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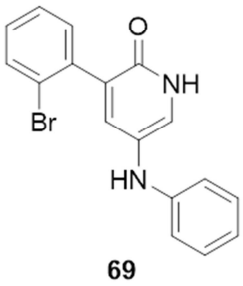
Graphical Abstract



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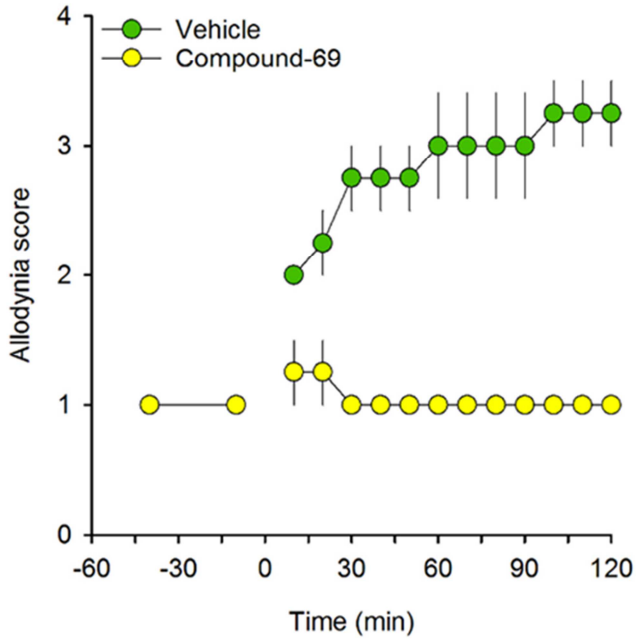

Pyridin-2(1*H*)one derivatives: a possible new class of therapeutics for mechanical allodynia

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Abstract

Mechanical Allodynia (MA), a frequent chronic pain symptom caused by innocuous stimuli, constitutes an unmet medical need, as treatments using analgesics available today are not always effective and can be associated with important side-effects. A series of 3,5-disubstituted pyridin-2(1*H*)-ones was designed, synthesized and evaluated *in vivo* toward a rat model of inflammatory MA. We found that the series rapidly and strongly prevented the development of MA. 3-(2-Bromophenyl)-5-(phenylamino)pyridin-2(1*H*)-one **69**, the most active compound of the series, was also able to quickly reverse neuropathic MA in rats. Next, when **69** was evaluated toward a panel of 50 protein kinases (PK) in order to identify its potential biological target(s), we found that **69** is a p38α MAPK inhibitor, a PK known to contribute to pain hypersensitivity in animal models. 3,5-Disubstituted pyridin-2(1*H*)-ones thus could represent a novel class of analgesic for the treatment of MA.

Keywords: Mechanical allodynia; pyridin-2(1*H*)-ones; p38 MAPK

1. Introduction

Chronic pain is a worldwide major health, social and economic problem. It has an important impact on quality of life across all ages, and is the most common reason for seeking medical care [1–5]. Global economic impact of pain is tremendous. Estimates show that chronic pain affects more than 20% of Europeans and costs several hundred billion each year in medical treatment and loss of productivity, with an expected increase due to population ageing.

Despite significant investments in research and development to study pain mechanisms and discover new treatments, most of the analgesics available today are still based on old drug classes: nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, anticonvulsants or antidepressants [6,7]. Moreover, these therapies have strong side-effects or abuse potentials, and are not always effective. Whereas most currently available treatments can alleviate inflammatory pain (initiated by tissue damage/inflammation), they are only partially effective for neuropathic pain (caused by nervous system lesion) [7]. Thus, chronic pain still constitutes an unmet medical need with a strong demand of the market for new efficient treatments.

Chronic pain syndromes, whether inflammatory or neuropathic, are characterized by persistent pain hypersensitivity such as spontaneous pain, hyperalgesia and allodynia. It is now well established that each of these pain symptoms relies on different cellular and molecular mechanisms. Thus a drug against spontaneous pain will not necessarily have an effect on allodynia and *vice versa*. Therefore, it is pivotal to discover drugs that specifically target the fundamental mechanisms causing the various pain symptoms.

Mechanical allodynia (MA), or touch-evoked pain, is one of the most prevalent pain symptoms, being present in almost half of neuropathic patients [8,9]. It was recently shown that it is associated with the activation, in the spinal dorsal horn (SDH) or medullary dorsal horn (MDH) (SDH trigeminal homologue in the brainstem), of a polysynaptic pathway whereby tactile inputs can gain access to the pain circuitry in superficial SDH/MDH. MA thus results from a miscoding, with cells that normally transmit and respond to noxious stimuli being activated by tactile inputs.

Activation of several neuronal protein kinases (PK) within the superficial SDH/MDH, such as extracellular signal-regulated protein kinases (ERK), the γ isoform of protein kinase C (PKCγ) or p38 mitogen-activated protein kinase (p38 MAPK), was shown to contribute to pain hypersensitivity in animal models of chronic inflammatory and neuropathic pain. Thus, inhibitors of ERK phosphorylation reduce mechanical allodynia and hyperalgesia [10]. Genetic [11] or pharmacological inactivation of PKCγ [12–15] prevents inflammatory MA whereas its activation is sufficient to produce MA [14]. Finally, inhibition of SDH/MDH p38 MAPK attenuates inflammatory [16–18] as well as neuropathic pain [18–20]. Therefore, PKs are possible cellular targets to alleviate MA.

Consequently, our goal was to design new ATP-competitive inhibitors of the catalytic domain of PKCγ for the treatment of MA. Based on the structures of two potent PKC inhibitors, bisindolylmaleimides BIM-1 and (2-methyl-indolyl)BIM-1 [21], we envisaged the preparation of 3,5-disubstituted pyridin-2(1*H*)-one derivatives: the central core pyridinone nucleus

features H-bond donor/acceptor atoms that could mimic maleimide (or ATP adenine) H-bond interactions with the hinge region of the targeted kinase. For the substitution of 3- and 5-positions, we considered aryl/heteroaryl(amino) groups. In order to assess the ability of this scaffold to interact the ATP-binding pocket of PKCγ, we performed a molecular modeling study using a PKCγ model generated by sequence homology from an X-ray crystal structure of highly homologous PKCβ available in the Protein Data Bank (PDB ID: 2I0E; no crystal structure of PKCγ available in the PDB). Then, we used an automated docking protocol of a virtual library of 255 pyridin-2(1*H*)-ones. This work led us to foresee the general structure **A** depicted in Figure 1, of a pyridin-2(1*H*)-one core substituted at the 3- and 5-positions by aryl/heteroaryl and phenylamino groups, respectively. This article reports the synthesis of a series of pyridin-2(1*H*)-one derivatives and their identification as potent anti-allodynic agents in rodent models of MA.

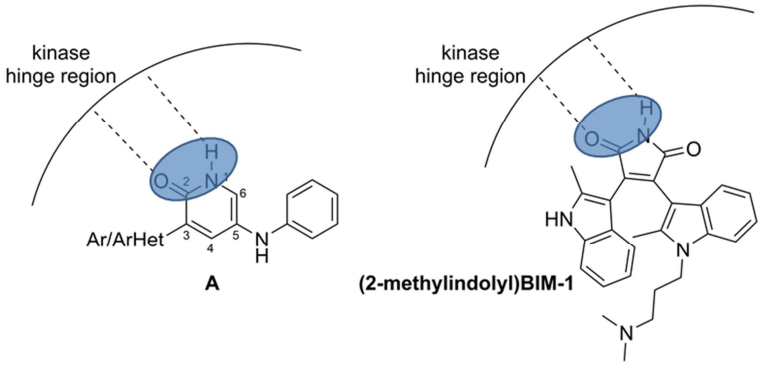
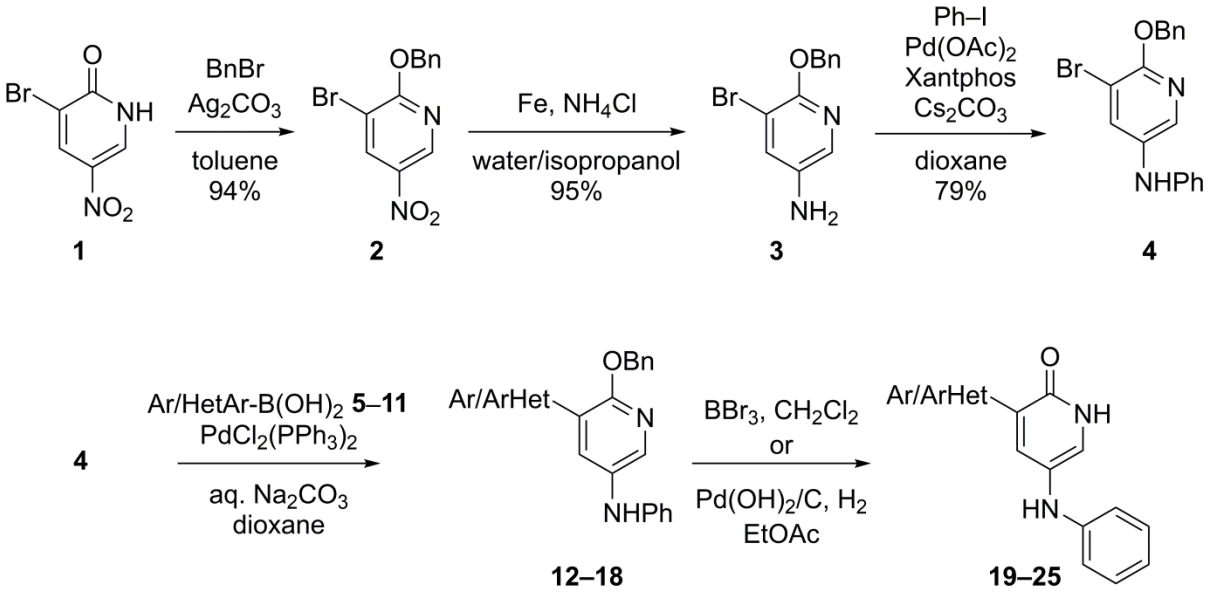


Figure 1. Comparison between the general structure **A** of 3,5-disubstituted pyridin-2(1*H*)-one derivatives and structure of (2-methylindolyl)BIM-1. Hydrogen bonds with the protein kinase hinge region are represented by dashed lines.

2. Results and discussion

2.1. Synthesis of 3,5-disubstituted pyridin-2(1*H*)-one derivatives

A series of **7** compounds of general structure **A** was initially prepared to work out the synthetic pathway as well as evaluate the potency of these compounds toward MA and PKCγ. The general synthetic pathway is indicated in Scheme 1. The synthesis started from commercially available 3-bromo-5-nitropyridin-2(1*H*)-one **1**, functionalized in such way that desired substituents could be easily introduced at the 3- and 5–positions. First, compound **1** was regioselectively *O*-benzylated in the presence of benzyl bromide and silver carbonate leading to pyridine **2** [22]. After reduction of the nitro group, Buchwald-Hartwig amination with iodobenzene afforded compound **4** in good yield.



Scheme 1. Synthesis of compounds **2**–**4** and **12**–**25**.

From intermediate **4**, aryl and heteroaryl substituents were then introduced at the 3-position using a Suzuki cross-coupling with the boronic acids **5**–**11** (Scheme 1, Table 1) leading to intermediates **12**–**18**. Finally, cleavage of the benzyl group using BBr_3 yielded final compounds **19**–**25** (Table 1). Compounds **19**–**25** were substituted by different aryl/heteroaryl groups leading to a preliminary library of pyridinone derivatives showing structural diversity at the 3-position.

Table 1. Isolated yields for compounds **12**–**25**.

Boronic acids[a]		Products **12**–**18**			Products **19**–**25**		
Cpd	Ar/HetAr	Cpd	Ar/HetAr	% yield	Cpd	Ar/HetAr	% yield
5	Phenyl	**12**	Phenyl	94	**19**	Phenyl	90
6	4-Fluorophenyl	**13**	4-Fluorophenyl	95	**20**	4-Fluorophenyl	97
7	Pyridin-4-yl	**14**	Pyridin-4-yl	93	**21**	Pyridin-4-yl	80
8	1-TIPS-1*H*-indol-3-yl	**15**	1*H*-Indolyl-3-yl	88	**22**	1*H*-Indolyl-3-yl	73
9	Quinolin-8-yl	**16**	Quinolin-8-yl	83	**23**	Quinolin-8-yl	19
10	Pyrimidin-5-yl	**17**	Pyrimidin-5-yl	94	**24**	Pyrimidin-5-yl	80
11	Isoquinolin-5-yl	**18**	Isoquinolin-5-yl	95	**25**	Isoquinolin-5-yl	44

[a]Boronic acids were either commercially available or prepared according to literature procedures (**8** [23], **9** [24], **11** [25]).

2.2. Preliminary evaluation of compounds 19–25

We first assessed the *in vivo* efficacy of compounds **19**–**24** on the face Complete Freund's Adjuvant (CFA) model (Fig. 2) [26]. Compound **25** was not tested due to its insufficient solubility. After receiving a subcutaneous injection of 25 µL of CFA (2.5 mg/kg) into the right vibrissa pad, rats develop a MA that lasts days. We found that intracisternally applied compounds prevented the development of inflammatory MA, particularly **19**–**21**, **23** and **24**. The most active compound was **21**, bearing a pyridin-4-yl moiety, with a rapid, strong and persistent anti-allodynic effect for the duration of the assay (90% inhibition at 120 min after CFA injection). The evaluation of this first series showed that the substituent at the 3-position of the pyridinone nucleus had an important impact on the anti-allodynic effect, and that changing its nature could lead to higher or lower activity.

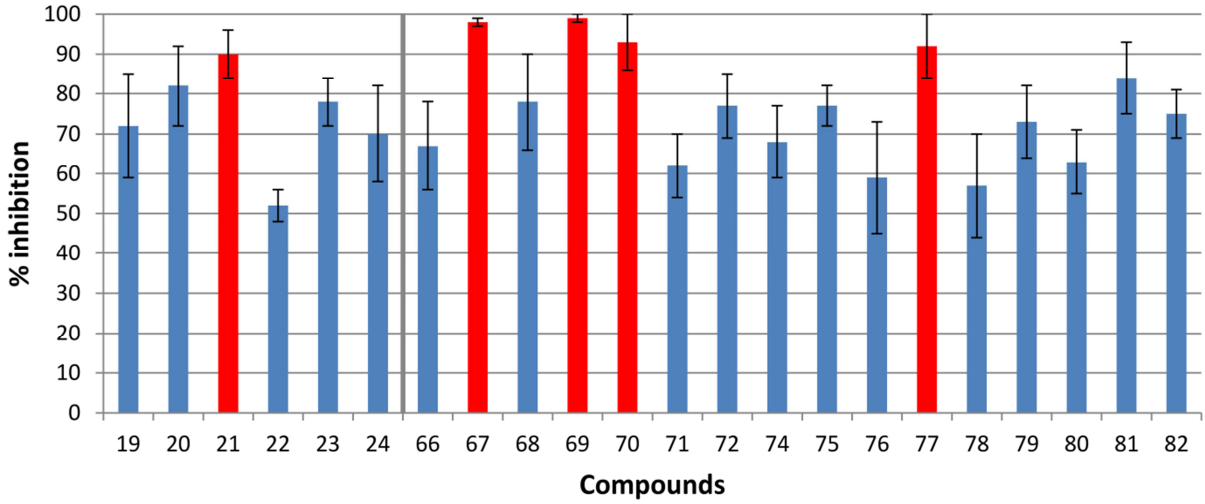


Figure 2. Intracisternal application of compounds **19**–**24**, **66**–**72** and **74**–**82** prevents face MA in a rat model of inflammatory pain (Complete Freund's Adjuvant (CFA), n=4–6 rats for each compound). For this assay, compounds (5 µL at 100 µM) or control vehicle were intra-cisternally administred 30 min before CFA injection. Compounds **67** and **69** (0.15 µg and 0.17 µg, respectively) induced 98% and 99% inhibition of inflammatory MA, respectively.

Compound series (**19**–**25**) was also tested toward PKCγ at 10 µM concentration at the International Centre for Kinase Profiling (ICKP, Dundee, Scotland) according to previously reported procedure [27]. Unfortunately, these compounds were not active toward this PK (≥85% mean residual kinase activity at 10 µM in duplicate assays). This indicated that the *in vivo* activity was due to an effect toward at least one other molecular target than PKCγ, possibly another PK. However, due to the promising anti-allodynic effect of compounds **19**–**24**, we aimed to prepare more efficient anti-allodynic drugs in this series, before identification of the potential molecular target. Thus, new products were synthesized and then evaluated on the rat model of inflammatory MA.

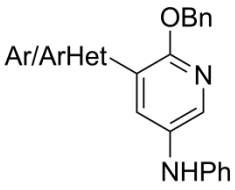
2.3. Identification of compound 69 as a potent anti-allodynic drug

According to the results presented above, we decided to synthesize other analogues of compounds **19**–**24**, bearing at the 3-position diversely substituted phenyl rings or

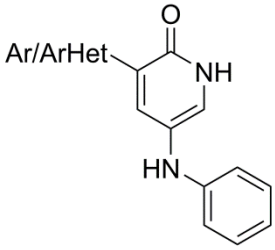
heteroaromatic moieties. Thus, using the same synthetic pathway presented in Scheme 1, intermediates **46**–**65** were prepared from compound **4** and debenzylation afforded final products **66**–**82** in modest to good yields (Table 2). Deprotection of compounds **63**–**65** led to products that could not be purified (**83**–**85**).

