

Synthesis of New 5- or 7-Substituted 3-Nitroimidazo[1,2-a]pyridine Derivatives Using SNAr and Palladium-Catalyzed Reactions To Explore Antiparasitic Structure–Activity Relationships

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- SNAr and palladium-catalyzed reactions to explore antiparasitic structure-activity
 relationships
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- 18

19 Graphical Abstract



20

21 Abstract

To study the antikinetoplastid structure-activity relationships in 3-nitroimidazo[1,2-a]pyridine series, we explored the substitution of positions 5 and 7 of the scaffold, developing nucleophilic aromatic substitution reactions and pallado-catalyzed Suzuki-Miyaura, Sonogashira and Buchwald-Hartwig cross-coupling reactions which had never been reported at these positions in this series. Thirty-five original compounds were obtained in 4 steps from 2-amino-bromopyridines, allowing a better definition of the antiparasitic pharmacophore.

28 **Key words** : Nitroaromatic, imidazo[1,2-a]pyridine, kinetoplastids, nucleophilic aromatic

- 29 substitution, palladium-catalyzed cross-coupling reaction, microwave irradiation.
- 30

31 Since the discovery in the 1940s of nitrofurazone, a 5-nitrofuran, as an antibacterial and 32 antiparasitic agent, 1-3 nitroaromatic compounds have been extensively studied for their anti-33 infective properties.4 Metronidazole, a 5-nitroimidazole identified in the 1960s (Figure 1).5 is 34 still widely used to treat infections caused by Gram-negative and Gram-positive anaerobic bacteria such as Bacteroides, Clostridioides or Helicobacter pylori and parasitic infections 35 caused by Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia.6-9 36 37 Nitroaromatic compounds are also well-known for their antikinetoplastid properties: 38 nifurtimox, a 5-nitrofuran derivative, and benznidazole, a 2-nitroimidazole derivative, are used to treat Chagas disease for more than 50 years (Figure 1).10-13 In 2019, fexinidazole, 39 40 belonging to the 5-nitroimidazole series (Figure 1), received marketing authorization as the 41 first all-oral treatment against Trypanosoma brucei gambiense,14,15 paving the way for the 42 development of new nitroheterocycles active against kinetoplastid infections, such as 43 leishmaniases, sleeping sickness and Chagas disease.16 Finally, two bicyclic nitroimidazoles 44 were approved for the treatment of multidrug-resistant tuberculosis: delamanid in 2014 and 45 pretomanid in 2019.17,18

In parallel, the imidazo[1,2-a]pyridine ring has drawn much attention since the discovery of zolpidem (Ambien®, Stilnox®), a hypnotic drug widely used for the treatment of severe insomnia.19-21 Some imidazo[1,2-a]pyridine derivatives substituted at positions 2 and 3 have been reported for their aptiloic participation of the several sector of the several sector.

49 have been reported for their antileishmanial activity.22,23

50



52 **Figure 1** Structures of metronidazole and antikinetoplastid nitroheterocyclic drug-53 compounds.

54 As part of this research, our team has previously identified two antileishmanial and two anti-55 T. brucei hit compounds in 3-nitroimidazo[1,2-a]pyridine series, thanks to pharmacomodulation work conducted on positions 2, 6 and 8 of the moiety (Figure 2). The 56 first antileishmanial hit (Hit A) was functionalized by a phenylsulfonylmethyl substituent at 57 position 2, a chlorine atom at position 6 and a 4-chlorophenylthioether group at position 8.24 58 The second (Hit B) is substituted at position 2 by a trifluoropropylsulfonylmethyl group and by 59 60 a 4-pyridyl substituent at position 8.25 The introduction of a 3-butyn-1-ol group at position 8 61 led to the identification of the first anti-T. brucei hit (Hit C).26 The second anti-T. brucei hit (Hit D) was functionalized by a methylsulfonylmethyl substituent at position 2 and a bromine atom 62 63 at position 8.27

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67 To go forward on the study of the antiparasitic structure-activity relationships, we explored 68 the position 5 and the position 7 of the 3-nitroimidazo[1,2-a]pyridine scaffold. Indeed, a 69 literature search of the imidazo[1,2-a]pyridine moiety showed that these two positions have 70 never been studied when a nitro group is present at position 3. Thus, we modulated the 71 position 5 and the position 7 separately, developing nucleophilic aromatic substitution reactions and Suzuki-Miyaura, Sonogashira and Buchwald-Hartwig cross-coupling reactions, 72 73 three of the most frequently used palladium-catalyzed reactions in medicinal chemistry 74 (Figure 3).28

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65

a) Previous work: Synthesis of 6,8-disubstituted antikinetoplastid hits



b) This work: Synthesis of 5- and 7-substituted compounds



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Figure 3 (a) Previous work: SNAr and palladium-catalyzed reactions used to modulate the position 8 of the 3-nitroimidazo[1,2-a]pyridine pharmacophore. **(b)** This work: SNAr and palladium-catalyzed reactions used to modulate the position 5 or 7 of the 3-nitroimidazo[1,2a]pyridine scaffold.

From commercially available 2-amino-4-bromopyridine and 2-amino-6-bromopyridine, the corresponding 2-chloromethylimidazo[1,2-a]pyridine intermediates 1a and 1b were obtained by cyclocondensation of 1,3-dichloroacetone in refluxing ethanol (Scheme 1).



86 **Scheme 1** Synthesis of imidazo[1,2-a]pyridine intermediates 1a and 1b. Reagents and 87 conditions: 1,3-dichloroacetone (1.1 equiv.), EtOH, 80 °C, 48 h, 38-39%.

Adapting a previously reported method described in our lab,29 the selective nitration at position 3 of 1a and 1b was conducted in a mixture of 68% nitric acid and concentrated sulfuric acid, giving the 2-chloromethyl-3-nitroimidazo[1,2-a]pyridines 2a and 2b (Scheme 2). For the nitration reaction of the 5-bromo intermediate 1a, the reaction mixture was stirred for

92 only 1 hour instead of 3 hours to avoid the formation of degradation products.



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Scheme 2 Synthesis of 3-nitroimidazo[1,2-a]pyridine intermediates 2a and 2b. Reagents and
 conditions: HNO3 68% (6 equiv.), H2SO4, 0 °C→RT, 1-3 h, 36-51%

97 To introduce a sulfonymethyl group at position 2, 1.5 equivalents of sodium benzenesulfinate

98 or sodium methanesulfinate were used to obtain intermediates 3a-c in moderate to good

99 yields (Scheme 3).

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Scheme 3 Synthesis of 2-sulfonylmethyl-3-nitroimidazo[1,2-a]pyridine intermediates 3a-c.
 Reagents and conditions: sodium sulfinate (1.5 equiv.), DMSO, RT, 15 h, 36-61%.

104 Unfortunately, the 5-bromo-2-methylsulfonylmethyl[1,2-a]pyridine derivative was not 105 obtained, since only the starting compound 2a and the 2,5-disubstituted derivative 4b were observed when 1.5 equivalents of sodium methanesulfinate stirred for 15 hours were used. 106 107 Only the starting compound 2a was observed using 1 equivalent of sodium methanesulfinate 108 with stirring for 24 hours and only the compound 4b was observed using 3 equivalents of 109 sodium methanesulfinate with stirring for 3 hours. The introduction of a methylsulfonylmethyl substituent at position 2 of the 2-chloromethyl-3-nitroimidazo[1,2-a]pyridine 2a is not a 110 regioselective reaction. Thus, using 3 equivalents of sodium benzenesulfinate or sodium 111 methanesulfinate with 2a, the substitution of both the chlorine atom of the chloromethyl group 112 at position 2 and the bromine atom at position 5 was performed, affording the 2,5-113 disubstituted compounds 4a and 4b in modest yields (Scheme 4). 114

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Scheme 4 Synthesis of 2,5-disubstituted derivatives 4a and 4b. Reagents and conditions:
sodium sulfinate (3 equiv.), DMSO, RT, 3 h, 20-27%.

Once the intermediates 3a-c were synthesized, positions 5 and 7 were modulated, using
 nucleophilic aromatic substitution reactions and pallado-catalyzed Suzuki-Miyaura,
 Sonogashira and Buchwald-Hartwig cross-coupling reactions.

Using a similar protocol previously reported,24 three derivatives bearing a 4chlorophenylthioether moiety were obtained in moderate to good yields, one bearing it at position 5 (compound 5a) and two at position 7 (Scheme 5).

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127 **Scheme 5** Synthesis of compounds 5a-c using SNAr reactions. Reagents and conditions: 4-128 chlorothiophenol (2 equiv.), NaH 60% (2 equiv.), DMSO, N2, RT, 15 h, 56-82%.

Under conditions adapted from a previously reported Suzuki-Miyaura cross-coupling
 reaction,25 compounds 6a-o were prepared in the presence of appropriated boronic acid,
 Pd(PPh3)4 and potassium carbonate in tetrahydrofuran, in a sealed tube under microwave
 (MW) irradiation, excepted for 4-pyridyl derivatives 6d, 6j and 6o for which Pd(dppf)Cl2 was
 used instead of Pd(PPh3)4 (Scheme 6).

