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Théo Frazier, Pauline Murail, Francis Giraud, Alain Artola, Radhouane Dallel, et al.. Improved Synthesis and Preparation of Analogues of a Pain-Relieving Pyridin-2(1H)-one. *Synthesis: Journal of Synthetic Organic Chemistry*, 2024, 56 (13), pp.2093-2099. 10.1055/s-0043-1763758 . hal-04741759

HAL Id: hal-04741759

<https://hal.science/hal-04741759v1>

Submitted on 17 Oct 2024

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Improved synthesis and preparation of analogues of a pain-relieving pyridin-2(1H)-one

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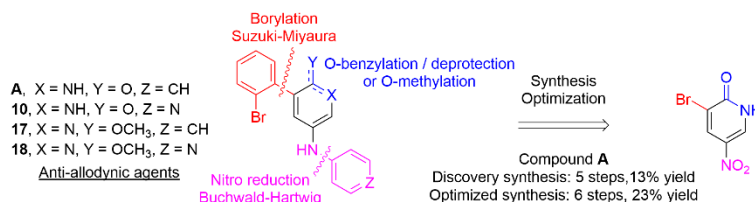
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Received:

Accepted:

Published online:

DOI:

Abstract. An optimization of the synthesis of 3,5-disubstituted pyridin-2(1H)-ones with in vivo anti-allodynic activity was conducted. The optimized synthesis was employed to prepare novel analogues which were then assessed for their efficacy in preventing cutaneous mechanical allodynia in a male rat hindpaw capsaicin model.

Key words Pyridin-2(1H)-one; Synthesis optimization; Palladium-catalyzed reactions; Mechanical allodynia; Analgesics

Chronic pain, characterized by painful symptoms lasting for an extended period,¹ poses a significant challenge for both individuals and healthcare systems worldwide. As a prevalent and possibly debilitating condition, chronic pain has emerged as a pressing public health concern, demanding urgent attention. According to recent studies, chronic pain affects millions of individuals globally, exerting profound physical, psychological, and socioeconomic impacts.^{2–4} Despite efforts in pain management, many patients continue to experience inadequate pain relief, often accompanied by undesirable side effects and the risk of dependence. To address this critical need, medicinal chemistry needs to focus on the discovery of novel analgesic compounds, with the aim to provide more effective and safe alternatives for the management of chronic pain.

One prevalent symptom found in chronic pain is mechanical allodynia (MA), that is characterized by the perception of pain in response to normally non-painful mechanical stimuli, such as light touch or gentle pressure. Recently, we discovered a series of pyridin-2-ones with potent anti-allodynic properties (Figure 1).^{5,6} As part of a structure-activity relationship study (SAR), a first series of derivatives was prepared with various aryl or heteroaryl groups at the pyridinone 3-position, while the 5-position remained substituted by a phenylamino group. This led to the identification of anti-allodynic hits **A** and **B**, substituted at the 3-position by 2-bromophenyl or indol-4-yl groups,

respectively. The latter was conserved for a second series of derivatives, the 5-position being substituted by various arylamino or heteroarylamino moieties. Superior anti-allodynic activity was found with a (pyridin-4-yl)amino group at the 5-position (compound **C**). Because of its interesting pain-relieving properties, compound **A** quickly emerged as a lead for further in-depth biological studies and synthesis of novel analogues. For example, inspired by compound **C**, we wanted to examine if the antalgic properties of **A** could be improved by substituting its phenylamino group by a (pyridin-4-yl)amino moiety (compound **10**, Figure 1). However, in part due to its 2-bromophenyl group, the synthesis of compound **A** was limited by poor overall yield and purification difficulties. In this work, this initial synthetic pathway to compound **A** was revised to get a more expedited and practical synthesis. In addition, we took advantage of these optimizations to prepare novel analogues and evaluate their antalgic properties toward a rat model of inflammatory MA.

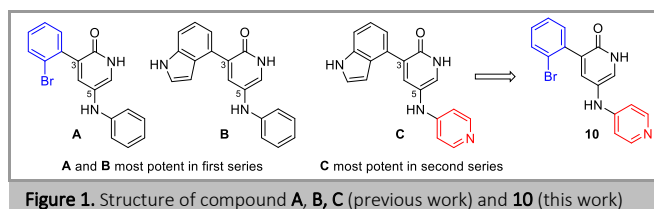
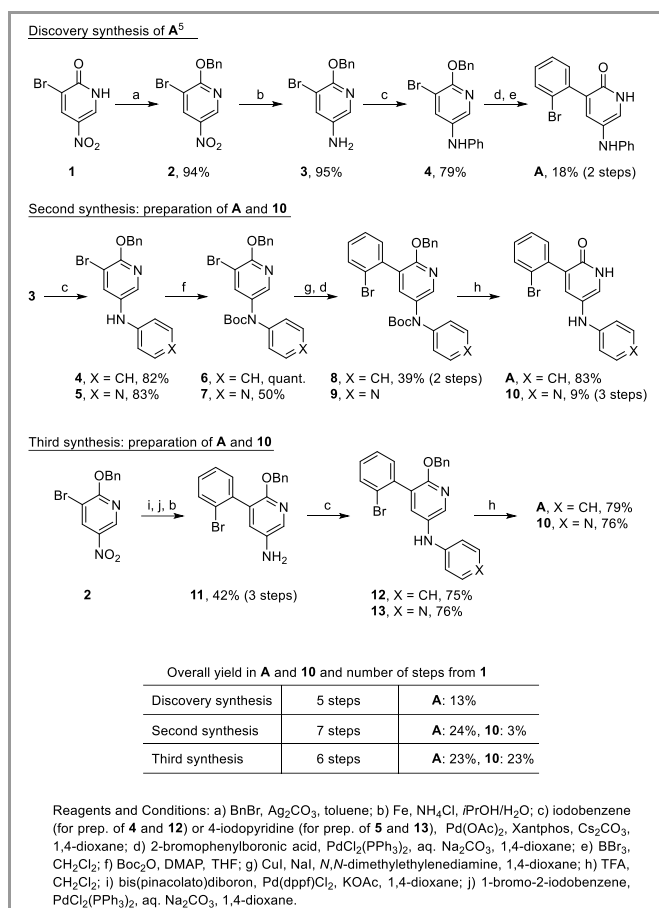