Table 2. Structure and isolated yields of compounds **46–85**.

26–45



46–65



66–85

Boronic acids/boronate[a,b]		Products **46–65**			Products **66–85**		
Cpd	Ar/HetAr	Cpd	Ar/HetAr	% yield	Cpd	Ar/HetAr	% yield
26	Quinolin-4-yl	**46**	Quinolin-4-yl	90	**66**	Quinolin-4-yl	69
27	1*H*-Indol-4-yl[b]	**47**	1*H*-Indol-4-yl	quant.	**67**	1*H*-Indol-4-yl	67
28	2-Cl-C_6H_4	**48**	2-Cl-C_6H_4	85	**68**	2-Cl-C_6H_4	50
29	2-Br-C_6H_4	**49**	2-Br-C_6H_4	–[c]	**69**	2-Br-C_6H_4	18[d]
30	2-(CO_2Et)C_6H_4	**50**	2-(CO_2Et)C_6H_4	75	**70**	2-(CO_2Et)C_6H_4	78
31	2-CNC_6H_4	**51**	2-CNC_6H_4	–[c]	**71**	2-($CONH_2$)C_6H_4	32[d]
32	2-NO_2-C_6H_4	**52**	2-NO_2-C_6H_4	37	**72**	2-NO_2-C_6H_4	89
33	(1,1'-biphenyl)-4-yl	**53**	(1,1'-biphenyl)-4-yl	91	**73**	(1,1'-biphenyl)-4-yl	80
34	3-Cl-C_6H_4	**54**	3-Cl-C_6H_4	95	**74**	3-Cl-C_6H_4	92
35	3-AcetylC_6H_4	**55**	3-AcetylC_6H_4	quant.	**75**	3-AcetylC_6H_4	70[e]
36	4-HOC_6H_4	**56**	4-HOC_6H_4	75	**76**	4-HOC_6H_4	91
37	4-$CH_3C_6H_4$	**57**	4-$CH_3C_6H_4$	86	**77**	4-$CH_3C_6H_4$	96
38	4-$CF_3C_6H_4$	**58**	4-$CF_3C_6H_4$	83	**78**	4-$CF_3C_6H_4$	95
39	4-$CF_3OC_6H_4$	**59**	4-$CF_3OC_6H_4$	91	**79**	4-$CF_3OC_6H_4$	91
40	4-(CO_2Me)C_6H_4	**60**	4-(CO_2Me)C_6H_4	60	**80**	4-(CO_2Me)C_6H_4	90
41	4-($CONH_2$)C_6H_4	**61**	4-($CONH_2$)C_6H_4	–[c]	**81**	4-($CONH_2$)C_6H_4	74[d]
42	2,4-diF-C_6H_3	**62**	2,4-diF-C_6H_3	–[c]	**82**	2,4-diF-C_6H_3	62[d]

43	1*H*-Indol-7-yl	**63**	1*H*-Indol-7-yl	49	**83**	1*H*-Indol-7-yl	–[f]
44	3-$NH_2C_6H_4$	**64**	3-$NH_2C_6H_4$	96	**84**	3-$NH_2C_6H_4$	–[f]
45	3-$CH_3OC_6H_4$	**65**	3-$CH_3OC_6H_4$	86	**85**	3-HOC_6H_4	–[f]

[a]Boronic acids/boronates were commercially available except **43** which was prepared according to literature procedures [28]. [b]Compound **27** was a pinacol boronate. [c]Compounds could not be fully purified by column chromatography and were engaged in the next step without further purification. [d]Yield over 2 steps from **4**. [e]Compound **55** was debenzylated using TMSI. [f]Compounds could not be purified.

The *in vivo* efficacy of all new compounds, except **73** which was not soluble enough for *in vivo* assays, was evaluated on the rat model of inflammatory MA (Fig. 2). We found that all the new compounds had an anti-allodynic activity. Interestingly, four 3,5-disubstituted pyridin-2(1*H*)-ones (**67**, **69**, **70** and **77**) were either as potent or even more effective than compound **21**. The most active pyridinones were **67** and **69** (Fig. 2), bearing at the 3-position an indol-4-yl or a 2-bromophenyl substituent, respectively. In this model of inflammatory MA, static MA was suppressed in compound **69** treated rats, in comparison to animals treated with vehicle (Fig. 3A). The results showed that the 3-position of the pyridinone moiety tolerated aryl/heteroaryl groups, including more sterically demanding groups such as indolyl group. However, the manner in which these groups are connected to the pyridinone moiety influenced the anti-allodynic activity (compare **22** and **67**). In addition, compared to phenyl substituted **19**, introduction of a nitrogen atom (**21**, bearing a pyridine-4-yl moiety) or a methyl group (**77**) at the 4-position led to comparable gains of activity. Similarly, substitution at the 2-position by a bromine atom (**69**) or an ethoxycarbonyl group (**70**) was favorable, with high activities similar to the one of compound **67** bearing an 1*H*-indol-4-yl substituent.

The most effective compound (**69**) was also evaluated in a rat model of facial neuropathic MA produced by the constriction injury of the rat infraorbital nerve (Fig. 3B) [29]. Rats develop MA within 2 weeks after constriction which then lasts for several weeks thereafter. Intracisternal administration of compounds **69** on day 14 reversed MA. The effect was fast (Fig. 3B), confirming the potential of this compound series in neuropathic pain management.

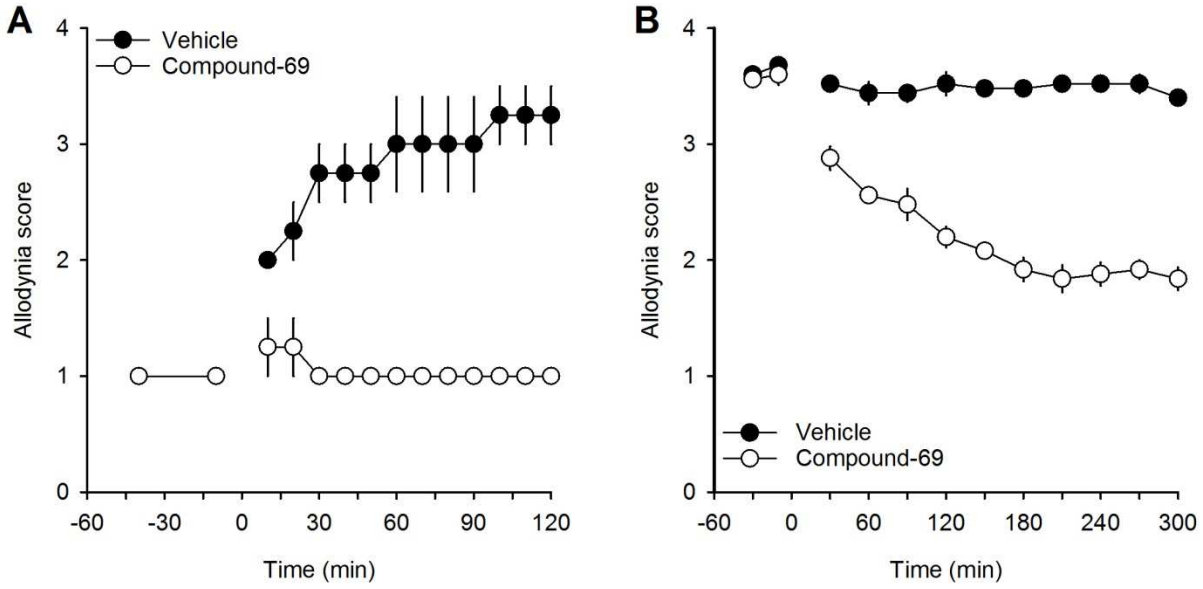


Figure 3. Intracisternal application of compound **69** both prevents inflammatory (A) and reverses neuropathic static MA (B). Time courses of changes in behavioral responses (allodynic score) evoked by static mechanical stimuli (6-g von Frey filament) applied on the face of rats intracisternally treated with 0.17 µg of compound **69** (5 µL at 100 µM) or vehicle. In A, compound **69** or vehicle was preemptively applied 30 min before subcutaneous injection of Complete Freund's Adjuvant (at time 0). In B, compound **69** or vehicle was applied (at time 0) 14 days after IoN-CCI; that is, once a stable MA was established. Static MA was completely suppressed (A) or quickly reversed (B) in compound **69**-treated rats. Results are presented as mean ± s.e.m.; n = 4 (A) and n = 5 (B) in each group. Allodynic score (from 0 to 4) according to Vos *et al.* [29].

2.4. Compounds 69 is a selective p38α MAPK inhibitor

Next, we undertook studies to identify the possible biological target(s) of the most active compound **69**. As previously indicated, the activation in neurons of PK such as PKCγ, ERK or p38 MAPK can contribute to pain hypersensitivity. Therefore, we decided to screen compound **69** toward a panel of 50 PKs that provide a representative sampling of the human kinome (Fig. 4, Table S1) [27]. In this panel, we identified p38α MAPK as the privileged target, with 19% of kinase residual activity at 10 µM compound concentration. Compound **69** was highly selective over the other protein kinases, as none of them showed a mean residual activity < 65% at the same concentration. IC_{50} toward p38α MAPK was determined and found to be in the micromolar range, with a value of 1.5 ± 0.7 µM (mean ± SD).

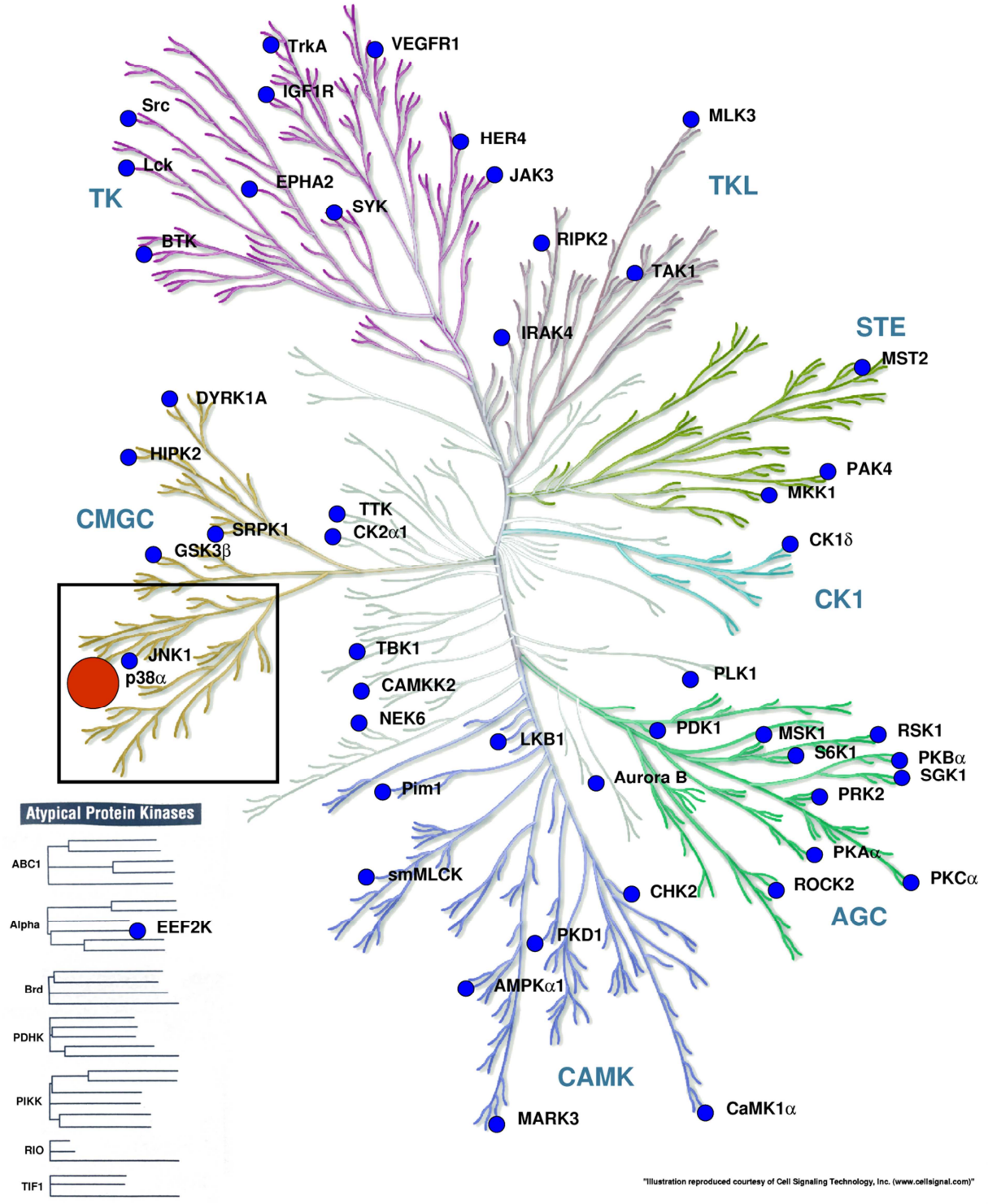


Figure 4. Compound **69** was evaluated at the International Center For Kinase Profiling (ICKP, Dundee, Scotland) toward a panel of 50 protein kinases that provide a representative sampling of the human kinome. The results were expressed as the mean percentage of residual activity at 10 µM concentration (duplicate assays). Blue disks: ≥ 65%, red disk: 19%. See Table S1 for screening values. The black square indicates the kinome region containing protein kinases evaluated in a second screening (Fig. 5, Table S2). The tree was generated using the Kinome Render software, and the illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) [30].

Next, we evaluated the selectivity of compound **69** toward another panel containing all four p38 MAPK isoforms, ERK1, ERK2 as well as other protein kinases close to p38α MAPK in the kinome phylogenetic tree (Fig. 5, Table S2). In addition, compound **67** that also exhibited strong anti-allodynic activity was also evaluated in this screening. The results showed that **69** was selective of p38α MAPK over the other protein kinases tested in this panel, including p38 MAPK isoforms. Compound **67** exhibited the same selectivity profile. Its IC_{50} toward p38α MAPK was determined and found to be in the micromolar range with a value of 3.0 ± 0.1 µM (mean ± SD).

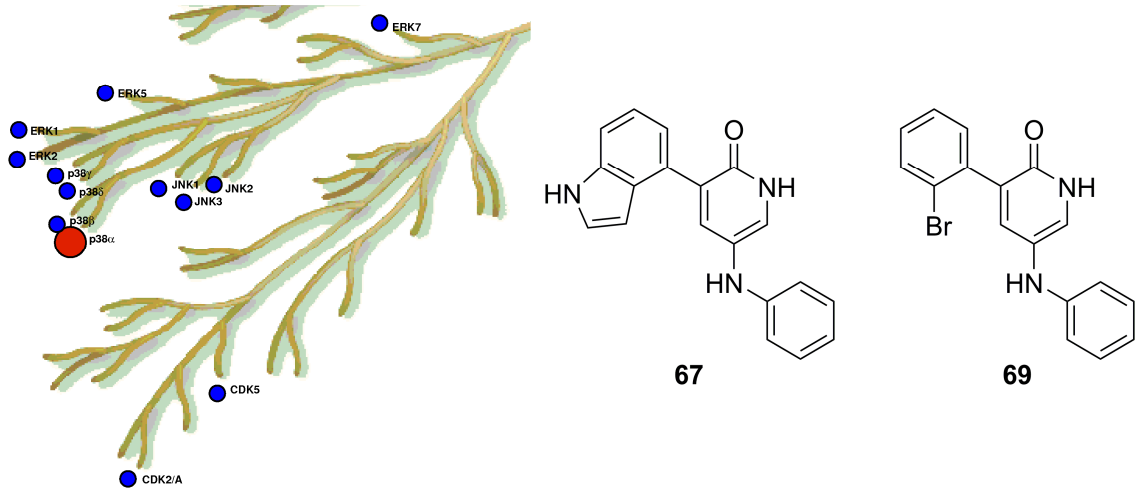


Figure 5. Compounds **67** and **69** were evaluated at the International Center For Kinase Profiling (ICKP, Dundee, Scotland) toward a panel of 13 protein kinases. The results were expressed as the mean percentage of residual activity at 1 µM concentration (duplicate assays). Blue disks: ≥ 90%, red disk: 59%, for both compounds. See Table S2 for screening values. The tree was generated using the Kinome Render software, and the illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) [30].

Hence, compound **69** appears as a highly selective inhibitor of p38α MAPK when considering the panel of 62 protein kinases evaluated. According to these results, besides not yet identified other biological targets, p38α MAPK could be reasonably considered as a target for this series of pyridin-2(1*H*)one derivatives, leading to the observed analgesia in the inflammatory and neuropathic rat models of MA.