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Scheme 6 Synthesis of compounds 6a-o using Suzuki-Miyaura cross-coupling reaction.
Reagents and conditions: boronic acid (1.5 equiv.), Pd(PPh3)4 (0.1 equiv.), K2CO3 (5 equiv.), THF, N2, 120 °C, MW, 2 h, 24-75%; or boronic acid (1.5 equiv.), Pd(PPh3)4 (0.1 equiv.), K2CO3 (5 equiv.), THF, N2, 75 °C, 48 h, 46%; or 4-Pyridinylboronic acid (1.5 equiv.),
Pd(dppf)Cl2 (0.1 equiv.), K2CO3 (5 equiv.), THF, N2, 120 °C, MW, 4 h, 35-60%.

141 Sonogashira cross-coupling reactions were performed using a previously described 142 protocol,26 giving compounds 7a-e in moderate yields (Scheme 7). Surprisingly, the 5-(but-3143 yn-1-ol) derivative was not obtained under these conditions, for which only the starting
144 compound 3a was observed, even though the reaction time was increased to 48 hours.
145 Heating the reaction up to 70 °C resulted in the formation of degradation products, without
146 the 5-(but-3-yn-1-ol) derivative being observed.

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Scheme 7 Synthesis of compounds 7a-e using Sonogashira cross-coupling reaction.
Reagents and conditions: alkyne (1.5 equiv.), Pd(PPh3)4 (0.1 equiv.), Cul (0.1 equiv.),
(iPr)2NH (12 equiv.), THF, RT, 24 h, 38-54%

Finally, by adapting a previously reported protocol27 by increasing the amount of aniline to 3 equivalents, three anilino-derivatives 8a-c were synthesized in moderate yields via Buchwald-Hartwig cross-coupling reaction (Scheme 8).



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Scheme 8 Synthesis of compounds 8a-c using Buchwald-Hartwig cross-coupling reaction.
Reagents and conditions: aniline (3 equiv.), Pd(OAc)2 (0.08 equiv.), BINAP (0.15 equiv.),
K2CO3 (2 equiv.), Toluene, N2, 140 °C, MW, 2 h, 35-52%.

160

161 Conclusion

162 In conclusion, this is the first time that 5- or 7-substituted 3-nitroimidazo[1,2-a]pyridine 163 derivatives have been synthesized. Thirty-five new compounds were obtained, including thirteen compounds 5-substituted and twenty-two 7-substituted. Modulation of the position 5 164 and the position 7 was performed with nucleophilic aromatic substitution, Suzuki-Miyaura, 165 166 Sonogashira and Buchwald-Hartwig reactions, using similar conditions to those used for the 167 substitution of the position 8 of the 3-nitroimidazo[1,2-a]pyridine scaffold. The antileishmanial 168 activity of these new compounds was evaluated in vitro, displaying weak activity against the 169 axenic amastigote form of L. infantum (EC50 > 10 μ M). This allowed a better definition of the 3-nitroimidazo[1,2-a]pyridine pharmacophore, showing that substitution of the position 5 or 7 170 171 was detrimental to the antileishmanial activity. In order to continue the study of the antikinetoplastid structure-activity relationships in 3-nitroimidazo[1,2-a]pyridine series, further 172 173 pharmacomodulation works are still in progress.

174 Experimental part.

175 Melting points were determined on a Köfler melting point apparatus (Wagner & Munz GmbH, 176 München, Germany) and were uncorrected. HRMS spectrum (ESI) was recorded on a SYNAPT G2 HDMS (Waters) at the Faculté des Sciences de Saint-Jérôme (Marseille). NMR 177 spectra were recorded on a Bruker Avance NEO 400MHz NanoBay spectrometer at the 178 179 Faculté de Pharmacie of Marseille. (1H NMR: reference DMSO-d6 δ = 2.50 ppm and 13C 180 NMR: reference DMSO-d6 δ = 39.52 ppm). The following adsorbent was used for column 181 chromatography: silica gel 60 (Merck KGaA, Darmstadt, Germany, particle size 0.063-0.200 182 mm, 70-230 mesh ASTM). TLC was performed on 5 cm x 10 cm aluminum plates coated 183 with silica gel 60F-254 (Merck) in an appropriate eluent. Visualization was performed with ultraviolet light (234 nm). Purity determination of synthesized compounds was checked by 184 185 LC/MS analyses, which were realized at the Faculté de Pharmacie of Marseille with a 186 Thermo Scientific Accela High Speed LC System® (Waltham, MA, USA) coupled using a single quadrupole mass spectrometer Thermo MSQ Plus®. The purity of all the synthesized 187 compounds was > 95%. The RP-HPLC column is a Thermo Hypersil Gold® 50 x 2.1 mm 188 189 (C18 bounded), with particles of a diameter of 1.9 mm. The volume of sample injected on the column was 1 µL. Chromatographic analysis, total duration of 8 min, was on the gradient of 190

191 the following solvents: t = 0 min, methanol/water 50:50; 0 < t < 4 min, linear increase in the 192 proportion of methanol to a methanol/water ratio of 95:5; 4 < t < 6 min, methanol/water 95:5; 193 6 < t < 7 min, linear decrease in the proportion of methanol to return to a methanol/water 194 ratio of 50:50; 6 < t < 7 min, methanol/water 50:50. The water used was buffered with 195 ammonium acetate 5 mM. The flow rate of the mobile phase was 0.3 mL/min. The retention 196 times (tR) of the molecules analyzed were indicated in min. Reagents were purchased from 197 Sigma-Aldrich or Fluorochem and used without further purification. Copies of 1H NMR and 198 13C NMR are available in the Supplementary Materials.

199 5-Bromo-2-chloromethylimidazo[1,2-a]pyridine (1a)

To a solution of 6-bromopyridin-2-amine (5 g, 28.90 mmol, 1 equiv.) in ethanol (80 mL), 1,3dichloroacetone (4.04 g, 31.79 mmol, 1.1 equiv.) was added. The reaction mixture was stirred and heated under reflux for 48 h. Then, the solvent was then evaporated in vacuo. Compound (1a) was obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a white solid in 38% yield (2.7 g). mp 128 °C.

- 205 1H NMR (400 MHz, DMSO-d6) δ = 8.06 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.31-7.23 (m, 2H), 206 4.88 (s, 2H).
- 207 13C NMR (100 MHz, DMSO-d6) δ = 145.0, 142.5, 126.0, 116.5, 115.9, 114.1, 112.5, 1C 208 (CH2CI) below DMSO-d6 signal.
- 209 MS (ESI+): m/z = 245.01/247.04/249.10 [M+H]+.
- 210 HRMS (ESI+): m/z [M+H]+ calcd for C8H7BrCIN2: 246.9453; found: 246.9453.
- 211 7-Bromo-2-chloromethylimidazo[1,2-a]pyridine (1b)

To a solution of 4-bromopyridin-2-amine (5 g, 28.90 mmol, 1 equiv.) in ethanol (80 mL), 1,3dichloroacetone (4.04 g, 31.79 mmol, 1.1 equiv.) was added. The reaction mixture was stirred and heated under reflux for 48 h. Then, the solvent was then evaporated in vacuo. Compound (1b) was obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a white solid in 39% yield (2.77 g). mp 199 °C.

- 217 1H NMR (400 MHz, DMSO-d6) δ: 8.82 (d, J = 7.2 Hz, 1H), 8.36 (s, 1H), 8.22 8.14 (m, 1H),
 218 7.58 (dd, J = 7.2, 1.9 Hz, 1H), 5.03 (s, 2H).
- 219 13C NMR (100 MHz, DMSO-d6) δ: 141.2, 135.3, 129.8, 125.7, 119.7, 115.4, 114.0, 35.6.
- 220 MS (ESI+): m/z = 245.03/247.00/249.11 [M+H]+.
- 221 HRMS (ESI+): m/z [M+H]+ calcd for C8H7BrClN2: 246.9453; found: 246.9450.
- 222 5-Bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2a)
- To a solution of 5-bromo-2-chloromethylimidazo[1,2-a]pyridine (1a) (2 g, 8.14 mmol, 1 equiv.) in concentrated sulfuric acid (20 mL) cooled by an ice-water bath, nitric acid 68% (2.2 mL, 48.88 mmol, 6 equiv.) was added dropwise. The reaction mixture was stirred for 1 h at room temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected by filtration and dried under reduced pressure. Compound (2a) was obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a yellow solid in 51% yield (1.2 g). mp 167 °C.
- 230 1H NMR (400 MHz, DMSO-d6) δ: 8.00 (dd, J = 8.6, 1.0 Hz, 1H), 7.88 7.67 (m, 2H), 5.01 (s, 2H).

