116.4(\mathrm{CH}), 105.9(\mathrm{C}), 68.1\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 400.0291$, 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 $\mathbf{3}$ ( $168.7 \mathrm{mg}, 0.604$ $\mathrm{mmol})$. The mixture was heated for 3 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, EtOAc/cyclohexane $1: 9$ to $17: 83$ ) to give $\mathbf{1 4}(184.2 \mathrm{mg}, 0.460 \mathrm{mmol}, 76 \%)$ as an orange solid. $R_{\mathrm{f}}=0.58$ (cyclohexane/EtOAc 7:3); Mp $105^{\circ} \mathrm{C}$; IR (ATR) 3387, 1519, 1448, 1340, 1235, $1052,976,845,743,730,691,667 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 8.65(\mathrm{~s}, 1 \mathrm{H}), 8.08$
(d, $J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.93(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.64(\mathrm{t}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.59\left(\mathrm{ddd}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=\right.$ $\left.2.2 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.49-7.38(\mathrm{~m}, 5 \mathrm{H}), 7.36-7.31(\mathrm{~m}, 1 \mathrm{H}) 7.31\left(\mathrm{ddd}, J_{1}=8.3 \mathrm{~Hz}, J_{2}=2.4 \mathrm{~Hz}\right.$, $\left.J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.41(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $\mathrm{d}_{6}$ ) $\delta(\mathrm{ppm}) 154.7(\mathrm{C}), 148.8(\mathrm{C}), 145.9$ (C), $137.8(\mathrm{CH}), 137.0(\mathrm{C}), 135.3(\mathrm{CH}), 133.3(\mathrm{C}), 130.6(\mathrm{CH}), 128.4(2 \mathrm{CH}), 127.8(\mathrm{CH}), 127.6$ $(2 \mathrm{CH}), 120.6(\mathrm{CH}), 113.2(\mathrm{CH}), 108.1(\mathrm{CH}), 106.2(\mathrm{C}), 67.9\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 400.0291$, found 400.0295 .

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

Compound $\mathbf{1 5}$ was prepared according to general procedure A, starting from $\mathbf{3}$ ( $200.8 \mathrm{mg}, 0.719$ $\mathrm{mmol})$. The mixture was heated for 2 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}, \mathrm{EtOAc} /$ cyclohexane $1: 9$ to $15 / 85$ ) to give $\mathbf{1 5}(217.5 \mathrm{mg}, 0.543 \mathrm{mmol}, 76 \%)$ as an orange solid. $R_{\mathrm{f}}=0.17$ (cyclohexane/EtOAc 9:1); Mp $153{ }^{\circ} \mathrm{C}$; IR (ATR) 3304, 1599, 1587, 1464, 1445, 1277, 1183, 1105, 1049, 983, 831, 738, $690 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 9.21$ (s, $1 \mathrm{H}), 8.13(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 8.09(\mathrm{~d}, J=9.3 \mathrm{~Hz}, 2 \mathrm{H}), 8.01(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.50-7.46(\mathrm{~m}, 2 \mathrm{H})$, 7.43-7.38 (m, 2H), 7.37-7.31 (m, 1H), $6.94(\mathrm{~d}, J=9.3 \mathrm{~Hz}, 2 \mathrm{H}), 5.43(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 155.6(\mathrm{C}), 151.3(\mathrm{C}), 139.6(\mathrm{CH}), 138.2(\mathrm{C}), 136.9(\mathrm{CH}), 136.8(\mathrm{C}), 131.8(\mathrm{C})$, $128.4(2 \mathrm{CH}), 127.8(\mathrm{CH}), 127.6(2 \mathrm{CH}), 126.2(2 \mathrm{CH}), 113.0(2 \mathrm{CH}), 106.2(\mathrm{C}), 68.1\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 400.0291$, 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 ( $161.4 \mathrm{mg}, 0.578$ 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 $\left(\mathrm{SiO}_{2}\right.$, cyclohexane to $\mathrm{EtOAc} /$ cyclohexane 5:95) to give 16 ( $157.1 \mathrm{mg}, 0.425 \mathrm{mmol}, 74 \%$ ) as a brown oil. $R_{\mathrm{f}}=0.77$ (EtOAc/cyclohexane 3:7); IR (ATR) 3398, 1586, 1498, 1464, 1443, 1358, 1291, 1236, 1051, 736, $696 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta$ (ppm) $7.84(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.62(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.47-7.44(\mathrm{~m}, 2 \mathrm{H}), 7.41-7.36(\mathrm{~m}, 2 \mathrm{H})$, $7.35(\mathrm{~s}, 1 \mathrm{H}), 7.34-7.29(\mathrm{~m}, 1 \mathrm{H}), 7.17(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.09\left(\mathrm{td}, J_{1}=7.7 \mathrm{~Hz}, J_{2}=1.5 \mathrm{~Hz}, 1 \mathrm{H}\right)$, $7.00\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=1.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.86\left(\mathrm{td}, J_{1}=7.3 \mathrm{~Hz}, J_{2}=1.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.36(\mathrm{~s}, 2 \mathrm{H}), 2.20(\mathrm{~s}$, $3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 152.8$ (C), 141.6 (C), 137.2 (C), 136.7 (C), 134.6 $(\mathrm{CH}), 132.2(\mathrm{CH}), 130.9(\mathrm{CH}), 128.4(2 \mathrm{CH}), 127.9(\mathrm{C}), 127.7(\mathrm{CH}), 127.5(2 \mathrm{CH}), 126.7(\mathrm{CH})$, $121.5(\mathrm{CH}), 117.3(\mathrm{CH}), 105.9(\mathrm{C}), 67.7\left(\mathrm{CH}_{2}\right), 17.8\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{18} \mathrm{BrN}_{2} \mathrm{O}$ $(\mathrm{M}+\mathrm{H})^{+} 369.0597$, found 369.0607 .

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

Compound $\mathbf{1 7}$ was prepared according to general procedure A, starting from 3 ( $250 \mathrm{mg}, 0.896$ $\mathrm{mmol})$. The mixture was heated for 5 h 30 min . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, cyclohexane to EtOAc/cyclohexane 2:8) to give $\mathbf{1 7}$ ( $177 \mathrm{mg}, 0.497 \mathrm{mmol}$, $55 \%$ ) as a red powder. $R_{\mathrm{f}}=0.12$ (EtOAc:cyclohexane $1: 9$ ); Mp> $132{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3250-2900, 1600, 1449, 1438, 1354, 1288, 1219, 1048, 992, 764, 736, $695 \mathrm{~cm}^{-1}$, ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 9.14(\mathrm{~s}, 1 \mathrm{H}), 8.55(\mathrm{~d}, J=2.4,1 \mathrm{H}), 8.37(\mathrm{~d}, J=2.4,1 \mathrm{H}), 8.15$ (ddd, $\left.J_{1}=5.0 \mathrm{~Hz}, J_{2}=1.9 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.58\left(\mathrm{ddd}, J_{1}=8.4 \mathrm{~Hz}, J_{2}=7.1 \mathrm{~Hz}, J_{3}=2.0 \mathrm{~Hz}, 1 \mathrm{H}\right)$, 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); ${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 155.4$ (C), 152.9 (C), $147.2(\mathrm{CH}), 137.5(\mathrm{CH}), 137.2(\mathrm{C})$, $134.9(\mathrm{CH}), 133.9(\mathrm{C}), 132.3(\mathrm{CH}), 128.4(2 \mathrm{CH}), 127.7(\mathrm{CH}), 127.5(2 \mathrm{CH}), 114.7(\mathrm{CH}), 110.7$
$(\mathrm{CH}), 105.1(\mathrm{C}), 67.6\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{17} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 356.0393$, 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 ( $201 \mathrm{mg}, 0.720$ $\mathrm{mmol})$. The mixture was heated for 2 h 45 min . The crude oil was purified by column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{EtOAc} /\right.$ cyclohexane $\left.3: 7+0.5 \% \mathrm{NEt}_{3}\right) . \mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added to the product and the solution was washed with aqueous saturated $\mathrm{NaHCO}_{3}$ solution, dried over $\mathrm{MgSO}_{4}$ and filtered. Evaporation gave compound $18(218.8 \mathrm{mg}, 0.614 \mathrm{mmol}, 85 \%)$ as a red powder. $R_{\mathrm{f}}=0.15$ (EtOAc/cyclohexane 3:7); Mp $68{ }^{\circ} \mathrm{C}$; IR (ATR) 3239, 1583, 1448, 1356, 1287, 1048, 992, 792, $732,691 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 8.31(\mathrm{~s}, 1 \mathrm{H}), 8.25(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 8.02$ $\left(\mathrm{dd}, J_{1}=4.6 \mathrm{~Hz}, J_{2}=1.4 \mathrm{~Hz}, 1 \mathrm{H}\right), 8.01(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.84(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.48-7.45(\mathrm{~m}$, $2 \mathrm{H}), 7.42-7.37(\mathrm{~m}, 2 \mathrm{H}), 7.37-7.30(\mathrm{~m}, 2 \mathrm{H}), 7.21\left(\mathrm{dd}, J_{1}=8.3 \mathrm{~Hz}, J_{2}=4.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.38(\mathrm{~s}, 2 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 153.9(\mathrm{C}), 140.5(\mathrm{CH}), 140.4(\mathrm{C}), 138.2(\mathrm{CH}), 137.1(\mathrm{C})$, $136.0(\mathrm{CH}), 134.3(\mathrm{C}), 133.4(\mathrm{CH}), 128.4(2 \mathrm{CH}), 127.7(\mathrm{CH}), 127.5(2 \mathrm{CH}), 123.9(\mathrm{CH}), 121.1$ $(\mathrm{CH}), 106.1(\mathrm{C}), 67.8\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{17} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 356.0393$, 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 ( $150.4 \mathrm{mg}, 0.539$ $\mathrm{mmol})$. The mixture was heated for 2 h 45 min . The crude oil was purified by column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{EtOAc} /\right.$ cyclohexane $9: 1+0.5 \% \mathrm{NEt}_{3}$ to $\left.\mathrm{EtOAc}+0.5 \% \mathrm{NEt}_{3}\right) . \mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added to the product and the solution was washed with aqueous saturated $\mathrm{NaHCO}_{3}$ solution, dried over $\mathrm{MgSO}_{4}$ and filtered. Evaporation gave compound 19 ( $138 \mathrm{mg}, 0.387 \mathrm{mmol}, 72 \%$ ) as an orange solid. $R_{\mathrm{f}}=0.23\left(\mathrm{EtOAc}+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp} 138{ }^{\circ} \mathrm{C}$; IR (ATR) 3500-3000, 1587, 1470, 1436, 1358, 1056, 992, 811, 729, $693 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 8.71(\mathrm{~s}, 1 \mathrm{H}), 8.19-8.16(\mathrm{~m}$, $2 \mathrm{H}), 8.08(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.94(\mathrm{~d}, J=2.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.49-7.45(\mathrm{~m}, 2 \mathrm{H}), 7.43-7.37(\mathrm{~m}, 2 \mathrm{H})$, 7.36-7.31 (m, 1H), 6.78-6.75 (m, 2H), $5.41(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm})$ 155.1 (C), 150.7 (C), 150.1 (2CH), 138.9 (CH), 136.9 (C), 136.3 (CH), 132.2 (C), 128.4 (2CH), $127.8(\mathrm{CH}), 127.6(2 \mathrm{CH}), 108.7(2 \mathrm{CH}), 106.1(\mathrm{C}), 68.0\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{17} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 356.0393$, 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 ( $191 \mathrm{mg}, 0.512$ $\mathrm{mmol})$. The mixture was refluxed for 17 h . The crude oil was purified by column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{EtOAc} /\right.$ cyclohexane $5: 95$ to 1:9) to give $21(198 \mathrm{mg}, 0.484 \mathrm{mmol}, 94 \%)$ as a beige solid. $R_{\mathrm{f}}=$ 0.36 (EtOAc/cyclohexane 2:8); Mp $56^{\circ} \mathrm{C}$; IR (ATR) 3406, 1619, 1507, 1443, 1231, 987, 742, 695 $\mathrm{cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $\mathrm{d}_{6}$ ) $\delta(\mathrm{ppm}) 11.19(\mathrm{~s}, 1 \mathrm{H}), 7.99(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.89(\mathrm{~d}, J=$ $1.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.54(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.42-7.10(\mathrm{~m}, 11 \mathrm{H}), 7.04\left(\mathrm{td}, J_{1}=7.6 \mathrm{~Hz}, J_{2}=1.4 \mathrm{~Hz}, 1 \mathrm{H}\right)$, 6.83 (dddd, $\left.J_{1}=8.0 \mathrm{~Hz}, J_{2}=7.5 \mathrm{~Hz}, J_{3}=4.8 \mathrm{~Hz}, J_{4}=1.7 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.32\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.0\right.$ $\left.\mathrm{Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.35(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.101 \mathrm{MHz}, \mathrm{DMSO}-d_{6}\right) \delta(\mathrm{ppm}) 155.0(\mathrm{C}), 152.6(\mathrm{~d}$, $\left.J_{\mathrm{CF}}=241 \mathrm{~Hz}, \mathrm{C}\right), 137.7(\mathrm{C}), 136.0(\mathrm{C}), 135.7(\mathrm{CH}), 133.6(\mathrm{C}), 132.4\left(\mathrm{~d}, J_{\mathrm{CF}}=11 \mathrm{~Hz}, \mathrm{C}\right), 131.6$ $(\mathrm{CH}), 128.1(2 \mathrm{CH}), 127.8(\mathrm{C}), 127.4(2 \mathrm{CH}), 127.3(\mathrm{CH}), 126.5(\mathrm{C}), 125.5(\mathrm{CH}), 124.8\left(\mathrm{~d}, J_{\mathrm{CF}}=3\right.$ $\mathrm{Hz}, \mathrm{CH}), 123.6(\mathrm{C}), 120.7(\mathrm{CH}), 120.05(\mathrm{CH}), 120.04\left(\mathrm{~d}, J_{\mathrm{CF}}=7 \mathrm{~Hz}, \mathrm{CH}\right), 116.9\left(\mathrm{~d}, J_{\mathrm{CF}}=3 \mathrm{~Hz}\right.$,