3. Conclusion

In summary, we synthesized a series of pyridin-2(1*H*)-one derivatives in 5 steps from 3-bromo-5-nitropyridin-2(1*H*)-one **1**. The heterocyclic core was substituted at the 5-position by a phenylamino group whereas the 3-position was substituted by various aryl/heteroaryl moieties. These compounds were evaluated *in vivo* toward a rat model of inflammatory MA. We found that the series rapidly and strongly prevented the development of MA. Compound **69**, the most active of the series, was also able to quickly reverse facial neuropathic MA in rats. Next, when **69** was evaluated toward a panel of 50 protein kinases in order to identify its potential biological target(s), we found that **69** is a p38α MAPK inhibitor, a PK known to

contribute to pain hypersensitivity in animal models. In conclusion, 3,5-disubstituted pyridin-2(1*H*)-ones thus could represent a novel class of analgesic for the treatment of MA.

4. Experimental section

4.1. Chemistry

4.1.1. General. Starting materials were obtained from commercial suppliers and used without further purification. IR spectra were recorded on a Perkin-Elmer Spectrum 65 FT-IR spectrometer ($\bar{\nu}$ in cm^{-1}). NMR spectra, performed on a Bruker AVANCE 400 III HD (^{1}H: 400 MHz, ^{13}C: 101 MHz) are reported in ppm using the solvent residual peak as an internal standard; the following abbreviations are used: singlet (s), doublet (d), triplet (t), quadruplet (q), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), triplet of doublets (td), triplet of triplets (tt), multiplet (m), broad signal (br s). Coupling constants are expressed in Hertz. Experiments under microwave irradiation were performed using a CEM Discover Benchmate apparatus. High resolution mass spectra were determined on a high-resolution Waters Micro Q-Tof or Thermo Scientific Q Exactive Q-Orbitrap apparatus (UCA START, Université Clermont Auvergne, Clermont-Ferrand, France). Chromatographic purifications were performed by column chromatography using 40–63 µm 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 **19**–**25** and **66**–**82** was established by HPLC analysis using a Agilent infinity 1260 chromatograph with DAD detector and an Agilent Zorbax SB-Phenyl column (4.6 mm x150 mm, 3.5 µm). Flow rate was 0.8 mL/min and the analysis was performed at 25 °C. Detection wavelength is indicated for each compound. Solvents were (A) water/0.1% formic acid, (B) Acetonitrile. Gradient was 100:0 A/B to 30:70 A/B in 8 min and then 30:70 A/B for 3 min.

4.1.2. 2-(Benzyloxy)-3-bromo-5-nitropyridine (2).

To a solution under argon of crushed 3-bromo-5-nitropyridin-2(1*H*)-one **1** (1.90 g, 8.68 mmol, 1 eq.) in anhydrous toluene (26 mL), benzyl bromide (2.2 mL, 18.5 mmol, 2.1 eq.) was added. The mixture was stirred at room temperature for 5 min. Then, the mixture was stirred at 70 °C and crushed Ag_2CO_3 was added in three portions of 0.35 eq. every hour (3x840 mg, 3x3.05 mmol, 3x0.35 eq.). After 3 h 30 min at 70 °C, the mixture was filtered through a pad of Celite and washed with ethyl acetate. The obtained yellow solid was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 95:5) to give the desired product **2** with a residual impurity which was eliminated by washing with cyclohexane, to give **2** (2.51 g, 8.12 mmol, 94%) as a white solid. R_f = 0.40 (EtOAc/cyclohexane 2:98); Mp 128 °C; IR (ATR) 3075, 1593, 1571, 1518, 1435, 1337, 1318, 1050, 1008, 725 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (d, J = 2.5, 1H), 8.85 (d, J = 2.5, 1H), 7.50 (d, J = 7.3, 2H), 7.45–7.34 (m, 3H), 5.57 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.3 (C), 142.8 (CH), 139.6 (C), 137.1 (CH), 135.7 (C), 128.50 (2CH), 128.22 (CH), 127.9 (2CH), 106.3 (C), 69.7 (CH_2); HRMS (ESI+) calcd for $C_{12}H_{10}BrN_2O_3$ $(M+H)^+$ 308.9869, found 308.9869.

4.1.3. 6-(Benzyloxy)-5-bromopyridin-3-amine (3).

To a solution of compound **2** (5.4 g, 17.5 mmol, 1 eq.) in a 10:1 propan-2-ol/water mixture (375 mL) were added Fe powder (5.89 g, 105 mmol, 6 eq.) and NH_4Cl (380 mg, 7.10 mmol, 0.4 eq.). The mixture was refluxed for 4 h. Then, the mixture was filtered through a pad of Celite which was then washed with ethyl acetate. The filtrate was washed with water, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered and then evaporated. The obtained orange oil was purified by column chromatography (SiO_2, EtOAc/cyclohexane 3:7 + 0.5% NEt_3) to give the desired product **3** (4.64 g, 16.6 mmol, 95%) as a brown oil which crystalized in beige solid. R_f = 0.38 (EtOAc/cyclohexane 3:7); Mp 81 °C; IR (ATR) 3390, 3305, 3208, 1625, 1452, 1356, 1216, 1046, 982 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, *J* = 2.5, 1H), 7.42 (d, *J* = 7.4, 2H), 7.37 (t, *J* = 7.4, 2H), 7.32 (d, *J* = 2.5, 1H), 7.32–7.27 (m, 1H), 5.26 (s, 2H), 5.04 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 150.4 (C), 141.2 (C), 137.6 (C), 130.1 (CH), 128.3 (2CH), 128.2 (CH), 127.6 (CH), 127.4 (2CH), 105.8 (C), 67.3 (CH_2); HRMS (ESI+) calcd for $C_{12}H_{12}BrN_2O$ $(M+H)^+$ 279.0128, found 279.0124.

4.1.4. 6-(Benzyloxy)-5-bromo-N-phenylpyridin-3-amine (4).

A 5 mL screw-cap tube under argon was charged with compound **3** (444 mg, 1.59 mmol, 1eq.), $Pd(OAc)_2$ (17.8 mg, 0.08 mmol, 0.05 eq.), Xantphos (46.2 mg, 0.08 mmol, 0.05 eq.) and Cs_2CO_3 (1.04 g, 3.19 mmol, 2 eq.). Then, anhydrous 1,4-dioxane degassed with argon (8 mL) and iodobenzene (180 µL, 1.61 mmol, 1 eq.) were added. The tube was sealed and the mixture was stirred at 100 °C for 4 h. 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 (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) to give a yellow-orange oil **4** (444 mg, 1.25 mmol, 79%) which solidify into a light brown solid after some days in freezer. R_f = 0.31 (EtOAc/cyclohexane 1:9); Mp 49 °C; IR (ATR) 3394, 1602, 1502, 1462, 1444, 1356, 1292, 1230, 1050, 738, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H, NH), 7.97 (d, *J* = 2.5, 1H), 7.78 (d, *J* = 2.5, 1H), 7.48–7.44 (m, 2H), 7.42–7.37 (m, 2H), 7.35–7.30 (m, 1H), 7.22 (dd, *J* = 8.6, 7.4, 2H), 6.96 (dd, *J* = 8.6, 1.1, 2H), 6.82 (tt, *J* = 7.4, 1.1, 1H), 5.37 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.3 (C), 143.7 (C), 137.2 (C), 135.4 (C), 135.2 (CH), 132.7 (CH), 129.4 (2CH), 128.4 (2CH), 127.8 (CH), 127.5 (2CH), 119.8 (CH), 115.7 (2CH), 106.0 (C), 67.7 (CH_2); HRMS (ESI+) calcd for $C_{18}H_{16}BrN_2O$ $(M+H)^+$ 355.0441, found 355.0440.

4.1.5. General Procedures for the preparation of compounds 12–18, 46–51 and 53–65.

Procedure A (conventional heating): To a solution under argon of brominated derivative in 1,4-dioxane (0.1–0.6 mmol, 1 eq., 0.1 M) were added the boronic acid or boronic ester (1.5 eq.) and a 2 M Na_2CO_3 aqueous solution (5 eq.). The mixture was degassed with argon for 10 min before the addition of $PdCl_2(PPh_3)_2$ (0.05 eq.). The solution was refluxed overnight. Ethyl acetate was added and the resulting mixture was washed with water. The organic phase was dried over $MgSO_4$ and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography.

Procedure B (microwave irradiation): A 10 mL microwave tube under argon was charged with brominated derivative (0.2–0.4 mmol, 1 eq.). 1,4-dioxane (0.1 M), boronic acid or boronic ester (1.5 eq.) and a 2 M Na_2CO_3 aqueous solution (5 eq.) were added. The solution was degassed with argon for 10 min before the addition of $PdCl_2(PPh_3)_2$ (0.05 eq.). The tube was sealed and the mixture was irradiated for 1 h (Discover mode, Dynamic control type, P_{max}

= 75 W, T = 100 °C). The mixture was then filtered through a pad of Celite which was then washed with ethyl acetate. The organic phase was washed with water and then dried over $MgSO_4$ and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography.

4.1.6. General Procedure for the preparation of compounds 19–21, 23–25, 66–74 and 76–82.

Procedure C: To a solution under argon and cooled to 0 °C of benzylated compound in anhydrous dichloromethane (0.1–0.5 mmol, 1 eq., 0.02 M) was added dropwise a 1 M BBr_3 solution in dichloromethane (4 eq.). The mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched by addition of methanol, or by addition of NEt_3 and methanol when indicated. After evaporation under reduced pressure, EtOAc was added. The mixture was washed with water, dried over $MgSO_4$, and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography.

4.1.7. 6-(Benzyloxy)-N,5-diphenylpyridin-3-amine (12).

Compound **12** was prepared according to general procedure B, starting from **4** (95 mg, 0.267 mmol). The crude oil was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) to give **12** (89 mg, 0.253 mmol, 94%). R_f = 0.70 (EtOAc/cyclohexane 3:7); Mp 118 °C; IR (ATR) 3380, 1601, 1514, 1497, 1466, 1424, 1359, 1298, 1255, 1218, 1022, 753, 728, 657, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.99 (d, J = 2.7, 1H), 7.62–7.59 (m, 2H), 7.53 (d, J = 2.8, 1H), 7.46–7.32 (m, 7H), 7.31–7.26 (m, 1H), 7.20 (t, J = 7.8, 2H), 6.98 (d, J = 8.0, 2H), 6.77 (t, J = 7.3, 1H), 5.37 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.3 (C), 144.4 (C), 137.7 (C), 136.1 (C), 135.7 (CH), 134.6 (C), 130.5 (CH), 129.3 (2CH), 129.0 (2CH), 128.32 (2CH), 128.27 (2CH), 127.6 (CH), 127.5 (CH), 127.4 (2CH), 123.8 (C), 119.1 (CH), 115.2 (2CH), 67.1 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{21}N_2O$ $(M+H)^+$ 353.1648, found 353.1641.

4.1.8. 6-(Benzyloxy)-5-(4-fluorophenyl)-N-phenylpyridin-3-amine (13).

Compound **13** was prepared according to general procedure A, starting from **4** (154 mg, 0.434 mmol) and the corresponding boronic acid. The mixture was refluxed for 18 h. The crude oil was purified by column chromatography (SiO_2, cyclohexane + 0.5% NEt_3 to EtOAc/cyclohexane 1:9 + 0.5% NEt_3) to give **13** (152 mg, 0.410 mmol, 95%) as a beige solid. R_f = 0.70 (EtOAc/cyclohexane 3:7); Mp 104 °C; IR (ATR) 3383, 1599, 1500, 1438, 1223, 843, 757, 734, 697 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.07 (s, 1H), 7.99 (d, J = 2.7, 1H), 7.68–7.62 (m, 2H), 7.53 (d, J = 2.7, 1H), 7.42–7.17 (m, 9H), 6.98 (d, J = 7.9, 2H), 6.77 (t, J = 7.3, 1H), 5.37 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6 (d, J_{CF} = 245, C), 154.2 (C), 144.3 (C), 137.6 (C), 135.7 (CH), 134.6 (C), 132.4 (d, J_{CF} = 3, C), 131.0 (d, J_{CF} = 8, 2CH), 130.4 (CH), 129.3 (2CH), 128.3 (2CH), 127.5 (CH), 127.4 (2CH), 122.8 (C), 119.1 (CH), 115.2 (2CH), 115.1 (d, J_{CF} = 21.5, 2CH), 67.1 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{20}FN_2O$ $(M+H)^+$ 371.1554, found 371.1562.

4.1.9. 2-(Benzyloxy)-N-phenyl-[3,4'-bipyridin]-5-amine (14).

Compound **14** was prepared according to general procedure B, starting from **4** (103 mg, 0.290 mmol) and the corresponding boronic acid. The mixture was irradiated for 45 min at 100 °C. The crude product was purified as above to give **14** (95.7 mg, 0.271 mmol, 93%). R_f = 0.30 (EtOAc/cyclohexane 5:5); Mp 129 °C; IR (ATR) 3261, 3189, 1594, 1443, 1262, 1229, 996, 829, 748, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.63–8.60 (m, 2H), 8.14 (s, 1H), 8.06

(d, *J* = 2.8, 1H), 7.66–7.63 (m, 3H), 7.43–7.40 (m, 2H), 7.39–7.34 (m, 2H), 7.32–7.27 (m, 1H), 7.21 (dd, *J* = 8.5, 7.4, 2H), 6.99 (dd, *J* = 8.6, 1.0, 2H), 6.79 (t, *J* = 7.3, 1H), 5.40 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.2 (C), 149.6 (2CH), 144.2 (C), 143.7 (C), 137.4 (C) 137.1 (CH), 134.7 (C), 130.3 (CH), 129.4 (2CH), 128.4 (2CH), 127.6 (CH), 127.5 (2CH), 123.7 (2CH), 121.0 (C), 119.3 (CH), 115.3 (2CH), 67.3 (CH_2); HRMS (ESI+) calcd for $C_{23}H_{20}N_3O$ $(M+H)^+$ 354.1601, found 354.1602.

4.1.10. 6-(Benzyloxy)-5-(1H-indol-3-yl)-N-phenylpyridin-3-amine (15).

1-(Triisopropylsilyl)-1*H*-indol-3-yl)boronic acid was prepared from 3-bromo-1-(triisopropylsilyl)-1*H*-indole according to literature procedure [23]. A solution under argon of 3-bromo-1-(triisopropylsilyl)-1*H*-indole (500 mg, 1.42 mmol, 1 eq.) in anhydrous THF (5 mL) was cooled to –60 °C. A 2.42 M n-butyllithium solution in hexane (0.73 mL, 1.77 mmol, 1.25 eq.) was added dropwise. The mixture was stirred at –60 °C for 1 h. Triisopropyl borate (0.4 mL, 1.73 mmol, 1.22 eq.) was added dropwise and the mixture was stirred at –60 °C for 1 h and at room temperature for 20 h. A saturated aqueous NH_4Cl solution (1.5 mL) and toluene (1.5 mL) were added and the mixture was washed with water. The organic phase was dried over $MgSO_4$, filtered and evaporated giving 1:1 mixture of 1-(triisopropylsilyl)-1*H*-indol-3-yl)boronic acid and 1-(triisopropylsilyl)-1*H*-indole (427 mg, ratio evaluated by ^{1}H NMR). The crude was used without purification.

Compound **15** was prepared according to general procedure A, starting from **4** (47.8 mg, 0.135 mmol) and the mixture of 1-(triisopropylsilyl)-1*H*-indol-3-yl)boronic acid and 1-(triisopropylsilyl)-1*H*-indole (128 mg). The reaction mixture was refluxed for 18 h. The obtained crude (170 mg) was directly engaged in the next step due to partial deprotection of the indolic part. To a solution of the crude product in THF (1 mL) was added a tetra-*n*-butylammonium fluoride solution in THF (1 M, 0.36 mL, 0.36 mmol, 2.7 eq.). The mixture was stirred for 1 h 30 min. EtOAc was added and the solution was washed with water and brine. The organic phase was dried over $MgSO_4$ and filtered. After evaporation, the solid was purified by column chromatography (SiO_2, cyclohexane + 0.5 % NEt_3 to EtOAc/cyclohexane 25:75 + 0.5 % NEt_3) to give **15** (46.4 mg, 0.119 mmol, 88%) as a mauve solid. R_f = 0.31 (EtOAc/cyclohexane 2:8); Mp 85 °C; IR (ATR) 3388, 3308, 1593, 1441, 1234, 1019, 740, 733, 693 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (br s, 1H), 8.06 (s, 1H), 7.90 (d, *J* = 2.7, 1H), 7.84 (d, *J* = 2.7, 1H), 7.78–7.74 (m, 2H), 7.47 (d, *J* = 7.4, 2H), 7.44 (d, *J* = 8.4, 1H), 7.39–7.34 (m, 2H), 7.33–7.28 (m, 1H), 7.22 (t, *J* = 7.8, 2H), 7.14 (t, *J* = 7.4, 1H), 7.06 (t, *J* = 7.5, 1H), 7.01 (d, *J* = 7.9, 2H), 6.77 (t, *J* = 7.3, 1H), 5.42 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.3 (C), 144.7 (C), 137.8 (C), 136.2 (C), 134.1 (C), 132.8 (CH), 129.3 (2CH), 128.8 (CH), 128.4 (2CH), 127.8 (2CH), 127.6 (CH), 126.4 (CH), 125.5 (C), 121.5 (CH), 119.6 (CH), 119.2 (CH), 118.91 (C), 118.89 (CH), 115.1 (2CH), 112.0 (CH), 109.1 (C), 67.2 (CH_2); HRMS (ESI+) calcd for $C_{26}H_{22}N_3O$ $(M+H)^+$ 392.1757, found 392.1765.