- 232 13C NMR (100 MHz, DMSO-d6) δ: 147.2, 146.9, 132.4, 130.8, 123.8, 117.4, 117.0, 38.1.
- 233 MS (ESI+): m/z = 289.74/291.87 [M+H]+.
- 234 HRMS (ESI+): m/z [M+H]+ calcd for C8H6BrCIN3O2: 291.9304; found: 291.9304.
- 235 7-Bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2b)

To a solution of 7-bromo-2-chloromethylimidazo[1,2-a]pyridine (1b) (2 g, 8.14 mmol, 1 equiv.) in concentrated sulfuric acid (20 mL) cooled by an ice-water bath, nitric acid 36% (2.2 mL, 48.88 mmol, 6 equiv.) was added dropwise. The reaction mixture was stirred for 3 h at room temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected by filtration and dried under reduced pressure. Compound (2b) was obtained after purification by chromatography on silica gel (eluent: cyclohexanedichloromethane 3:7) as a yellow solid in 36 % yield (0.85 g). mp 158 °C.

- 243 1H NMR (400 MHz, DMSO-d6) δ : 9.22 (dd, J = 7.4, 0.5 Hz, 1H), 8.36 (d, J = 1.4 Hz, 1H), 244 7.65 (dd, J = 7.4, 2.0 Hz, 1H), 5.11 (s, 2H).
- 245 13C NMR (100 MHz, DMSO-d6) δ: 147.4, 144.3, 129.0, 128.8, 125.4, 120.8, 120.2, 39.0.
- 246 MS (ESI+): m/z = 289.71/291.83 [M+H]+.
- 247 HRMS (ESI+): m/z [M+H]+ calcd for C8H6BrCIN3O2: 291.9304; found: 291.9301.
- 248 5-Bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3a)

To a solution of 5-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2a) (0.5 g, 1.72 mmol, 1 equiv.) in dimethylsulfoxide (20 mL), sodium benzenesulfinate (0.42 g, 2.58 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 15 h at room temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected by filtration and dried under reduced pressure. Compound (3a) was obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a yellow solid in 36% yield (0.245 g). mp 194 °C.

- 256 1H NMR (400 MHz, DMSO-d6) δ: 7.92 (d, J = 8.7 Hz, 1H), 7.83 7.66 (m, 5H), 7.60 (t, J = 257 7.7 Hz, 2H), 5.10 (s, 2H).
- 13C NMR (100 MHz, DMSO-d6) δ: 147.0, 139.0, 138.5, 134.3, 132.8, 132.2, 129.4 (2C),
 128.0 (2C), 123.6, 117.2, 116.8, 55.2.
- 260 MS (ESI+): m/z = 395.98/397.88 [M+H]+.
- 261 HRMS (ESI+): m/z [M+H]+ calcd for C14H11BrN3O4S: 397.9628; found: 397.9622.
- 262 7-Bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3b)
- To a solution of 7-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2b) (0.5 g, 1.72 mmol, 1 equiv.) in dimethylsulfoxide (20 mL), sodium benzenesulfinate (0.42 g, 2.58 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 15 h at room temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected by filtration and dried under reduced pressure. Compound (3b) was obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a yellow solid in 59% yield (0.40 g). mp 254 °C.
- 270 1H NMR (400 MHz, DMSO-d6) δ: 9.20 (d, J = 7.4 Hz, 1H), 8.33 (d, J = 1.4 Hz, 1H), 7.80 –
 271 7.54 (m, 6H), 5.23 (s, 2H).

272 13C NMR (100 MHz, DMSO-d6) δ: 144.4, 139.9, 138.8, 134.3, 130.7, 129.3 (2C), 128.8,
273 128.0 (2C), 125.5, 120.8, 120.2, 56.0.

- 274 MS (ESI+): m/z = 395.99/397.71 [M+H]+.
- 275 HRMS (ESI+): m/z [M+H]+ calcd for C14H11BrN3O4S: 397.9628; found: 397.9626.
- 276 7-Bromo-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (3c)

To a solution of 7-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2b) (0.5 g, 1.72 mmol, 1 equiv.) in dimethylsulfoxide (20 mL), sodium methanesulfinate (0.27 g, 2.58 mmol, 1.5 equiv.) was added. The reaction mixture was stirred for 15 h at room temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected by filtration and dried under reduced pressure. Compound (3c) was obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a beige solid in 61% yield (0.35 g). mp 210 °C.

- 284 1H NMR (400 MHz, DMSO-d6) δ : 9.25 (dd, J = 7.4, 0.6 Hz, 1H), 8.40 (dd, J = 2.0, 0.6 Hz, 285 1H), 7.67 (dd, J = 7.4, 2.0 Hz, 1H), 5.09 (s, 2H), 3.13 (s, 3H).
- 286 13C NMR (100 MHz, DMSO-d6) δ: 144.6, 140.7, 130.9, 128.9, 125.5, 120.7, 120.2, 54.3,
 287 41.1.
- 288 MS (ESI+): m/z = 334.74/336.64 [M+H]+.
- 289 HRMS (ESI+): m/z [M+H]+ calcd for C9H9BrN3O4S: 335.9471; found: 335.9469.
- 290 3-Nitro-5-(phenylsulfonyl)-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (4a)

To a solution of 5-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2a) (0.5 g, 1.72 mmol, 1 equiv.) in dimethylsulfoxide (20 mL), sodium benzenesulfinate (0.85 g, 5.16 mmol, 3 equiv.) was added. The reaction mixture was stirred for 3 h at room temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected by filtration and dried under reduced pressure. Compound (4a) was obtained after purification by chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as a yellow solid in 27% yield (0.21 g). mp 230 °C.

- 298 1H NMR (400 MHz, DMSO-d6) δ : 8.22 8.12 (m, 2H), 8.02 (d, J = 7.6 Hz, 2H), 7.91 (dd, J = 299 8.6, 7.7 Hz, 1H), 7.85 7.65 (m, 6H), 7.61 (t, J = 7.8 Hz, 2H), 5.13 (s, 2H).
- 300 13C NMR (100 MHz, DMSO-d6) δ: 144.7, 139.9, 138.5, 138.2, 137.1, 134.5, 134.3, 133.1,
 301 130.2, 129.4 (2C), 129.3 (2C), 128.0 (2C), 127.1 (2C), 125.4, 123.3, 55.1.
- 302 MS (ESI+): m/z = 457.85 [M+H]+.
- 303 HRMS (ESI+): m/z [M+H]+ calcd for C20H16N3O6S2: 458.0475; found: 458.0475.
- 304 5-(Methylsulfonyl)-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (4b)

To a solution of 5-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2a) (0.5 g, 1.72 mmol, 1 equiv.) in dimethylsulfoxide (20 mL), sodium methanesulfinate (0.53 g, 5.16 mmol, 3 equiv.) was added. The reaction mixture was stirred for 3 h at room temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected by filtration and dried under reduced pressure. Compound (4b) was obtained after purification by chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as a yellow solid in 20% yield (0.12 g). mp 257 °C.

- 312 1H NMR (400 MHz, DMSO-d6) δ: 8.31 8.18 (m, 2H), 7.99 (t, J = 8.1 Hz, 1H), 4.97 (s, 2H), 3.70 (s, 3H), 3.17 (s, 3H).
- 314 13C NMR (100 MHz, DMSO-d6) δ: 144.8, 139.1, 138.5, 133.1, 130.5, 123.7, 123.2, 53.3,
 315 43.6, 40.9.
- 316 MS (ESI+): m/z = 333.98 [M+H]+.
- 317 HRMS (ESI+): m/z [M+H]+ calcd for C10H12N3O6S2: 334.0162; found: 334.0160.
- 318 5-[(4-Chlorophenyl)thio]-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (5a)
- 319 To a sealed 20 mL flask containing sodium hydride (60% dispersion in mineral oil) (40 mg, 1.00 mmol, 2 equiv.) in dimethylsulfoxide (3 mL), 4-chlorobenzenethiol (145 mg, 1.00 mmol, 320 321 2 equiv.) was added under N2 atmosphere. The reaction mixture was stirred at room 322 temperature for 30 min. Then а solution of 5-bromo-3-nitro-2-323 [(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3a) (0.2 g, 0.50 mmol, 1 equiv.) in dimethylsulfoxide (6 mL) was injected. The reaction mixture was stirred for 15 h at room 324 temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. 325 Compound (5a) was obtained after purification by chromatography on silica (eluent: 326 327 dichloromethane) as a yellow solid in 56% yield (0.13 g). mp 187 °C.
- 328 1H NMR (400 MHz, DMSO-d6) δ : 7.83-7.72 (m, 5H), 7.61 (t, J = 7.7 Hz, 2H), 7.56 7.48 (m, 329 4H), 7.09 (d, J = 7.2 Hz, 1H), 5.15 (s, 2H).
- 330 13C NMR (100 MHz, DMSO-d6) δ: 146.2, 140.7, 140.3, 138.6, 135.5 (2C), 135.0, 134.3,
 331 132.4, 132.1, 130.9, 130.2 (2C), 129.3 (2C), 128.1 (2C), 121.0, 115.3, 55.7.
- 332 MS (ESI+): m/z = 459.94/461.75 [M+H]+.
- 333 HRMS (ESI+): m/z [M+H]+ calcd for C20H15CIN3O4S2: 460.0187; found: 460.0188.
- 334 7-[(4-Chlorophenyl)thio]-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (5b)
- 335 To a sealed 20 mL flask containing sodium hydride (60% dispersion in mineral oil) (40 mg, 1.00 mmol, 2 equiv.) in dimethylsulfoxide (3 mL), 4-chlorobenzenethiol (145 mg, 1.00 mmol, 336 337 2 equiv.) was added under N2 atmosphere. The reaction mixture was stirred at room 338 temperature for 30 min. Then а solution of 7-bromo-3-nitro-2-339 [(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3b) (0.2 g, 0.50 mmol, 1 equiv.) in 340 dimethylsulfoxide (6 mL) was injected. The reaction mixture was stirred for 15 h at room 341 temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. 342 Compound (5b) was obtained after purification by chromatography on silica (eluent: dichloromethane) as a yellow solid in 82% yield (0.19 g). mp 238 °C. 343
- 3441H NMR (400 MHz, DMSO-d6) δ: 9.16 (d, J = 7.4 Hz, 1H), 7.73 (m, 3H), 7.69 7.55 (m, 6H),3457.44 (d, J = 1.4 Hz, 1H), 7.21 (dd, J = 7.4, 1.9 Hz, 1H), 5.18 (s, 2H).
- 346 13C NMR (100 MHz, DMSO-d6) δ: 144.4, 144.0, 140.2, 138.9, 136.2 (2C), 135.2, 134.2,
 347 130.5 (2C), 129.3 (2C), 128.1, 128.0, 127.9 (2C), 116.3, 113.2, 56.1, 54.9.
- 348 MS (ESI+): m/z = 459.79/461.46 [M+H]+.
- 349 HRMS (ESI+): m/z [M+H]+ calcd for C20H15CIN3O4S2: 460.0187; found: 460.0189.
- 350 7-[(4-Chlorophenyl)thio]-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (5c)
- To a sealed 20 mL flask containing sodium hydride (60% dispersion in mineral oil) (48 mg, 1.20 mmol, 2 equiv.) in dimethylsulfoxide (3 mL), 4-chlorobenzenethiol (173 mg, 1.20 mmol,