CH), $115.7\left(\mathrm{~d}, J_{\mathrm{CF}}=19 \mathrm{~Hz}, \mathrm{CH}\right), 111.1(\mathrm{CH}), 100.5(\mathrm{CH}), 66.9\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{26} \mathrm{H}_{21} \mathrm{FN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 410.1663$, 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 ( $112 \mathrm{mg}, 0.300$ mmol ). The mixture was refluxed for 16 h . The crude oil was purified by column chromatography $\left(\mathrm{SiO}_{2}\right.$, cyclohexane to EtOAc/cyclohexane 2:8) to give 22 ( $122 \mathrm{mg}, 0.298 \mathrm{mmol}, 99 \%$ ) as a light green powder. $R_{\mathrm{f}}=0.31$ (EtOAc/cyclohexane 2:8); Mp $62^{\circ} \mathrm{C}$; IR (ATR) 3391, 1615, 1592, 1443, $1228,1140,750 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.20(\mathrm{~s}, 1 \mathrm{H}), 8.30(\mathrm{~s}, 1 \mathrm{H}), 8.05(\mathrm{~d}$, $J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.60(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.43-7.11(\mathrm{~m}, 10 \mathrm{H}), 6.77\left(\mathrm{dd}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=2.1 \mathrm{~Hz}\right.$, $1 \mathrm{H}), 6.68\left(\mathrm{dt}, J_{1}=11.9 \mathrm{~Hz}, J_{2}=2.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.52\left(\mathrm{td}, J_{1}=8.5 \mathrm{~Hz}, J_{2}=2.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.32-6.30(\mathrm{~m}$, 1 H ), $5.36(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 163.3$ (d, $\left.J_{\mathrm{CF}}=241 \mathrm{~Hz}, \mathrm{C}\right), 155.4$ (C), $147.1\left(\mathrm{~d}, J_{\mathrm{CF}}=11 \mathrm{~Hz}, \mathrm{C}\right), 137.6(\mathrm{C}), 136.6(\mathrm{CH}), 136.0(\mathrm{C}), 133.0(\mathrm{C}), 132.5(\mathrm{CH}), 130.9\left(\mathrm{~d}, J_{\mathrm{CF}}=\right.$ $10 \mathrm{~Hz}, \mathrm{CH}), 128.1(2 \mathrm{CH}), 127.7(\mathrm{C}), 127.5(2 \mathrm{CH}), 127.4(\mathrm{CH}), 126.5(\mathrm{C}), 125.6(\mathrm{CH}), 123.9(\mathrm{C})$, $120.7(\mathrm{CH}), 120.1(\mathrm{CH}), 111.2(\mathrm{CH}), 110.6\left(\mathrm{~d}, J_{\mathrm{CF}}=2 \mathrm{~Hz}, \mathrm{CH}\right), 104.9\left(\mathrm{~d}, J_{\mathrm{CF}}=21 \mathrm{~Hz}, \mathrm{CH}\right), 101.0$ $\left(\mathrm{d}, J_{\mathrm{CF}}=25 \mathrm{~Hz}, \mathrm{CH}\right), 100.5(\mathrm{CH}), 67.0\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{26} \mathrm{H}_{21} \mathrm{FN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+}$ 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 $\mathbf{6}$ ( $166.2 \mathrm{mg}, 0.445$ $\mathrm{mmol})$. The mixture was refluxed for 16 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, $\mathrm{EtOAc} /$ cyclohexane $1: 9$ to EtOAc/cyclohexane 2:8) to give 23 ( $170.2 \mathrm{mg}, 0.416 \mathrm{mmol}, 93 \%$ ) as a grey-green solid. $R_{\mathrm{f}}=0.21$ (EtOAc/cyclohexane 2:8); Mp>82 ${ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3395, 1505, 1213, $751 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.18(\mathrm{~s}, 1 \mathrm{H}), 8.00(\mathrm{~s}, 1 \mathrm{H})$, $7.98(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.53(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.42-7.10(\mathrm{~m}, 9 \mathrm{H}), 7.05(\mathrm{t}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.01$ $\left(\mathrm{dd}, J_{1}=9.2 \mathrm{~Hz}, J_{2}=4.9 \mathrm{~Hz}, 2 \mathrm{H}\right), 6.30\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.34(\mathrm{~s}$, $2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 156.0$ (d, $\left.J_{\mathrm{CF}}=235 \mathrm{~Hz}, \mathrm{C}\right), 154.6$ (C), 140.9 (d, $J_{\mathrm{CF}}$ $=2 \mathrm{~Hz}, \mathrm{C}), 137.7(\mathrm{C}), 136.0(\mathrm{C}), 134.7(\mathrm{C}), 134.6(\mathrm{CH}), 130.7(\mathrm{CH}), 128.1(2 \mathrm{CH}), 127.9(\mathrm{C}), 127.4$ $(2 \mathrm{CH}), 127.3(\mathrm{CH}), 126.5(\mathrm{C}), 125.5(\mathrm{CH}), 123.8(\mathrm{C}), 120.7(\mathrm{CH}), 120.0(\mathrm{CH}), 117.1\left(\mathrm{~d}, J_{\mathrm{CF}}=8\right.$ $\mathrm{Hz}, 2 \mathrm{CH}), 115.8\left(\mathrm{~d}, J_{\mathrm{CF}}=22 \mathrm{~Hz}, 2 \mathrm{CH}\right), 111.1(\mathrm{CH}), 100.6(\mathrm{CH}), 66.9\left(\mathrm{CH}_{2}\right) ;$ HRMS (ESI+) calcd for $\mathrm{C}_{26} \mathrm{H}_{21} \mathrm{FN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 410.1663$, 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 ( $115 \mathrm{mg}, 0.269$ mmol ). The mixture was refluxed for 14 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, cyclohexane to $\mathrm{EtOAc} /$ cyclohexane 12:88) to give 24 ( $97.6 \mathrm{mg}, 0.211 \mathrm{mmol}, 78 \%$ ) as a beige solid. $R_{\mathrm{f}}=0.13$ (EtOAc/cyclohexane 1:9); Mp $63{ }^{\circ} \mathrm{C}$; IR (ATR) 3411, 3311, 1677, 1582, 1500, 1444, 1227, 1079, 746, $696 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.19$ (br s, 1H), 9.23 (s, $1 \mathrm{H}), 8.15(\mathrm{~d}, J=2.7,1 \mathrm{H}), 7.90\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.70(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.43-$ $7.22(\mathrm{~m}, 8 \mathrm{H}), 7.17-7.11(\mathrm{~m}, 2 \mathrm{H}), 7.01\left(\mathrm{dd}, J_{1}=8.6 \mathrm{~Hz}, J_{2}=0.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.77\left(\mathrm{ddd}, J_{1}=8.1 \mathrm{~Hz}, J_{2}\right.$ $\left.=7.1 \mathrm{~Hz}, J_{3}=1.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.33\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.40(\mathrm{~s}, 2 \mathrm{H}), 4.33$ $(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.34(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $\left.d_{6}\right) \delta(\mathrm{ppm}) 167.6(\mathrm{C}=\mathrm{O})$, 157.0 (C), 148.3 (C), $140.7(\mathrm{CH}), 137.4$ (C), $136.04(\mathrm{CH}), 136.02(\mathrm{C}), 134.6(\mathrm{CH}), 131.3(\mathrm{CH})$, 131.1 (C), $128.2(2 \mathrm{CH}), 127.5(2 \mathrm{CH}), 127.4(\mathrm{C}+\mathrm{CH}), 126.5(\mathrm{C}), 125.6(\mathrm{CH}), 124.1(\mathrm{C}), 120.7$
(CH), $120.1(\mathrm{CH}), 117.1(\mathrm{CH}), 113.3(\mathrm{CH}), 111.5(\mathrm{C}), 111.2(\mathrm{CH}), 100.6(\mathrm{CH}), 67.2\left(\mathrm{CH}_{2}\right), 60.5$ $\left(\mathrm{CH}_{2}\right)$, $14.1\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{29} \mathrm{H}_{26} \mathrm{~N}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 464.1969$, 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 ( $250 \mathrm{mg}, 0.585$ mmol ). The mixture was refluxed for 14 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}, \mathrm{EtOAc} /$ cyclohexane $1: 9$ to $15: 85$ ) to give $25(212.9 \mathrm{mg}, 0.459 \mathrm{mmol}, 79 \%)$ as a beige solid. $R_{\mathrm{f}}=0.16$ (EtOAc/cyclohexane 2:8); Mp>186 ${ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3345, 3177, 1697, 1436, 1300, 1223, $746 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.20(\mathrm{~s}, 1 \mathrm{H}), 8.33(\mathrm{~s}, 1 \mathrm{H})$, $8.05(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.61(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.58-7.56(\mathrm{~m}, 1 \mathrm{H}), 7.43-7.19(\mathrm{~m}, 10 \mathrm{H}), 7.16-$ $7.11(\mathrm{~m}, 2 \mathrm{H}), 6.34\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.37(\mathrm{~s}, 2 \mathrm{H}), 4.29(\mathrm{q}, J=7.1 \mathrm{~Hz}$, $2 \mathrm{H}), 1.30(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 165.9(\mathrm{C}=\mathrm{O}), 155.3(\mathrm{C})$, 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 $(2 \mathrm{CH}), 127.7(\mathrm{C}), 127.5(2 \mathrm{CH}), 127.4(\mathrm{CH}), 126.5(\mathrm{C}), 125.6(\mathrm{CH}), 123.9(\mathrm{C}), 120.7(\mathrm{CH}), 120.1$ $(\mathrm{CH}), 119.3(\mathrm{CH}), 119.2(\mathrm{CH}), 114.7(\mathrm{CH}), 111.2(\mathrm{CH}), 100.5(\mathrm{CH}), 67.0\left(\mathrm{CH}_{2}\right), 60.7\left(\mathrm{CH}_{2}\right), 14.2$ $\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{29} \mathrm{H}_{26} \mathrm{~N}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 464.1969$, 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 ( $152 \mathrm{mg}, 0.356$ mmol ). The mixture was refluxed for 15 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, $\mathrm{EtOAc} /$ cyclohexane $1: 9$ to $2: 8$ ) to give $26(144.5 \mathrm{mg}, 0.312 \mathrm{mmol}, 88 \%)$ as a light yellow solid. $R_{\mathrm{f}}=0.3$ (EtOAc/cyclohexane 3:7); Mp> $188{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3390, 3314, 1683, 1597, 1456, 1283, 1229, 1174, 1120, $980,746,697 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta$ (ppm) $11.20(\mathrm{~s}, 1 \mathrm{H}), 8.69(\mathrm{~s}, 1 \mathrm{H}), 8.11(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.79(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.64(\mathrm{~d}, J=2.7$ $\mathrm{Hz}, 1 \mathrm{H}), 7.43-7.22(\mathrm{~m}, 6 \mathrm{H}), 7.38(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.17-7.11(\mathrm{~m}, 2 \mathrm{H}), 6.97(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H})$, $6.32\left(\mathrm{ddd}, J_{1}=2.9 \mathrm{~Hz}, J_{2}=1.9 \mathrm{~Hz}, J_{3}=0.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.38(\mathrm{~s}, 2 \mathrm{H}), 4.23(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.28(\mathrm{t}$, $J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 165.6$ (C=O), 156.0 (C), 149.5 (C), 137.7 $(\mathrm{CH}), 137.5(\mathrm{C}), 136.0(\mathrm{C}), 133.5(\mathrm{CH}), 132.0(\mathrm{C}), 131.2(2 \mathrm{CH}), 128.2(2 \mathrm{CH}), 127.53(\mathrm{C}), 127.50$ (2CH), $127.4(\mathrm{CH}), 126.5(\mathrm{C}), 125.6(\mathrm{CH}), 124.0(\mathrm{C}), 120.7(\mathrm{CH}), 120.1(\mathrm{CH}), 119.0(\mathrm{C}), 113.1$ $(2 \mathrm{CH}), 111.2(\mathrm{CH}), 100.5(\mathrm{CH}), 67.1\left(\mathrm{CH}_{2}\right), 59.9\left(\mathrm{CH}_{2}\right), 14.3\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{29} \mathrm{H}_{26} \mathrm{~N}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 464.1969$, 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 10 ( $200 \mathrm{mg}, 0.519 \mathrm{mmol}$ ). The mixture was refluxed for 3 h . The crude oil was purified by two successive chromatography columns $\left(\mathrm{SiO}_{2}, \mathrm{EtOAc} /\right.$ cyclohexane 1:9 to 2:8 and $\mathrm{SiO}_{2}, \mathrm{Et}_{2} \mathrm{O} /$ pentane 1:9 to 7:3) to give 27 (175.5 $\mathrm{mg}, 0.416 \mathrm{mmol}, 80 \%$ ) as a white powder. $R_{\mathrm{f}}=0.20$ (EtOAc/cyclohexane $2: 8$ ); $\mathrm{Mp} 73{ }^{\circ} \mathrm{C}$; IR (ATR) $3402,1595,1507,1446,1228,1114,1022,736,696 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO$\left.d_{6}\right) \delta(\mathrm{ppm}) 11.18(\mathrm{~s}, 1 \mathrm{H}), 8.00(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.56(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.41-7.21(\mathrm{~m}, 8 \mathrm{H})$, 7.15-7.10 (m, 2H), 7.07-7.03 (m, 1H), 6.99-6.95 (m, 1H), 6.83-6.77 (m, 2H), $6.32\left(\mathrm{ddd}, \mathrm{J}_{1}=3.0\right.$ $\left.\mathrm{Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.34(\mathrm{~s}, 2 \mathrm{H}), 3.84(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta$ (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), $128.2(2 \mathrm{CH}), 128.0(\mathrm{C}), 127.5(2 \mathrm{CH}), 127.3(\mathrm{CH}), 126.6(\mathrm{C}), 125.5(\mathrm{CH}), 123.5(\mathrm{C}), 120.8(\mathrm{CH})$, $120.7(\mathrm{CH}), 120.1(\mathrm{CH}), 119.8(\mathrm{CH}), 114.3(\mathrm{CH}), 111.3(\mathrm{CH}), 111.0(\mathrm{CH}), 100.7(\mathrm{CH}), 66.9\left(\mathrm{CH}_{2}\right)$, $55.5\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{27} \mathrm{H}_{24} \mathrm{~N}_{3} \mathrm{O}_{2}(\mathrm{M}+\mathrm{H})^{+} 422.1863$, 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 $\mathbf{1 1}$ ( $125.4 \mathrm{mg}, 0.325$ $\mathrm{mmol})$. The mixture was refluxed for 15 h . The crude oil was purified by column chromatography $\left(\mathrm{SiO}_{2}\right.$, pentane $/ \mathrm{Et}_{2} \mathrm{O} 9: 1$ to $\left.45: 55\right)$ to give $28(116 \mathrm{mg}, 0.275 \mathrm{mmol}, 85 \%)$ as a pink powder. $R_{\mathrm{f}}=$ 0.14 (EtOAc/cyclohexane 2:8); Mp > $53{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3390, 1594, 1494, 1445, 1226, 1154, 750, $692 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.19(\mathrm{~s}, 1 \mathrm{H}), 8.07(\mathrm{~s}, 1 \mathrm{H})$, $8.01(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.58(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.42-7.21(\mathrm{~m}, 6 \mathrm{H}), 7.36(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.16-$ $7.11(\mathrm{~m}, 2 \mathrm{H}), 7.09(\mathrm{t}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.56\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=1.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.51(\mathrm{t}, J=2.2 \mathrm{~Hz}$, $1 \mathrm{H}), 6.35\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=2.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.32-6.30(\mathrm{~m}, 1 \mathrm{H}), 5.35(\mathrm{~s}, 2 \mathrm{H}), 3.70(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 160.4$ (C), 154.9 (C), 145.9 (C), 137.7 (C), 136.0 (C), 135.7 (CH), 133.9 (C), $131.6(\mathrm{CH}), 130.1(\mathrm{CH}), 128.1(2 \mathrm{CH}), 127.8(\mathrm{C}), 127.4(2 \mathrm{CH}), 127.3(\mathrm{CH}), 126.5$ (C), $125.5(\mathrm{CH}), 123.7(\mathrm{C}), 120.7(\mathrm{CH}), 120.0(\mathrm{CH}), 111.1(\mathrm{CH}), 107.6(\mathrm{CH}), 104.5(\mathrm{CH}), 100.8$ $(\mathrm{CH}), 100.5(\mathrm{CH}), 66.9\left(\mathrm{CH}_{2}\right), 54.8\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{27} \mathrm{H}_{24} \mathrm{~N}_{3} \mathrm{O}_{2}(\mathrm{M}+\mathrm{H})^{+} 422.1863$, found 422.1862.