4.1.11. 6-(Benzyloxy)-N-phenyl-5-(quinolin-8-yl)pyridin-3-amine (16) .

Quinolin-8-ylboronic acid was prepared from 8-iodoquinoline according to literature procedure [24]. To a solution under argon of 8-iodoquinoline (434 mg, 1.70 mmol, 1 eq.) in anhydrous THF (1.35 mL) was added *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (0.26 mL, 1.73 mmol, 1 eq.). The mixture was cooled to –78 °C a 2.5 M *n*-butyllithium solution in hexane (0.68 mL, 1.70 mmol, 1 eq.) was added dropwise. The mixture was stirred at –78 °C for 4 h. Trimethyl borate (0.57 mL, 5.11 mmol, 3 eq.) was added dropwise and the mixture was

stirred at room temperature for 2 h. A 3 M aqueous HCl solution (4 mL) was added and the aqueous layer was washed with diethyl ether and neutralized by solid $NaHCO_3$. The resulting precipitate was filtered and washed with acetone to give quinolin-8-ylboronic acid (112 mg) which was used without further purification.

Compound **16** was prepared according to general procedure A, starting from **4** (145 mg, 0.408 mmol) and the quinolin-8-ylboronic acid (114 mg). The mixture was refluxed for 21 h. The crude solid was purified by column chromatography (SiO_2, cyclohexane + 0.5% NEt_3 to EtOAc/cyclohexane 3:7 + 0.5% NEt_3) to give **16** (137 mg, 0.340 mmol, 83%) as a yellow solid. R_f = 0.41 (EtOAc/cyclohexane 3:7); Mp 162 °C; IR (ATR) 3252, 3180, 1592, 1497, 1461, 1228, 1003, 796, 736, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.90 (dd, *J* = 4.1, 1.8, 1H), 8.42 (dd, *J* = 8.3, 1.8, 1H), 8.05 (s, 1H), 8.03–8.00 (m, 2H), 7.81 (dd, *J* = 7.1, 1.5, 1H), 7.67 (dd, *J* = 8.1, 7.2, 1H), 7.56 (dd, *J* = 8.3, 4.1, 1H), 7.56 (d, *J* = 2.7, 1H), 7.24–7.12 (m, 7H), 7.01 (dd, *J* = 8.6, 1.0, 2H), 6.74 (tt, *J* = 7.3, 1.1, 1H), 5.27 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.3 (C), 150.2 (CH), 145.7 (C), 144.6 (C), 137.8 (C), 136.3 (CH), 135.8 (CH), 135.4 (C), 133.6 (C), 132.6 (CH), 130.6 (CH), 129.2 (2CH), 128.3 (CH), 128.0 (2CH + C), 127.1 (CH), 126.9 (2CH), 126.1 (CH), 122.7 (C), 121.4 (CH), 118.8 (CH), 114.9 (2CH), 66.59 (CH_2); HRMS (ESI+) calcd for $C_{27}H_{22}N_3O$ $(M+H)^+$ 404.1757, found 404.1755.

4.1.12. 6-(Benzyloxy)-N-phenyl-5-(pyrimidin-5-yl)pyridin-3-amine (17).

Compound **17** was prepared according to general procedure A, starting from **4** (122 mg, 0.343 mmol) and the corresponding boronic acid. The mixture was refluxed for 18 h. The crude oil was purified by column chromatography (SiO_2, EtOAc/cyclohexane 1:9 to 65:35) to give **17** (115 mg, 0.324 mmol, 94%) as a yellow solid. R_f = 0.20 (EtOAc/cyclohexane 3:7); Mp 115 °C; IR (ATR) 3299, 1595, 1536, 1408, 1261, 1228, 1015, 747, 722, 692 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 9.05 (s, 2H), 8.17 (s, 1H), 8.07 (d, *J* = 2.7, 1H), 7.75 (d, *J* = 2.8, 1H), 7.43–7.40 (m, 2H), 7.39–7.34 (m, 2H), 7.33–7.28 (m, 1H), 7.21 (t, *J* = 7.8, 2H), 7.01 (d, *J* = 7.9, 2H), 6.79 (t, *J* = 7.3, 1H), 5.38 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.2 (CH), 156.5 (2CH), 154.3 (C), 144.2 (C), 137.3 (CH), 137.2 (C), 134.8 (C), 130.3 (CH), 130.0 (C), 129.3 (2CH), 128.4 (2CH), 127.68 (CH), 127.65 (2CH), 119.2 (CH), 117.2 (C), 115.3 (2CH), 67.5 (CH_2); HRMS (ESI+) calcd for $C_{22}H_{19}N_4O$ $(M+H)^+$ 355.1553, found 355.1560.

4.1.13. 6-(Benzyloxy)-5-(isoquinolin-5-yl)-N-phenylpyridin-3-amine (18).

Isoquinolin-5-ylboronic acid was prepared from 5-bromoisoquinoline according to literature procedure [25]. Anhydrous THF (19 mL) was cooled to –78 °C then a 2.5 M *n*-butyllithium solution in hexane (1.2 mL, 3.0 mmol, 1.25 eq.) was added under argon. A solution of 5-bromoisoquinoline (502 mg, 2.41 mmol, 1 eq.) in anhydrous THF (5 mL) was added. The mixture was stirred at –78 °C for 1 h. Triisopropyl borate (0.70 mL, 3.0 mmol, 1.25 eq.) was added dropwise and the mixture was stirred at room temperature for 2 h. A 5% aqueous NaOH solution (1 mL) was slowly added to quench the reaction. Aqueous phase was acidified to pH 5 at 0 °C with a 10% aqueous HCl solution, then was extracted with EtOAc. The organic phase was dried over $MgSO_4$ and filtered. After evaporation, the obtained solid was washed with diethyl ether to give isoquinolin-5-ylboronic acid (135.5 mg, 0.783 mmol, 32%).

Compound **18** was prepared according to general procedure A, starting from **4** (161 mg, 0.453 mmol) and isoquinolin-5-ylboronic acid. The mixture was refluxed for 18 h. The crude solid was purified by column chromatography (SiO_2, EtOAc/cyclohexane 1:9 to 65:35) to give **18**

(173 mg, 0.429 mmol, 95%) as a white solid. R_f = 0.22 (EtOAc/cyclohexane 3:7); Mp 162 °C; IR (ATR) 3279, 1603, 1441, 1361, 1227, 995, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 1H), 8.46 (d, *J* = 5.9, 1H), 8.16 (dd, *J* = 7.5, 1.9, 1H), 8.14 (d, *J* = 2.7, 1H), 8.12 (s, 1H), 7.79–7.72 (m, 2H), 7.51 (d, *J* = 2.8, 1H), 7.43 (d, *J* = 5.9, 1H), 7.24–7.17 (m, 5H), 7.15–7.11 (m, 2H), 7.02 (d, *J* = 7.9, 2H), 6.77 (t, *J* = 7.3, 1H), 5.38–5.22 (br s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.7 (C), 152.7 (CH), 144.2 (C), 143.1 (CH), 137.3 (C), 136.4 (CH), 134.5 (C), 133.42 (C), 133.41 (C), 131.7 (CH), 131.6 (CH), 129.3 (2CH), 128.2 (C), 128.1 (2CH), 127.8 (CH), 127.39 (CH), 127.35 (2CH), 127.1 (CH), 121.4 (C), 119.3 (CH), 118.5 (CH), 115.4 (2CH), 66.90 (CH_2); HRMS (ESI+) calcd for $C_{27}H_{22}N_3O$ $(M+H)^+$ 404.1757, found 404.1763.

4.1.14. 3-Phenyl-5-(phenylamino)pyridin-2(1H)-one (19).

Compound **19** was prepared according to general procedure C, starting from **12** (46.3 mg, 0.131 mmol). The mixture was stirred for 4 h and was quenched with NEt_3 (12 eq.) and MeOH (4 eq.). The crude was purified by column chromatography (SiO_2, EtOAc/MeOH 99.9:0.1 to 99.2:0.8) to give **19** (31.0 mg, 0.118 mmol, 90%) as a yellow solid. R_f = 0.20 (CH_2Cl_2/MeOH 97:3); Mp > 153 °C (decomposition); IR (ATR) 3294, 1592, 1549, 1495, 1456, 1441, 863, 796, 784, 738 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.64 (br s, 1H), 7.73–7.69 (m, 2H), 7.52 (d, *J* = 2.9, 1H), 7.51 (s, 1H), 7.41–7.36 (m, 2H), 7.34–7.28 (m, 1H), 7.19 (d, *J* = 2.8, 1H), 7.14 (dd, *J* = 8.4, 7.4, 2H), 6.75 (d, *J* = 8.0, 2H), 6.68 (t, *J* = 7.3, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.5 (C), 146.5 (C), 137.5 (CH), 136.5 (C), 129.9 (C), 129.2 (2CH), 128.2 (2CH), 127.9 (2CH), 127.5 (CH), 127.1 (CH), 122.8 (C), 117.9 (CH), 113.81 (2CH); HRMS (ESI+) calcd for $C_{17}H_{15}N_2O$ $(M+H)^+$ 263.1179, found 263.1173; HPLC purity ≥ 99 %, t_R = 8.18 min, λ = 284 nm.

4.1.15. 3-(4-Fluorophenyl)-5-(phenylamino)pyridin-2(1H)-one (20).

Compound **20** was prepared according to general procedure C, starting from **13** (80.5 mg, 0.217 mmol). The mixture was stirred for 1 h. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 99.5:0.5 to 97:3) to give **20** (58.9 mg, 0.210 mmol, 97%) as a yellow solid. R_f = 0.35 (CH_2Cl_2/MeOH 94:6); Mp > 198 °C (decomposition); IR (ATR) 3276, 1593, 1549, 1451, 1226, 830 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.69 (br s, 1H), 7.81–7.75 (m, 2H), 7.53 (d, *J* = 2,9, 1H), 7,51 (s, 1H), 7.24–7,11 (m, 5H), 6.74 (d, *J* = 7.9, 2H), 6.68 (t, *J* = 7.3, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6 (d, J_{CF} = 245, C), 159.5 (C), 146.5 (C), 137.5 (CH), 132.8 (d, J_{CF} = 3, C), 130.2 (d, J_{CF} = 8, 2CH), 129.2 (2CH), 128.8 (C), 127.1 (CH), 122.8 (C), 117.9 (CH), 114.8 (d, J_{CF} = 21, 2CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{17}H_{14}FN_2O$ $(M+H)^+$ 281.1085, found 281.1087; HPLC purity ≥ 99%, t_R = 8.30 min, λ = 282 nm.

4.1.16. 5-(Phenylamino)-[3,4'-bipyridin]-2(1H)-one (21).

Compound **21** was prepared according to general procedure C, starting from **14** (59.2 mg, 0.168 mmol). The mixture was stirred for 2 h 30 min. The crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 99:1 to 95:5) to give **21** (35.5 mg, 0.135 mmol, 80%) as a yellow solid. R_f = 0.37 (CH_2Cl_2/MeOH 94:6); Mp > 230 °C (decomposition); IR (ATR) 3220, 1661, 1631, 1596, 1460, 1325, 1258, 830 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.85 (br s, 1H), 8.56 (d, *J* = 5.4, 2H), 7.82–7.79 (m, 2H), 7.76 (d, *J* = 2.8, 1H), 7.54 (s, 1H), 7.30 (d, *J* = 2.8, 1H), 7.15 (t, *J* = 7.8, 2H), 6.75 (d, *J* = 7.9, 2H), 6.69 (t, *J* = 7.3, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.2 (C), 149.4 (2CH), 146.4 (C), 143.6 (C), 138.9 (CH), 129.3

(2CH), 129.2 (CH), 126.6 (C), 122.8 (C), 122.4 (2CH), 118.0 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{16}H_{14}N_3O$ $(M+H)^+$ 264.1131, found 264.1134; HPLC purity ≥ 97%, t_R = 6.04 min, λ = 270 nm.

4.1.17. 3-(1H-Indol-3-yl)-5-(phenylamino)pyridin-2(1H)-one (22).

To a mixture under argon of 20% $Pd(OH)_2/C$ (13.61 mg, 0.019 mmol, 0.25 eq.) and ethyl acetate (1 mL), previously degassed with argon, was added a solution of compound **15** (30.9 mg, 0.079 mmol, 1 eq.) in ethyl acetate (4.5 mL) previously degassed with argon. The mixture was then hydrogenated at room temperature for 15 h. The mixture was filtered through a pad of Celite which was then washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the obtained red solid was purified by column chromatography (SiO_2, EtOAc + 0.5 % NEt_3 to EtOAc/MeOH 95:5 + 0.5% NEt_3) to give **22** (17.4 mg, 0.058 mmol, 73%) a red powder. R_f = 0.37 (EtOAc/MeOH 95:5 + 0.5% NEt_3); Mp > 181 °C (decomposition); IR (ATR) 3450–3150, 1597, 1497, 1431, 734, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.51 (br s, 1H), 11.39 (br s, 1H), 8.32 (d, *J* = 2.6, 1H), 7.82–7.79 (m, 2H), 7.58 (s, 1H), 7.46 (d, *J* = 8.0, 1H), 7.21–7.11 (m, 3H), 7.10–7.04 (m, 2H), 6.82 (d, *J* = 8.0, 2H), 6.69 (t, *J* = 7.3, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.5 (C), 146.5 (C), 136.2 (C), 132.6 (CH), 129.3 (2CH), 127.5 (CH), 126.3 (C), 125.1 (C), 122.7 (C), 122.2 (CH), 121.4 (CH), 119.7 (CH), 119.2 (CH), 117.9 (CH), 113.9 (2CH), 112.1 (CH), 109.6 (C); HRMS (ESI+) calcd for $C_{19}H_{16}N_3O$ $(M+H)^+$ 302.1288, found 302.1292; HPLC purity ≥ 97 %, t_R = 8.19 min, λ = 280 nm.

4.1.18. 5-(Phenylamino)-3-(quinolin-8-yl)pyridin-2(1H)-one (23).

Compound **23** was prepared according to general procedure C, starting from **16** (80.3 mg, 0.199 mmol). The mixture was stirred for 2 h 40 min and was quenched with NEt_3 (12 eq.) and MeOH (4 eq.). After evaporation, EtOAc was added. The mixture was washed once with water and twice with a saturated aqueous $NaHCO_3$ solution, dried over MgSO4 and filtered. After evaporation, the crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 99:1 + 0.5% NEt_3 to 96:4 + 0.5% NEt_3). The residue was dissolved in EtOAc and washed with water to eliminate the remaining triethylamine salts. After drying over $MgSO_4$, filtration and evaporation, **23** (11.9 mg, 0.0380 mmol, 19%) was obtained as a kaki powder. The poor yield could be explained by the poor solubility of the final product.

Compound **23** was again prepared according to general procedure C, starting from **16** (133.8 mg, 0.332 mmol). The mixture was stirred for 3 h, quenched with NEt_3 (12 eq.) and MeOH (4 eq.) and then concentrated. The crude was filtered and washed with water, acetone and CH_2Cl_2. The compound **23** with important traces of CH_2Cl_2 was obtained (70 mg, containing about 10.5% wt CH_2Cl_2).

R_f = 0.27 (CH_2Cl_2/MeOH 95:5); Mp > 255 °C (decomposition); IR (ATR) 3245, 1649, 1578, 1557, 1494, 1335, 1258, 795, 750, 705 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.52 (br s, 1H), 8.88 (dd, *J* = 4.1, 1.8, 1H), 8.39 (dd, *J* = 8.3, 1.8, 1H), 7.97 (dd, *J* = 8.2, 1.5, 1H), 7.85 (dd, *J* = 7.1, 1.5, 1H), 7.63 (dd, *J* = 8.1, 7.2, 1H), 7.56–7.51 (m, 3H), 7.23 (br s, 1H), 7.15 (dd, *J* = 8.5, 7.3, 2H), 6.83 (dd, *J* = 8.6, 1.0, 2H), 6.66 (tt, *J* = 7.3, 1.0, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.8 (C), 150.0 (CH), 146.4 (C), 145.8 (C), 140.2 (CH), 136.3 (CH), 135.5 (C), 130.6 (CH), 129.3 (C), 129.2 (2CH), 128.1 (C), 127.9 (CH), 126.6 (CH), 125.9 (CH), 122.3 (C), 121.3 (CH), 117.8 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{20}H_{16}N_3O$ $(M+H)^+$ 314.1288, found 314.1291; HPLC purity ≥ 96%, t_R = 6.77 min, λ = 282 nm.

4.1.19. 5-(Phenylamino)-3-(pyrimidin-5-yl)pyridin-2(1H)-one (24).