Figure 1. Structure of compound **A**, **B**, **C** (previous work) and **10** (this work)

In its discovery synthesis, compound **A** was obtained in five steps and 13% overall yield from the 3-bromo-5-nitropyridin-2-one **1**,⁵ with poor yields and purification issues in the last two steps (Scheme 1). From **4**, these problems could be due to 2-bromophenylboronic acid homocoupling and its coupling with the product of the reaction. Therefore, we looked for another synthetic pathway to **A**. For this second method (Scheme 1), we started from bromopyridine **4**, obtained in 82% yield from **3**. After Boc-protection of the amino group of **4**, aromatic Finkelstein reaction was performed to obtain a more reactive iodine intermediate.⁷ This allowed us to carry out further Suzuki-

Miyaura cross-coupling at lower temperature (60 °C) and then avoid reaction at the halogen position of product **8** 2-bromophenyl group. However, despite numerous attempts, we found that halogen exchange remained incomplete (~2:1 I/Br ratio from **6**). Next, Suzuki-Miyaura coupling from iodinated intermediate and 2-bromophenylboronic acid led to **8**, still in perfectible 39% yield over two steps. The cleavage of the protecting groups resulted in the formation of **A**, achieved in 24% yield over a sequence of seven steps starting from **1**.



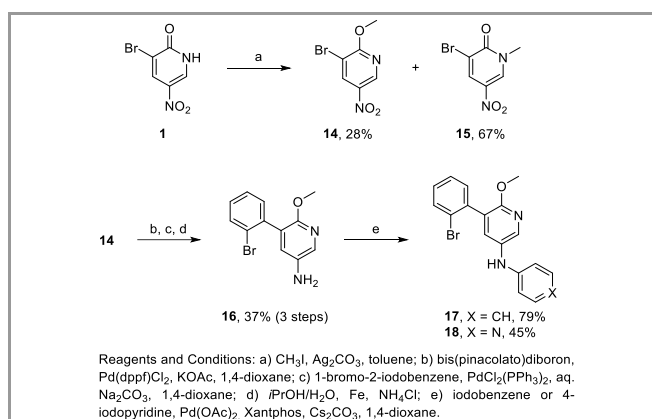
Scheme 1. Synthetic pathways to **A** and **10**.

This second method was also used to prepare **10**, a novel analogue taking advantage of the best substituents we previously identified in this series, namely 2-bromophenyl and (pyridin-4-yl)amino groups at the 3- and 5-positions, respectively (Scheme 1). Indeed, in a first work,⁵ we found that the best anti-allodynic properties were obtained with a 2-bromophenyl group at the 3-position of the pyridinone, while the 5-position was substituted with a phenylamino group. Then, we found that the anti-allodynic activity could be improved by introducing a (pyridin-4-yl)amino group at the 5-position when the 3-position was substituted by an indol-4-yl moiety.⁶ Unfortunately, when the second synthetic pathway was applied to the preparation of **10**, we obtained only 3% overall yield from **1**, due to the poor efficiency of steps such as Boc-protection of intermediate **5**⁶ and subsequent halogen exchange.

Therefore, we investigated an alternative synthetic route to **A** and **10**. We thought that the 2-bromophenyl moiety could be introduced from 1-bromo-2-iodobenzene and a borylated pyridine derived from compound **2**. Thus, the third strategy

started from benzyl-protected compound **2** (Scheme 1). Three steps were then subsequently performed: borylation to give pinacol boronate intermediate,⁸ Suzuki-Miyaura coupling with 1-bromo-2-iodobenzene, and reduction of the nitro group, providing **11** with a yield of 42% over three steps. Then, Buchwald-Hartwig reaction with iodobenzene or 4-iodopyridine and benzyl cleavage in acidic conditions led to **A** and **10** in 23% yield, over a sequence of six steps starting from **1**. This third synthetic pathway was far superior for the preparation of compound **10** (23% yield from **1**, instead of 3%). Regarding compound **A**, the third and second methods provided similar yields, but the third one was more practical and straightforward.