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

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

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

Compound $\mathbf{3 0}$ was prepared according to general procedure B , starting from $\mathbf{1 3}$ ( $248 \mathrm{mg}, 0.620$ $\mathrm{mmol})$. The mixture was refluxed for 14 h 20 min . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, EtOAc/cyclohexane 1:9 to 2:8) to give 30 ( $234 \mathrm{mg}, 0.536 \mathrm{mmol}, 87 \%$ ) as an orange solid. $R_{\mathrm{f}}=0.24$ (cyclohexane/EtOAc 8:2); Mp $87^{\circ} \mathrm{C}$; IR (ATR) 3414, 3347, 3177, 1615, 1571, 1495, 1345, 1260, 1218, 735, $693 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.20$ (s, $1 \mathrm{H}), 9.43(\mathrm{~s}, 1 \mathrm{H}), 8.20(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.12\left(\mathrm{dd}, J_{1}=8.6 \mathrm{~Hz}, J_{2}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.76(\mathrm{~d}, J=2.7$ $\mathrm{Hz}, 1 \mathrm{H}), 7.51\left(\mathrm{ddd}, J_{1}=8.6 \mathrm{~Hz}, J_{2}=6.7 \mathrm{~Hz}, J_{3}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.41\left(\mathrm{ddd}, J_{1}=7.3 \mathrm{~Hz}, J_{2}=1.7 \mathrm{~Hz}\right.$, $\left.J_{3}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.38-7.23(\mathrm{~m}, 6 \mathrm{H}), 7.19-7.12(\mathrm{~m}, 2 \mathrm{H}), 7.08\left(\mathrm{dd}, J_{1}=8.7 \mathrm{~Hz}, J_{2}=1.2 \mathrm{~Hz}, 1 \mathrm{H}\right)$, $6.84\left(\mathrm{ddd}, J_{1}=8.4 \mathrm{~Hz}, J_{2}=6.9 \mathrm{~Hz}, J_{3}=1.2 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.37\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=1.9 \mathrm{~Hz}, J_{3}=0.8\right.$ $\mathrm{Hz}, 1 \mathrm{H}), 5.42(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 157.7(\mathrm{C}), 143.4(\mathrm{C}), 142.3(\mathrm{CH})$, $137.6(\mathrm{CH}), 137.3(\mathrm{C}), 136.2(\mathrm{CH}), 136.0(\mathrm{C}), 132.9(\mathrm{C}), 130.0(\mathrm{C}), 128.2(2 \mathrm{CH}), 127.53(2 \mathrm{CH})$, $127.49(\mathrm{CH}), 127.2(\mathrm{C}), 126.5(\mathrm{C}), 126.2(\mathrm{CH}), 125.6(\mathrm{CH}), 124.2(\mathrm{C}), 120.7(\mathrm{CH}), 120.1(\mathrm{CH})$, $117.5(\mathrm{CH}), 116.2(\mathrm{CH}), 111.3(\mathrm{CH}), 100.6(\mathrm{CH}), 67.3\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{26} \mathrm{H}_{21} \mathrm{~N}_{4} \mathrm{O}_{3}$ $(\mathrm{M}+\mathrm{H})^{+} 437.1608$, found 437.1617.

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

Compound 31 was prepared according to general procedure B , starting from $\mathbf{1 4}$ ( $170 \mathrm{mg}, 0.425$ $\mathrm{mmol})$. The mixture was refluxed for 15 h . The crude oil was purified by column chromatography
 solid. $R_{\mathrm{f}}=0.35$ (cyclohexane/EtOAc 7:3); Mp > $189^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3364, 1532, $1341,983,747,735,689 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.21(\mathrm{~s}, 1 \mathrm{H}), 8.64(\mathrm{~s}, 1 \mathrm{H})$, $8.12(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.70(\mathrm{t}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.66(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.55\left(\mathrm{ddd}, J_{1}=7.9 \mathrm{~Hz}, J_{2}\right.$ $\left.=2.3 \mathrm{~Hz}, J_{3}=0.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.45(\mathrm{t}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.40\left(\mathrm{ddd}, J_{1}=6.7 \mathrm{~Hz}, J_{2}=2.3 \mathrm{~Hz}, J_{3}=0.8 \mathrm{~Hz}\right.$, $1 \mathrm{H}), 7.37(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.36-7.22(\mathrm{~m}, 6 \mathrm{H}), 7.18-7.11(\mathrm{~m}, 2 \mathrm{H}), 6.36-6.34(\mathrm{~m}, 1 \mathrm{H}), 5.39(\mathrm{~s}$, $2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 156.0$ (C), 148.8 (C), 146.6 (C), 137.5 (C+CH), $136.1(\mathrm{C}), 133.2(\mathrm{CH}), 132.2(\mathrm{C}), 130.6(\mathrm{CH}), 128.2(2 \mathrm{CH}), 127.5(2 \mathrm{CH}+\mathrm{C}), 127.4(\mathrm{CH}), 126.5$ (C), $125.6(\mathrm{CH}), 124.1(\mathrm{C}), 120.7(\mathrm{CH}), 120.4(\mathrm{CH}), 120.1(\mathrm{CH}), 112.6(\mathrm{CH}), 111.2(\mathrm{CH}), 107.5$ $(\mathrm{CH}), 100.5(\mathrm{CH}), 67.1\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{26} \mathrm{H}_{21} \mathrm{~N}_{4} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 437.1608$, found 437.1614.

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

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

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

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

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

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

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

Compound 35 was prepared according to general procedure B , starting from $\mathbf{1 8}(150 \mathrm{mg}, 0.421$ mmol ). The mixture was refluxed for 15 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, $\left.\mathrm{EtOAc} / c y c l o h e x a n e ~ 1: 9 ~ t o ~ 6: 4\right) . ~ \mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added to the product and the solution was washed with aqueous saturated $\mathrm{NaHCO}_{3}$ solution, dried over $\mathrm{MgSO}_{4}$ and filtered. Evaporation gave compound 35 ( $156 \mathrm{mg}, 0.397 \mathrm{mmol}, 94 \%$ ) as a green solid. $R_{\mathrm{f}}=0.21$ (EtOAc/cyclohexane 6:4); $\mathrm{Mp}>79{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3374, 1579, 1447, 1423, 1229, 751, $694 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.20(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 8.29(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 8.26(\mathrm{~s}, 1 \mathrm{H}), 8.06(\mathrm{~d}, J=$ $2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.97\left(\mathrm{dd}, J_{1}=4.6 \mathrm{~Hz}, J_{2}=1.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.68-7.51(\mathrm{~m}, 1 \mathrm{H}), 7.59(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H})$, $7.44-7.09(\mathrm{~m}, 10 \mathrm{H}), 6.31\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=1.9 \mathrm{~Hz}, J_{3}=0.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.36(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 155.3$ (C), 141.1 (C), 139.9 (CH), 138.0 (CH), 137.6 (C), 136.0 (C), $135.8(\mathrm{CH}), 133.1(\mathrm{C}), 131.7(\mathrm{CH}), 128.1(2 \mathrm{CH}), 127.7(\mathrm{C}), 127.5(2 \mathrm{CH}), 127.4(\mathrm{CH}), 126.5(\mathrm{C})$, $125.6(\mathrm{CH}), 124.0(\mathrm{C}), 123.9(\mathrm{CH}), 120.7(\mathrm{CH}), 120.6(\mathrm{CH}), 120.1(\mathrm{CH}), 111.2(\mathrm{CH}), 100.5(\mathrm{CH})$, $67.0\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{25} \mathrm{H}_{21} \mathrm{~N}_{4} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 393.1710$, found 393.1708.