Compound **24** was prepared according to general procedure C, starting from **17** (80.5 mg, 0.227 mmol). The mixture was stirred for 3 h 20 min and was quenched with NEt_3 (12 eq.) and MeOH (4 eq.). After evaporation, EtOAc was added. The mixture was washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and filtered. After evaporation, the crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2 to 95:5) to give **24** (47.8 mg, 0.181 mmol, 80%) as a yellow solid. R_f = 0.12 (CH_2Cl_2/MeOH 95:5); Mp > 160 °C (decomposition); IR (ATR) 3408, 3287, 1597, 1548, 1475, 742, 717, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.90 (br s, 1H), 9.15 (s, 2H), 9.10 (s, 1H), 7.82 (d, *J* = 2.9, 1H), 7.56 (s, 1H), 7.30 (d, *J* = 2.8, 1H), 7.14 (t, *J* = 7.8, 2H), 6.76 (d, *J* = 8.0, 2H), 6.68 (t, *J* = 7.3, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.2 (C), 156.9 (CH), 155.7 (2CH), 146.4 (C), 138.8 (CH), 130.2 (C), 129.2 (2CH), 128.9 (CH), 123.8 (C), 123.0 (C), 118.0 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{15}H_{13}N_4O$ $(M+H)^+$ 265.1084, found 265.1090; HPLC purity ≥ 96%, t_R = 7.61 min, λ = 284 nm.

4.1.20. 3-(Isoquinolin-5-yl)-5-(phenylamino)pyridin-2(1H)-one (25).

Compound **25** was prepared according to general procedure C, starting from **18** (172 mg, 0.426 mmol). The mixture was stirred for 2 h 30 min and was quenched with NEt_3 (16 eq.) and MeOH (6 eq.). After evaporation, EtOAc was added. The mixture was washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$, and filtered. After evaporation, the crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2 to 90:10) to give **25** (58.6 mg, 0.187 mmol, 44%) as a yellow solid. R_f = 0.16 (CH_2Cl_2/MeOH 94:6); Mp > 209 °C (decomposition); IR (ATR) 3274, 1646, 1583, 1554, 1496, 1462, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.73 (br s, 1H), 9.34 (s, 1H), 8.47 (d, *J* = 5,9, 1H), 8.15–8.11 (m, 1H), 7.74–7.70 (m, 2H), 7.56–7.53 (m, 2H), 7.44 (d, *J* = 2.9, 1H), 7.35 (d, *J* = 2.9, 1H), 7.15 (dd, *J* = 8.5, 7.4, 2H), 6.80 (dd, *J* = 8.6, 1.0, 2H), 6.68 (tt, *J* = 7.3, 1.0, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.4 (C), 152.6 (CH), 146.3 (C), 142.8 (CH), 139.9 (CH), 134.3 (C), 133.6 (C), 131.5 (CH), 129.3 (C), 129.2 (2CH), 128.3 (C), 128.0 (CH), 127.6 (CH), 127.0 (CH), 122.8 (C), 118.7 (CH), 118.0 (CH), 114.0 (2CH); HRMS (ESI+) calcd for $C_{20}H_{16}N_3O$ $(M+H)^+$ 314.1288, found 314.1292; HPLC purity ≥ 96%, t_R = 6.47 min, λ = 278 nm.

4.1.21. 6-(Benzyloxy)-5-(quinolin-4-yl)-N-phenylpyridin-3-amine (46).

Compound **46** was prepared according to general procedure A, starting from **4** (201 mg, 0.566 mmol) and the corresponding boronic acid. The mixture was refluxed for 16 h. The crude oil was purified by column chromatography (SiO_2, EtOAc/cyclohexane 1:9 to 3:7) to give **46** (205 mg, 0.508 mmol, 90%) as a yellow powder. R_f = 0.16 (EtOAc/cyclohexane 2:8); Mp 156 °C; IR (ATR) 3232, 3179, 1597, 1438, 1229, 1022, 730, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, *J* = 4.4, 1H), 8.17 (s, 1H), 8.16 (d, *J* = 2.8, 1H), 8.09 (d, *J* = 8.4, 1H), 7.79 (ddd, *J* = 8.4, 6.8, 1.6, 1H), 7.66 (dd, *J* = 8.4, 1.4, 1H), 7.58 (ddd, *J* = 8.3, 6.8, 1.4, 1H), 7.54 (d, *J* = 2.8, 1H), 7.52 (d, *J* = 4.4, 1H), 7.24–7.17 (m, 5H), 7.14–7.10 (m, 2H), 7.02 (dd, *J* = 8.7, 1.1, 2H), 6.78 (tt, *J* = 7.3, 1.0, 1H), 5.39–5.21 (br s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.3 (C), 150.1 (CH), 147.7 (C), 144.0 (C), 142.9 (C), 137.3 (C), 136.9 (CH), 134.5 (C), 131.0 (CH), 129.5 (CH), 129.4 (CH), 129.3 (2CH), 128.1 (2CH), 127.4 (CH), 127.3 (2CH), 126.8 (CH), 126.2 (C), 125.9 (CH), 122.2 (CH), 120.3 (C), 119.4 (CH), 115.5 (2CH), 67.0 (CH_2); HRMS (ESI+) calcd for $C_{27}H_{22}N_3O$ $(M+H)^+$ 404.1757, found 404.1763.

4.1.22. 6-(Benzyloxy)-5-(1H-indol-4-yl)-N-phenylpyridin-3-amine (47).

Compound **47** was prepared according to general procedure A, starting from **4** (189 mg, 0.53 mmol) and the corresponding pinacol boronic ester. The mixture was refluxed for 16 h. The crude oil was purified by column chromatography (SiO_2, EtOAc/cyclohexane 5:95 to EtOAc/cyclohexane 15:85) to give **47** (207 mg, 0.53 mmol, quant.) as a grey powder. R_f = 0.30 (EtOAc/cyclohexane 2:8); Mp 66 °C; IR (ATR) 3394, 1595, 1496, 1441, 1350, 1228, 748, 694 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.06 (s, 1H), 8.02 (d, *J* = 2.7, 1H), 7.58 (d, *J* = 2.7, 1H), 7.43–7.10 (m, 11H), 6.99 (d, *J* = 7.9, 2H), 6.76 (t, *J* = 7.3, 1H), 6.32–6.30 (m, 1H), 5.35 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.7 (C), 144.5 (C), 137.7 (C), 136.0 (C), 135.3 (CH), 134.1 (C), 131.3 (CH), 129.3 (2CH), 128.1 (2CH), 127.9 (C), 127.4 (2CH), 127.3 (CH), 126.5 (C), 125.5 (CH), 123.7 (C), 120.7 (CH), 120.0 (CH), 119.0 (CH), 115.2 (2CH), 111.1 (CH), 100.5 (CH), 66.9 (CH_2); HRMS (ESI+) calcd for $C_{26}H_{22}N_3O$ $(M+H)^+$ 392.1757, found 392.1751.

4.1.23. 6-(Benzyloxy)-5-(2-chlorophenyl)-N-phenylpyridin-3-amine (48).

Compound **48** was prepared according to general procedure A, starting from **4** (125.2 mg, 0.352 mmol) and the corresponding boronic acid. The mixture was refluxed for 15 h 30 min. The crude oil was purified by column chromatography (SiO_2, pentane to EtOAc/pentane 1:9) to give **48** (116 mg, 0.300 mmol, 85%) a red oil. R_f = 0.34 (EtOAc/cyclohexane 1:9); IR (ATR) 3390, 1599, 1497, 1425, 1231, 736, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 8.03 (d, *J* = 2.8, 1H), 7.58–7.53 (m, 1H), 7.47–7.38 (m, 4H), 7.33–7.23 (m, 5H), 7.20 (dd, *J* = 8.5, 7.3, 2H), 6.97 (d, *J* = 8.7, 1.1, 2H), 6.77 (tt, *J* = 7.3, 1.0, 1H), 5.30 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.4 (C), 144.2 (C), 137.6 (C), 136.4 (CH), 135.2 (C), 134.0 (C), 132.6 (C), 131.8 (CH), 131.2 (CH), 129.6 (CH), 129.32 (2CH), 129.28 (CH), 128.2 (2CH), 127.4 (CH), 127.3 (2CH), 127.1 (CH), 121.9 (C), 119.2 (CH), 115.2 (2CH), 67.0 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{20}ClN_2O$ $(M+H)^+$ 387.1259, found 387.1248.

4.1.24. 6-(Benzyloxy)-5-(2-bromophenyl)-N-phenylpyridin-3-amine (49).

Compound **49** was prepared according to general procedure A, starting from **4** (114.7 mg, 0.323 mmol) and the corresponding boronic acid. The mixture was refluxed for 16 h. The crude was chromatographed (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) but some impurity remained in the obtained orange oil (71 mg). Compound **49** was used for the next step without further purification. R_f = 0.29 (EtOAc/cyclohexane 1:9).

4.1.25. Ethyl 2-(2-(benzyloxy)-5-(phenylamino)pyridin-3-yl)benzoate (50).

Compound **50** was prepared according to general procedure A, starting from **4** (123.5 mg, 0.348 mmol) and the corresponding boronic acid. The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) to give **50** (110 mg, 0.259 mmol, 75%) an orange-brown oil. R_f = 0.40 (EtOAc/cyclohexane 2:8); IR (ATR) 3372, 1708, 1598, 1430, 1253, 746, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.98 (d, *J* = 2.7, 1H), 7.85 (dd, *J* = 7.7, 1.4, 1H), 7.65 (td, *J* = 7.6, 1.5, 1H), 7.50 (td, *J* = 7.6, 1.3, 1H), 7.41 (dd, *J* = 7.6, 1.3, 1H), 7.39 (d, *J* = 2.7, 1H), 7.33–7.22 (m, 5H), 7.20 (dd, *J* = 8.6, 7.3, 2H), 6.96 (dd, *J* = 8.6, 1.1, 2H), 6.76 (tt, *J* = 7.3, 1.1, 1H), 5.24 (s, 2H), 3.98 (q, *J* = 7.1, 2H), 0.95 (t, *J* = 7.1, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.8 (C), 154.3 (C), 144.6 (C), 137.4 (C), 136.6 (C), 135.5 (CH), 134.1 (C), 132.1 (CH), 131.1 (CH), 131.0 (C), 130.4 (CH), 129.5 (CH), 129.3 (2CH), 128.1 (2CH), 128.0 (CH), 127.4 (CH), 127.3 (2CH), 124.9 (C), 118.9 (CH), 115.0 (2CH), 66.8 (CH_2), 60.4 (CH_2), 13.6 (CH_3); HRMS (ESI+) calcd for $C_{27}H_{25}N_2O_3$ $(M+H)^+$ 425.1860, found 425.1857.

4.1.26. 2-(2-(Benzyloxy)-5-(phenylamino)pyridin-3-yl)benzonitrile (51).

Compound **51** was prepared according to general procedure A, starting from **4** (152 mg, 0.428 mmol) and the corresponding boronic acid. The mixture was refluxed for 15 h. The crude was chromatographed (SiO_2, pentane to EtOAc/pentane) but some impurities remained in the obtained white solid (131.6 mg). Compound **51** was used for the next step without further purification. R_f = 0.35 (EtOAc/pentane 5:5).

4.1.27. 6-(Benzyloxy)-5-(2-nitrophenyl)-N-phenylpyridin-3-amine (52).

To a solution under argon of **4** (201.4 mg, 0.567 mmol, 1 eq.) in 1,4-dioxane (0.5 mL) were added the 2-nitrophenylboronic acid (95.1 mg, 0.57, 1 eq.) and a 2 M aqueous K_2CO_3 solution (4 eq.). The mixture was degassed with argon for 10 min before the addition of $Pd(dppf)Cl_2$ (24.4 mg, 0.033 mmol, 0.06 eq.). The solution was stirred at 100 °C. Additional portions of boronic acid were added after 2 h 30 min (47.3 mg, 0.283 mmol, 0.5 eq.), 17 h 30 min (31.6 mg, 0.189 mmol, 0.33 eq.) and 24 h (47.4 mg, 0.284 mmol, 0.5 eq.). The mixture was then stirred at 100 °C overnight. Ethyl acetate was added and the resulting mixture was washed with water. The organic phase was dried over $MgSO_4$ and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) to give the desired product **52** (83.1 mg, 0.209 mmol, 37%) as an orange powder. R_f = 0.41 (EtOAc/cyclohexane 2:8); Mp 141 °C; IR (ATR) 3370, 1453, 1351, 1295, 1250, 1219, 990, 730, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 8.05 (dd, *J* = 8.1, 1.2, 1H), 8.01 (d, *J* = 2.7, 1H), 7.80 (td, *J* = 7.6, 1.3, 1H), 7.64 (ddd, *J* = 8.1, 7.5, 1.5, 1H), 7.60 (dd, *J* = 7.6, 1.3, 1H), 7.55 (d, *J* = 2.7, 1H), 7.33–7.19 (m, 7H), 7.00 (dd, *J* = 8.6, 1.1, 2H), 6.79 (tt, *J* = 7.3, 1.1, 1H), 5.21 (br s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.5 (C), 148.6 (C), 144.2 (C), 137.0 (C), 136.1 (CH), 134.7 (C), 133.8 (CH), 132.6 (CH), 130.6 (C), 129.9 (CH), 129.4 (CH), 129.3 (2CH), 128.2 (2CH), 127.5 (CH), 127.4 (2CH), 124.3 (CH), 121.3 (C), 119.3 (CH), 115.3 (2CH), 67.2(CH_2); HRMS (ESI+) calcd for $C_{24}H_{20}N_3O_3$ $(M+H)^+$ 398.1499, found 398.1487.

4.1.28. 5-([1,1'-biphenyl]-4-yl)-6-(benzyloxy)-N-phenylpyridin-3-amine (53).

Compound **53** was prepared according to general procedure A, starting from **4** (119 mg, 0.335 mmol) and the corresponding boronic acid. The mixture was refluxed for 16 h. The crude oil was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) to give **53** (30.8 mg) and a second fraction containing trace of 4-phenylphenol. CH_2Cl_2 was added to the second fraction which was washed with a 0.5 M aqueous NaOH solution, and then with water. The organic phase was dried over $MgSO_4$, filtered and evaporated to give pure **53** (99.8 mg). Compound **53** (130.6 mg, 0.305 mmol, 91%) was obtained as a light brown solid. R_f = 0.27 (EtOAc/cyclohexane 1:9); Mp 109 °C; IR (ATR) 3304, 1595, 1437, 1232, 1006, 841, 721, 690 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 8.00 (d, *J* = 2.7, 1H), 7.76–7.69 (m, 6H), 7.60 (d, *J* = 2.8, 1H), 7.51–7.41 (m, 4H), 7.40–7.34 (m, 3H), 7.32–7.26 (m, 1H), 7.21 (dd, *J* = 8.6, 7.3, 2H), 7.00 (dd, *J* = 8.7, 1.1, 2H), 6.78 (tt, *J* = 7.3, 1.1, 1H), 5.41 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.3 (C), 144.4 (C), 139.6 (C), 139.3 (C), 137.7 (C), 135.7 (CH), 135.2 (C), 134.6 (C), 130.3 (CH), 129.5 (2CH), 129.3 (2CH), 129.0 (2CH), 128.3 (2CH), 127.6 (CH), 127.5 (CH), 127.4 (2CH), 126.6 (2CH), 126.5 (2CH), 123.3 (C), 119.1 (CH), 115.2 (2CH), 67.1 (CH_2); HRMS (ESI+) calcd for $C_{30}H_{25}N_2O$ $(M+H)^+$ 429.1961, found 429.1972.

4.1.29. 6-(Benzyloxy)-5-(3-chlorophenyl)-N-phenylpyridin-3-amine (54).

Compound **54** was prepared according to general procedure A, starting from **4** (117 mg, 0.329 mmol). The mixture was refluxed for 16 h. The crude oil was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) to give **54** (121.3 mg, 0.314 mmol, 95%) as a red oil. R_f = 0.40 (EtOAc/cyclohexane 1:9); IR (ATR) 3378, 1602, 1589, 1439, 1409, 1359, 1298, 1256, 1217, 1013, 894, 754, 728, 692 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 8.02 (d, *J* = 2.7, 1H), 7.71 (t, *J* = 1.7, 1H), 7.58 (d, *J* = 2.7, 1H), 7.56 (dt, *J* = 7.5, 1.5, 1H), 7.46 (t, *J* = 7.7, 1H), 7.44–7.40 (m, 3H), 7.39–7.33 (m, 2H), 7.32–7.27 (m, 1H), 7.21 (dd, *J* = 8.5, 7.4, 2H), 6.99 (dd, *J* = 8.6, 1.0, 2H), 6.78 (tt, *J* = 7.3, 1.1, 1H), 5.38 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.1 (C), 144.3 (C), 138.2 (C), 137.5 (C), 136.3 (CH), 134.6 (C), 132.9 (C), 130.4 (CH), 130.2 (CH), 129.4 (2CH), 128.9 (CH), 128.3 (2CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (2CH), 122.2 (C), 119.2 (CH), 115.2 (2CH), 67.2 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{20}ClN_2O$ $(M+H)^+$ 387.1259, found 387.1268.

4.1.30. 1-(3-(2-(Benzyloxy)-5-(phenylamino)pyridin-3-yl)phenyl)ethan-1-one (55).