Finally, as we found that *O*-methylation could improve the anti-allodynic activity in this series (unpublished results), the third synthetic method was used to prepare **17** and **18**, the *O*-methyl analogues of compounds **A** and **10**. Thus, 2-methoxypyridine **14** was prepared in 28% yield from **1** in toluene in the presence of silver carbonate whereas the *N*-methylated regioisomer **15** was isolated in 67% yield (Scheme 2). A procedure to achieve high yield of **14** could not be found. In THF with silver carbonate under microwave irradiation,⁹ **14** and **15** were obtained in 16% and 62% yield, respectively, alongside an *O*-(methoxybutyl) side-product (20%) resulting from THF alkylation with methyl iodide, subsequently followed by attack of **1** and ring opening. From **14**, the following steps were similar to those used for the preparation of compounds **A** and **10** via the third method (Scheme 1).



Scheme 2. Synthesis of compounds **17** and **18**.

In vivo anti-mechanical allodynia evaluation.

To emphasize the impact of novel structural modifications made to the pyridin-2-ones on their analgesic potency, the ability of compounds **10**, **17** and **18** to prevent cutaneous mechanical allodynia in the male rat hindpaw capsaicin model was assessed. Solution of compound (**10** μL at 5 μM) was administered intrathecally 30 min before subcutaneous capsaicin injection. Behavioral responses to a graded series of von Frey filaments were then observed and quantified. Compound **10** appeared to be the most effective of the three tested compounds, with a percentage of MA inhibition as high as 86%, indicating that **10** provided a better antalgic effect than the best compound previously reported (compound **C**: 56% inhibition).⁶

In summary, an optimization of the synthesis of 3,5-disubstituted pyridin-2(1*H*)-one **A** was conducted. Novel analogues of compound **A** were also prepared and assessed for their efficacy

in preventing cutaneous mechanical allodynia in a male rat hindpaw capsaicin model, identifying compound **10** as a potent anti-allodynic agent.

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 (^1H : 400 MHz, ^{13}C : 101 MHz) or Bruker AVANCE 500 III HD (^1H : 500 MHz, ^{13}C : 126 MHz) are reported in ppm using the solvent residual peak as an internal standard; the following abbreviations are used: singlet (s), doublet (d), triplet (t), doublet of doublets (dd), doublet of doublet of doublet (ddd), triplet of doublet (t), multiplet (m), broad signal (br s). Coupling constants are expressed in Hertz. High resolution mass spectra were determined on a Thermo Scientific Q Exactive Q-Orbitrap apparatus (UCA Partner, Université Clermont Auvergne, Clermont-Ferrand, France). Chromatographic purifications were performed by column chromatography using 40–63 μm silica gel or by flash column chromatography using puriFlash® XS 520 Plus with IR-50SI-F0004, IR-50SI-F0012, IR-50SI-F0025 or IR-50SI-F0040 columns. Reactions were monitored by TLC using fluorescent silica gel plates (60 F254 from Macherey Nagel). Melting points were measured on a Stuart SMP3 apparatus and are uncorrected.

Procedures

Procedure A. Buchwald-Hartwig cross-coupling from compound **3**, **11** or **16**, and iodide derivatives.

A screw-cap tube under argon was charged with compound **3**, **11** or **16**, Pd(OAc)₂ (0.05 eq.), Xantphos (0.05 eq.) and Cs₂CO₃ (2 eq.). Then, anhydrous 1,4-dioxane (amount for 0.2 M starting material concentration) degassed with argon and the iodide derivative (1 eq.) were added. The tube was sealed and the mixture was stirred at 100 °C for several hours. The resulting suspension was filtered through a pad of Celite which was then washed with ethyl acetate. After evaporation of the filtrate, the brown residue was purified by column chromatography.

Procedure B. Boc protection.

To a solution under argon of secondary amine derivative (1 eq.) in THF (amount for 0.175 M starting material concentration) were added Boc₂O (1.5 eq.) and DMAP (0.4 eq.). The mixture was stirred for several hours. After evaporation of THF under reduced pressure, the crude was purified by column chromatography.

Procedure C. Halogen exchange.

A screw-cap tube under argon was charged with brominated derivative (1 eq.), CuI (0.05 eq.) and NaI (2 eq.). Then, anhydrous 1,4-dioxane (amount for 1 M starting material concentration) degassed with argon and *N,N*-dimethylethylenediamine (0.1 eq.) were added. The tube was sealed and the mixture was stirred at 100 °C for several hours. The resulting suspension was filtered through a pad of Celite which was then washed with EtOAc. After evaporation of the filtrate, the crude was purified by column chromatography.

Procedure D. Suzuki cross-coupling.

To a solution under argon of iodide derivative (1 eq.) in 1,4-dioxane (amount for 0.1 M substrate concentration) were added 2-bromophenylboronic acid (1 eq.) and 2 M Na₂CO₃ aqueous solution (5 eq.). The mixture was degassed with argon for 10 min before the addition of PdCl₂(PPh₃)₂ (0.05 eq.). The solution was stirred at 60 °C overnight. The resulting mixture was filtered through a pad of Celite which was then washed with EtOAc. The organic layer was washed with water and then with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was purified by column chromatography.

Procedure E. Debenzylation and Boc cleavage.

TFA was added to the benzylated derivative. The solution was stirred at 45 °C for 30 minutes. The resulting solution was concentrated under reduced pressure. CH₂Cl₂ was added the solution was washed with a saturated aqueous solution of Na₂CO₃, dried over MgSO₄, filtered and

concentrated under reduced pressure. The crude was purified by column chromatography.

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

Compound **4** was prepared according to general procedure A, starting from **3** (600 mg, 2.15 mmol). The mixture was heated for 4 h. The crude oil was purified by column chromatography (SiO₂, cyclohexane/EtOAc 99:1 to 90:10) to give **3** (628 mg, 1.77 mmol, 82%) as a brown solid. *R*_f = 0.31 (cyclohexane/EtOAc 9:1). For characterization data, see Ref. 5.

6-(Benzyloxy)-5-bromo-*N*-(pyridin-4-yl)pyridin-3-amine **5**

Compound **5** was prepared according to general procedure A, starting from **3** (2.394 g, 8.58 mmol). The mixture was heated for 5 h. The crude oil was purified by column chromatography (SiO₂, cyclohexane/EtOAc 10:90 + 0.5% NEt₃ to 0:100 + 0.5% NEt₃) to give **5** (2.550 g, 7.16 mmol, 83%) as an orange solid. *R*_f = 0.23 (EtOAc + 0.5% NEt₃); For characterization data, see Ref. 6.

Tert-butyl [6-(benzyloxy)-5-bromopyridin-3-yl]phenylcarbamate **6**

Compound **6** was prepared according to general procedure B, starting from **4** (200 mg, 0.563 mmol). The mixture was stirred for 24 h at room temperature. The crude oil was purified by column chromatography (SiO₂, cyclohexane/EtOAc 98:2) to give **6** (256 mg, 0.562 mmol, quantitative) as a colorless oil. *R*_f = 0.44 (cyclohexane/EtOAc 95:5); IR (ATR) 2981, 1707, 1440, 1291, 1240, 1153, 1049, 734, 693 cm^{-1} ; ^1H NMR (400 MHz, DMSO-*d*₆) δ 8.11–8.07 (m, 2H), 7.46 (d, *J* = 7.1, 2H), 7.42–7.28 (m, 7H), 7.23 (t, *J* = 6.9, 1H), 5.41 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, DMSO-*d*₆) δ 156.7 (C), 152.8 (C), 144.1 (CH), 142.1 (C), 141.2 (CH), 136.6 (C), 134.4 (C), 128.9 (2CH), 128.4 (2CH), 127.9 (CH), 127.6 (2CH), 127.0 (2CH), 126.3 (CH), 105.2 (C), 81.0 (C), 68.2 (CH₂), 27.8 (3CH₃); HRMS (ESI+) *m/z* calcd for C₂₃H₂₄BrN₂O₃ (M + H)⁺ 455.0965, found 455.0959.

Tert-butyl [6-(benzyloxy)-5-bromopyridin-3-yl]pyridin-4-ylcarbamate **7**

Compound **7** was prepared according to general procedure B, starting from **5** (200 mg, 0.561 mmol). The mixture was refluxed for 24 h. The crude oil was purified by column chromatography (SiO₂, cyclohexane/EtOAc 7:3) to give **7** (128 mg, 0.280 mmol, 50%) as an orange oil. *R*_f = 0.24 (cyclohexane/EtOAc 7:3); IR (ATR) 2976, 1706, 1295, 1243, 1153, 1018, 751, 738, 693 cm^{-1} ; ^1H NMR (400 MHz, DMSO-*d*₆) δ 8.46 (m, 2H), 8.20 (d, *J* = 2.4, 1H), 8.15 (d, *J* = 2.3, 1H), 7.48 (d, *J* = 7.4, 2H), 7.41 (t, *J* = 7.4, 2H), 7.34 (t, *J* = 7.2, 1H), 7.23 (m, 2H), 5.45 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, DMSO-*d*₆) δ 157.6 (C), 151.9 (C), 150.2 (2CH), 149.2 (C), 145.2 (CH), 142.3 (CH), 136.5 (C), 132.4 (C), 128.4 (2CH), 127.9 (CH), 127.7 (2CH), 118.3 (2CH), 105.7 (C), 82.3 (C), 68.4 (CH₂), 27.6 (3CH₃); HRMS (ESI+) *m/z* calcd for C₂₂H₂₃BrN₃O₃ (M + H)⁺ 456.0917, found 456.0908.

Tert-butyl [6-(benzyloxy)-5-(2-bromophenyl)pyridin-3-yl]phenylcarbamate **8**

Halogen exchange was first performed according to general procedure C, starting from **6** (770 mg, 1.69 mmol). The mixture was refluxed for 66 h. The crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 95:5), but some starting material remained in the obtained yellow wax (776 mg, ~2:1 I/Br molar ratio) which was used for the next step without further purification. *R*_f = 0.44 (cyclohexane/EtOAc 95:5).

Compound **8** was prepared according to general procedure D, starting from iodinated intermediate (770 mg, ~2:1 I/Br molar ratio) and 2-bromophenylboronic acid (200 mg, 1.00 mmol). The crude oil was purified by column chromatography (SiO₂, CH₂Cl₂) to give **8** (350 mg, 0.659 mmol, 39% in two steps from **6**) as a grey solid. *R*_f = 0.33 (cyclohexane/EtOAc 95:5); Mp 49 °C; IR (ATR) 2974, 2934, 1706, 1444, 1426, 1295, 1243, 1153, 1019 cm^{-1} ; ^1H NMR (400 MHz, DMSO-*d*₆) δ 8.13 (d, *J* = 2.6, 1H), 7.71 (dd, *J* = 8.0, 1.0, 1H), 7.59 (d, *J* = 2.6, 1H), 7.45 (td, *J* = 7.5, 1.1, 1H), 7.40–7.19 (m, 12H), 5.34 (s, 2H), 1.38 (s, 9H); ^{13}C NMR (101 MHz, DMSO-*d*₆) δ 157.4 (C), 153.0 (C), 144.8 (CH), 142.5 (C), 138.9 (CH), 137.1 (C), 136.7 (C), 133.6 (C), 132.4 (CH), 131.6 (CH), 129.9 (CH), 128.9 (2CH), 128.2 (2CH), 127.7 (CH), 127.5 (CH), 127.4 (2CH), 126.9 (2CH), 126.0 (CH), 123.6 (C), 123.1 (C), 80.7 (C), 67.4 (CH₂), 27.8 (3CH₃); HRMS (ESI+) *m/z* calcd for C₂₉H₂₈BrN₂O₃ (M + H)⁺ 531.1278, found 531.1274.

5-(Phenylamino)-3-(2-bromophenyl)pyridin-2(1H)-one A

Compound **A** was prepared according to general procedure E, starting from **8** (330 mg, 0.621 mmol) and TFA (4 mL). The crude was purified by column chromatography (SiO₂, EtOAc). After evaporation, the solid was washed with CH₂Cl₂ to give **A** (176 mg, 0.516 mmol, 83%) as a pale-yellow solid.

Alternatively, Compound **A** was prepared according to general procedure E, starting from **12** (530 mg, 1.23 mmol) and TFA (9 mL). The crude was washed with CH₂Cl₂ to give **A** (332 mg, 0.97 mmol, 79%) as a pale-yellow solid. For characterization data, see Ref. 5.

3-(2-Bromophenyl)-5-(pyridin-4-ylamino)pyridin-2(1H)-one 10

Halogen exchange was first performed according to general procedure C, starting from **7** (290 mg, 0.635 mmol). The mixture was refluxed for 66 h. The crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 7:3), but some starting material remained in the obtained orange wax (92 mg, ~55:45 I/Br molar ratio) which was used for the next step without further purification. *R_f* = 0.24 (cyclohexane/EtOAc 7:3).

Compound **9** was prepared according to general procedure D, starting from iodinated intermediate (90 mg, ~55:45 I/Br molar ratio) and 2-bromophenylboronic acid (18 mg, 0.090 mmol). The crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 7:3), but some starting material remained in the obtained orange wax (109 mg). *R_f* = 0.24 (cyclohexane/EtOAc 7:3). Compound **9** was used for the next step without further purification.

Compound **10** was prepared according to general procedure E, starting from **9** (107 mg) and TFA (1 mL). The crude was purified by column chromatography (SiO₂, CH₂Cl₂/MeOH 9:1 + 0.5% NEt₃). After evaporation, the solid was washed with CH₂Cl₂ to give **10** (18 mg, 0.053 mmol, 9% in three steps from **7**) as a light-grey solid.

Alternatively, compound **10** can be prepared according to general procedure E, starting from **13** (200 mg, 0.463 mmol) and TFA (4 mL). The crude was purified by column chromatography (SiO₂, CH₂Cl₂/MeOH 9:1 + 0.5% NEt₃). After evaporation, the solid was washed with CH₂Cl₂ to give **10** (121 mg, 0.354 mmol, 76%) as a white solid. *R_f* = 0.26 (CH₂Cl₂/MeOH 9:1 + 0.5% NEt₃). Mp > 158 °C (decomposition); IR (ATR) 2922, 2852, 1593, 1517, 1349, 1200, 996, 815 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.79 (br s, 1H), 8.25 (s, 1H), 8.11 (d, *J* = 5.6, 2H), 7.68 (d, *J* = 7.9, 1H), 7.44–7.35 (m, 3H), 7.33–7.26 (m, 2H), 6.62 (d, *J* = 6.0, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 159.2 (C), 152.8 (C), 149.1 (2CH), 139.7 (CH), 137.6 (C), 132.3 (CH), 131.8 (CH), 131.6 (C), 131.0 (CH), 129.6 (CH), 127.4 (CH), 123.2 (C), 119.0 (C), 108.1 (2CH); HRMS (ESI+) *m/z* calcd for C₁₆H₁₃BrN₃O (M + H)⁺ 342.0237, found 342.0233; HPLC purity ≥ 97%, *t_R* = 18.70 min, λ = 280 nm.

6-(Benzyloxy)-5-(2-bromophenyl)pyridin-3-amine 11

To a solution of **2** (500 mg, 1.62 mmol) in dioxane (10 mL) under argon were added bis(pinacolato)diboron (1.24 g, 4.9 mmol, 3 eq.), potassium acetate (320 mg, 3.26 mmol, 2 eq.) and Pd(dppf)Cl₂ (115 mg, 0.16 mmol, 0.1 eq.). The mixture was stirred at 80 °C for 4 h. The resulting solution was diluted with water and extracted three times with EtOAc. Combined organic extracts were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The resulting brown residue was solubilized in dioxane (16 mL) under argon and 2 M Na₂CO₃ aqueous solution (4 mL, 8.0 mmol, 5 eq.), 1-bromo-2-iodobenzene (210 μL, 1.64 mmol, 1 eq.), Pd(PPh₃)₂Cl₂ (55 mg, 0.08 mmol, 0.05 eq.) were added. The mixture was stirred at 60 °C overnight. The resulting mixture was filtered through a pad of Celite which was then washed with EtOAc. The filtrate was washed with water and then with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 98:2 to 95:5), but some impurities remained in the obtained brown solid (301 mg) which was used for the next step without further purification. *R_f* = 0.36 (cyclohexane/EtOAc 98:2).