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

Compound 36 was prepared according to general procedure B, starting from 19 ( $117 \mathrm{mg}, 0.328$ mmol ). The mixture was refluxed for 16 h . The crude oil was purified by column chromatography $\left(\mathrm{SiO}_{2}\right.$, acetone/cyclohexane $+0.1 \% \mathrm{NEt}_{3} 5: 5$ to $\left.7: 3\right) . \mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added to the product and the solution was washed with aqueous saturated $\mathrm{NaHCO}_{3}$ solution, dried over $\mathrm{MgSO}_{4}$ and filtered. Evaporation gave compound $36(82.9 \mathrm{mg}, 0.211 \mathrm{mmol}, 64 \%)$ as an orange solid. $R_{\mathrm{f}}=0.34$ (EtOAc/cyclohexane 7:3 + 0.1\% NEt 3 ); Mp $90{ }^{\circ} \mathrm{C}$; IR (ATR) 3500-3000, 1593, 1512, 1445, 1353, $1214,995,816,752,733 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.21(\mathrm{~s}, 1 \mathrm{H}), 8.69(\mathrm{~s}, 1 \mathrm{H})$, 8.17-8.14 (m, 2H), 8.11 (d, $J=2.7 \mathrm{~Hz}, 1 \mathrm{H}$ ), 7.64 (d, $J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.43-7.22(\mathrm{~m}, 6 \mathrm{H}), 7.37$ (dd, $\left.J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.17-7.12(\mathrm{~m}, 2 \mathrm{H}), 6.82-6.79(\mathrm{~m}, 2 \mathrm{H}), 6.32\left(\mathrm{ddd}, J_{1}=2.9 \mathrm{~Hz}, J_{2}=\right.$ $\left.1.9 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.39(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 156.3(\mathrm{C}), 151.1$ (C), 150.1 (2CH), 138.4 (CH), 137.5 (C), 136.0 (C), $134.0(\mathrm{CH}), 131.2$ (C), 128.2 (2CH), 127.5 $(2 \mathrm{CH}), 127.46(\mathrm{C}), 127.44(\mathrm{CH}), 126.5(\mathrm{C}), 125.7(\mathrm{CH}), 124.1(\mathrm{C}), 120.7(\mathrm{CH}), 120.1(\mathrm{CH}), 111.3$
$(\mathrm{CH}), 108.5(2 \mathrm{CH}), 100.5(\mathrm{CH}), 67.1\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{25} \mathrm{H}_{21} \mathrm{~N}_{4} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+}$393.1710, found 393.1710.

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

Compound $\mathbf{3 8}$ was prepared according to general procedure B , starting from $37(1 \mathrm{~g}, 3.24 \mathrm{mmol})$. The mixture was refluxed for 14 h 30 min . The crude oil was purified by three column chromatographies $\left(\mathrm{SiO}_{2}, \mathrm{EtOAc} /\right.$ cyclohexane $1: 9$ to $15: 85 ; \mathrm{SiO}_{2}$, cyclohexane/ $\mathrm{Et}_{2} \mathrm{O} 9: 1$ to $75: 25$, $\mathrm{SiO}_{2}$; cyclohexane/acetone $75: 25$ ) to give 38 ( $899.9 \mathrm{mg}, 2.61 \mathrm{mmol}, 81 \%$ ) as an orange solid. $R_{\mathrm{f}}=$ 0.25 (EtOAc/cyclohexane 2:8); Mp $161^{\circ} \mathrm{C}$; $\operatorname{IR}$ (ATR) 3277, 1584, 1506, 1332, 1303, 1215, 998, $758,719 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.30(\mathrm{~s}, 1 \mathrm{H}), 9.13(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H})$, $8.47(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.47\left(\mathrm{dd}, J_{1}=6.8 \mathrm{~Hz}, J_{2}=2.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.41(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.37-7.24$ $(\mathrm{m}, 5 \mathrm{H}), 7.21-7.15(\mathrm{~m}, 2 \mathrm{H}), 6.35-6.33(\mathrm{~m}, 1 \mathrm{H}), 5.55(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $\mathrm{d}_{6}$ ) $\delta$ (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), $127.8(2 \mathrm{CH}), 126.4$ (C), $126.1(\mathrm{CH}), 125.5(\mathrm{C}), 124.2(\mathrm{C}), 120.8(\mathrm{CH}), 120.2(\mathrm{CH}), 112.1$ $(\mathrm{CH}), 100.2(\mathrm{CH}), 68.8\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{20} \mathrm{H}_{16} \mathrm{~N}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 346.1186$, found 346.1195.

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

To a solution of compound $\mathbf{3 8}(72 \mathrm{mg}, 0.208 \mathrm{mmol}, 1$ equiv) in a $10: 1$ propan- 2 -ol/water mixture $(4.4 \mathrm{~mL})$ were added Fe powder ( $70.5 \mathrm{mg}, 1.26 \mathrm{mmol}, 6.1$ equiv) and $\mathrm{NH}_{4} \mathrm{Cl}(4.5 \mathrm{mg}, 0.084 \mathrm{mmol}$, 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 $\mathrm{MgSO}_{4}$, filtered and then evaporated. The obtained orange oil was purified by column chromatography $\left(\mathrm{SiO}_{2}\right.$, EtOAc/cyclohexane 3:7 to 5:5) to give $39(46 \mathrm{mg}, 0.146 \mathrm{mmol}, 70 \%)$ as a brown solid. $R_{\mathrm{f}}=0.13$ (EtOAc/cyclohexane 3:7); Mp $68{ }^{\circ} \mathrm{C}$; IR (ATR) 3404, 1608, 1582, 1455, 1423, 1407, 1355, 1220, $751,731,695 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.13(\mathrm{~s}, 1 \mathrm{H}), 7.54(\mathrm{~d}, J=2.8 \mathrm{~Hz}$, $1 \mathrm{H}), 7.36\left(\mathrm{dt}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.33(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.29-7.18(\mathrm{~m}, 5 \mathrm{H}), 7.15(\mathrm{~d}, J=$ $2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.11(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.05\left(\mathrm{dd}, J_{1}=7.3 \mathrm{~Hz}, J_{2}=1.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.27\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}\right.$, $\left.J_{2}=1.9 \mathrm{~Hz}, J_{3}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.24(\mathrm{~s}, 2 \mathrm{H}), 4.85(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}\right.$, DMSO- $\left.d_{6}\right) \delta(\mathrm{ppm})$ 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 $(\mathrm{CH}), 126.9(\mathrm{CH}), 126.6(\mathrm{C}), 125.2(\mathrm{CH}), 123.3(\mathrm{C}), 120.6(\mathrm{CH}), 119.9(\mathrm{CH}), 110.7(\mathrm{CH}), 100.8$ $(\mathrm{CH}), 66.5\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 316.1444$, 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 ( $149.5 \mathrm{mg}, 0.474$ $\mathrm{mmol})$. The mixture was heated for $24 \mathrm{~h} . \mathrm{Pd}(\mathrm{OAc})_{2}(0.05$ 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 $\left(\mathrm{SiO}_{2}\right.$, cyclohexane to $\mathrm{EtOAc} /$ cyclohexane $15: 85$ and $\mathrm{SiO}_{2}$, pentane/ $\mathrm{Et}_{2} \mathrm{O} 9: 1$ to 8:2) to give 40 ( 105.8 mg , $0.225 \mathrm{mmol}, 47 \%$ ) as a white solid. $R_{\mathrm{f}}=0.42$ (EtOAc/cyclohexane 3:7); Mp $74^{\circ} \mathrm{C}$; IR (ATR) 3384, 3500-3100, 1593, 1494, 1441, 1353, 1021, 744, 728, $693 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta$ $(\mathrm{ppm}) 11.18(\mathrm{~s}, 1 \mathrm{H}), 8.03(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.57(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.55\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=\right.$ $1.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.46(\mathrm{~s}, 1 \mathrm{H}), 7.41-7.18(\mathrm{~m}, 7 \mathrm{H}), 7.36\left(\mathrm{dd}, J_{1}=3.1 \mathrm{~Hz}, J_{2}=2.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.15-7.10(\mathrm{~m}$, $2 \mathrm{H}), 7.06\left(\mathrm{dd}, J_{1}=8.2 \mathrm{~Hz}, J_{2}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.79-6.74(\mathrm{~m}, 1 \mathrm{H}), 6.33\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.0 \mathrm{~Hz}\right.$,
$\left.J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.37(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 155.6(\mathrm{C}), 142.9(\mathrm{C}), 137.8$ $(\mathrm{CH}), 137.6(\mathrm{C}), 136.0(\mathrm{C}), 133.5(\mathrm{CH}), 133.3(\mathrm{C}), 133.2(\mathrm{CH}), 128.6(\mathrm{CH}), 128.1(2 \mathrm{CH}), 127.7$ (C), $127.5(2 \mathrm{CH}), 127.4(\mathrm{CH}), 126.5(\mathrm{C}), 125.5(\mathrm{CH}), 123.8(\mathrm{C}), 121.1(\mathrm{CH}), 120.7(\mathrm{CH}), 120.1$ $(\mathrm{CH}), 116.5(\mathrm{CH}), 111.9(\mathrm{C}), 111.1(\mathrm{CH}), 100.6(\mathrm{CH}), 67.0\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{26} \mathrm{H}_{21} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 470.0863$, 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 ( $150.2 \mathrm{mg}, 0.476$ mmol ). The mixture was heated for 5 h . The crude oil was purified by column chromatography ( $\mathrm{SiO}_{2}$, EtOAc/cyclohexane $1: 9$ to $15: 85$ ) to give $41(104.1 \mathrm{mg}, 0.221 \mathrm{mmol}, 46 \%)$ as an orange solid. $R_{\mathrm{f}}=0.52$ (EtOAc/cyclohexane 3:7); Mp > $155{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3383, 1589, 1446, 1421, 1406, 1229, 989, 751, $695 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.21(\mathrm{~s}, 1 \mathrm{H})$, $8.28(\mathrm{~s}, 1 \mathrm{H}), 8.04(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.60(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.42-7.37(\mathrm{~m}, 1 \mathrm{H}), 7.37(\mathrm{t}, J=2.8$ $\mathrm{Hz}, 1 \mathrm{H}), 7.35-7.21(\mathrm{~m}, 5 \mathrm{H}), 7.16-7.11(\mathrm{~m}, 3 \mathrm{H}), 7.08(\mathrm{t}, J=2.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.93\left(\mathrm{ddd}, J_{1}=8.3 \mathrm{~Hz}, J_{2}=\right.$ $\left.2.3 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.89\left(\mathrm{ddd}, J_{1}=7.9 \mathrm{~Hz}, J_{2}=1.9 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.32$ (ddd, $J_{1}=3.0$ $\left.\mathrm{Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.37(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 155.5(\mathrm{C})$, 146.8 (C), 137.6 (C), $136.8(\mathrm{CH}), 136.1(\mathrm{C}), 132.8(\mathrm{C}), 132.6(\mathrm{CH}), 131.2(\mathrm{CH}), 128.2(2 \mathrm{CH})$, 127.6 (C), $127.5(2 \mathrm{CH}), 127.4(\mathrm{CH}), 126.5(\mathrm{C}), 125.6(\mathrm{CH}), 123.9(\mathrm{C}), 122.4(\mathrm{C}), 121.0(\mathrm{CH})$, $120.7(\mathrm{CH}), 120.1(\mathrm{CH}), 116.7(\mathrm{CH}), 113.4(\mathrm{CH}), 111.2(\mathrm{CH}), 100.4(\mathrm{CH}), 67.0\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{26} \mathrm{H}_{21} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 470.0863$, 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 ( $150.8 \mathrm{mg}, 0.478$ mmol ). The mixture was heated for 5 h . The crude oil was purified by two successive chromatography columns $\left(\mathrm{SiO}_{2}\right.$, cyclohexane to $\mathrm{EtOAc} /$ cyclohexane $2: 8$ and $\mathrm{SiO}_{2}$, pentane/ $\mathrm{Et}_{2} \mathrm{O} 9: 1$ to 8:2) to give 42 ( $103.8 \mathrm{mg}, 0.221 \mathrm{mmol}, 46 \%$ ) as a beige solid. $R_{\mathrm{f}}=0.35(\mathrm{EtOAc} /$ cyclohexane 3:7); Mp $161{ }^{\circ} \mathrm{C}$; IR (ATR) 3398, 3171, 1586, 1496, 1447, 1353, 1225, 1007, 748, 724, $688 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.19(\mathrm{~s}, 1 \mathrm{H}), 8.21(\mathrm{~s}, 1 \mathrm{H}), 8.03(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.57$ (d, $J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.42-7.21(\mathrm{~m}, 8 \mathrm{H}), 7.36\left(\mathrm{dd}, J_{1}=3.1 \mathrm{~Hz}, J_{2}=2.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.16-7.11(\mathrm{~m}, 2 \mathrm{H})$, $6.92(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.30\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 5.36(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 155.2(\mathrm{C}), 144.2(\mathrm{C}), 137.6(\mathrm{C}), 136.1(\mathrm{CH}), 136.0(\mathrm{C}), 133.4$ (C), $132.0(\mathrm{CH}), 131.9(2 \mathrm{CH}), 128.1(2 \mathrm{CH}), 127.7(\mathrm{C}), 127.5(2 \mathrm{CH}), 127.4(\mathrm{CH}), 126.5(\mathrm{C}), 125.6$ $(\mathrm{CH}), 123.9(\mathrm{C}), 120.7(\mathrm{CH}), 120.1(\mathrm{CH}), 116.8(2 \mathrm{CH}), 111.1(\mathrm{CH}), 109.4(\mathrm{C}), 100.5(\mathrm{CH}), 67.0$ $\left(\mathrm{CH}_{2}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{26} \mathrm{H}_{21} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 470.0863$, 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 $21(65.0 \mathrm{mg}, 0.159$ mmol ) and with 3.2 equiv of $\mathrm{BBr}_{3}$. The mixture was stirred for 1 h and was quenched with $\mathrm{NEt}_{3}$ ( 12 equiv) and MeOH (4 equiv). The crude was purified by column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{EtOAc}+\right.$ $0.5 \% \mathrm{NEt}_{3}$ ) to give $43(41 \mathrm{mg}, 0.128 \mathrm{mmol}, 81 \%)$ as a beige solid. $R_{\mathrm{f}}=0.22(\mathrm{EtOAc}) ; \mathrm{Mp}>141^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3353, 1649, 1609, 1505, 1337, 881, $739 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.61(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 11.13(\mathrm{~s}, 1 \mathrm{H}), 7.54(\mathrm{~d}, J=2.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.39(\mathrm{~d}, J=1.6 \mathrm{~Hz}$, $1 \mathrm{H}), 7.36\left(\mathrm{dt}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.34(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.28\left(\mathrm{dd}, J_{1}=7.3 \mathrm{~Hz}, J_{2}=1.0\right.$ $\mathrm{Hz}, 1 \mathrm{H}), 7.23(\mathrm{~d}, J=2.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.12\left(\mathrm{ddd}, J_{1}=12.2 \mathrm{~Hz}, J_{2}=8.1 \mathrm{~Hz}, J_{3}=1.4 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.10(\mathrm{t}, J=$ $7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.00\left(\mathrm{td}, J_{1}=7.7 \mathrm{~Hz}, J_{2}=1.4 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.89\left(\mathrm{td}, J_{1}=8.5 \mathrm{~Hz}, J_{2}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.74-$
$6.67(\mathrm{~m}, 1 \mathrm{H}), 6.40-6.38(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( $\left.101 \mathrm{MHz}, \mathrm{DMSO}-d_{6}\right) \delta(\mathrm{ppm}) 159.7(\mathrm{C}), 151.5\left(\mathrm{~d}, J_{\mathrm{CF}}\right.$ $=240 \mathrm{~Hz}, \mathrm{C}), 138.4(\mathrm{CH}), 136.1(\mathrm{C}), 134.7\left(\mathrm{~d}, J_{\mathrm{CF}}=11 \mathrm{~Hz}, \mathrm{C}\right), 130.5(\mathrm{C}), 128.3(\mathrm{C}), 127.6(\mathrm{CH})$, $126.1(\mathrm{C}), 125.3(\mathrm{CH}), 124.8\left(\mathrm{~d}, J_{\mathrm{CF}}=3 \mathrm{~Hz}, \mathrm{CH}\right), 121.7(\mathrm{C}), 120.4(\mathrm{CH}), 119.9(\mathrm{CH}), 118.2\left(\mathrm{~d}, J_{\mathrm{CF}}\right.$ $=7 \mathrm{~Hz}, \mathrm{CH}), 115.3\left(\mathrm{~d}, J_{\mathrm{CF}}=18 \mathrm{~Hz}, \mathrm{CH}\right), 114.6\left(\mathrm{~d}, J_{\mathrm{CF}}=3 \mathrm{~Hz}, \mathrm{CH}\right), 110.9(\mathrm{CH}), 100.6(\mathrm{CH}) ;$ HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{FN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 320.1194$, found 320.1195 ; HPLC purity $\geq 96 \%$, $\mathrm{t}_{\mathrm{R}}=$ $7.93 \mathrm{~min}, \lambda=272 \mathrm{~nm}$.