Compound **55** was prepared according to general procedure A, starting from **4** (117.5 mg, 0.331 mmol) and the corresponding boronic acid. The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 15:85) to give **55** (130.6 mg, 0.331 mmol, quant.) a brown oil. R_f = 0.41 (EtOAc/cyclohexane 2:8); IR (ATR) 3367, 1669, 1596, 1535, 1497, 1490, 1442, 1417, 1246, 1218, 1009, 734, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.21 (td, *J* = 1.8, 0.5, 1H), 8.10 (s, 1H), 8.04 (d, *J* = 2.7, 1H), 7.93 (ddd, *J* = 7.8, 1.8, 1.1, 1H), 7.86 (ddd, *J* = 7.7, 1.9, 1.1, 1H), 7.62 (d, *J* = 2.8, 1H), 7.59 (td, *J* = 7.8, 0.5, 1H), 7.45–7.41 (m, 2H), 7.38–7.32 (m, 2H), 7.32–7.26 (m, 1H), 7.21 (dd, *J* = 8.6, 7.3, 2H), 6.99 (dd, *J* = 8.7, 1.1, 2H), 6.78 (tt, *J* = 7.3, 1.1, 1H), 5.38 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.7 (C), 154.3 (C), 144.4 (C), 137.5 (C), 136.8 (C), 136.4 (C), 136.2 (CH), 134.6 (C), 133.6 (CH), 130.6 (CH), 129.3 (2CH), 129.0 (CH), 128.7 (CH), 128.3 (2CH), 127.58 (2CH), 127.57 (CH), 127.2 (CH), 122.8 (C), 119.1 (CH), 115.2 (2CH), 67.2 (CH_2), 26.7 (CH_3); HRMS (ESI+) calcd for $C_{26}H_{23}N_2O_2$ $(M+H)^+$ 395.1754, found 395.1748.

4.1.31. 4-(2-(Benzyloxy)-5-(phenylamino)pyridin-3-yl)phenol (56).

Compound **56** was prepared according to general procedure A, starting from **4** (147 mg, 0.414 mmol) and the corresponding boronic acid. The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO_2, EtOAc/cyclohexane 5:95 to 2:8). The obtained yellow solid was then dissolved in ethyl acetate and washed with water. The organic phase was dried over $MgSO_4$, filtered and evaporated to give **56** (115 mg, 0.312 mmol, 75%) as a pale yellow solid. R_f = 0.24 (EtOAc/cyclohexane 8:2); Mp 172°C; IR (ATR) 3389, 1597, 1528, 1249, 1211, 1023, 725, 689 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 7.99 (s, 1H), 7.92 (d, *J* = 2.7, 1H), 7.47 (d, *J* = 2.7, 1H), 7.43 (d, *J* = 8.7, 2H), 7.43–7.39 (m, 2H), 7.38–7.33 (m, 2H), 7.31–7.26 (m, 1H), 7.20 (dd, *J* = 8.4, 7.4, 2H), 6.96 (dd, *J* = 8.6, 1.0, 2H), 6.80 (d, *J* = 8.7, 2H), 6.76 (tt, *J* = 7.3, 1.0, 1H), 5.36 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.0 (C), 154.3 (C), 144.5 (C), 137.8 (C), 134.8 (CH), 134.4 (C), 130.2 (2CH), 130.0 (CH), 129.3 (2CH), 128.3 (2CH), 127.4 (CH), 127.3 (2CH), 126.6 (C), 123.9 (C), 118.9 (CH), 115.10 (2CH), 115.06 (2CH), 67.0 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{21}N_2O_2$ $(M+H)^+$ 369.1598, found 369.1587.

4.1.32. 6-(Benzyloxy)-N-phenyl-5-(p-tolyl)pyridin-3-amine (57).

Compound **57** was prepared according to general procedure A, starting from **4** (120 mg, 0.338 mmol) and the corresponding boronic acid. The mixture was refluxed for 15 h. The crude oil was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) to give **57** containing trace of 4-methylphenol. EtOAc was added and the organic phase washed with a 0.5 M aqueous NaOH solution, and then with water. The organic phase was dried over $MgSO_4$, filtered and evaporated to give **57** (106 mg, 0.289 mmol, 86%) as an orange solid. R_f = 0.37 (EtOAc/cyclohexane 1:9); Mp 72 °C; IR (ATR) 3313, 1594, 1440, 1231, 1025, 868, 822, 730, 692 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.05 (s, 1H), 7.97 (d, *J* = 2.7, 1H), 7.51 (d, *J* = 2.8, 1H), 7.50 (d, *J* = 8.2, 2H), 7.42–7.39 (m, 2H), 7.38–7.33 (m, 2H), 7.31–7.26 (m, 1H), 7.23 (d, *J* = 7.8, 2H), 7.20 (dd, *J* = 8.6, 7.3, 2H), 6.97 (dd, *J* = 8.7, 1.1, 2H), 6.76 (tt, *J* = 7.3, 1.1, 1H), 5.36 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.3 (C), 144.5 (C), 137.7 (C), 137.0 (C), 135.4 (CH), 134.5 (C), 133.2 (C), 130.4 (CH), 129.3 (2CH), 128.85 (2×2CH), 128.3 (2CH), 127.49 (CH), 127.46 (2CH), 123.8 (C), 119.0 (CH), 115.1 (2CH), 67.1 (CH_2), 20.8 (CH_3); HRMS (ESI+) calcd for $C_{25}H_{23}N_2O$ $(M+H)^+$ 367.1805, found 367.1797.

4.1.33. 6-(Benzyloxy)-N-phenyl-5-(4-(trifluoromethyl)phenyl)pyridin-3-amine (58).

Compound **58** was prepared according to general procedure A, starting from **4** (152 mg, 0.43 mmol) and the corresponding boronic acid. The mixture was refluxed for 18 h. The crude green oil was purified by column chromatography (SiO_2, EtOAc/cyclohexane 5:95 to 2:8) to give **58** (149 mg, 0.35 mmol, 83%) as a pale yellow oil which solidified to a yellow solid.

R_f = 0.51 (EtOAc/cyclohexane 2:8); Mp 109 °C; IR (ATR) 3383, 3336, 1598, 1442, 1322, 1123, 1111, 1068, 845, 738, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 8.05 (d, *J* = 2.8, 1H), 7.84 (d, *J* = 8.2, 2H), 7.78 (d, *J* = 8.4, 2H), 7.61 (d, *J* = 2.8, 1H), 7.42–7.39 (m, 2H), 7.38–7.33 (m, 2H), 7,31–7,26 (m, 1H), 7.21 (dd, *J* = 8.5, 7.3, 2H), 7.00 (dd, *J* = 8.6, 1.1, 2H), 6.78 (tt, *J* = 7.3, 1.1, 1H), 5.40 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.1 (C), 144.2 (C), 140.3 (C), 137.5 (C), 136.5 (CH), 134.7 (C), 130.5 (CH), 129.8 (2CH), 129.3 (2CH), 128.3 (2CH), 127.9 (q, J_{CF} = 32, C), 127.52 (CH), 127.46 (2CH), 125.1 (q, J_{CF} = 4, 2CH), 124.2 (q, J_{CF} = 272, C), 122.2 (C), 119.2 (CH), 115.3 (2CH), 67.2 (CH_2); HRMS (ESI+) calcd for $C_{25}H_{20}F_3N_2O$ $(M+H)^+$ 421.1522, found 421.1539.

4.1.34. 6-(Benzyloxy)-N-phenyl-5-(4-(trifluoromethoxy)phenyl)pyridin-3-amine (59).

Compound **59** was prepared according to general procedure A, starting from **4** (115.1 mg, 0.324 mmol) and the corresponding boronic acid. The mixture was refluxed for 16 h. The crude was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 1:9) to give **59** (128.1 mg, 0.293 mmol, 91%) as a grey solid. R_f = 0.36 (EtOAc/cyclohexane 1:9); Mp 83 °C; IR (ATR) 3394, 1598, 1443, 1258, 1206, 1163, 1047, 1017, 734, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 8.01 (d, *J* = 2.7, 1H), 7.74 (d, *J* = 8.9, 2H), 7.57 (d, *J* = 2.8, 1H), 7.45–7.33 (m, 6H), 7.31–7.26 (m, 1H), 7.20 (dd, *J* = 8.5, 7.4, 2H), 6.99 (dd, *J* = 8.6, 1.0, 2H), 6.78 (tt, *J* = 7.4, 1.0, 1H), 5.38 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.1 (C), 147.7 (q, *J* = 2, C), 144.3 (C), 137.6 (C), 136.1 (CH), 135.4 (C), 134.6 (C), 131.0 (2CH), 130.4 (CH), 129.3 (2CH), 128.3 (2CH), 127.5 (CH), 127.4 (2CH), 122.3 (C), 120.8 (2CH), 120,1 (q, *J* = 256, C), 119.2 (CH), 115.3 (2CH), 67.1 (CH_2); HRMS (ESI+) calcd for $C_{25}H_{20}F_3N_2O_2$ $(M+H)^+$ 437.1463, found 437.1471.

4.1.35. Methyl 4-(2-(benzyloxy)-5-(phenylamino)pyridin-3-yl)benzoate (60).

Compound **60** was prepared according to general procedure A, starting from **4** (98.9 mg, 0.278 mmol) and the corresponding boronic acid. The mixture was refluxed for 16 h. The crude was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 15:85) to give **60** (68.8 mg, 0.168 mmol, 60%) as a yellow powder. R_f = 0.46 (EtOAc/cyclohexane 2:8); Mp 139 °C; IR (ATR) 3374, 1707, 1695, 1598, 1280, 1261, 861, 729, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.11 (s, 1H), 8.04 (d, J = 2.7, 1H), 8.00 (d, J = 8.6, 2H), 7.77 (d, J = 8.6, 2H), 7.60 (d, J = 2.7, 1H), 7.43–7.39 (m, 2H), 7.39–7.33 (m, 2H), 7.32–7.26 (m, 1H), 7.21 (dd, J = 8.5, 7.3, 2H), 6.99 (dd, J = 8.6, 1.1, 2H), 6.78 (tt, J = 7.3, 1.1, 1H), 5.38 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0 (C), 154.2 (C), 144.3 (C), 141.0 (C), 137.5 (C), 136.5 (CH), 134.7 (C), 130.5 (CH), 129.39 (2CH), 129.35 (2CH), 129.1 (2CH), 128.6 (C), 128.4 (2CH), 127.6 (CH), 127.5 (2CH), 122.6 (C), 119.2 (CH), 115.3 (2CH), 67.3 (CH_2), 52.2 (CH_3); HRMS (ESI+) calcd for $C_{26}H_{23}N_2O_3$ $(M+H)^+$ 411.1703, found 411.1702.

4.1.36. 4-(2-(Benzyloxy)-5-(phenylamino)pyridin-3-yl)benzamide (61).

Compound **61** was prepared according to general procedure A, starting from **4** (115 mg, 0.324 mmol) and the corresponding boronic acid. The mixture was refluxed for 16 h. The crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 3:7 to 6:4) but some impurities remained in the obtained white powder (133 mg). Compound **61** was used for the next step without further purification. R_f = 0.09 (EtOAc/cyclohexane 3:7).

4.1.37. 6-(Benzyloxy)-5-(2,4-difluorophenyl)-N-phenylpyridin-3-amine (62).

Compound **62** was prepared according to general procedure A, starting from **4** (115 mg, 0.324 mmol) and the corresponding boronic acid. The mixture was refluxed for 22 h. Due to the presence of residual starting material **4**, catalyst $PdCl_2(PPh_3)_2$ was added (5.1 mg, 0.0073 mmol, 0.02 eq.) and the mixture was refluxed for additional 17 h. The crude was chromatographed (SiO_2, pentane to EtOAc/pentane 6:94) but some impurities remained in the obtained pink-brown oil (97.6 mg). Compound **62** was used for the next step without further purification. R_f = 0.21 (EtOAc/pentane 5:95).

4.1.38. 6-(Benzyloxy)-5-(1H-indol-7-yl)-N-phenylpyridin-3-amine (63).

Indole-7-boronic acid was prepared from 7-bromoindole according to literature procedure [28]. To a solution under argon cooled to 0 °C of 7-bromoindole (171 mg, 0.87 mmol, 1 eq.) in anhydrous THF (1.4 mL) was added a suspension of KH (30% dispersion in mineral oil, 121.6 mg, 0.91 mmol, 1 eq.) in anhydrous THF (0.33 mL) cooled to 0 °C. The mixture was stirred at 0 °C for 20 min then was cooled to –78 °C and a 1.08 M *t*-butyllithium solution in pentane (1.65 mL, 1.78 mmol, 2 eq.) cooled to –78 °C was added dropwise. The mixture was then stirred at room temperature for 15 min in the dark. The mixture was cooled to –78 °C and trimethyl borate was added (0.19 mL, 1.7 mmol, 2 eq.). The mixture was stirred at room temperature for 3 h. Water was added and the mixture was washed with EtOAc. Aqueous phase was acidified with a 10% HCl solution (pH 1) and was extracted with EtOAc. The organic phase was dried over $MgSO_4$, filtered and evaporated giving a 46:54 mixture of indole-7-boronic acid and indole (213 mg, ratio evaluated by ^1H-NMR). The obtained crude was used without purification.

Compound **63** was prepared according to general procedure A, starting from **4** (105.1 mg, 0.296 mmol) and the mixture of indole-7-boronic acid and indole obtained in the preceding step. The reaction mixture was refluxed for 15.5 h. The crude oil was purified by column

chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 2:8) to give **63** (57 mg, 0.146 mmol, 49%) as a beige powder. R_f = 0.32 (EtOAc/cyclohexane 2:8); Mp 135 °C; IR (ATR) 3389, 3316, 1596, 1497, 1420, 1230, 1023, 798, 722, 692 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 8.09 (s, 1H), 8.08 (d, *J* = 2.8, 1H), 7.57–7.53 (m, 1H), 7.55 (d, *J* = 2.8, 1H), 7.30 (t, *J* = 2.9, 1H), 7.24–7.17 (m, 7H), 7.08–6.99 (m, 4H), 6.76 (tt, *J* = 7.3, 1.1, 1H), 6.47 (dd, *J* = 3.1, 1.9, 1H), 5.34 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.9 (C), 144.5 (C), 137.5 (C), 135.7 (CH), 134.3 (C), 133.6 (C), 131.2 (CH), 129.3 (2CH), 128.0 (2CH), 127.9 (C), 127.5 (2CH), 127.3 (CH), 125.5 (CH), 122.2 (CH), 122.0 (C), 120.6 (C), 119.9 (CH), 119.0 (CH), 118.8 (CH), 115.1 (2CH), 101.1 (CH), 67.1 (CH_2); HRMS (ESI+) calcd for $C_{26}H_{22}N_3O$ $(M+H)^+$ 392.1757, found 392.1754.

4.1.39. 5-(3-Aminophenyl)-6-(benzyloxy)-N-phenylpyridin-3-amine (64).

Compound **64** was prepared according to general procedure A, starting from **4** (121.6 mg, 0.342 mmol) and the corresponding boronic acid. The mixture was refluxed for 15 h 30 min. The crude oil was purified by column chromatography (SiO_2, EtOAc/cyclohexane 2:8 to 25:75) to give **64** (120.2 mg, 0.327 mmol, 96%) a light yellow oil. R_f = 0.07 (EtOAc/cyclohexane 1:9); Mp 106 °C; IR (ATR) 3380, 1586, 1426, 1360, 1020, 754, 735, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.02 (s, 1H), 7.93 (d, *J* = 2.8, 1H), 7.45 (d, *J* = 2.8, 1H), 7.43–7.39 (m, 2H), 7.37–7.32 (m, 2H), 7.30–7.25 (m, 1H), 7.20 (dd, *J* = 8.6, 7.4, 2H), 7.05 (t, *J* = 7.8, 1H), 6.96 (dd, *J* = 8.6, 1.1, 2H), 6.79–6.72 (m, 3H), 6.54 (ddd, *J* = 8.0, 2.3, 1.0, 1H), 5.36 (s, 2H), 5.11 (br s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.3 (C), 148.5 (C), 144.4 (C), 137.8 (C), 136.7 (C), 135.2 (CH), 134.3 (C), 130.2 (CH), 129.3 (2CH), 128.6 (CH), 128.3 (2CH), 127.4 (CH), 127.3 (2CH), 124.7 (C), 119.0 (CH), 116.6 (CH), 115.2 (2CH), 114.4 (CH), 113.2 (CH), 66.9 (CH_2); HRMS (ESI+) calcd for $C_{24}H_{22}N_3O$ $(M+H)^+$ 368.1757, found 368.1743.

4.1.40. 6-(Benzyloxy)-5-(3-methoxyphenyl)-N-phenylpyridin-3-amine (65).