To a solution of intermediate (301 mg) in a 10:1 propan-2-ol/water mixture (35 mL) were added Fe powder (550 mg, 9.8 mmol, 6 eq.) and NH₄Cl (35 mg, 0.65 mmol, 0.4 eq.). The mixture was refluxed for 1 h. Then,

the mixture was filtered through a pad of Celite which was then washed with EtOAc. After evaporation, the crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 8:2) to give **11** (239 mg, 0.67 mmol, 42% in three steps from **2**) as a white solid. *R_f* = 0.41 (cyclohexane/EtOAc 6:4); Mp = 124 °C; IR (ATR) 3451, 3310, 3201, 1449, 1425, 1353, 1232, 1214, 991, 744, 692 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.69 (dd, *J* = 8.0, 1.0, 1H), 7.57 (d, *J* = 2.8, 1H), 7.42 (td, *J* = 7.5, 1.2, 1H), 7.35–7.19 (m, 7H), 6.89 (d, *J* = 2.8, 1H), 5.21 (s, 2H), 4.89 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 151.5 (C), 139.6 (C), 138.1 (C), 138.0 (C), 132.3 (CH), 131.5 (CH), 130.9 (CH), 129.4 (CH), 128.1 (2CH), 127.5 (CH), 127.2 (CH), 127.1 (2CH), 126.5 (CH), 123.4 (C), 123.2 (C), 66.6 (CH₂); HRMS (ESI+) *m/z* calcd for C₁₈H₁₆BrN₂O (M + H)⁺ 355.0441, found 355.0439.

6-(Benzyloxy)-5-(2-bromophenyl)-N-(phenyl)pyridin-3-amine 12

Compound **12** was prepared according to general procedure A, starting from **11** (640 mg, 1.80 mmol). The mixture was heated for 8 h. The crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 97:3 to 62:38). Evaporation provided compound **12** (580 mg, 1.34 mmol, 75%) as an orange oil. IR (ATR) 3395, 3049, 3032, 1596, 1497, 1439, 1426, 1230, 1216, 1023, 990, 732, 692 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 (s, 1H), 8.04 (d, *J* = 2.7, 1H), 7.72 (d, *J* = 8.0, 1H), 7.47–7.40 (m, 2H), 7.37 (d, *J* = 2.7, 1H), 7.35–7.23 (m, 6H), 7.20 (t, *J* = 7.8, 2H), 6.98 (d, *J* = 7.9, 2H), 6.77 (t, *J* = 7.3, 1H), 5.32 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 154.3 (C), 144.3 (C), 137.6 (C), 137.3 (C), 136.4 (CH), 134.0 (C), 132.4 (CH), 131.7 (CH), 131.0 (CH), 129.8 (CH), 129.3 (2CH), 128.2 (2CH), 127.6 (CH), 127.4 (CH), 127.3 (2CH), 123.7 (C), 123.1 (C), 119.2 (CH), 115.2 (2CH), 67.0 (CH₂); HRMS (ESI+) *m/z* calcd for C₂₄H₂₀BrN₂O (M + H)⁺ 431.0754, found 431.0749.

6-(Benzyloxy)-5-(2-bromophenyl)-N-(pyridin-4-yl)pyridin-3-amine 13

Compound **13** was prepared according to general procedure A, starting from **11** (238 mg, 0.67 mmol). The mixture was heated for 5 h. The crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 2:8 + 0.5% NEt₃ to EtOAc + 0.5% NEt₃). Evaporation provided compound **13** (219 mg, 0.507 mmol, 76%) as white solid. *R_f* = 0.19 (EtOAc + 0.5% NEt₃); Mp = 181–182 °C; IR (ATR) 3234, 3153, 3032, 2940, 1588, 1446, 1426, 1216, 991, 740 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 8.16 (m, 2H), 8.12 (d, *J* = 2.7, 1H), 7.73 (d, *J* = 7.9, 1H), 7.49 (d, *J* = 2.7, 1H), 7.44–7.47 (m, 2H), 7.36–7.24 (m, 6H), 6.79 (m, 2H), 5.35 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 156.0 (C), 150.9 (C), 150.1 (2CH), 139.7 (CH), 137.3 (C), 136.9 (C), 134.1 (CH), 132.4 (CH), 131.7 (CH), 131.0 (C), 129.9 (CH), 128.2 (2CH), 127.7 (CH), 127.5 (CH), 127.3 (2CH), 123.9 (C), 123.1 (C), 108.5 (2CH), 67.2 (CH₂); HRMS (ESI+) *m/z* calcd for C₂₃H₁₉BrN₃O (M + H)⁺ 432.0706, found 432.0701.

3-Bromo-2-methoxy-5-nitropyridine 14 and 3-bromo-1-methyl-5-nitropyridin-2(1H)-one 15

To a solution of **1** (1.26 g, 5.75 mmol) in anhydrous toluene (57 mL) under argon atmosphere were added crushed Ag₂CO₃ (2.15 g, 7.8 mmol, 1.4 eq.) and Mel (3.52 mL, 57 mmol, 10 eq.). The mixture was stirred at room temperature overnight. The mixture was filtered through a pad of Celite which was then washed with ethyl acetate. After evaporation under reduced pressure, the crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 95:5 to 6:4) to give the desired *O*-methylated product **14** (378 mg, 1.62 mmol, 28%) as a pale-yellow solid and the *N*-methylated product **15** (897 mg, 3.85 mmol, 67%) as a pale-yellow solid. **14**: *R_f* = 0.55 (cyclohexane/EtOAc 9:1); Mp 89 °C; IR (ATR) 3065, 1587, 1508, 1475, 1334, 1312, 1128, 1047, 990, 758, 704 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.08 (d, *J* = 2.4, 1H), 8.80 (d, *J* = 2.4, 1H), 4.08 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 162.9 (C), 142.9 (CH), 139.5 (C), 136.9 (CH), 106.1 (C), 56.0 (CH₃); HRMS (ESI+) *m/z* calcd for C₆H₆BrN₂O₃ (M + H)⁺ 232.9556, found 232.9555. **15**: *R_f* = 0.11 (cyclohexane/EtOAc 8:2); Mp 124 °C; IR (ATR) 3085, 1653, 1618, 1508, 1334, 1298, 1115, 915, 759 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.27 (d, *J* = 2.9, 1H), 8.59 (d, *J* = 2.9, 1H), 3.62 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 158.3 (C), 141.8 (CH), 135.0 (CH), 129.3 (C), 113.0 (C), 39.1 (CH₃); HRMS (ESI+) *m/z* calcd for C₆H₆BrN₂O₃ (M + H)⁺ 232.9556, found 232.9552.

5-(2-Bromophenyl)-6-methoxy-pyridin-3-amine 16

To a solution of **14** (560 mg, 2.40 mmol) in dioxane (15 mL) under argon were added bis(pinacolato)diboron (1.83 g, 7.21 mmol, 3 eq.), potassium acetate (471 mg, 4.80 mmol, 2 eq.) and Pd(dppf)Cl₂ (176 mg, 0.24 mmol, 0.1 eq.). The mixture was stirred at 80 °C for 4 h. The resulting solution was diluted with water and extracted three times with ethyl acetate. Combined organic extracts were washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The resulting brown residue was solubilized in dioxane (24 mL) under argon and 2 M Na₂CO₃ aqueous solution (6 mL, 12.0 mmol, 5 eq.), 1-bromo-2-iodobenzene (311 µL, 2.42 mmol, 1 eq.), Pd(PPh₃)₂Cl₂ (81 mg, 0.12 mmol, 0.05 eq.) were added. The mixture was stirred at 60 °C overnight. The resulting mixture was filtered through a pad of Celite which was then washed with EtOAc. The filtrate was washed with water and then with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 99:1 to 8:2), but some impurities remained in the obtained brown solid (471 mg) which was used for the next step without further purification. *R*_f = 0.50 (cyclohexane/EtOAc 9:1).

To a solution of intermediate (465 mg) in a 10:1 propan-2-ol/water mixture (52 mL) were added Fe powder (804 mg, 14.4 mmol, 6 eq.) and NH₄Cl (51 mg, 0.95 mmol, 0.4 eq.). The mixture was refluxed for 1 h. Then, the mixture was filtered through a pad of Celite which was then washed with ethyl acetate. After evaporation, the crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 94:6 to 43:57) to give **16** (250 mg, 0.90 mmol, 37% in three steps from **14**) as a colorless wax. *R*_f = 0.20 (cyclohexane/EtOAc 7:3); IR (ATR) 3443, 3311, 3200, 2944, 2880, 1449, 1425, 1241, 1232, 1214, 991, 744, 693 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.67 (m, 1H), 7.57 (d, *J* = 2.8, 1H), 7.44–7.39 (m, 1H), 7.32–7.26 (m, 2H), 6.85 (d, *J* = 2.8, 1H), 4.85 (s, 2H), 3.68 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.2 (C), 139.3 (C), 138.2 (C), 132.3 (CH), 131.5 (CH), 131.0 (CH), 129.4 (CH), 127.6 (CH), 126.5 (CH), 123.3 (C), 123.1 (C), 52.8 (CH₃); HRMS (ESI⁺) *m/z* calcd for C₁₂H₁₂BrN₂O (M + H)⁺ 279.0128, found 279.0122.