2 equiv.) was added under N2 atmosphere. The reaction mixture was stirred at room temperature for 30 min. Then a solution of 7-bromo-2-[(methylsulfonyl)methyl]-3nitroimidazo[1,2-a]pyridine (3c) (0.2 g, 0.60 mmol, 1 equiv.) in dimethylsulfoxide (6 mL) was injected. The reaction mixture was stirred for 15 h at room temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated. Compound (5c) was obtained after purification by chromatography on silica (eluent: dichloromethane-ethyl acetate 9:1) as a yellow solid in 69% yield (0.165 g). mp 192 °C.

360 1H NMR (400 MHz, DMSO-d6) δ : 9.22 (d, J = 7.4 Hz, 1H), 7.65 (td, J = 8.7, 2.2 Hz, 4H), 7.47 361 (d, J = 1.3 Hz, 1H), 7.25 (dd, J = 7.4, 2.0 Hz, 1H), 5.05 (s, 2H), 3.11 (s, 3H).

362 13C NMR (100 MHz, DMSO-d6) δ: 144.5, 144.1, 141.0, 136.2 (2C), 135.2, 130.6, 130.5
363 (2C), 128.2, 128.1, 116.3, 113.2, 54.4, 41.2.

- 364 MS (ESI+): m/z = 398.74/400.67 [M+H]+.
- 365 HRMS (ESI+): m/z [M+H]+ calcd for C15H13CIN3O4S2: 398.0031; found: 398.0027.
- 366 General procedure for the preparation of 5-arylimidazo[1,2-a]pyridine derivatives (6a-6e)

367 A mixture of 5-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3a) (200 mg, 368 0.5 mmol, 1 equiv.), tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol, 0.1 equiv.), 369 potassium carbonate (348 mg, 2.52 mmol, 5 equiv.), and appropriate boronic acid (1.5 equiv.) 370 in THF (7 mL) under N2 atmosphere was heated at 120 °C under microwave irradiation for 2 371 h (except for compounds 6d and 6e). Water was then added and the mixture was extracted 372 three times with dichloromethane. The organic layer was washed three times with water, dried over anhydrous Na2SO4, filtered and evaporated. The crude residue was purified by 373 374 column chromatography.

375 3-Nitro-5-phenyl-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (6a)

Compound (6a) was obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a yellow solid in 51% yield (0.10 g). mp 220 °C.

- 3781H NMR (400 MHz, DMSO-d6) δ: 7.90 (d, J = 4.1 Hz, 2H), 7.79-7.74 (m, 3H), 7.61 (t, J = 7.8379Hz, 2H), 7.49 7.43 (m, 3H), 7.42 7.36 (m, 3H), 5.08 (s, 2H).
- 380 13C NMR (100 MHz, DMSO-d6) δ: 146.4, 140.1, 139.4, 138.3, 135.0, 134.2, 132.3, 132.0,
 381 129.7, 129.3 (2C), 129.0 (2C), 128.3 (2C), 124.3 (2C), 119.6, 116.6, 55.7.
- 382 MS (ESI+): m/z = 394.04 [M+H]+.
- 383 HRMS (ESI+): m/z [M+H]+ calcd for C20H16N3O4S: 394.0856; found: 394.0857.
- 384 4-{3-Nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridin-5-yl}phenol (6b)
- Compound (6b) was obtained after purification by chromatography on silica gel (eluent: dichloromethane-ethyl acetate 8:2) as a yellow solid in 43% yield (0.09 g). mp 251 °C.
- 387 1H NMR (400 MHz, DMSO-d6) δ: 9.94 (s, 1H), 7.87-7.74 (m, 5H), 7.60 (t, J = 7.7 Hz, 2H),
 388 7.29 (d, J = 6.6 Hz, 1H), 7.21 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 5.07 (s, 2H).
- 389 13C NMR (100 MHz, DMSO-d6) δ: 158.6, 146.6, 140.7, 139.4, 138.4, 134.2, 132.3, 132.1,
 390 129.3 (2C), 128.3 (2C), 125.9, 125.8 (2C), 118.8, 115.7 (2C), 115.6, 55.7.
- 391 MS (ESI+): m/z = 409.94 [M+H]+.
- 392 HRMS (ESI+): m/z [M+H]+ calcd for C20H16N3O5S: 410.0805; found: 410.0804.

- 393 5-(4-Fluorophenyl)-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (6c)
- Compound (6c) was obtained after purification by chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as a yellow solid in 53% yield (0.11 g). mp 210 °C.

396 1H NMR (400 MHz, DMSO-d6) δ: 7.95 – 7.84 (m, 2H), 7.80-7.74 (m, 3H), 7.61 (t, J = 7.8 Hz, 2H), 7.48 (dd, J = 8.6, 5.3 Hz, 2H), 7.43 – 7.27 (m, 3H), 5.08 (s, 2H).

398 13C NMR (100 MHz, DMSO-d6) $\overline{0}$: 162.4 (d, J = 247.3 Hz), 146.4, 139.6, 139.2, 138.3, 399 134.3, 132.2, 131.9, 131.6 (d, J = 3.4 Hz), 129.3 (2C), 128.3 (2C), 127.0 (d, J = 8.6 Hz) (2C), 400 119.7, 116.7, 116.0 (d, J = 22.1 Hz) (2C), 55.7.

- 401 MS (ESI+): m/z = 411.63 [M+H]+.
- 402 HRMS (ESI+): m/z [M+H]+ calcd for C20H15FN3O4S: 412.0762; found: 412.0762.
- 403 3-Nitro-2-[(phenylsulfonyl)methyl]-5-(pyridin-4-yl)imidazo[1,2-a]pyridine (6d)

404 [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (37 mg, 0.05 mmol, 0.1 equiv.)
405 was used instead of tetrakis(triphenylphosphine)palladium(0). The reaction mixture was
406 heated at 120 °C under microwave irradiation for 4h. Compound (6d) was obtained after
407 purification by chromatography on silica gel (eluent: dichloromethane-ethyl acetate 6:4) as a
408 khaki solid in 60% yield (0.12 g). mp 201 °C.

409 1H NMR (400 MHz, DMSO-d6) δ : 8.69 (d, J = 4.5 Hz, 2H), 8.04 – 7.89 (m, 2H), 7.77 (d, J = 410 8.0 Hz, 3H), 7.62 (t, J = 7.7 Hz, 2H), 7.53 (d, J = 6.8 Hz, 1H), 7.42 (d, J = 5.4 Hz, 2H), 5.11 (s, 2H).

- 412 13C NMR (100 MHz, DMSO-d6) δ: 150.3 (2C), 146.2, 142.2, 139.9, 138.3, 137.4, 134.3,
 413 132.2, 131.9, 129.4 (2C), 128.3 (2C), 120.4, 118.8 (2C), 118.0, 55.7.
- 414 MS (ESI+): m/z = 394.98 [M+H]+.
- 415 HRMS (ESI+): m/z [M+H]+ calcd for C19H15N4O4S: 395.0809; found: 395.0808.
- 416 (E)-3-Nitro-2-[(phenylsulfonyl)methyl]-5-styrylimidazo[1,2-a]pyridine (6e)

The reaction mixture was stirred and heated at 75 °C for 48 h. Compound (6e) was obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a yellow solid in 46% yield (0.097 g). mp 229 °C.