Compound **65** was prepared according to general procedure A, starting from **4** (114 mg, 0.321 mmol) and the corresponding boronic acid. The mixture was refluxed for 15 h 30 min. The crude oil was purified by column chromatography (SiO_2, cyclohexane to EtOAc/cyclohexane 8:92) to give a mixture of **65** and 3-methoxyphenol. Ethyl acetate was added and the organic phase was washed with an 0.5 M NaOH aqueous solution of and then with water. The organic phase was dried over $MgSO_4$, filtered and then evaporated to give **65** (106 mg, 0.277 mmol, 86%) a brown oil. R_f = 0.57 (EtOAc/cyclohexane 2:8); IR (ATR) 3375, 1587, 1418, 1360, 1262, 1014, 864, 754, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 8.00 (d, *J* = 2.7, 1H), 7.55 (d, *J* = 2.7, 1H), 7.44–7.41 (m, 2H), 7.38–7.27 (m, 4H), 7.23–7.18 (m, 3H), 7.14 (ddd, *J* = 7.7, 1.5, 1.0, 1H), 6.98 (dd, *J* = 8.6, 1.0, 2H), 6.91 (ddd, *J* = 8.3, 2.6, 0.9, 1H), 6.77 (tt, *J* = 7.3, 1.1, 1H), 5.36 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.9 (C), 154.3 (C), 144.4 (C), 137.6 (C), 137.4 (C), 135.7 (CH), 134.5 (C), 130.5 (CH), 129.31 (2CH), 129.30 (CH), 128.3 (2CH), 127.61 (2CH), 127.56 (CH), 123.6 (C), 121.2 (CH), 119.1 (CH), 115.1 (2CH), 114.3 (CH), 113.6 (CH), 67.1 (CH_2), 55.0 (CH_3); HRMS (ESI+) calcd for $C_{25}H_{23}N_2O_2$ $(M+H)^+$ 383.1751, found 383.1754.

4.1.41. 5-(Phenylamino)-3-(quinolin-4-yl)pyridin-2(1H)-one (66).

Compound **66** was prepared according to general procedure C, starting from **46** (100 mg, 0.248 mmol). The mixture was stirred for 3 h and was quenched with NEt_3 (12 eq.) and MeOH (4 eq.). After evaporation, EtOAc was added. The mixture was washed with brine,

then the organic phase was dried over $MgSO_4$, and filtered. After evaporation, the crude was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2). EtOAc was added to the obtained product which was then washed with water to remove residual NEt_3 salts. The organic phase was dried over $MgSO_4$, filtered and concentrated to give **66** (54 mg, 0.172 mmol, 69%) as a light brown solid. R_f = 0.17 (CH_2Cl_2/MeOH 95:5); Mp > 275 °C (decomposition); IR (ATR) 1627, 1592, 1561, 1479, 1337, 1255, 836, 742, 689 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (br s, 1H), 8.91 (d, *J* = 4.4, 1H), 8.06 (d, *J* = 8.3, 1H), 7.80–7.74 (m, 2H), 7.60–7.55 (m, 2H), 7.49 (d, *J* = 3.0, 1H), 7.46 (d, *J* = 4.4, 1H), 7.38 (br s, 1H), 7.15 (dd, *J* = 8.6, 7.3, 2H), 6.80 (dd, *J* = 8.6, 1.0, 2H), 6.68 (tt, *J* = 7.3, 1.1, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.0 (C), 150.1 (CH), 147.8 (C), 146.2 (C), 143.5 (C), 139.9 (CH), 129.30 (CH), 129.27 (CH), 129.25 (2CH), 128.7 (CH), 128.1 (C), 126.4 (CH), 126.3 (C), 126.0 (CH), 122.9 (C), 122.1 (CH), 118.1 (CH), 114.0 (2CH); HRMS (ESI+) calcd for $C_{20}H_{16}N_3O$ $(M+H)^+$ 314.1288, found 314.1291; HPLC purity ≥ 96%, t_R = 6.83 min, λ = 280 nm.

4.1.42. 3-(1H-Indol-4-yl)-5-(phenylamino)pyridin-2(1H)-one (67).

Compound **67** was prepared according to general procedure C, starting from **47** (96.6 mg, 0.247 mmol). The mixture was stirred for 6 h and was quenched with NEt_3 (15 eq.) and MeOH (5 eq.). After evaporation, EtOAc was added. The mixture was washed with H_2O, dried over $MgSO_4$, and filtered. After evaporation, the crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 6:4 to 9:1) to give **67** (49.9 mg, 0.166 mmol, 67%) as a yellow solid. R_f = 0.13 (EtOAc/cyclohexane 6:4); Mp > 143 °C (decomposition); IR (ATR) 3500–3000, 1595, 1495, 1333, 1250, 746, 691 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.56 (br s, 1H), 11.14 (s, 1H), 7.52 (d, *J* = 3.0, 1H), 7.51 (s, 1H), 7.37–7.33 (m, 2H), 7.27 (dd, *J* = 7.3, 0.9, 1H), 7.20 (br s, 1H), 7.15 (dd, *J* = 8.5, 7.3, 2H), 7.09 (t, *J* = 7.7, 1H), 6.77 (dd, *J* = 8.6, 1.0, 2H), 6.68 (tt, *J* = 7.3, 1.1, 1H), 6.37–6.35 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.6 (C), 146.6 (C), 138.3 (CH), 136.1 (C), 130.6 (C), 129.2 (2CH), 128.3 (C), 126.7 (CH), 126.1 (C), 125.4 (CH), 122.5 (C), 120.5 (CH), 119.9 (CH), 117.9 (CH), 113.9 (2CH), 110.9 (CH), 100.5 (CH); HRMS (ESI+) calcd for $C_{19}H_{16}N_3O$ $(M+H)^+$ 302.1288, found 302.1282. HPLC purity ≥ 95%, t_R = 7.82 min, λ = 278 nm.

4.1.43. 3-(2-Chlorophenyl)-5-(phenylamino)pyridin-2(1H)-one (68).

Compound **68** was prepared according to general procedure C, starting from **48** (82.1 mg, 0.212 mmol). The mixture was stirred for 2 h 40 min and was quenched with NEt_3 (12 eq.) and MeOH (6 eq.). The crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 6:4 to 75:25). The product was washed with CH_2Cl_2 to give **68** (31.4 mg, 0.106 mmol, 50%) as a light yellow-green powder. R_f = 0.12 (EtOAc/cyclohexane 7:3); Mp > 231 °C; IR (ATR) 3267, 1654, 1593, 1563, 745, 696 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (br s, 1H), 7.53–7.48 (m, 2H), 7.41–7.34 (m, 3H), 7.32 (d, *J* = 2.9, 1H), 7.27–7.23 (br s, 1H), 7.14 (dd, *J* = 8.5, 7.4, 2H), 6.75 (dd, *J* = 8.6, 1.0, 2H), 6.68 (tt, *J* = 7.3, 1.0, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.9 (C), 146.4 (C), 139.4 (CH), 135.8 (C), 132.6 (C), 131.9 (CH), 129.5 (C), 129.3 (CH), 129.23 (CH), 129.22 (2CH), 128.0 (CH), 126.9 (CH), 122.3 (C), 118.0 (CH), 113.9 (2CH); HRMS (ESI+) calcd for $C_{17}H_{14}ClN_2O$ $(M+H)^+$ 297.0789, found 297.0781; HPLC purity ≥ 98%, t_R = 8.19 min, λ = 280 nm.

4.1.44. 3-(2-Bromophenyl)-5-(phenylamino)pyridin-2(1H)-one (69).

Compound **69** was prepared according to general procedure C, starting from impure compound **49** (65 mg). The mixture was stirred for 3 h and was quenched with NEt_3 (13 eq.) and MeOH (7 eq.). After work-up, the crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 7:3 to EtOAc). The product was washed with CH_2Cl_2 to give **69** (18.6 mg, 0.055 mmol, 18% over 2 steps from **29**) as a white solid. R_f = 0.32 (EtOAc); Mp > 236 °C (decomposition); IR (ATR) 3272, 1596, 744 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.63 (br s, 1H), 7.67 (d, *J* = 7.9, 1H), 7.52 (s, 1H), 7.44–7.34 (m, 2H), 7.32–7.22 (m, 3H), 7.14 (t, *J* = 7.6, 2H), 6.75 (d, *J* = 7.9, 2H), 6.67 (t, *J* = 7.1, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8 (C), 146.4 (C), 139.3 (CH), 137.8 (C), 132.4 (CH), 131.8 (CH), 131.3 (C), 129.5 (CH), 129.2 (2CH), 127.9 (CH), 127.4 (CH), 123.2 (C), 122.3 (C), 118.0 (CH), 113.9 (2CH); HRMS (ESI+) calcd for $C_{17}H_{14}BrN_2O$ $(M+H)^+$ 341.0284, found 341.0281; HPLC purity ≥ 95%, t_R = 8.24 min, λ = 280 nm.

4.1.45. Ethyl 2-(2-oxo-5-(phenylamino)-1,2-dihydropyridin-3-yl)benzoate (70).

Compound **70** was prepared according to general procedure C, starting from **50** (83.2 mg, 0.196 mmol). The mixture was stirred for 3 h and was quenched with NEt_3 (15 eq.) and MeOH (6 eq.). The crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 5:5 to AcOEt) to give **70** (51.4 mg, 0.154 mmol, 78%) as a brown powder. R_f = 0.28 (EtOAc); Mp > 83 °C (decomposition); IR (ATR) 3450–3150, 1705, 1595, 1495, 1283, 1250, 748, 693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.54 (br s, 1H), 7.75 (dd, *J* = 7.5, 1.5, 1H), 7.59 (td, *J* = 7.5, 1.4, 1H), 7.51 (s, 1H), 7.45 (td, *J* = 7.6, 1.3, 1H), 7.35–7.32 (m, 2H), 7.19–7.5 (br s, 1H), 7.14 (dd, *J* = 8.6, 7.3, 2H), 6.74 (dd, *J* = 8.6, 1.1, 2H), 6.67 (tt, *J* = 7.3, 1.0, 1H), 4.10 (q, *J* = 7.1, 2H), 1.13 (t, *J* = 7.1, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.1 (C), 159.7 (C), 146.6 (C), 136.9 (CH), 136.8 (C), 133.0 (C), 131.8 (CH), 131.7 (C), 130.5 (CH), 129.2 (2CH), 128.9 (CH), 127.7 (CH), 126.7 (CH), 122.5 (C), 117.9 (CH), 113.7 (2CH), 60.3 (CH_2), 13.8 (CH_3); HRMS (ESI+) calcd for $C_{20}H_{19}N_2O_3$ $(M+H)^+$ 335.1390, found 335.1397; HPLC purity ≥ 95 %, t_R = 8.13 min, λ = 272 nm.

4.1.46. 2-(2-Oxo-5-(phenylamino)-1,2-dihydropyridin-3-yl)benzamide (71).

Compound **71** was prepared according to general procedure C, starting from impure compound **51** (76.6 mg). The mixture was stirred for 5 h 30 min and was quenched with NEt_3 (10 eq.) and MeOH (6 eq.). After work-up, the crude was purified by column chromatography (SiO_2, EtOAc/MeOH 95:5 to 85:15) to give **71** (24.6 mg, 0.081 mmol, 32% over 2 steps from **31**) as a yellow powder. R_f = 0.29 (EtOAc/MeOH 85:15); Mp > 226 °C (decomposition); IR (ATR) 3500–3000, 1657, 1596, 1494, 746, 691 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.41 (br s, 1H), 7.65 (br s, 1H), 7.50–7.47 (m, 2H), 7.43 (td, *J* = 7.5, 1.5, 1H), 7.36 (td, *J* = 7.5, 1.4, 1H), 7.36–7.33 (m, 1H), 7.26 (d, *J* = 2.9, 1H), 7.15 (dd, *J* = 8.5, 7.3, 2H), 7.11 (br s, 2H), 6.75 (dd, *J* = 8.6, 1.0, 2H), 6.66 (tt, *J* = 7.3, 1.1, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.4 (C), 159.5 (C), 146.4 (C), 137.4 (CH), 137.2 (C), 135.3 (C), 132.0 (C), 130.6 (CH), 129.2 (2CH), 129.1 (CH), 127.4 (CH), 127.2 (CH), 126.2 (CH), 122.4 (C), 117.8 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{18}H_{16}N_3O_2$ $(M+H)^+$ 306.1237, found 306.1233; HPLC purity ≥ 94%, t_R = 6.88 min, λ = 294 nm.

4.1.47. 3-(2-Nitrophenyl)-5-(phenylamino)pyridin-2(1H)-one (72).

Compound **72** was prepared according to general procedure C, starting from **52** (80.5 mg, 0.203 mmol). The mixture was stirred for 4 h and was quenched with NEt_3 (18 eq.) and MeOH (6 eq.). After work-up, the crude was purified by column chromatography (SiO_2,

EtOAc/cyclohexane 3:7 to 5:5) to give **72** (55.6 mg, 0.181 mmol, 89%) as a red powder. R_f = 0.58 (Acetone/cyclohexane 5:5); Mp > 224 °C (decomposition); IR (ATR) 3375, 1658, 1597, 1519, 1488, 1465, 1336, 741, 695 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.63 (br s, 1H), 7.98 (dd, *J* = 8.1, 1.3, 1H), 7.75 (td, *J* = 7.6, 1.3, 1H), 7.60 (ddd, *J* = 8.1, 7.5, 1.4, 1H), 7.56 (br s, 1H), 7.55 (d, *J* = 2.9, 1H), 7.51 (dd, *J* = 7.6, 1.5, 1H), 7.23 (br s, 1H), 7.16 (dd, *J* = 8.5, 7.3, 2H), 6.77 (dd, *J* = 8.6, 1.0, 2H), 6.69 (tt, *J* = 7.3, 1.1, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.6 (C), 148.9 (C), 146.3 (C), 137.7 (CH), 133.5 (CH), 132.1 (CH), 131.0 (C), 129.7 (C), 129.3 (2CH), 129.1 (CH), 127.4 (CH), 123.9 (CH), 122.6 (C), 118.0 (CH), 133.9 (2CH); HRMS (ESI+) calcd for $C_{17}H_{14}N_3O_3$ $(M+H)^+$ 308.1030, found 308.1030; HPLC purity ≥ 97%, t_R = 8.07 min, λ = 276 nm.

4.1.48. 3-([1,1'-biphenyl]-4-yl)-5-(phenylamino)pyridin-2(1H)-one (73).

Compound **73** was prepared according to general procedure C, starting from **53** (77.6 mg, 0.181 mmol) and the corresponding boronic acid. The mixture was stirred for 3 h and was quenched with NEt_3 (14 eq.) and MeOH (7 eq.). After evaporation, EtOAc was added. A precipitate appeared in the organic phase and was filtered and washed with EtOAc and CH_2Cl_2 to give **73** (48.8 mg, 0.144 mmol, 80%) was obtained as a beige solid. R_f = 0.09 (EtOAc/cyclohexane 5:5); Mp > 245 °C (decomposition); IR (ATR) 3412, 1599, 749, 691 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.67 (br s, 1H), 7.85 (d, *J* = 7.8, 2H), 7.73–7.66 (m, 4H), 7.60 (s, 1H), 7.52 (s, 1H), 7.48 (t, *J* = 7.3, 2H), 7.37 (t, *J* = 6.8, 1H), 7.21 (s, 1H), 7.15 (t, *J* = 7.5, 2H), 6.76 (d, *J* = 7.8, 2H), 6.68 (t, *J* = 7.2, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.5 (C), 146.5 (C), 139.8 (C), 139.1 (C), 137.4 (CH), 135.6 (C), 129.4 (C), 129.2 (2CH), 129.0 (2CH), 128.7 (2CH), 127.5 (CH), 127.1 (CH), 126.6 (2CH), 126.2 (2CH), 122.8 (C), 117.9 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{23}H_{19}N_2O$ $(M+H)^+$ 339.1492, found 339.1487; HPLC purity ≥ 97%, t_R = 9.16 min, λ = 284 nm.

4.1.49. 3-(3-Chlorophenyl)-5-(phenylamino)pyridin-2(1H)-one (74).

Compound **74** was prepared according to general procedure C, starting from **54** (78.8 mg, 0.204 mmol). The mixture was stirred for 2 h 40 min and was quenched with NEt_3 (10 eq.) and MeOH (6 eq.). The crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 5:5 to 7:3) to give **74** (55.4 mg, 0.187 mmol, 92%) as a yellow-brown powder. R_f = 0.34 (EtOAc/cyclohexane 7:3); Mp > 187 °C (decomposition); IR (ATR) 3275, 1596, 1547, 1449, 1350, 1286, 746, 703, 683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.75 (br s, 1H), 7.89 (t, *J* = 1.7, 1H), 7.66 (dt, *J* = 7.4, 1.6, 1H), 7.62 (d, *J* = 2.9, 1H), 7.51 (s, 1H), 7.41 (t, *J* = 7.7, 1H), 7.37 (ddd, *J* = 8.0, 2.0, 1.5, 1H), 7.23 (d, *J* = 2.9, 1H), 7.15 (dd, *J* = 8.6, 7.3, 2H), 6.75 (dd, *J* = 8.6, 1.1, 2H), 6.68 (tt, *J* = 7.3, 1.1, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.3 (C), 146.4 (C), 138.5 (C), 138.2 (CH), 132.6 (C), 129.9 (CH), 129.2 (2CH), 128.1 (C), 127.9 (CH), 127.8 (CH), 127.3 (CH), 126.6 (CH), 122.8 (C), 118.0 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{17}H_{14}ClN_2O$ $(M+H)^+$ 297.0789, found 297.0796; HPLC purity ≥ 99%, t_R = 8.59 min, λ = 284 nm.

4.1.50. 3-(3-Acetylphenyl)-5-(phenylamino)pyridin-2(1H)-one (75).