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

Compound 44 was prepared according to general procedure C 1 , starting from $22(91.0 \mathrm{mg}, 0.222$ mmol ) and with 3 equiv of $\mathrm{BBr}_{3}$. The mixture was stirred for 3 h and was quenched with $\mathrm{NEt}_{3}$ ( 10 equiv) and MeOH (6 equiv). The crude was filtered and washed with water, acetone and a mixture of $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ and cyclohexane to give $\mathbf{4 4}$ as a dark green solid ( $40.8 \mathrm{mg}, 0.128 \mathrm{mmol}, 57 \%$ ). $R_{\mathrm{f}}=0.20$ $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5\right) ; \mathrm{Mp}>166{ }^{\circ} \mathrm{C}$; IR (ATR) 3181, 1651, 1602, 1139, $751 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.63(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 11.14(\mathrm{~s}, 1 \mathrm{H}), 7.78(\mathrm{~s}, 1 \mathrm{H}), 7.50(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H})$, $7.36(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.34(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.27\left(\mathrm{dd}, J_{1}=7.3 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.26(\mathrm{br} \mathrm{s}$, $1 \mathrm{H}), 7.16\left(\mathrm{td}, J_{1}=8.2 \mathrm{~Hz}, J_{2}=7.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.10(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.57\left(\mathrm{dd}, J_{1}=8.3 \mathrm{~Hz}, J_{2}=2.2\right.$ $\left.\mathrm{Hz}, J_{3}=0.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.48\left(\mathrm{dt}, J_{1}=11.9 \mathrm{~Hz}, J_{2}=2.3 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.47-6.41(\mathrm{~m}, 1 \mathrm{H}), 6.37-6.34(\mathrm{~m}$, $1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 163.3\left(\mathrm{~d}, J_{\mathrm{CF}}=240 \mathrm{~Hz}, \mathrm{C}\right), 159.8(\mathrm{C}), 149.0\left(\mathrm{~d}, J_{\mathrm{CF}}\right.$ $=11 \mathrm{~Hz}, \mathrm{C}), 138.6(\mathrm{CH}), 136.1(\mathrm{C}), 130.78(\mathrm{C}), 130.76\left(\mathrm{~d}, J_{\mathrm{CF}}=10 \mathrm{~Hz}, \mathrm{CH}\right), 128.2(\mathrm{C}), 128.1$ $(\mathrm{CH}), 126.1(\mathrm{C}), 125.4(\mathrm{CH}), 121.4(\mathrm{C}), 120.5(\mathrm{CH}), 119.9(\mathrm{CH}), 111.0(\mathrm{CH}), 109.6(\mathrm{CH}), 103.8(\mathrm{~d}$, $\left.J_{\mathrm{CF}}=21 \mathrm{~Hz}, \mathrm{CH}\right), 100.4(\mathrm{CH}), 99.9\left(\mathrm{~d}, J_{\mathrm{CF}}=25 \mathrm{~Hz}, \mathrm{CH}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{FN}_{3} \mathrm{O}$ $(\mathrm{M}+\mathrm{H})^{+} 320.1194$, found 320.1211 ; HPLC purity $\geq 95 \%, \mathrm{t}_{\mathrm{R}}=7.93 \mathrm{~min}, \lambda=288 \mathrm{~nm}$.

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

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

### 4.1.43. Ethyl 2-((5-(1H-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 ( $104.6 \mathrm{mg}, 0.226$ 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 ( $84 \mathrm{mg}, 0.225 \mathrm{mmol}$, quant.) was obtained as an orange solid. $R_{\mathrm{f}}=$ $0.35\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 98: 2+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>263{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3285, 1680,

1654, 1627, 1452, 1238, $750 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.79$ (br s, 1H), 11.13 $(\mathrm{s}, 1 \mathrm{H}), 8.88(\mathrm{~s}, 1 \mathrm{H}), 7.87\left(\mathrm{dd}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=1.7 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.51(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.43-7.37(\mathrm{~m}$, $2 \mathrm{H}), 7.36\left(\mathrm{dt}, J=8.1 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.33(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.26\left(\mathrm{dd}, J_{1}=7.4 \mathrm{~Hz}, J_{2}=0.9\right.$ $\mathrm{Hz}, 1 \mathrm{H}), 7.09(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.82\left(\mathrm{dd}, J_{1}=8.6 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.72\left(\mathrm{ddd}, J_{1}=8.2 \mathrm{~Hz}, J_{2}\right.$ $\left.=7.2 \mathrm{~Hz}, J_{3}=1.2 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.38-6.35(\mathrm{~m}, 1 \mathrm{H}), 4.31(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.33(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;$ ${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 167.5(\mathrm{C}=\mathrm{O}), 160.3(\mathrm{C}=\mathrm{O}), 149.8(\mathrm{C}), 140.0(\mathrm{CH}), 136.1$ (C), $134.6(\mathrm{CH}), 131.5(\mathrm{CH}), 131.2(\mathrm{CH}), 130.9(\mathrm{C}), 128.2(\mathrm{C}), 126.1(\mathrm{C}), 125.3(\mathrm{CH}), 120.4(\mathrm{CH})$, $119.9(\mathrm{CH}), 119.3(\mathrm{C}), 116.4(\mathrm{CH}), 113.2(\mathrm{CH}), 110.9(\mathrm{CH}), 110.7(\mathrm{C}), 100.5(\mathrm{CH}), 60.4\left(\mathrm{CH}_{2}\right)$, $14.2\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{22} \mathrm{H}_{20} \mathrm{~N}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 374.1499$, found 374.1490 ; HPLC purity $\geq 96 \%, \mathrm{t}_{\mathrm{R}}=8.65 \mathrm{~min}, \lambda=270 \mathrm{~nm}$.

### 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 $25(169.3 \mathrm{mg}, 0.365$ 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 ( $\mathrm{NEt}_{3}-$ treated $\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5$ ) to give $\mathbf{4 7}$ containing $\mathrm{NEt}_{3}$ salts. The product was washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $47(72.1 \mathrm{mg}, 0.193 \mathrm{mmol}, 53 \%)$ as a beige solid. $R_{\mathrm{f}}=0.35\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>244{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3365, 3207, 1691, 1660, 1601, 1539, 1465, 1285, 846, $746 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm})$ $11.61(\mathrm{~s}, 1 \mathrm{H}), 11.15(\mathrm{~s}, 1 \mathrm{H}), 7.82(\mathrm{~s}, 1 \mathrm{H}), 7.50(\mathrm{~d}, J=2.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.38-7.25(\mathrm{~m}, 7 \mathrm{H}), 7.10(\mathrm{t}, J=$ $7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.02\left(\mathrm{dt}, J_{1}=6.6 \mathrm{~Hz}, J_{2}=2.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.39\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=1.0 \mathrm{~Hz}\right.$, $1 \mathrm{H}), 4.28(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.29(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm})$ $166.0(\mathrm{C}=\mathrm{O})$, 159.8 ( $\mathrm{C}=\mathrm{O}$ ), 147.2 (C), $138.5(\mathrm{CH}), 136.1$ (C), 130.83 (C), 130.76 (C), $129.6(\mathrm{CH})$, 128.2 (C), $127.8(\mathrm{CH}), 126.1$ (C), 125.4 (CH), 121.6 (C), 120.4 (CH), 119.9 (CH), $118.4(\mathrm{CH})$, $118.2(\mathrm{CH}), 113.5(\mathrm{CH}), 111.0(\mathrm{CH}), 100.4(\mathrm{CH}), 60.6\left(\mathrm{CH}_{2}\right), 14.2\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{22} \mathrm{H}_{20} \mathrm{~N}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 374.1499$, found 374.1499; HPLC purity $\geq 96 \%, \mathrm{t}_{\mathrm{R}}=8.03 \mathrm{~min}, \lambda=278 \mathrm{~nm}$.