- 420 1H NMR (400 MHz, DMSO-d6) δ: 7.87 (dd, J = 8.6, 7.4 Hz, 1H), 7.76 (ddd, J = 9.4, 7.4, 4.6 421 Hz, 5H), 7.66 – 7.57 (m, 4H), 7.50 – 7.33 (m, 4H), 6.95 (d, J = 16.1 Hz, 1H), 5.18 (s, 2H).
- 422 13C NMR (100 MHz, DMSO-d6) δ: 146.0, 140.4, 138.8, 135.9, 134.2, 132.4, 132.1, 132.0,
 423 129.4 (2C), 129.1, 128.9 (2C), 128.0 (2C), 127.3 (2C), 122.0, 116.6, 116.0, 55.7, 1C missing.
- 424 MS (ESI+): m/z = 419.94 [M+H]+.
- 425 HRMS (ESI+): m/z [M+H]+ calcd for C22H18N3O4S: 420.1013; found: 420.1013.
- 426 General procedure for the preparation of 7-aryl-2-(phenylsulfonylmethyl)imidazo[1,2-427 a]pyridine derivatives (6f-6j)

A mixture of 7-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3b) (200 mg,
0.5 mmol, 1 equiv.), tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol, 0.1 equiv.),
potassium carbonate (348 mg, 2.52 mmol, 5 equiv.), and appropriate boronic acid (1.5 equiv.)
in THF (7 mL) under N2 atmosphere was heated at 120 °C under microwave irradiation for 2
h (except for compound 6j). Water was then added and the mixture was extracted three

- times with dichloromethane. The organic layer was washed three times with water, dried over
 anhydrous Na2SO4, filtered and evaporated. The crude residue was purified by column
 chromatography.
- 436 3-Nitro-7-phenyl-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (6f)

437 Compound (6f) was obtained after purification by chromatography on silica gel (eluent: 438 cyclohexane-dichloromethane 2:8) as a yellow solid in 75% yield (0.15 g). mp 219 °C.

439 1H NMR (400 MHz, DMSO-d6) δ: 9.33 (d, J = 7.3 Hz, 1H), 8.28 (s, 1H), 7.96 (d, J = 7.2 Hz, 440 2H), 7.90 (dd, J = 7.3, 1.4 Hz, 1H), 7.76 (dd, J = 16.4, 7.6 Hz, 3H), 7.66 – 7.48 (m, 5H), 5.26 441 (s, 2H).

- 442 13C NMR (100 MHz, DMSO-d6) δ: 145.1, 143.1, 140.3, 138.9, 135.9, 134.2, 130.4, 129.8,
 443 129.4 (4C), 128.2, 128.0 (2C), 127.2 (2C), 116.2, 114.0, 56.2.
- 444 MS (ESI+): m/z = 394.03 [M+H]+.
- 445 HRMS (ESI+): m/z [M+H]+ calcd for C20H16N3O4S: 394.0856; found: 394.0855.
- 446 3-Nitro-2-[(phenylsulfonyl)methyl]-7-(p-tolyl)imidazo[1,2-a]pyridine (6g)

447 Compound (6g) was obtained after purification by chromatography on silica gel (eluent: 448 cyclohexane-dichloromethane 2:8) as a yellow solid in 44% yield (0.09 g). mp 240 °C.

- 449 1H NMR (400 MHz, DMSO-d6) δ: 9.31 (dd, J = 7.3, 0.7 Hz, 1H), 8.25 (d, J = 1.1 Hz, 1H), 450 7.92 - 7.83 (m, 3H), 7.81 - 7.72 (m, 3H), 7.65 - 7.56 (m, 2H), 7.38 (d, J = 7.9 Hz, 2H), 5.25 451 (s, 2H), 2.39 (s, 3H).
- 452 13C NMR (100 MHz, DMSO-d6) δ: 145.7, 143.5, 140.8, 140.2, 139.4, 134.7, 133.5, 130.4 453 (2C), 129.8 (2C), 128.6, 128.5 (2C), 127.5 (2C), 116.5, 113.9, 56.7, 21.3, 1C missing.
- 454 MS (ESI+): m/z = 407.92 [M+H]+.
- 455 HRMS (ESI+): m/z [M+H]+ calcd for C21H18N3O4S: 408.1013; found: 408.1016.
- 456 4-{3-Nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridin-7-yl}phenol (6h)
- 457 Compound (6h) was obtained after purification by chromatography on silica gel (eluent: 458 dichloromethane-ethyl acetate 8:2) as a yellow solid in 24% yield (0.05 g). mp 262 °C.
- 459 1H NMR (400 MHz, DMSO-d6) δ: 10.01 (s, 1H), 9.26 (d, J = 7.0 Hz, 1H), 8.14 (s, 1H), 7.91 460 7.68 (m, 6H), 7.60 (t, J = 6.9 Hz, 2H), 6.92 (d, J = 7.7 Hz, 2H), 5.24 (s, 2H).
- 461 13C NMR (100 MHz, DMSO-d6) δ: 159.3, 145.4, 143.2, 140.5, 138.9, 134.2, 130.2, 129.3
 462 (2C), 128.7 (2C), 128.0 (3C), 126.3, 116.2 (2C), 115.7, 112.2, 56.2.
- 463 MS (ESI+): m/z = 409.90 [M+H]+.
- 464 HRMS (ESI+): m/z [M+H]+ calcd for C20H16N3O5S: 410.0805; found: 410.0805.
- 465 7-(4-Fluorophenyl)-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (6i)
- 466 Compound (6i) was obtained after purification by chromatography on silica gel (eluent: 467 dichloromethane) as a yellow solid in 68% yield (0.14 g). mp 250 °C.
- 468 1H NMR (400 MHz, DMSO-d6) δ: 9.32 (d, J = 7.3 Hz, 1H), 8.28 (d, J = 1.2 Hz, 1H), 8.08 469 7.96 (m, 2H), 7.88 (dd, J = 7.4, 1.9 Hz, 1H), 7.83 – 7.70 (m, 3H), 7.62 - 7.59 (m, 2H), 7.47 – 470 7.33 (m, 2H), 5.26 (s, 2H).

- 471 13C NMR (100 MHz, DMSO-d6) δ: 163.2 (d, J = 247.9 Hz), 145.0, 142.0, 140.3, 138.9,
- 472 134.2, 132.4 (d, J = 3.0 Hz), 130.4, 129.6 (d, J = 8.6 Hz, 2C), 129.4 (2C), 128.1, 128.0 (2C),
- 473 116.3 (d, J = 23.4 Hz, 2C), 116.2, 114.0, 56.2.
- 474 MS (ESI+): m/z = 411.92 [M+H]+.
- 475 HRMS (ESI+): m/z [M+H]+ calcd for C20H15FN3O4S: 412.0762; found: 412.0763.
- 476 3-Nitro-2-[(phenylsulfonyl)methyl]-7-(pyridin-4-yl)imidazo[1,2-a]pyridine (6j)
- [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (37 mg, 0.05 mmol, 0.1 equiv.)
 was used instead of tetrakis(triphenylphosphine)palladium(0). The reaction mixture was
 heated at 120 °C under microwave irradiation for 4 h. Compound (6j) was obtained after
 purification by chromatography on neutral alumina gel (eluent: dichloromethane-ethyl acetate
 9:1) as a yellow solid in 35% yield (0.07 g). mp 254 °C.
- 482 1H NMR (400 MHz, DMSO-d6) δ : 9.38 (dd, J = 7.3, 0.7 Hz, 1H), 8.76 (dd, J = 4.5, 1.6 Hz, 483 2H), 8.52 - 8.46 (m, 1H), 8.01 - 7.92 (m, 3H), 7.76 (ddd, J = 8.6, 5.3, 1.1 Hz, 3H), 7.60 (dd, J 484 = 10.7, 4.9 Hz, 2H), 5.27 (s, 2H).
- 485 13C NMR (100 MHz, DMSO-d6) δ: 150.7 (2C), 144.7, 143.0, 140.2, 140.0, 138.9, 134.3,
 486 130.7, 129.4 (2C), 128.5, 128.0 (2C), 121.4 (2C), 115.7, 115.4, 56.1.
- 487 MS (ESI+): m/z = 395.10 [M+H]+.
- 488 HRMS (ESI+): m/z [M+H]+ calcd for C19H15N4O4S: 395.0809; found: 395.0809.
- 489 General procedure for the preparation of 7-aryl-2-(methylsulfonylmethyl)imidazo[1,2-490 a]pyridine derivatives (6k-6o)
- 491 A mixture of 7-bromo-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (3c) (200 mg, 492 0.6 mmol, 1 equiv.), tetrakis(triphenylphosphine)palladium(0) (69 mg, 0.05 mmol, 0.1 equiv.), 493 potassium carbonate (413 mg, 2.99 mmol, 5 equiv.), and appropriate boronic acid (1.5 equiv.) 494 in THF (7 mL) under N2 atmosphere was heated at 120 °C under microwave irradiation for 2 495 h (except for compound 6o). Water was then added and the mixture was extracted three times with dichloromethane. The organic layer was washed three times with water, dried over 496 497 anhydrous Na2SO4, filtered and evaporated. The crude residue was purified by column 498 chromatography on silica gel.
- 499 2-[(Methylsulfonyl)methyl]-3-nitro-7-phenylimidazo[1,2-a]pyridine (6k)
- 500 Compound (6k) was obtained after purification by chromatography on silica gel (eluent: 501 cyclohexane-dichloromethane 2:8) as a yellow solid in 63% yield (0.125 g). mp 234 °C.
- 505 13C NMR (100 MHz, DMSO-d6) δ: 145.2, 143.1, 141.2, 136.0, 130.5, 129.8, 129.4 (2C), 506 128.3, 127.2 (2C), 116.2, 114.0, 54.5, 41.2.
- 507 MS (ESI+): m/z = 332.10 [M+H]+.
- 508 HRMS (ESI+): m/z [M+H]+ calcd for C15H14N3O4S: 332.0700; found: 332.0702.
- 509 2-[(Methylsulfonyl)methyl]-3-nitro-7-(p-tolyl)imidazo[1,2-a]pyridine (6l)