5-(2-Bromophenyl)-6-methoxy-*N*-phenylpyridin-3-amine **17**

Compound **17** was prepared according to general procedure A, starting from **16** (100 mg, 0.358 mmol). The mixture was heated for 5 h. The crude was purified by column chromatography (SiO₂, cyclohexane/EtOAc 95:5 to 6:4). Evaporation provided compound **17** (100 mg, 0.281 mmol, 79%) as an orange wax. *R*_f = 0.44 (cyclohexane/EtOAc 8:2); IR (ATR) 3389, 1599, 1464, 1409, 1233, 1015, 746, 692 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.07–8.02 (m, 2H), 7.71 (dd, *J* = 8.0, 1.0, 1H), 7.44 (td, *J* = 7.4, 1.2, 1H), 7.39 (dd, *J* = 7.6, 1.9, 1H), 7.35–7.29 (m, 2H), 7.22–7.16 (m, 2H), 6.99–6.94 (m, 2H), 6.76 (t, *J* = 7.3, 1H), 3.79 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 155.0 (C), 144.4 (C), 137.3 (C), 136.7 (CH), 133.7 (C), 132.4 (CH), 131.6 (CH), 131.1 (CH), 129.7 (CH), 129.3 (2CH), 127.7 (CH), 123.5 (C), 123.2 (C), 119.1 (CH), 115.1 (2CH), 53.2 (CH₃); HRMS (ESI⁺) *m/z* calcd for C₁₈H₁₆BrN₂O (M + H)⁺ 355.0441, found 355.0434; HPLC purity ≥ 99%, *t*_R = 34.49 min, λ = 240 nm.

5-(2-Bromophenyl)-6-methoxy-*N*-(pyridin-4-yl)pyridin-3-amine **18**

Compound **18** was prepared according to general procedure A, starting from **16** (100 mg, 0.358 mmol). The mixture was heated for 24 h. The crude was purified by column chromatography (SiO₂, CH₂Cl₂/MeOH 99:1 to 78:22). Evaporation provided compound **18** (58 mg, 0.163 mmol, 45%) as a brown solid. *R*_f = 0.51 (CH₂Cl₂/MeOH 9:1); Mp = 184 °C; IR (ATR) 3350, 1595, 1464, 1410, 1391, 1212, 993 cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.71 (s, 1H), 8.15 (m, 2H), 8.12 (d, *J* = 2.7, 1H), 7.72 (dd, *J* = 8.0, 1.1, 1H), 7.48–7.40 (m, 3H), 7.34 (ddd, *J* = 8.0, 7.1, 2.1, 1H), 6.78 (m, 2H), 3.83 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 156.6 (C), 151.1 (C), 149.9 (2CH), 140.0 (CH), 136.9 (C), 134.1 (CH), 132.4 (CH), 131.7 (CH), 130.7 (C), 129.8 (CH), 127.7 (CH), 123.8 (C), 123.2 (C), 108.4 (2CH), 53.4 (CH₃); HRMS (ESI⁺) *m/z* calcd for C₁₇H₁₅BrN₃O (M + H)⁺ 356.0393, found 356.0389; HPLC purity ≥ 98%, *t*_R = 22.10 min, λ = 240 nm.

Behavioral study in rat

Study approval

Animal protocols were approved by the Committee of Animal Research at the University of Clermont Auvergne, France, and authorized by the

French Superior Education and Research Ministry (#41113). They were in accordance with the International Association for the Study of Pain (https://www.iasp-pain.org/resources/guidelines/iasp-guidelines-for-the-use-of-animals-in-research/) and the European Directive 2010/63/EU and ARRIVE guidelines.

Rat capsaicin model

Capsaicin (Sigma-Aldrich) was dissolved in endolipid solution and conserved at 4 °C. For behavioral testing, animals received a subcutaneous injection of capsaicin (25 µg in 25 µL) solution into the right hindpaw using a 27 gauge needle coupled to a 100 µL Hamilton syringe, as described previously.¹⁰

Intrathecal injection

For investigation of the effects of synthesized compounds upon capsaicin-induced mechanical hypersensitivity, animals were briefly (about 3 min) anesthetized using a mask with 2% isoflurane and received an intrathecal injection of either compound (5 µM in 10 µL saline) or vehicle alone (saline + 0.01% DMSO) using a 10 µL Hamilton syringe (*n* = 5 or 6 rats in each group). After recovery (about 2 min), rats were placed in an observation field (0.6 x 0.6 m²) under red light for a 30 min habituation session. During this period, rats were adapted to the observation field and red light. Immediately after the 30 min habituation period, animals received the subcutaneous injection of capsaicin.

Behavioral responses

Behavioral sensory testing was performed as previously described.¹¹ Briefly, rats were first allowed to acclimatize to the 0.6x0.6 m² glass chambers used for behavioral testing as well as to innocuous mechanical stimulation for 3 days before the start of the behavioral sensory testing. The mechanical withdrawal threshold was determined using von Frey (VF) filaments (Bioseb, France) applied to the plantar surface of the right hindpaw via the descending-ascending method. Each filament was applied to the skin for 5 times for 3 s (at 10 s intervals). The VF filament threshold (VFT, in grams) was equal to the filament evoking a hindpaw withdrawal response in three out of five trials. After the injection of capsaicin, the VFT were recorded at 10-minute intervals for 65-minutes. The level of mechanical hypersensitivity inhibition of a given compound was computed as follows: [(AUC vehicle - AUC compound)/AUC vehicle] x 100 (AUC being the area under the curve).

Funding Information

This research was financed by the French government IDEX-ISITE initiative 16-IDEX-0001 (CAP 20-25), Université Clermont Auvergne, Inserm and CNRS, and the Région Auvergne-Rhône-Alpes (Pack Ambition Recherche). The authors also thank WeylChem InnoTec (Frankfurt, Germany) for financial support.

Acknowledgment

The authors thank Aurélie Job for HPLC analysis.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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