### 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 $26(145.4 \mathrm{mg}, 0.314$ 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 $\mathbf{4 8}(116.6 \mathrm{mg}, 0.312 \mathrm{mmol}$, quant.) as a yellow-brown solid. $R_{\mathrm{f}}=0.30\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>255{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3200, 3280, 1687, 1656, 1595, 1454, 1257, 1168, 1098, $756 \mathrm{~cm}^{-1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.57(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 11.14(\mathrm{~s}, 1 \mathrm{H}), 8.21(\mathrm{~s}, 1 \mathrm{H}), 7.76(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.50(\mathrm{~d}, J$ $=2.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.37-7.33(\mathrm{~m}, 2 \mathrm{H}), 7.33(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.28\left(\mathrm{dd}, J_{1}=7.3 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.09(\mathrm{t}, J$ $=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.78(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.37-6.35(\mathrm{~m}, 1 \mathrm{H}), 4.22(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 1.27(\mathrm{t}, J=7.1$ $\mathrm{Hz}, 3 \mathrm{H})$; ${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 165.7$ (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 $(\mathrm{CH}), 120.36(\mathrm{C}), 119.9(\mathrm{CH}), 118.1(\mathrm{C}), 112.3(2 \mathrm{CH}), 110.9(\mathrm{CH}), 100.5(\mathrm{CH}), 59.8\left(\mathrm{CH}_{2}\right), 14.3$ $\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{22} \mathrm{H}_{20} \mathrm{~N}_{3} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 374.1499$, found 374.1486; HPLC purity $\geq$ $98 \%, \mathrm{t}_{\mathrm{R}}=7.95 \mathrm{~min}, \lambda=310 \mathrm{~nm}$.

Compound 49 was prepared according to general procedure D , starting from 27 ( $148 \mathrm{mg}, 0.351$ 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $\mathbf{4 9}(97.8 \mathrm{mg}, 0.295 \mathrm{mmol}, 84 \%)$ as a beige solid. $R_{\mathrm{f}}=0.51\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>240^{\circ} \mathrm{C}$ (decomposition); IR (ATR) $3395,3351,3314,1653,1619,1595,1556,1503,1454,1342,1251,1116,1021,738 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.51(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 11.13(\mathrm{~s}, 1 \mathrm{H}), 7.53(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.35\left(\mathrm{dt}, J_{1}\right.$ $\left.=8.1 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.33(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.27\left(\mathrm{dd}, J_{1}=7.4 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.20(\mathrm{br}$ d, $J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.09\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=7.4 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.91\left(\mathrm{dd}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=1.4 \mathrm{~Hz}, 1 \mathrm{H}\right)$, $6.85(\mathrm{~s}, 1 \mathrm{H}), 6.80-6.66(\mathrm{~m}, 3 \mathrm{H}), 6.39-6.37(\mathrm{~m}, 1 \mathrm{H}), 3.82(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 159.7(\mathrm{C}=\mathrm{O}), 147.3$ (C), $138.8(\mathrm{CH}), 136.1$ (C), 136.0 (C), 130.3 (C), 128.4 (C), 127.5 $(\mathrm{CH}), 126.1(\mathrm{C}), 125.3(\mathrm{CH}), 122.2(\mathrm{C}), 120.8(\mathrm{CH}), 120.4(\mathrm{CH}), 119.9(\mathrm{CH}), 118.0(\mathrm{CH}), 111.9$ $(\mathrm{CH}), 110.83(\mathrm{CH}), 110.82(\mathrm{CH}), 100.6(\mathrm{CH}), 55.4\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{3} \mathrm{O}_{2}$ $(\mathrm{M}+\mathrm{H})^{+} 332.1394$, found 332.1393 ; HPLC purity $\geq 97 \%, \mathrm{t}_{\mathrm{R}}=8.00 \mathrm{~min}, \lambda=276 \mathrm{~nm}$.

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

Compound 50 was prepared according to general procedure D, starting from 28 ( $204.5 \mathrm{mg}, 0.485$ 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 $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $\mathbf{5 0}$ ( $129.3 \mathrm{mg}, 0.390 \mathrm{mmol}, 80 \%$ ) as a brown solid. $R_{\mathrm{f}}=0.45\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>141{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3000, 1650, 1591, 1153, 752, $688 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm})$ $11.52(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 11.14(\mathrm{~s}, 1 \mathrm{H}), 7.52(\mathrm{~s}, 1 \mathrm{H}), 7.51(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.36\left(\mathrm{dt}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=0.9\right.$ $\mathrm{Hz}, 1 \mathrm{H}), 7.34(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.26\left(\mathrm{dd}, J_{1}=7.3 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.20(\mathrm{br} \mathrm{d}, J=2.6 \mathrm{~Hz}$, $1 \mathrm{H}), 7.09(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.05(\mathrm{t}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 6.37-6.33(\mathrm{~m}, 2 \mathrm{H}), 6.30(\mathrm{t}, J=2.2 \mathrm{~Hz}, 1 \mathrm{H})$, $6.27\left(\mathrm{ddd}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=2.5 \mathrm{~Hz}, J_{3}=0.8 \mathrm{~Hz}, 1 \mathrm{H}\right), 3.68(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}\right.$, DMSO- $\left.d_{6}\right)$ $\delta(\mathrm{ppm}) 160.4(\mathrm{C}=\mathrm{O}), 159.6$ (C), $148.0(\mathrm{C}), 138.5$ (CH), 136.1 (C), 130.5 (C), 130.0 (CH), 128.3 (C), $127.0(\mathrm{CH}), 126.1(\mathrm{C}), 125.3(\mathrm{CH}), 122.3(\mathrm{C}), 120.5(\mathrm{CH}), 119.9(\mathrm{CH}), 110.9(\mathrm{CH}), 106.6$ $(\mathrm{CH}), 103.4(\mathrm{CH}), 100.5(\mathrm{CH}), 99.7(\mathrm{CH}), 54.8\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{3} \mathrm{O}_{2}$ $(\mathrm{M}+\mathrm{H})^{+} 332.1394$, found 332.1392 ; HPLC purity $\geq 97 \%, \mathrm{t}_{\mathrm{R}}=7.81 \mathrm{~min}, \lambda=278 \mathrm{~nm}$.

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

Compound 51 was prepared according to general procedure D, starting from 29 ( $100.6 \mathrm{mg}, 0.239$ 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 $51(78.4 \mathrm{mg}, 0.237 \mathrm{mmol}, 99 \%)$ was obtained as a red solid. $R_{\mathrm{f}}=0.39$ $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>132{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3000, 1651, $1605,1506,1233,1036,820,756 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.44(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, $11.13(\mathrm{~s}, 1 \mathrm{H}), 7.49(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.37-7.33(\mathrm{~m}, 2 \mathrm{H}), 7.25(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.19(\mathrm{~s}, 1 \mathrm{H})$, 7.09 (br s, 1H), $7.09(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.83-6.76(\mathrm{~m}, 4 \mathrm{H}), 6.36-6.34(\mathrm{~m}, 1 \mathrm{H}), 3.66(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ) $\delta$ (ppm) 159.3 (C=O), 152.5 (C), 139.7 (C), 137.2 (CH), 136.1 (C), $130.5(\mathrm{C}), 128.5(\mathrm{C}), 126.1(\mathrm{C}), 125.3(\mathrm{CH}), 124.6(\mathrm{C}), 124.0(\mathrm{CH}), 120.4(\mathrm{CH}), 119.9(\mathrm{CH}), 116.5$ $(2 \mathrm{CH}), 114.7(2 \mathrm{CH}), 110.8(\mathrm{CH}), 100.6(\mathrm{CH}), 55.3\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{3} \mathrm{O}_{2}$ $(\mathrm{M}+\mathrm{H})^{+} 332.1394$, found 332.1398 ; HPLC purity $\geq 96 \%, \mathrm{t}_{\mathrm{R}}=7.71 \mathrm{~min}, \lambda=280 \mathrm{~nm}$.

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

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

Compound $\mathbf{5 3}$ was prepared according to general procedure C2, starting from $\mathbf{3 0}$ ( $119 \mathrm{mg}, 0.273$ mmol ) and 3.7 equiv of $\mathrm{BBr}_{3}$. The mixture was stirred for 3 h 15 min . The reaction mixture was then quenched by addition of $\mathrm{NEt}_{3}$ ( 13 equiv) and MeOH ( 5 equiv). The crude was purified by column chromatography ( $\mathrm{NEt}_{3}$-treated $\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 98: 2$ to $95: 5$ ). To eliminate traces of $\mathrm{NEt}_{3}$ salts, the product was washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $\mathbf{5 3}$ ( $31 \mathrm{mg}, 0.090 \mathrm{mmol}, 33 \%$ ) as an orange solid. $R_{\mathrm{f}}=0.33\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>268^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3350, $3232,1653,1606,1498,1470,1257,744,726,696 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm})$ $11.87(\mathrm{~s}, 1 \mathrm{H}), 11.13(\mathrm{~s}, 1 \mathrm{H}), 9.18(\mathrm{~s}, 1 \mathrm{H}), 8.10\left(\mathrm{dd}, J_{1}=8.5 \mathrm{~Hz}, J_{2}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.55(\mathrm{~d}, J=2.9$ $\mathrm{Hz}, 1 \mathrm{H}), 7.53\left(\mathrm{ddd}, J_{1}=8.5 \mathrm{~Hz}, J_{2}=7.0 \mathrm{~Hz}, J_{3}=1.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.48(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.36\left(\mathrm{dt}, J_{1}=8.1 \mathrm{~Hz}\right.$, $\left.J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.33\left(\mathrm{dd}, J_{1}=3.1 \mathrm{~Hz}, J_{2}=2.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.28\left(\mathrm{dd}, J_{1}=7.4 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right)$, $7.10(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.01\left(\mathrm{dd}, J_{1}=8.7 \mathrm{~Hz}, J_{2}=1.2 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.81\left(\mathrm{ddd}, J_{1}=8.4 \mathrm{~Hz}, J_{2}=6.9 \mathrm{~Hz}\right.$, $\left.J_{3}=1.2 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.42-6.40(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 160.3(\mathrm{C}=\mathrm{O}), 144.5$ (C), 140.1 (CH), 136.3 (CH), 136.1 (C), 132.4 (C), 132.3 (CH), 131.0 (C), 128.0 (C), 126.2 $(\mathrm{CH}+\mathrm{C}), 125.4(\mathrm{CH}), 120.4(\mathrm{CH}), 119.9(\mathrm{CH}), 118.4(\mathrm{C}), 117.0(\mathrm{CH}), 116.2(\mathrm{CH}), 111.0(\mathrm{CH})$, $100.7(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{~N}_{4} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 347.1139$, found 347.1150; HPLC purity $\geq 96 \%, \mathrm{t}_{\mathrm{R}}=8.11 \mathrm{~min}, \lambda=276 \mathrm{~nm}$.

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

Compound $\mathbf{5 4}$ was prepared according to general procedure C 2 , starting from $\mathbf{3 1}$ ( $90 \mathrm{mg}, 0.206$ $\mathrm{mmol})$. The mixture was stirred for 5 h . The reaction mixture was then quenched by addition of $\mathrm{NEt}_{3}$ ( 17 equiv) and MeOH ( 6 equiv). The crude was purified by column chromatography ( $\mathrm{NEt}_{3}-$ treated $\mathrm{SiO}_{2}, 98: 2 \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ to $9: 1 \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}$ ) to give $54(65.1 \mathrm{mg}, 0.188 \mathrm{mmol}, 91 \%)$ as an orange brown solid. $R_{\mathrm{f}}=0.25\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>295{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3396, 3283, 1604, 1655, 1604, 1509, 1455, 1337, 761, $724 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.74(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 11.15(\mathrm{~s}, 1 \mathrm{H}), 8.15(\mathrm{~s}, 1 \mathrm{H}), 7.53(\mathrm{~d}, J=3.0$ $\mathrm{Hz}, 1 \mathrm{H}), 7.51-7.47(\mathrm{~m}, 2 \mathrm{H}), 7.42(\mathrm{t}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.37(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.37-7.32(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, $7.33(\mathrm{t}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.27(\mathrm{~d}, J=7.1 \mathrm{~Hz}, 1 \mathrm{H}), 7.18-7.14(\mathrm{~m}, 1 \mathrm{H}), 7.10(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.38-$ $6.36(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 159.9(\mathrm{C}=\mathrm{O}), 148.9$ (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), $120.4(\mathrm{CH}), 120.0(\mathrm{CH}), 119.7(\mathrm{CH}), 111.8(\mathrm{CH}), 111.0(\mathrm{CH}), 106.6(\mathrm{CH}), 100.4(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{~N}_{4} \mathrm{O}_{3}(\mathrm{M}+\mathrm{H})^{+} 347.1139$, found 347.1140; HPLC purity $\geq 95 \%$, $\mathrm{t}_{\mathrm{R}}=7.92$ $\min , \lambda=260 \mathrm{~nm}$.

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

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

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

Compound 56 was prepared according to general procedure D , starting from 30 ( $50.4 \mathrm{mg}, 0.115$ mmol ) in 3 mL of MeOH . The mixture was stirred under $\mathrm{H}_{2}$ for 4 h 30 min in the dark. The crude was purified by column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5\right)$ to give 56 ( $22.1 \mathrm{mg}, 0.070$ $\mathrm{mmol}, 60 \%)$ as a brown solid. $R_{\mathrm{f}}=0.20\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>208{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3000, 1649, 1597, 1556, 1500, 1452, $747 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR (400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.34(\mathrm{~s}, 1 \mathrm{H}), 11.11(\mathrm{~s}, 1 \mathrm{H}), 7.45(\mathrm{~d}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.36-7.31(\mathrm{~m}, 2 \mathrm{H})$, $7.26(\mathrm{~d}, J=7.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.08(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.83(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 6.76(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.72-$ $6.65(\mathrm{~m}, 2 \mathrm{H}), 6.54(\mathrm{~s}, 1 \mathrm{H}), 6.53-6.48(\mathrm{~m}, 1 \mathrm{H}), 6.40-6.37(\mathrm{~m}, 1 \mathrm{H}), 4.73(\mathrm{~s}, 2 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 159.0$ (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), $121.9(\mathrm{CH}), 121.8(\mathrm{CH}), 120.4(\mathrm{CH}), 119.9(\mathrm{CH})$, $118.3(\mathrm{CH}), 116.8(\mathrm{CH}), 115.0(\mathrm{CH}), 110.7(\mathrm{CH}), 100.6(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{17} \mathrm{~N}_{4} \mathrm{O}$ $(\mathrm{M}+\mathrm{H})^{+} 317.1397$, 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 ( $69.4 \mathrm{mg}, 0.171$ 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 ( $\mathrm{NEt}_{3}$-treated $\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5$ ) to give $\mathbf{5 7}$ containing $\mathrm{NEt}_{3}$ salts. $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added and the solution was washed with saturated $\mathrm{NaHCO}_{3}$ solution and water. The organic phase was dried over $\mathrm{MgSO}_{4}$ and filtered. After evaporation under reduced pressure, product $57(41.8 \mathrm{mg}, 0.133 \mathrm{mmol}, 77 \%)$ was obtained as a red powder. $R_{\mathrm{f}}=0.18$ $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>199{ }^{\circ} \mathrm{C}$; IR (ATR) 3500-3000, 1650, 1599, 1557, 1498, $1113,747,614 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.53$ (br s, 1H), 11.13 (s, 1H), 7.51 $(\mathrm{d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.35\left(\mathrm{dt}, J_{1}=8.1 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.33(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.27\left(\mathrm{dd}, J_{1}\right.$ $\left.=7.3 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.13(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.09(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.07(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}), 7.02(\mathrm{t}$,
$J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.75(\mathrm{~s}, 1 \mathrm{H}), 6.72(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 1 \mathrm{H}), 6.67\left(\mathrm{td}, J_{1}=7.2 \mathrm{~Hz}, J_{2}=1.1 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.36$ $\left(\mathrm{ddd}, J_{1}=3.1 \mathrm{~Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 2.20(\mathrm{~s}, 3 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}\right.$, DMSO- $\left.d_{6}\right) \delta$ (ppm) 159.6 (C=O), 144.8 (C), $138.7(\mathrm{CH}), 136.1$ (C), $130.5(\mathrm{CH}), 130.4(\mathrm{C}), 128.3$ (C), 126.9 $(\mathrm{CH}), 126.6(\mathrm{CH}), 126.1(\mathrm{C}), 125.3(\mathrm{CH}), 124.3(\mathrm{C}), 123.1(\mathrm{C}), 120.4(\mathrm{CH}), 119.9(\mathrm{CH}), 118.5$ $(\mathrm{CH}), 113.1(\mathrm{CH}), 110.8(\mathrm{CH}), 100.5(\mathrm{CH}), 17.8\left(\mathrm{CH}_{3}\right)$; HRMS (ESI+) calcd for $\mathrm{C}_{20} \mathrm{H}_{18} \mathrm{~N}_{3} \mathrm{O}$ $(\mathrm{M}+\mathrm{H})^{+} 316.1444$, found 316.1449 ; HPLC purity $\geq 96 \%, \mathrm{t}_{\mathrm{R}}=8.09 \mathrm{~min}, \lambda=278 \mathrm{~nm}$.

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

Compound $\mathbf{5 8}$ was prepared according to general procedure C1, starting from $\mathbf{3 4}$ ( $102.6 \mathrm{mg}, 0.261$ mmol ). The mixture was stirred for 4 h 40 min and was quenched with $\mathrm{NEt}_{3}$ ( 14 equiv) and MeOH (9 equiv). The crude was purified by column chromatography $\left(\mathrm{SiO}_{2}\right.$, acetone/cylohexane $5: 5+0.5 \%$ $\mathrm{NEt}_{3}$ to $\left.6: 4+0.5 \% \mathrm{NEt}_{3}\right)$ to give $\mathbf{5 8}(48.5 \mathrm{mg}, 0.160 \mathrm{mmol}, 61 \%)$ as a light orange solid. $R_{\mathrm{f}}=0.38$ (acetone/cyclohexane 7:3); $\mathrm{Mp}>171^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3000, 1652, 1596, 1338, $754 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.44(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 11.13(\mathrm{~s}, 1 \mathrm{H}), 8.67(\mathrm{~s}, 1 \mathrm{H})$, $8.10\left(\mathrm{dd}, J_{1}=5.0 \mathrm{~Hz}, J_{2}=1.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.97(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.78(\mathrm{~d}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.51$ (ddd, $\left.J_{1}=8.7 \mathrm{~Hz}, J_{2}=7.1 \mathrm{~Hz}, J_{3}=2.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.38-7.35(\mathrm{~m}, 2 \mathrm{H}), 7.31\left(\mathrm{dd}, J_{1}=7.4 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}\right.$, $1 \mathrm{H}), 7.10(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.71-6.68(\mathrm{~m}, 1 \mathrm{H}), 6.67\left(\mathrm{ddd}, J_{1}=7.1 \mathrm{~Hz}, J_{2}=5.1 \mathrm{~Hz}, J_{3}=0.9 \mathrm{~Hz}\right.$, 1H), 6.51-6.49 (m, 1H); ${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 159.1$ (C=O), $158.5(\mathrm{CH}), 156.3$ (C), $147.2(\mathrm{CH}), 137.1(\mathrm{CH}), 136.1(\mathrm{C}), 136.0(\mathrm{CH}), 129.8(\mathrm{C}), 128.5(\mathrm{C}), 126.2(\mathrm{C}), 125.2(\mathrm{CH})$, $122.1(\mathrm{C}), 120.4(\mathrm{CH}), 120.0(\mathrm{CH}), 113.5(\mathrm{CH}), 110.8(\mathrm{CH}), 110.0(\mathrm{CH}), 100.8(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{~N}_{4} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 303.1240$, found 303.1247; HPLC purity $\geq 98 \%, \mathrm{t}_{\mathrm{R}}=5.82$ $\min , \lambda=320 \mathrm{~nm}$.

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

Compound $\mathbf{5 9}$ was prepared according to general procedure D , starting from $\mathbf{3 5}$ ( $114.6 \mathrm{mg}, 0.292$ $\mathrm{mmol})$ in 2 mL of MeOH and with 0.14 equiv of $\mathrm{Pd}(\mathrm{OH})_{2} / \mathrm{C}$. The mixture was stirred under $\mathrm{H}_{2}$ for 3 days in the dark. The crude was purified by column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5\right.$ to 9:1) to give $\mathbf{5 9}(42 \mathrm{mg}, 0.139 \mathrm{mmol}, 48 \%)$ as a light orange solid. $R_{\mathrm{f}}=0.35\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 9: 1+\right.$ $0.5 \% \mathrm{NEt}_{3}$ ); Mp > $179^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3000, 1651, 1579, 1336, 752, $706 \mathrm{~cm}^{-}$ ${ }^{1}$; ${ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.63(\mathrm{~s}, 1 \mathrm{H}), 11.14(\mathrm{~s}, 1 \mathrm{H}), 8.13\left(\mathrm{dd}, J_{1}=2.6 \mathrm{~Hz}, J_{2}=\right.$ $0.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.90\left(\mathrm{dd}, J_{1}=4.4 \mathrm{~Hz}, J_{2}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.73(\mathrm{~s}, 1 \mathrm{H}), 7.51(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.36(\mathrm{dt}$, $\left.J_{1}=8.0 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.34(\mathrm{t}, J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.28(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.26\left(\mathrm{dd}, J_{1}=7.4 \mathrm{~Hz}, J_{2}=\right.$ $1.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.18-7.09(\mathrm{~m}, 2 \mathrm{H}), 7.10(\mathrm{t}, J=7.8 \mathrm{~Hz}, 1 \mathrm{H}), 6.37-6.35(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz , DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 159.7(\mathrm{C}=\mathrm{O}), 143.0(\mathrm{C}), 138.9(\mathrm{CH}), 138.1(\mathrm{CH}), 136.7(\mathrm{CH}), 136.1(\mathrm{C}), 130.9$ (C), 128.2 (C), $127.6(\mathrm{CH}), 126.1(\mathrm{C}), 125.4(\mathrm{CH}), 123.9(\mathrm{CH}), 121.4(\mathrm{C}), 120.5(\mathrm{CH}), 119.9(\mathrm{CH})$, $119.4(\mathrm{CH}), 111.0(\mathrm{CH}), 100.5(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{~N}_{4} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+}$303.1240, found 303.1246 ; HPLC purity $\geq 96 \%, \mathrm{t}_{\mathrm{R}}=5.71 \mathrm{~min}, \lambda=268 \mathrm{~nm}$.

### 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 $36(61 \mathrm{mg}, 0.155 \mathrm{mmol})$ in $\mathrm{MeOH}(6 \mathrm{~mL})$ was engaged in reaction $\left(\mathrm{Pd}(\mathrm{OH})_{2} / \mathrm{C}\right.$ cartridge, room temperature, $1 \mathrm{~mL} / \mathrm{min}, 3$ cycles $)$. The crude was purified by column chromatography ( $\mathrm{NEt}_{3}$-treated $\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5$ to $8: 2$ ) to give $\mathbf{6 0}$ after evaporation a $\sim 1: 1$ solvate with MeOH ( 29 mg , containing $10.4 \% \mathrm{w} / \mathrm{w}$ of MeOH as measured by NMR, $0.086 \mathrm{mmol}, 55 \%)$ as a light brown solid. $R_{\mathrm{f}}=0.03\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5\right) ; \mathrm{Mp}>200{ }^{\circ} \mathrm{C}$
(decomposition); IR (ATR) 3400-2900, 1655, 1587, 1357, 1332, 1215, 1027, 1000, 808, 755, 638 $\mathrm{cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.71(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 11.15(\mathrm{~s}, 1 \mathrm{H}), 8.22(\mathrm{~s}, 1 \mathrm{H}), 8.13-$ $8.10(\mathrm{~m}, 2 \mathrm{H}), 7.50(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.37\left(\mathrm{dt}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.35(\mathrm{t}, J=2.7 \mathrm{~Hz}$, $1 \mathrm{H}), 7.33(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.27\left(\mathrm{dd}, J_{1}=7.4 \mathrm{~Hz}, J_{2}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.10(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.65-6.63(\mathrm{~m}$, $2 \mathrm{H}), 6.36\left(\mathrm{ddd}, J_{1}=3.0 \mathrm{~Hz}, J_{2}=2.0 \mathrm{~Hz}, J_{3}=0.8 \mathrm{~Hz}, 1 \mathrm{H}\right) ;{ }^{13} \mathrm{C} \mathrm{NMR}\left(101 \mathrm{MHz}\right.$, DMSO- $\left.d_{6}\right) \delta(\mathrm{ppm})$ $159.9(\mathrm{C}=\mathrm{O}), 152.6(\mathrm{C}), 149.8(2 \mathrm{CH}), 138.6(\mathrm{CH}), 136.1(\mathrm{C}), 130.9(\mathrm{C}), 129.4(\mathrm{CH}), 128.1(\mathrm{C})$, $126.1(\mathrm{C}), 125.4(\mathrm{CH}), 120.5(\mathrm{CH}), 119.9(\mathrm{CH}), 119.5(\mathrm{C}), 111.0(\mathrm{CH}), 108.1(2 \mathrm{CH}), 100.5(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{18} \mathrm{H}_{15} \mathrm{~N}_{4} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 303.1240$, found 303.1236 ; HPLC purity $\geq 95 \%$, $\mathrm{t}_{\mathrm{R}}=$ $5.66 \mathrm{~min}, \lambda=270 \mathrm{~nm}$.

### 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 ( $105 \mathrm{mg}, 0.223$ mmol ). The mixture was stirred for 3 h 30 min . The reaction mixture was then quenched by addition of $\mathrm{NEt}_{3}$ ( 16 equiv) and MeOH ( 6 equiv). The crude was purified by column chromatography ( $\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 98: 2$ to $94: 6$ ). After evaporation, $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added and the solution was washed with saturated aqueous NaCl solution. The organic phase was dried over $\mathrm{MgSO}_{4}$, filtered and evaporated to give $\mathbf{6 1}(49.8 \mathrm{mg}, 0.131 \mathrm{mmol}, 59 \%)$ as a beige powder. $R_{\mathrm{f}}=$ $0.39\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right) ; \mathrm{Mp}>227{ }^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3000, 1650, 1611, 1589, 1555, 1491, 1449, 1020, $743 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm})$ $11.68(\mathrm{~s}, 1 \mathrm{H}), 11.13(\mathrm{~s}, 1 \mathrm{H}), 7.49\left(\mathrm{dd}, J_{1}=7.9 \mathrm{~Hz}, J_{2}=1.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.49(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.36$ $\left(\mathrm{dt}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.33(\mathrm{t}, J=2.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.29(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.28(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H})$, $7.18\left(\mathrm{ddd}, J_{1}=8.8 \mathrm{~Hz}, J_{2}=7.4 \mathrm{~Hz}, J_{3}=1.5 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.09(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.01(\mathrm{~s}, 1 \mathrm{H}), 6.78$ (dd, $\left.J_{1}=8.1 \mathrm{~Hz}, J_{2}=1.4 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.66\left(\mathrm{ddd}, J_{1}=7.9 \mathrm{~Hz}, J_{2}=7.3 \mathrm{~Hz}, J_{3}=1.6 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.40-6.38$ $(\mathrm{m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 159.9(\mathrm{C}=\mathrm{O}), 144.4(\mathrm{C}), 139.4(\mathrm{CH}), 136.1(\mathrm{C})$, $132.9(\mathrm{CH}), 130.6(\mathrm{C}), 129.6(\mathrm{CH}), 128.5(\mathrm{CH}), 128.2(\mathrm{C}), 126.1(\mathrm{C}), 125.3(\mathrm{CH}), 121.1(\mathrm{C}), 120.4$ $(\mathrm{CH}), 119.9(\mathrm{CH}), 119.4(\mathrm{CH}), 114.3(\mathrm{CH}), 110.9(\mathrm{CH}), 109.6(\mathrm{C}), 100.5(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 380.0393$, found 380.0388 ; HPLC purity $\geq 98 \%, \mathrm{t}_{\mathrm{R}}=8.35 \mathrm{~min}, \lambda=$ 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 C 2 , starting from $41(81 \mathrm{mg}, 0.172$ mmol ). The mixture was stirred for 3 h 30 min . The reaction mixture was then quenched by addition of $\mathrm{NEt}_{3}$ ( 21 equiv) and MeOH ( 7 equiv). The crude was purified by column chromatography $\left(\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 97: 3\right.$ to $\left.94: 6\right)$. After evaporation, the product was washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $\mathbf{6 2}(44.7 \mathrm{mg}, 0.118 \mathrm{mmol}, 68 \%)$ as light green powder. $R_{\mathrm{f}}=0.31$ $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 95: 5+0.5 \% \mathrm{NEt}_{3}\right.$ ); $\mathrm{Mp}>155^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3000, 1649, $1614,1588,1556,1333,892,755 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.64(\mathrm{br} \mathrm{s}, 1 \mathrm{H})$, $11.15(\mathrm{~s}, 1 \mathrm{H}), 7.77(\mathrm{~s}, 1 \mathrm{H}), 7.50(\mathrm{~d}, J=2.9 \mathrm{~Hz}, 1 \mathrm{H}), 7.36\left(\mathrm{dt}, J_{1}=8.0 \mathrm{~Hz}, J_{2}=0.9 \mathrm{~Hz}, 1 \mathrm{H}\right), 7.35(\mathrm{t}$, $J=2.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.27(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H}), 7.26(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.12-7.07(\mathrm{~m}, 2 \mathrm{H}), 6.89(\mathrm{t}, J=2.1 \mathrm{~Hz}$, $1 \mathrm{H}), 6.82\left(\mathrm{ddd}, J_{1}=7.9 \mathrm{~Hz}, J_{2}=2.1 \mathrm{~Hz}, J_{3}=1.0 \mathrm{~Hz}, 1 \mathrm{H}\right), 6.73\left(\mathrm{dd}, J_{1}=8.3 \mathrm{~Hz}, J_{2}=2.2 \mathrm{~Hz}, 1 \mathrm{H}\right)$, 6.37-6.35 (m, 1H); ${ }^{13} \mathrm{C}$ NMR ( 101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 159.8(\mathrm{C}=\mathrm{O}), 148.7(\mathrm{C}), 138.6(\mathrm{CH})$, 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), $120.4(\mathrm{CH}), 120.0(\mathrm{CH}), 119.9(\mathrm{CH}), 115.6(\mathrm{CH}), 112.5(\mathrm{CH}), 111.0(\mathrm{CH}), 100.4(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 380.0393$, found 380.0396 ; HPLC purity $\geq 99 \%$, $\mathrm{t}_{\mathrm{R}}=8.26$ $\min , \lambda=278 \mathrm{~nm}$.

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

Compound $\mathbf{6 3}$ was prepared according to general procedure C2, starting from $\mathbf{4 2}$ ( $74.8 \mathrm{mg}, 0.159$ mmol ). The mixture was stirred for 3 h 30 min . The reaction mixture was then quenched by addition of $\mathrm{NEt}_{3}$ ( 23 equiv) and MeOH ( 8 equiv). The crude was purified by column chromatography ( $\mathrm{SiO}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH} 97: 3$ to $95: 5$ ). After evaporation, the product was washed with $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ to give $63(31.4 \mathrm{mg}, 0.083 \mathrm{mmol}, 52 \%)$ as yellow solid. $R_{\mathrm{f}}=0.30\left(\mathrm{CH}_{2} \mathrm{Cl}_{2} / \mathrm{MeOH}\right.$ $95: 5+0.5 \% \mathrm{NEt}_{3}$ ); $\mathrm{Mp}>167^{\circ} \mathrm{C}$ (decomposition); IR (ATR) 3500-3000, 1651, 1610, 1586, 1556, 1487, 1333, $752 \mathrm{~cm}^{-1} ;{ }^{1} \mathrm{H}$ NMR ( 400 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 11.61(\mathrm{~s}, 1 \mathrm{H}), 11.14(\mathrm{~s}, 1 \mathrm{H}), 7.68(\mathrm{~s}$, $1 \mathrm{H}), 7.49(\mathrm{~d}, J=3.0 \mathrm{~Hz}, 1 \mathrm{H}), 7.38-7.33(\mathrm{~m}, 2 \mathrm{H}), 7.29(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.26(\mathrm{~d}, J=7.2 \mathrm{~Hz}, 1 \mathrm{H})$, $7.23(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 7.09(\mathrm{t}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 6.71(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.36-6.34(\mathrm{~m}, 1 \mathrm{H}) ;{ }^{13} \mathrm{C}$ NMR (101 MHz, DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}) 159.7(\mathrm{C}=\mathrm{O}), 146.2(\mathrm{C}), 138.3(\mathrm{CH}), 136.1(\mathrm{C}), 131.8(2 \mathrm{CH}), 130.8(\mathrm{C})$, $128.2(\mathrm{C}), 127.6(\mathrm{CH}), 126.1(\mathrm{C}), 125.4(\mathrm{CH}), 121.7(\mathrm{C}), 120.4(\mathrm{CH}), 119.9(\mathrm{CH}), 115.6(2 \mathrm{CH})$, $110.9(\mathrm{CH}), 108.4(\mathrm{C}), 100.5(\mathrm{CH})$; HRMS (ESI+) calcd for $\mathrm{C}_{19} \mathrm{H}_{15} \mathrm{BrN}_{3} \mathrm{O}(\mathrm{M}+\mathrm{H})^{+} 380.0393$, found 380.0396 ; HPLC purity $\geq 97 \%, \mathrm{t}_{\mathrm{R}}=8.27 \mathrm{~min}, \lambda=278 \mathrm{~nm}$.

### 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 $4{ }^{\circ} \mathrm{C}$. For behavioral testing, animals were briefly ( $<2 \mathrm{~min}$ ) anesthetized using a mask with $2 \%$ isoflurane and received a subcutaneous injection of $25 \mu \mathrm{~L}$ of CFA ( $2.5 \mathrm{mg} / \mathrm{kg}$,) solution into the right vibrissa pad using a 27 Ga needle coupled to a $25 \mu \mathrm{~L}$ Hamilton syringe, as described previously [15]. After recovery from anesthesia ( $<2 \mathrm{~min}$ ), rats were placed into an observation field ( $0.6 \times 0.6 \mathrm{~m}$ 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 synthetized compounds upon CFA-induced MA, animals were briefly ( $\approx 3 \mathrm{~min}$ ) anesthetized using a mask with $2 \%$ isoflurane and received an intracisternal injection of either compound ( $10 \mu \mathrm{M}$ in $5 \mu \mathrm{~L}$ aCSF) or vehicle alone (aCSF $+1 \%$ DMSO) using a $10 \mu \mathrm{~L}$ Hamilton syringe [25]. aCSF consisted of $150 \mathrm{mM} \mathrm{Na}^{+}, 3 \mathrm{mM} \mathrm{K}{ }^{+}, 0.8 \mathrm{mM} \mathrm{Mg}{ }^{2+}, 1.4 \mathrm{mM}$ $\mathrm{Ca}^{2+}, 155 \mathrm{mM} \mathrm{Cl}, \mathrm{pH} 7.4,295$ mosmol. $\mathrm{kg}^{-1}$. After recovery ( $\approx 2 \mathrm{~min}$ ), rats were placed in an observation field ( $0.6 \times 0.6$ msquare) under red light for a $30-\mathrm{min}$ 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 ( $6-\mathrm{g}$ 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 ( $\approx 3 \mathrm{~min}$ ) anesthetized using a mask with $2 \%$ isoflurane and received intradermal injection of CFA. Behavioral responses to the very same $6-\mathrm{g}$ 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 vehicle - AUC compound)/AUC vehicle]x 100 (AUC being the area under the curve; see Figure 2A)

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## 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-fiberinduced 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. Miraucourt, R. Dallel, D.L. Voisin, D.L. Glycine Inhibitory Dysfunction Turns Touch into Pain through PKCgamma Interneurons. PLoS One 2 (2007) e1116, doi: 10.1371/journal.pone. 0001116.
[15] C. Alba-Delgado, S. Mountadem, N. Mermet-Joret, L. Monconduit, R. Dallel, A. Artola, M. Antri. 5- $\mathrm{HT}_{2 \mathrm{~A}}$ receptor-induced morphological reorganization of $\mathrm{PKC} \gamma$-expressing interneurons gates inflammatory mechanical allodynia in rat. J. Neurosci. 38 (2018) 1048910504, 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. AbrunhosaThomas, A. Artola, F. Anizon, R. Dallel, P. Moreau. Pyridin-2(1H)one derivatives: a possible new class of therapeutics for mechanical allodynia. Eur. J. Med. Chem. 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) 40174022, 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 mitogenactivated 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 webaccessible 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.392308.2009.