- 510 Compound (6l) was obtained after purification by chromatography on silica gel (eluent: 511 dichloromethane) as a yellow solid in 70% yield (0.145 g). mp 244 °C.
- 512 1H NMR (400 MHz, DMSO-d6) δ : 9.33 (d, J = 7.3 Hz, 1H), 8.28 (d, J = 1.1 Hz, 1H), 7.92 7.77 (m, 3H), 7.36 (d, J = 8.0 Hz, 2H), 5.11 (s, 2H), 3.18 (s, 3H), 2.38 (s, 3H).
- 514 13C NMR (100 MHz, DMSO-d6) δ: 145.3, 143.1, 141.2, 139.7, 132.9, 130.5, 129.9 (2C), 515 128.2, 127.0 (2C), 115.9, 113.4, 54.5, 41.2, 20.8.
- 516 MS (ESI+): m/z = 346.12 [M+H]+.
- 517 HRMS (ESI+): m/z [M+H]+ calcd for C16H16N3O4S: 346.0856; found: 346.0861.
- 518 4-{2-[(Methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridin-7-yl}phenol (6m)
- 519 Compound (6m) was obtained after purification by chromatography on silica gel (eluent: 520 dichloromethane-ethyl acetate 8:2) as a yellow solid in 34% yield (0.07 g). mp > 260 °C.
- 521 1H NMR (400 MHz, DMSO-d6) δ: 10.01 (s, 1H), 9.32 (d, J = 7.3 Hz, 1H), 8.21 (s, 1H), 7.84 522 (d, J = 8.2 Hz, 3H), 6.93 (d, J = 8.3 Hz, 2H), 5.10 (s, 2H), 3.17 (s, 3H).
- 523 13C NMR (100 MHz, DMSO-d6) δ: 159.4, 145.5, 143.3, 141.3, 130.4, 128.7 (2C), 128.1, 126.3, 116.2 (2C), 115.6, 112.2, 54.5, 41.2.
- 525 MS (ESI+): m/z = 348.16 [M+H]+.
- 526 HRMS (ESI+): m/z [M+H]+ calcd for C15H14N3O5S: 348.0649; found: 348.0652.
- 527 7-(4-Fluorophenyl)-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (6n)
- 528 Compound (6n) was obtained after purification by chromatography on silica gel (eluent: 529 dichloromethane) as a yellow solid in 33% yield (0.14 g). mp 252 °C.
- 530 1H NMR (400 MHz, DMSO-d6) δ: 9.36 (d, J = 7.2 Hz, 1H), 8.33 (s, 1H), 8.13 7.96 (m, 2H),
 531 7.89 (d, J = 7.0 Hz, 1H), 7.40 (t, J = 8.4 Hz, 2H), 5.12 (s, 2H), 3.18 (s, 3H).
- 532 13C NMR (100 MHz, DMSO-d6) δ: 163.2 (d, J = 247.9 Hz), 145.1, 142.0, 141.2, 132.4 (d, J 533 = 3.0 Hz), 130.5, 129.5 (d, J = 8.6 Hz, 2C), 128.2, 116.3 (d, J = 21.6 Hz, 2C), 116.0, 114.0, 534 54.5, 41.2.
- 535 MS (ESI+): m/z = 350.05 [M+H]+.
- 536 HRMS (ESI+): m/z [M+H]+ calcd for C15H13FN3O4S: 350.0605; found: 350.0610.
- 537 2-[(Methylsulfonyl)methyl]-3-nitro-7-(pyridin-4-yl)imidazo[1,2-a]pyridine (60)

[1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (44 mg, 0.06 mmol, 0.1 equiv.)
was used instead of tetrakis(triphenylphosphine)palladium(0). The reaction mixture was
heated at 120 °C under microwave irradiation for 4 h. Compound (60) was obtained after
purification by chromatography on neutral alumina gel (eluent: dichloromethane-ethyl acetate
8:2) as a yellow solid in 36% yield (0.07 g). mp > 260 °C.

- 543 1H NMR (400 MHz, DMSO-d6) δ: 9.44 (d, J = 7.3 Hz, 1H), 8.77 (d, J = 4.9 Hz, 2H), 8.56 (s, 1H), 7.99 (d, J = 5.7 Hz, 3H), 5.14 (s, 2H), 3.17 (s, 3H).
- 545 13C NMR (100 MHz, DMSO-d6) δ: 150.7 (2C), 144.8, 143.0, 141.0, 140.0, 130.8, 128.6, 121.4 (2C), 115.6, 115.3, 54.4, 41.1.
- 547 MS (ESI+): m/z = 333.17 [M+H]+.

- 548 HRMS (ESI+): m/z [M+H]+ calcd for C14H13N4O4S: 333.0652; found: 333.0652.
- 549 3-Nitro-5-(phenylethynyl)-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (7a)

550 A mixture of 5-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3a) (0.2 g, 551 0.50 mmol, 1 equiv.), tetrakis(triphenylphosphine) palladium(0) (58 mg, 0.05 mmol, 0.1 equiv.), copper iodide (9.5 mg, 0.05 mmol, 0.1 equiv.), diisopropylamine (850 µL, 6.05 mmol, 552 553 12 equiv.) and phenylacetylene (83 µL, 0.76 mmol, 1.5 equiv.) in THF (7 mL) was stirred under N2 at room temperature for 24 h. Then, the mixture was slowly poured into an ice-554 555 water mixture and precipitated. Compound (7a) was obtained after purification by 556 chromatography on silica gel (eluent: dichloromethane) as a yellow solid in 38% yield (0.08 557 g). mp 202 °C.

- 558 1H NMR (400 MHz, DMSO-d6) δ: 7.96 (d, J = 8.5 Hz, 1H), 7.87 7.69 (m, 5H), 7.62-7.52 (m, 559 7H), 5.13 (s, 2H).
- 560 13C NMR (100 MHz, DMSO-d6) δ: 145.0, 138.6, 138.4, 134.3, 132.5, 131.6 (2C), 131.1, 130.5, 129.4 (2C), 129.1 (2C), 128.0 (2C), 123.3, 121.7, 120.3, 118.5, 103.9, 81.2, 55.2.
- 562 MS (ESI+): m/z = 417.93 [M+H]+.
- 563 HRMS (ESI+): m/z [M+H]+ calcd for C22H16N3O4S: 418.0856; found: 418.0854.
- 564 3-Nitro-7-(phenylethynyl)-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (7b)

565 A mixture of 7-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3b) (0.2 g, 0.50 mmol, 1 equiv.), tetrakis(triphenylphosphine) palladium(0) (58 mg, 0.05 mmol, 0.1 566 equiv.), copper iodide (9.5 mg, 0.05 mmol, 0.1 equiv.), diisopropylamine (850 µL, 6.05 mmol, 567 568 12 equiv.) and phenylacetylene (83 µL, 0.76 mmol, 1.5 equiv.) in THF (7 mL) was stirred 569 under N2 at room temperature for 24 h. Then, the mixture was slowly poured into an ice-570 water mixture and precipitated. Compound (7b) was obtained after purification by 571 chromatography on silica gel (eluent: dichloromethane) as a yellow solid in 57% yield (0.12 572 g). mp 254 °C.

- 573 1H NMR (400 MHz, DMSO-d6) δ : 9.29 (d, J = 7.2 Hz, 1H), 8.14 (s, 1H), 7.85 7.41 (m, 11H), 5.25 (s, 2H).
- 575 13C NMR (100 MHz, DMSO-d6) δ: 143.9, 140.3, 138.8, 134.3, 131.8 (3C), 130.0, 129.3 (2C), 129.0 (2C), 128.1, 128.0 (2C), 125.4, 121.0, 120.1, 119.3, 95.1, 86.7, 56.1.
- 577 MS (ESI+): m/z = 417.91 [M+H]+.
- 578 HRMS (ESI+): m/z [M+H]+ calcd for C22H16N3O4S: 418.0856; found: 418.0858.
- 579 4-{3-Nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridin-7-yl}but-3-yn-1-ol (7c)
- 580 A mixture of 7-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3b) (0.2 g, 581 0.50 mmol, 1 equiv.), tetrakis(triphenylphosphine) palladium(0) (58 mg, 0.05 mmol, 0.1 equiv.), copper iodide (9.5 mg, 0.05 mmol, 0.1 equiv.), diisopropylamine (850 µL, 6.05 mmol, 582 12 equiv.) and but-3-yn-1-ol (58 µL, 0.76 mmol, 1.5 equiv.) in THF (7 mL) was stirred under 583 584 N2 at room temperature for 24 h. Then, the mixture was slowly poured into an ice-water 585 mixture and precipitated. Compound (7c) was obtained after purification by chromatography 586 on neutral aluminum gel (eluent: dichloromethane-ethyl acetate 9:1) as a yellow solid in 52% 587 yield (0.10 g). mp 205 °C.

- 588 1H NMR (400 MHz, DMSO-d6) δ : 9.23 (dd, J = 7.2, 0.8 Hz, 1H), 7.93 (s, 1H), 7.82 7.68 (m, 589 3H), 7.66 7.52 (m, 2H), 7.41 (dd, J = 7.2, 1.7 Hz, 1H), 5.22 (s, 2H), 4.99 (t, J = 5.7 Hz, 1H), 590 3.63 (dd, J = 12.3, 6.5 Hz, 2H), 2.66 (t, J = 6.6 Hz, 2H).
- 591 13C NMR (100 MHz, DMSO-d6) δ: 144.1, 140.2, 138.8, 134.2, 130.8, 129.3 (2C), 128.0 (2C), 128.0, 126.5, 119.8, 119.7, 96.2, 78.8, 59.3, 56.1, 23.5.
- 593 MS (ESI+): m/z = 386.13 [M+H]+.
- 594 HRMS (ESI+): m/z [M+H]+ calcd for C18H16N3O5S: 386.0805; found: 386.0807.
- 595 2-[(Methylsulfonyl)methyl]-3-nitro-7-(phenylethynyl)imidazo[1,2-a]pyridine (7d)
- 596 A mixture of 7-bromo-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (3c) (0.2 g, 597 0.60 mmol, 1 equiv.), tetrakis(triphenylphosphine) palladium(0) (69 mg, 0.06 mmol, 0.1 equiv.), copper iodide (11.4 mg, 0.06 mmol, 0.1 equiv.), diisopropylamine (1 mL, 7.18 mmol, 598 599 12 equiv.) and phenylacetylene (99 µL, 0.90 mmol, 1.5 equiv.) in THF (7 mL) was stirred 600 under N2 at room temperature for 24 h. Then, the mixture was slowly poured into an icewater mixture and precipitated. Compound (7d) was obtained after purification by 601 602 chromatography on silica gel (eluent: dichloromethane) as a yellow solid in 50% yield (0.105 603 g). mp 236 °C.
- 604 1H NMR (400 MHz, DMSO-d6) δ: 9.33 (d, J = 7.2 Hz, 1H), 8.21 (s, 1H), 7.75 7.41 (m, 6H), 605 5.11 (s, 2H), 3.16 (s, 3H).
- 606 13C NMR (100 MHz, DMSO-d6) δ: 144.1, 141.1, 131.8 (2C), 131.0, 129.9, 128.9 (2C), 128.2, 125.4, 121.0, 120.1, 119.2, 95.1, 86.7, 54.4, 41.1.
- 608 MS (ESI+): m/z = 356.07 [M+H]+.
- 609 HRMS (ESI+): m/z [M+H]+ calcd for C17H14N3O4S: 356.0700; found: 356.0706.
- 610 4-{2-[(Methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridin-7-yl}but-3-yn-1-ol (7e)
- 611 A mixture of 7-bromo-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (3c) (0.2 g, 612 0.60 mmol, 1 equiv.), tetrakis(triphenylphosphine) palladium(0) (69 mg, 0.06 mmol, 0.1 613 equiv.), copper iodide (11.4 mg, 0.06 mmol, 0.1 equiv.), diisopropylamine (1 mL, 7.18 mmol, 12 equiv.) and but-3-yn-1-ol (68 µL, 0.90 mmol, 1.5 equiv.) in THF (7 mL) was stirred under 614 615 N2 at room temperature for 24 h. Then, the mixture was slowly poured into an ice-water 616 mixture and precipitated. Compound (7e) was obtained after purification by chromatography 617 on silica gel with 0.5% triethylamine (eluent: dichloromethane-ethyl acetate 9:1) as a yellow 618 solid in 54% vield (0.105 a), mp 192 °C.
- 619 1H NMR (400 MHz, DMSO-d6) δ: 9.27 (d, J = 6.7 Hz, 1H), 7.99 (s, 1H), 7.42 (d, J = 6.3 Hz, 620 1H), 5.08 (s, 2H), 5.00 (s, 1H), 3.64 (d, J = 4.4 Hz, 2H), 3.14 (s, 3H), 2.67 (s, 2H).
- 621 13C NMR (100 MHz, DMSO-d6) δ: 144.2, 141.0, 130.9, 128.0, 126.5, 119.8, 119.7, 96.2,
 622 78.8, 59.3, 54.4, 41.1, 23.6.
- 623 MS (ESI+): m/z = 324.10 [M+H]+.
- 624 HRMS (ESI+): m/z [M+H]+ calcd for C13H14N3O5S: 324.0649; found: 324.0652.
- 625 3-Nitro-N-phenyl-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridin-5-amine (8a)
- A mixture of 5-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3a) (0.2 g, 0.50 mmol, 1 equiv.), palladium(II) acetate (9 mg, 0.04 mmol, 0.08 equiv.), rac-BINAP (47 mg, 0.075 mmol, 0.15 equiv.), potassium carbonate (138 mg, 1.00 mmol, 2 equiv.) and

- aniline (140 μL, 1.50 mmol, 3 equiv.) in toluene (7 mL) was stirred under N2 atmosphere and
 heated at 140 °C under microwave irradiation for 2 h. Then, the mixture was slowly poured
 into an ice-water mixture, extracted three times with dichloromethane, dried over anhydrous
 Na2SO4, filtered and evaporated. Compound (8a) was obtained after purification by
 chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as a red solid in
 48% yield (0.11 g). mp 123 °C.
- 635 1H NMR (400 MHz, DMSO-d6) δ: 8.75 (s, 1H), 7.86 7.70 (m, 4H), 7.63 (t, J = 7.7 Hz, 2H), 636 7.39 (t, J = 7.9 Hz, 2H), 7.32 (d, J = 8.4 Hz, 1H), 7.24 – 7.09 (m, 3H), 7.00 (d, J = 8.0 Hz, 637 1H), 5.19 (s, 2H).
- 13C NMR (100 MHz, DMSO-d6) δ: 147.8, 142.3, 142.2, 139.3, 139.0, 134.4, 134.2, 131.9,
 129.6 (2C), 129.4 (2C), 127.9 (2C), 123.9, 120.7 (2C), 107.2, 102.5, 56.0.
- 640 MS (ESI+): m/z = 409.01 [M+H]+.
- 641 HRMS (ESI+): m/z [M+H]+ calcd for C20H17N4O4S: 409.0965; found: 409.0965.
- 642 3-Nitro-N-phenyl-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridin-7-amine (8b)

643 A mixture of 7-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3b) (0.2 g, 644 0.50 mmol, 1 equiv.), palladium(II) acetate (9 mg, 0.04 mmol, 0.08 equiv.), rac-BINAP (47 645 mg, 0.075 mmol, 0.15 equiv.), potassium carbonate (138 mg, 1.00 mmol, 2 equiv.) and 646 aniline (140 µL, 1.50 mmol, 3 equiv.) in toluene (7 mL) was stirred under N2 atmosphere and heated at 140 °C under microwave irradiation for 2 h. Then, the mixture was slowly poured 647 648 into an ice-water mixture, extracted three times with dichloromethane, dried over anhydrous 649 Na2SO4, filtered and evaporated. Compound (8b) was obtained after purification by 650 chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as an orange solid 651 in 52% yield (0.07 g). mp 232 °C.

652 1H NMR (400 MHz, DMSO-d6) δ: 9.51 (s, 1H), 9.08 (d, J = 7.6 Hz, 1H), 7.74 (dd, J = 16.4, 653 7.5 Hz, 3H), 7.59 (t, J = 7.7 Hz, 2H), 7.43 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 7.7 Hz, 2H), 7.23 – 654 7.08 (m, 2H), 7.02 (d, J = 2.0 Hz, 1H), 5.15 (s, 2H).

- 655 13C NMR (100 MHz, DMSO-d6) δ: 147.9, 147.6, 141.6, 139.3, 139.0, 134.1, 129.7 (2C), 656 129.3 (2C), 129.0, 127.9 (2C), 124.1, 121.2 (2C), 109.4, 94.2, 56.3, 1C missing.
- 657 MS (ESI+): m/z = 409.04 [M+H]+.
- 658 HRMS (ESI+): m/z [M+H]+ calcd for C20H17N4O4S: 409.0965; found: 409.0964.
- 659 2-[(Methylsulfonyl)methyl]-3-nitro-N-phenylimidazo[1,2-a]pyridin-7-amine (8c)
- 660 A mixture of 7-bromo-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (3c) (0.2 g, 661 0.60 mmol, 1 equiv.), palladium(II) acetate (11 mg, 0.05 mmol, 0.08 equiv.), rac-BINAP (56 662 mg, 0.09 mmol, 0.15 equiv.), potassium carbonate (166 mg, 1.20 mmol, 2 equiv.) and aniline 663 (168 µL, 1.80 mmol, 3 equiv.) in toluene (7 mL) was stirred under N2 atmosphere and heated 664 at 140 °C under microwave irradiation for 2 h. Then, the mixture was slowly poured into an 665 ice-water mixture, extracted three times with dichloromethane, dried over anhydrous Na2SO4, filtered and evaporated. Compound (8c) was obtained after purification by 666 chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as an orange solid 667 668 in 35% yield (0.10 g). mp 255 °C.
- 669 1H NMR (400 MHz, DMSO-d6) δ: 9.52 (s, 1H), 9.15 (d, J = 7.4 Hz, 1H), 7.37 (dd, J = 39.6, 7.4 Hz, 4H), 7.26 7.01 (m, 3H), 5.01 (s, 2H), 3.14 (s, 3H).

671 13C NMR (100 MHz, DMSO-d6) δ: 148.0, 147.7, 142.6, 139.4, 129.8 (2C), 129.7, 129.1,
672 124.1, 121.2 (2C), 109.4, 94.2, 54.5, 41.3.

- 673 MS (ESI+): m/z = 347.13 [M+H]+.
- 674 HRMS (ESI+): m/z [M+H]+ calcd for C15H15N4O4S: 347.0809; found: 347.0810.

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683 Conflict of Interest

684 The authors declare no conflict of interest.

685 References

- 686 (1) Dodd, M. C.; Stillman W. B.; Roys M.; Crosby C. J. Pharmacol. Exp. Ther. 1944, 82,
 687 11-18.
- 688 (2) Dodd, M. C. J. Pharmacol. Exp. Ther. 1946, 86, 311-323.
- 689 (3) Evens, F.; Niemegeers, K.; Packchanian, A. Am. J. Trop. Med. Hyg. 1957, 6, 665.
- 690 (4) Nepali, K.; Lee, H.-Y.; Liou, J.-P. J. Med. Chem. 2019, 62, 2851.
- 691 (5) Durel, P.; Couture, J.; Collart, P.; Girot, C. Sex. Transm. Infect. 1960, 36, 154.
- 692 (6) King, A.J. Practitioner 1960, 185, 808–812.
- 693 (7) Cohen, J. Lancet 1996, 348, 273.
- 694 (8) Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. Drugs 1978, 16, 387.
- 695 (9) Löfmark, S.; Edlund, C.; Nord, C. E. Clin. Infect. Dis. 2010, 50, S16-S23.
- 696 (10) R. Wilkinson, S.; Bot, C.; M. Kelly, J.; S. Hall, B. Curr. Top. Med. Chem. 2011, 11, 697 2072.
- 698 (11) Patterson, S.; Wyllie, S. Trends Parasitol. 2014, 30, 289.
- 699 (12) Thakare, R.; Dasgupta, A.; Chopra, S. Drugs Today 2021, 57, 251.
- Müller Kratz, J.; Garcia Bournissen, F.; Forsyth, C. J.; Sosa-Estani, S. Expert Rev.
 Clin. Pharmacol. 2018, 11, 943.
- 702 (14) Pelfrene, E.; Harvey Allchurch, M.; Ntamabyaliro, N.; Nambasa, V.; Ventura, F. V.;
- Nagercoil, N.; Cavaleri, M. PLoS Negl. Trop. Dis. 2019, 13, e0007381.
- 704 (15) Deeks, E. D. Drugs 2019, 79, 215.
- 705 (16) Allocco, J. J.; Donald, R.; Zhong, T.; Lee, A.; Tang, Y. S.; Hendrickson, R. C.;
- 706 Liberator, P.; Nare, B. Int. J. Parasitol. 2006, 36, 1249.

- 707 (17) Ryan, N. J.; Lo, J. H. Drugs 2014, 74, 1041.
- 708 (18) Keam, S. J. Drugs 2019, 79, 1797.
- 709 (19) Deep, A.; Bhatia, R.; Kaur, R.; Kumar, S.; Jain, U.; Singh, H.; Batra, S.; Kaushik, D.;
 710 Deb, P. Curr. Top. Med. Chem. 2016, 17, 238.
- (20) Vanelle, P.; Maldonado, J.; Madadi, N.; Gueiffier, A.; Teulade, J.-C.; Chapat, J.-P.;
 Crozet, M. P. Tetrahedron Lett. 1990, 31, 3013.
- 713 (21) Holm, K. J.; Goa, K. L. Drugs 2000, 59, 865.
- 714 (22) Kannigadu, C.; N'Da, David. D. Curr. Pharm. Des. 2020, 26, 4658.
- 715 (23) Marhadour, S.; Marchand, P.; Pagniez, F.; Bazin, M.-A.; Picot, C.; Lozach, O.;
- Ruchaud, S.; Antoine, M.; Meijer, L.; Rachidi, N.; Le Pape, P. Eur. J. Med. Chem. 2012, 58,
 543.
- 718 (24) Fersing, C.; Basmaciyan, L.; Boudot, C.; Pedron, J.; Hutter, S.; Cohen, A.; Castera-
- 719 Ducros, C.; Primas, N.; Laget, M.; Casanova, M.; Bourgeade-Delmas, S.; Piednoel, M.;
- Sournia-Saquet, A.; Belle Mbou, V.; Courtioux, B.; Boutet-Robinet, É.; Since, M.; Milne, R.;
- Wyllie, S.; Fairlamb, A. H.; Valentin, A.; Rathelot, P.; Verhaeghe, P.; Vanelle, P.; Azas, N. ACS
 Med. Chem. Lett. 2019, 10, 34.
- (25) Paoli-Lombardo, R.; Primas, N.; Bourgeade-Delmas, S.; Hutter, S.; Sournia-Saquet,
 A.; Boudot, C.; Brenot, E.; Castera-Ducros, C.; Corvaisier, S.; Since, M.; Malzert-Fréon, A.;
 Courtioux, B.; Valentin, A.; Verhaeghe, P.; Azas, N.; Rathelot, P.; Vanelle, P. Pharmaceuticals
 2022, 15, 998.
- 727 (26) Fersing, C.; Boudot, C.; Castera-Ducros, C.; Pinault, E.; Hutter, S.; Paoli-Lombardo,
- R.; Primas, N.; Pedron, J.; Seguy, L.; Bourgeade-Delmas, S.; Sournia-Saquet, A.; Stigliani,
- J.-L.; Brossas, J.-Y.; Paris, L.; Valentin, A.; Wyllie, S.; Fairlamb, A. H.; Boutet-Robinet, É.;
- Corvaisier, S.; Since, M.; Malzert-Fréon, A.; Destere, A.; Mazier, D.; Rathelot, P.; Courtioux, R: Azea, N.; Verbaarba, B.; Venella, P. Eur. J. Med. Chem. 2020, 202, 112558
- 731 B.; Azas, N.; Verhaeghe, P.; Vanelle, P. Eur. J. Med. Chem. 2020, 202, 112558.
- 732 (27) Fersing, C.; Boudot, C.; Paoli-Lombardo, R.; Primas, N.; Pinault, E.; Hutter, S.;
 733 Castera-Ducros, C.; Kabri, Y.; Pedron, J.; Bourgeade-Delmas, S.; Sournia-Saquet, A.;
 734 Stigliani, J.-L.; Valentin, A.; Azqueta, A.; Muruzabal, D.; Destere, A.; Wyllie, S.; Fairlamb, A.
- H.; Corvaisier, S.; Since, M.; Malzert-Fréon, A.; Di Giorgio, C.; Rathelot, P.; Azas, N.;
- 736 Courtioux, B.; Vanelle, P.; Verhaeghe, P. Eur. J. Med. Chem. 2020, 206, 112668.
- 737 (28) Buskes, M. J.; Blanco, M.-J. Molecules 2020, 25, 3493.
- (29) Castera-Ducros, C.; Paloque, L.; Verhaeghe, P.; Casanova, M.; Cantelli, C.; Hutter,
 S.; Tanguy, F.; Laget, M.; Remusat, V.; Cohen, A.; Crozet, M. D.; Rathelot, P.; Azas, N.;
- 740 Vanelle, P. Bioorg. Med. Chem. 2013, 21, 7155.
- 741
- 742
- 743
- 744