To a solution under argon of **55** (46 mg, 0.117 mg, 1 eq.) in anhydrous CH_2Cl_2 (0.75 mL) was added dropwise iodotrimethylsilane (20 µL, 0.141 mmol, 1.2 eq.). The mixture was stirred at room temperature overnight. Due to the presence of residual starting material **55**, additional iodotrimethylsilane (10 µL, 0.07 mmol, 0.6 eq.) was added and the mixture was stirred for 2 h. The reaction was quenched by addition of NEt_3 (0.05 mL) and MeOH (0.75 mL) and the

mixture was concentrated. Ethyl acetate was added and the organic phase was washed with water, dried over $MgSO_4$ and filtered. After evaporation under reduced pressure, the crude was purified by column chromatography (SiO_2, acetone/cyclohexane 4:6 to 45:55) to give **75** (25 mg, 0.082 mmol, 70%) a yellow powder. R_f = 0.53 (acetone/cyclohexane 6:4); Mp > 188 °C (decomposition); IR (ATR) 3310, 1673, 1621, 1599, 1243, 752, 697 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.74 (br s, 1H), 8.28 (t, *J* = 1.8, 1H), 8.00 (ddd, *J* = 7.8, 1.8, 1.2, 1H), 7.91 (ddd, *J* = 7.8, 1.8, 1.2, 1H), 7.63 (d, *J* = 3.0, 1H), 7.54 (t, *J* = 7.8, 1H), 7.53 (s, 1H), 7.24 (d, *J* = 2.8, 1H), 7.15 (dd, *J* = 8.6, 7.3, 2H), 6.75 (dd, *J* = 8.7, 1.1, 2H), 6.68 (tt, *J* = 7.3, 1.1, 1H), 2.60 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 197.9 (C), 159.4 (C), 146.5 (C), 138.1 (CH), 136.8 (C), 136.6 (C), 132.9 (CH), 129.3 (2CH), 129.0 (C), 128.4 (CH), 127.9 (CH), 127.6 (CH), 127.3 (CH), 122.9 (C), 118.0 (CH), 113.8 (2CH), 26.9 (CH_3); HRMS (ESI+) calcd for $C_{19}H_{17}N_2O_2$ $(M+H)^+$ 305.1285, found 305.1277; HPLC purity ≥ 98%, t_R = 7.99 min, λ = 282 nm.

4.1.51. 3-(4-Hydroxyphenyl)-5-(phenylamino)pyridin-2(1H)-one (76).

Compound **76** was prepared according to general procedure C, starting from **56** (90 mg, 0.24 mmol). The mixture was stirred for 2 h and was quenched with NEt_3 (27 eq.) and MeOH (9 eq.). After evaporation, EtOAc was added. The mixture was washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and evaporated. The crude was purified by column chromatography (SiO_2, EtOAc) to give **76** (62 mg, 0.22 mmol, 91%) as a yellow solid. R_f = 0.29 (EtOAc); Mp >238 °C (decomposition); IR (ATR) 3415, 3374, 1598, 1513, 1495, 1173, 1163, 862, 834, 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.50 (br s, 1H), 9.51 (s, 1H), 7.57 (d, *J* = 8.8, 2H), 7.46 (s, 1H), 7.42 (d, *J* = 2.9, 1H), 7.14 (dd, *J* = 8.5, 7.3, 2H), 7.11 (d, *J* = 2.9, 1H), 6.76 (d, *J* = 8.8, 2H), 6.73 (dd, *J* = 8.6, 1.0, 2H), 6.67 (tt, *J* = 7.3, 1.0, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.7 (C), 157.0 (C), 146.6 (C), 136.0 (CH), 130.0 (C), 129.4 (2CH), 129.2 (2CH), 127.2 (C), 125.8 (CH), 122.7 (C), 117.8 (CH), 114.7 (2CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{17}H_{15}N_2O_2$ $(M+H)^+$ 279.1128, found 279.1132; HPLC purity ≥ 97%, t_R = 7.34 min, λ = 284 nm.

4.1.52. 5-(Phenylamino)-3-(p-tolyl)pyridin-2(1H)-one (77).

Compound **77** was prepared according to general procedure C, starting from **57** (80.3 mg, 0.219 mmol). The mixture was stirred for 3 h and was quenched with NEt_3 (13 eq.) and MeOH (6 eq.). After evaporation, EtOAc was added. The mixture was washed with water and brine. The organic phase was dried over $MgSO_4$, filtered and evaporated. The crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 5:5 to EtOAc/cyclohexane 8:2) to give **77** (58.3 mg, 0.211 mmol, 96%) as a yellow powder. R_f = 0.17 (EtOAc/cyclohexane 7:3); Mp > 195 °C (decomposition); IR (ATR) 3290, 1586, 1550, 818, 797, 744, 622 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.59 (br s, 1H), 7.62 (d, *J* = 8.2, 2H), 7.49 (s, 1H), 7.48 (d, *J* = 2.8, 1H), 7.21–7.11 (m, 5H), 6.74 (dd, *J* = 8.6, 1.0, 2H), 6.67 (tt, *J* = 7.3, 1.1, 1H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.6 (C), 146.5 (C), 137.0 (CH), 136.8 (C), 133.6 (C), 129.9 (C), 129.2 (2CH), 128.5 (2CH), 128.0 (2CH), 126.7 (CH), 122.8 (C), 117.9 (CH), 113.80 (2CH), 20.8 (CH_3); HRMS (ESI+) calcd for $C_{18}H_{17}N_2O$ $(M+H)^+$ 277.1335, found 277.1338; HPLC purity ≥ 97%, t_R = 8.46 min, λ = 284 nm.

4.1.53. 5-(Phenylamino)-3-(4-(trifluoromethyl)phenyl)pyridin-2(1H)-one (78).

Compound **78** was prepared according to general procedure C, starting from **58** (110 mg, 0.26 mmol). The mixture was stirred for 2 h and was quenched with NEt_3 (27 eq.) and MeOH (9

eq.). After work-up, the crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 8:2) to give **78** (82 mg, 0.25 mmol, 95%) as a yellow solid. R_f = 0.45 (EtOAc/cyclohexane 8:2); Mp > 229 °C (decomposition); IR (ATR) 3292, 1595, 1550, 1455, 1318, 1167, 1123, 1111, 1068, 834, 750 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.77 (br s, 1H), 7.98 (d, *J* = 8.1, 2H), 7.73 (d, *J* = 8.3, 2H), 7.66 (d, *J* = 2.9, 1H), 7.52 (br s, 1H), 7.27 (d, *J* = 2.9, 1H), 7.15 (dd, *J* = 8.6, 7.3, 2H), 6.76 (dd, *J* = 8.6, 1.0, 2H), 6.69 (tt, *J* = 7.3, 1.0, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.3 (C), 146.4 (C), 140.5 (C), 138.6 (CH), 129.2 (2CH), 128.8 (2CH), 128.3 (CH), 128.1 (C), 127.6 (q, J_{CF} = 32, C), 124.8 (q, J_{CF} = 4, 2CH), 124.3 (q, J_{CF} = 272, C), 122.9 (C), 118.0 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{18}H_{14}F_3N_2O$ $(M+H)^+$ 331.1053, found 331.1042; HPLC purity ≥ 97 %, t_R = 8.73 min, λ = 284 nm.

4.1.54. 5-(Phenylamino)-3-(4-(trifluoromethoxy)phenyl)pyridin-2(1H)-one (79).

Compound **79** was prepared according to general procedure C, starting from **59** (68 mg, 0.156 mmol). The mixture was stirred for 3 h 40 min and was quenched with NEt_3 (14 eq.) and MeOH (8 eq.). After work-up, the crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 8:2) to give **79** (49.2 mg, 0.142 mmol, 91%) as a yellow solid. R_f = 0.55 (EtOAc); Mp > 210 °C (decomposition); IR (ATR) 3282, 1595, 1549, 1454, 1208, 1152, 910, 806, 744 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.74 (br s, 1H), 7.87 (d, *J* = 8.9, 2H), 7.59 (d, *J* = 2.9, 1H), 7.51 (s, 1H), 7.37 (d, *J* = 8.4, 2H), 7.22 (d, *J* = 2.8, 1H), 7.14 (dd, *J* = 8.5, 7.4, 2H), 6.75 (dd, *J* = 8.6, 1.0, 2H), 6.68 (tt, *J* = 7.3, 1.0, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.4 (C), 147.5 (q, *J* = 2, C), 146.5 (C), 138.0 (CH), 135.7 (C), 130.1 (2CH), 129.2 (2CH), 128.4 (C), 127.7 (CH), 122.8 (C), 120.5 (2CH), 120.1 (q, *J* = 256, C), 118.0 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{18}H_{14}F_3N_2O_2$ $(M+H)^+$ 347.1002, found 347.1002; HPLC purity ≥ 97%, t_R = 8.80 min, λ = 284 nm.

4.1.55. Methyl 4-(2-oxo-5-(phenylamino)-1,2-dihydropyridin-3-yl)benzoate (80).

Compound **80** was prepared according to general procedure C, starting from **60** (51.4 mg, 0.125 mmol). The mixture was stirred for 5 h 20 min and was quenched with NEt_3 (29 eq.) and MeOH (10 eq.). After work-up, the crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 9:1 to AcOEt) to give **80** (36.3 mg, 0.113 mmol, 90%) as a yellow-brown solid. R_f = 0.31 (EtOAc); Mp > 230 °C (decomposition); IR (ATR) 3375, 1694, 1593, 1274, 1106, 746, 706, 689 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.79 (br s, 1H), 7.96 (d, *J* = 8.5, 2H), 7.91 (d, *J* = 8.5, 2H), 7.65 (d, *J* = 2.9, 1H), 7.53 (s, 1H), 7.26 (d, *J* = 2.9, 1H), 7.15 (dd, *J* = 8.6, 7.3, 2H), 6.75 (dd, *J* = 8.6, 1.1, 2H), 6.68 (tt, *J* = 7.3, 1.1, 1H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.1 (C), 159.3 (C), 146.5 (C), 141.2 (C), 138.6 (CH), 129.3 (2CH), 128.9 (2CH), 128.5 (C), 128.34 (3CH), 128.27 (C), 122.9 (C), 118.0 (CH), 113.8 (2CH), 52.2 (CH_2); HRMS (ESI+) calcd for $C_{19}H_{17}N_2O_3$ $(M+H)^+$ 321.1234, found 321.1230; HPLC purity ≥ 97%, t_R = 8.22 min, λ = 284 nm.

4.1.56. 4-(2-Oxo-5-(phenylamino)-1,2-dihydropyridin-3-yl)benzamide (81).

Compound **81** was prepared according to general procedure C, starting from impure compound **61** (101 mg). The mixture was stirred for 23 h and was quenched with NEt_3 (14 eq.) and MeOH (5 eq.). After work-up, the crude was purified by column chromatography (SiO_2, acetone/cyclohexane 5:5 to acetone) to give **81** (55.3 mg, 0.181 mmol, 74% over 2 steps from **41**) as a yellow-brown solid. R_f = 0.14 (acetone/cyclohexane 5:5); Mp > 222 °C (decomposition); IR (ATR) 3421, 3272, 3252, 3162, 1664, 1596, 1393, 846, 758, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 11.73 (br s, 1H), 7.98 (br s, 1H), 7.88 (d, *J* = 8.5, 2H), 7.81

(d, *J* = 8.5, 2H), 7.61 (d, *J* = 2.9, 1H), 7.52 (s, 1H), 7.36 (br s, 1H), 7.23 (br s, 1H), 7.15 (dd, *J* = 8.5, 7.4, 2H), 6.75 (d, *J* = 8.0, 2H), 6.68 (t, *J* = 7.3, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.6 (C), 159.4 (C), 146.5 (C), 139.2 (C), 138.1 (CH), 133.0 (C), 129.3 (2CH), 129.0 (C), 127.9 (2CH), 127.8 (CH), 127.2 (2CH), 122.9 (C), 118.0 (CH), 113.8 (2CH); HRMS (ESI+) calcd for $C_{18}H_{16}N_3O_2$ $(M+H)^+$ 306.1237, found 306.1232; HPLC purity ≥ 96%, t_R = 6.97 min, λ = 284 nm.

4.1.57. 3-(2,4-Difluorophenyl)-5-(phenylamino)pyridin-2(1H)-one (82).

Compound **82** was prepared according to general procedure C, starting from impure compound **62** (65 mg). The mixture was stirred for 2 h 30 min and was quenched with NEt_3 (13 eq.) and MeOH (7 eq.). After work-up, the crude was purified by column chromatography (SiO_2, EtOAc/cyclohexane 5:5 to 7:3) to give **82** (39.7 mg, 0.133 mmol, 62% over 2 steps from **42**) as a green powder. R_f = 0.25 (EtOAc/cyclohexane 7:3); Mp > 202 °C (decomposition); IR (ATR) 3290, 1593, 1544, 1496, 1454, 1444, 1424, 1362, 1265, 1100, 819, 750 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (br s, 1H), 7.59 (dt, *J* = 8.6, 6.8, 1H), 7.51 (br s, 1H), 7.43 (d, *J* = 2.9, 1H), 7.28 (ddd, *J* = 10.6, 9.5, 2.6, 1H), 7.27–7.23 (br s, 1H), 7.14 (t, *J* = 7.9, 2H), 7.15–7.08 (m, 1H), 6.74 (d, *J* = 8.0, 2H), 6.68 (t, *J* = 7.3, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.8 (dd, J_{CF} = 247, 12.5, C), 160.8 (dd, J_{CF} = 249, 12.5, C), 158.9 (C), 146.4 (C), 139.7 (CH), 132.8 (dd, J_{CF} = 10, 5, CH), 129.2 (2CH), 128.1 (CH), 124.8 (C), 122.4 (C), 120.8 (dd, J_{CF} = 14.5, 4, C), 118.0 (CH), 113.8 (2CH), 111.1 (dd, J_{CF} = 21, 3.5, CH), 104.0 (t, J_{CF} = 26, CH); HRMS (ESI+) calcd for $C_{17}H_{13}F_2N_2O$ $(M+H)^+$ 299.0991, found 299.0992; HPLC purity ≥ 97%, t_R = 8.19 min, λ = 282 nm.

4.2. Anti-allodynic activity

4.2.1. Study approval

The experiments followed the ethical guidelines of the International Association for the Study of Pain [31] and ethical guidelines of the Directive 2010/63/UE of the European Parliament and of the Council and French Decree 2013–118 on the protection of animals used for scientific purposes. Protocols used in this study were approved by the local animal experimentation committee: CEMEAA "Comité d'Ethique en Matière d'Expérimentation Animale Auvergne" (#CE 28-12) and the French Ministry for Research.

4.2.2. Face Complete Freund's Adjuvant (CFA) model

CFA (Becton Dickinson) was dissolved in saline solution containing Tween 80 and paraffin oil and conserved at 4 °C. For the behavioral tests, animals were briefly (<2 min) anesthetized using a mask with 2% isoflurane and received a subcutaneous injection of 25 µL of CFA (2.5 mg/kg,) solution into the right vibrissa pad using a 27 Ga needle coupled to a 25 µL Hamilton syringe, as described previously. After injection, animals were awakened from anesthesia and placed in the behavioral experimental room, followed by a 120 min mechanical testing period.

4.2.3. Rat model of neuropathic MA: chronic constriction injury of the rat's infraorbital nerve (IoN-CCI)

IoN-CCI was performed following a previously established surgical procedure [29]. Briefly, after animals were anesthetized using chloral hydrate (400 mg/kg i.p.), IoN was exposed just caudal to the vibrissal pad and two ligatures (4/0 chromic catgut) were loosely tied around the nerve just cranial to its exit from the infraorbital foramen. The ligatures were separated by a 1 mm interval. This procedure was performed under 16 × surgical microscope magnification

(Jenoptik, Germany) to allow for the control of the degree of nerve constriction. The nerve diameter was only slightly reduced and ligatures diminished, but did not occlude circulation through the superficial vasculature. Skin incision was closed with single suture points (4/0 nylon).

4.2.4. Intracisternal injection

For investigating the effects of synthetized compounds upon mechanical allodynia, animals were briefly (<2 min) anesthetized using a mask with 2% isoflurane and received an intracisternal injection of 5 µL of compound (100 µM) or vehicle alone (saline + 1% DMSO) using a 10 µL Hamilton syringe [13]. After recovery (<2 min), rats were placed in an observation field (0.6 x0.6 m square) under red light for a period test. 6-g von Frey filament was gently applied every 15 or 30 min onto the orofacial region by a first experimenter. The behavioral responses were observed and quantified by a second experimenter (see below).

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

The behavioral responses procedure was previously developed by Vos *et al.* [29]. 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.

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Abbreviations

CFA, complete Freund's adjuvant; ERK, Extracellular signal-regulated kinases; IoN-CCI, chronic constriction injury of the rat's infraorbital nerve; MA, mechanical allodynia; MDH, medullary dorsal horn; p38 MAPK, p38 mitogen-activated protein kinases; PDB, protein data bank; PK, protein kinases; PKC, protein kinase C; SDH, spinal dorsal horn.

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New 3,5-disubstituted pyridin-2(1*H*)-ones were synthesized

Hit compound **69** is a selective P38α MAPK inhibitor

Hit compound **69** potently prevented/reversed mechanical allodynia *in vivo*

3,5-Disubstituted pyridin-2(1*H*)-ones could represent a novel class of analgesics

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: