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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

Romain Paoli-Lombardo, Nicolas Primas, Sandra Bourgeade-Delmas, Alix Sournia-Saquet, Caroline Castera-Ducros, Inès Jacquet, Pierre Verhaeghe,
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1 **Synthesis of new 5- and 7-substituted 3-nitroimidazo[1,2-a]pyridine derivatives using**
2 **SNAr and palladium-catalyzed reactions to explore antiparasitic structure-activity**
3 **relationships**

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11

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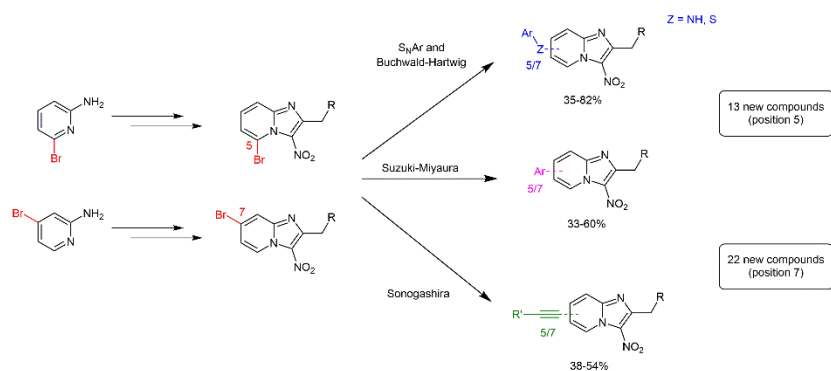
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18

19 **Graphical Abstract**



20

21 **Abstract**

22 To study the antikinoplastid structure-activity relationships in 3-nitroimidazo[1,2-a]pyridine
23 series, we explored the substitution of positions 5 and 7 of the scaffold, developing
24 nucleophilic aromatic substitution reactions and pallado-catalyzed Suzuki-Miyaura,
25 Sonogashira and Buchwald-Hartwig cross-coupling reactions which had never been reported
26 at these positions in this series. Thirty-five original compounds were obtained in 4 steps from
27 2-amino-bromopyridines, allowing a better definition of the antiparasitic pharmacophore.

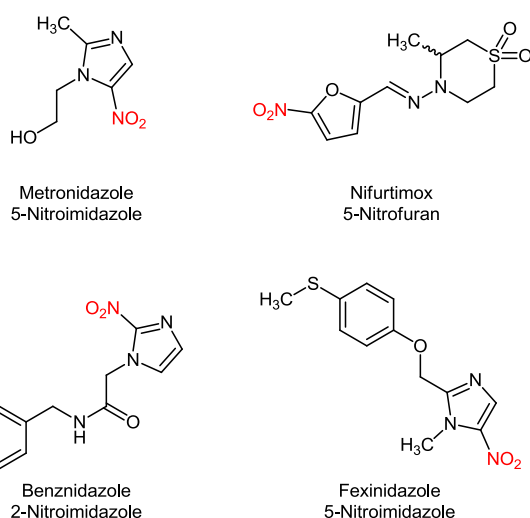
28 **Key words** : Nitroaromatic, imidazo[1,2-a]pyridine, kinetoplastids, nucleophilic aromatic
29 substitution, palladium-catalyzed cross-coupling reaction, microwave irradiation.

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
35 bacteria such as Bacteroides, Clostridioides or Helicobacter pylori and parasitic infections
36 caused by Trichomonas vaginalis, Entamoeba histolytica and Giardia lamblia.⁶⁻⁹
37 Nitroaromatic compounds are also well-known for their antikinetoplastid properties:
38 nifurtimox, a 5-nitrofuran derivative, and benznidazole, a 2-nitroimidazole derivative, are
39 used to treat Chagas disease for more than 50 years (Figure 1).¹⁰⁻¹³ In 2019, fexinidazole,
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 leishmaniasis, 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}

46 In parallel, the imidazo[1,2-a]pyridine ring has drawn much attention since the discovery of
47 zolpidem (Ambien®, Stilnox®), a hypnotic drug widely used for the treatment of severe
48 insomnia.¹⁹⁻²¹ Some imidazo[1,2-a]pyridine derivatives substituted at positions 2 and 3
49 have been reported for their antileishmanial activity.^{22,23}

50

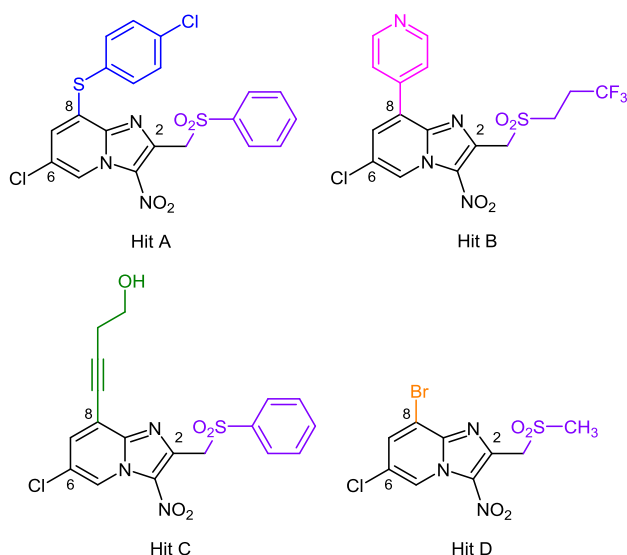


51

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 the 3-nitroimidazo[1,2-a]pyridine series, thanks to
56 pharmacomodulation work conducted on positions 2, 6 and 8 of the moiety (Figure 2). The
57 first antileishmanial hit (Hit A) was functionalized by a phenylsulfonylmethyl substituent at
58 position 2, a chlorine atom at position 6 and a 4-chlorophenylthioether group at position 8.²⁴
59 The second (Hit B) is substituted at position 2 by a trifluoropropylsulfonylmethyl group and by
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
62 D) was functionalized by a methylsulfonylmethyl substituent at position 2 and a bromine atom
63 at position 8. ²⁷

64



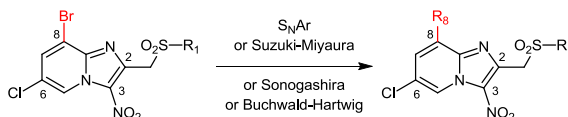
65

66 **Figure 2** Structures of previously identified antikinoplastid hit compounds.

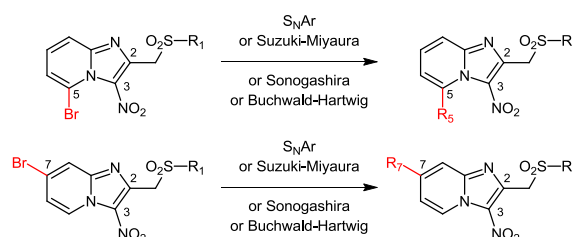
67 To go forward on the study of the antiparasitic structure-activity relationships, we explored
 68 the position 5 and the position 7 of the 3-nitroimidazo[1,2-a]pyridine scaffold. Indeed, a
 69 literature search of the imidazo[1,2-a]pyridine moiety showed that these two positions have
 70 never been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

75

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



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

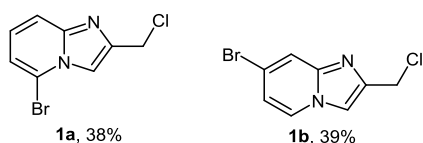
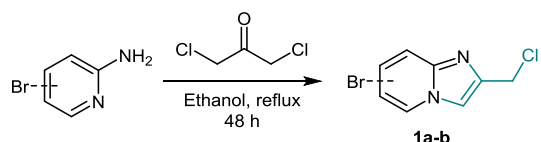


76

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

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

84

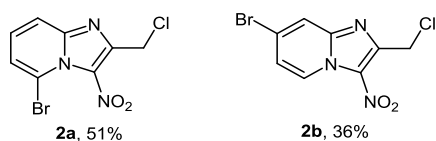
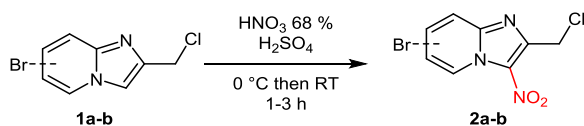


85

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%.

88 Adapting a previously reported method described in our lab,²⁹ the selective nitration at
89 position 3 of 1a and 1b was conducted in a mixture of 68% nitric acid and concentrated
90 sulfuric acid, giving the 2-chloromethyl-3-nitroimidazo[1,2-a]pyridines 2a and 2b (Scheme 2).
91 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.

93

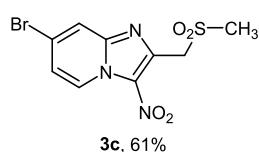
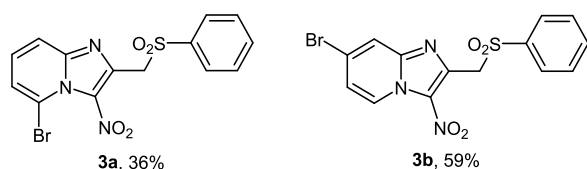


94

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

97 To introduce a sulfonmethyl 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).

100

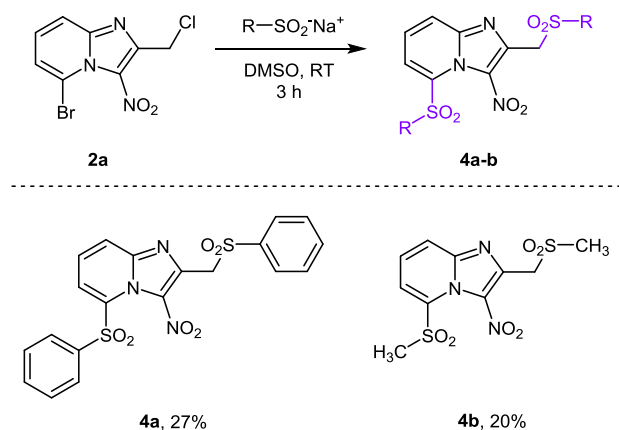


101

102 **Scheme 3** Synthesis of 2-sulfonylmethyl-3-nitroimidazo[1,2-a]pyridine intermediates 3a-c.
103 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
106 observed when 1.5 equivalents of sodium methanesulfinate stirred for 15 hours were used.
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
110 substituent at position 2 of the 2-chloromethyl-3-nitroimidazo[1,2-a]pyridine 2a is not a
111 regioselective reaction. Thus, using 3 equivalents of sodium benzenesulfinate or sodium
112 methanesulfinate with 2a, the substitution of both the chlorine atom of the chloromethyl group
113 at position 2 and the bromine atom at position 5 was performed, affording the 2,5-
114 disubstituted compounds 4a and 4b in modest yields (Scheme 4).

115

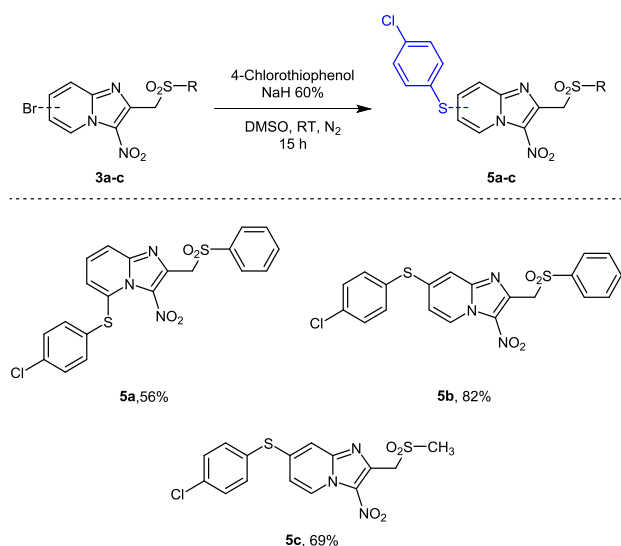


117 **Scheme 4** Synthesis of 2,5-disubstituted derivatives 4a and 4b. Reagents and conditions:
118 sodium sulfinate (3 equiv.), DMSO, RT, 3 h, 20-27%.

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

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

125

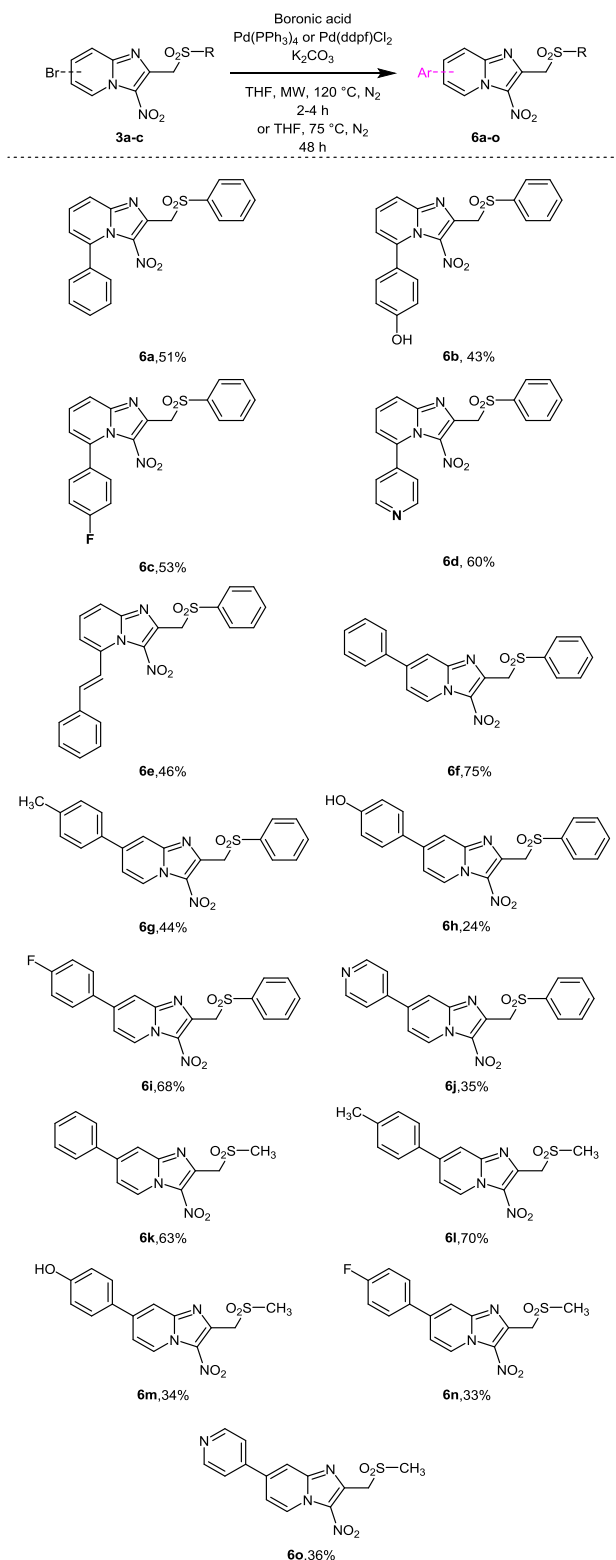


126

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

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

134



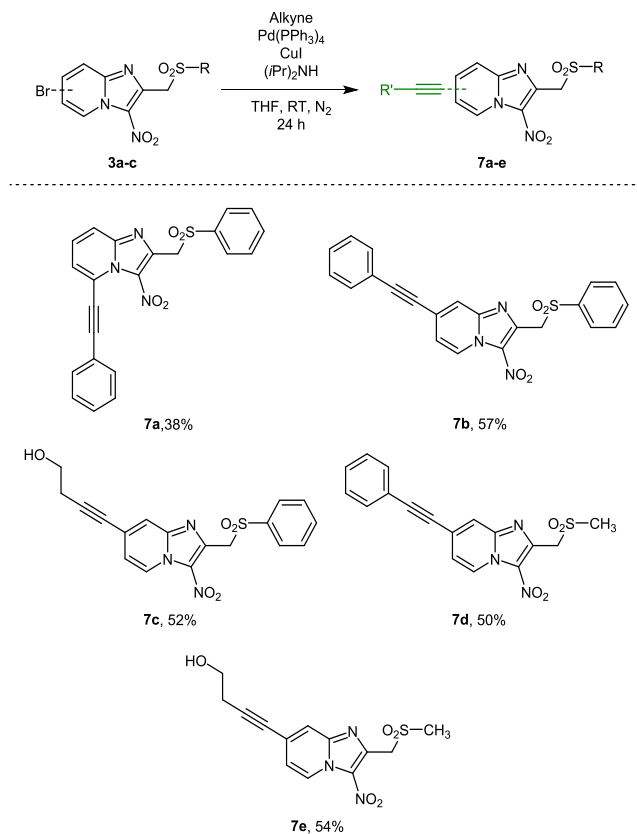
135

136 **Scheme 6** Synthesis of compounds 6a-o using Suzuki-Miyaura cross-coupling reaction.
 137 Reagents and conditions: boronic acid (1.5 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (0.1 equiv.), K_2CO_3 (5
 138 equiv.), THF, N_2 , 120 °C, MW, 2 h, 24-75%; or boronic acid (1.5 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (0.1
 139 equiv.), K_2CO_3 (5 equiv.), THF, N_2 , 75 °C, 48 h, 46%; or 4-Pyridinylboronic acid (1.5 equiv.),
 140 $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.1 equiv.), K_2CO_3 (5 equiv.), THF, N_2 , 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-3-

143 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.

147

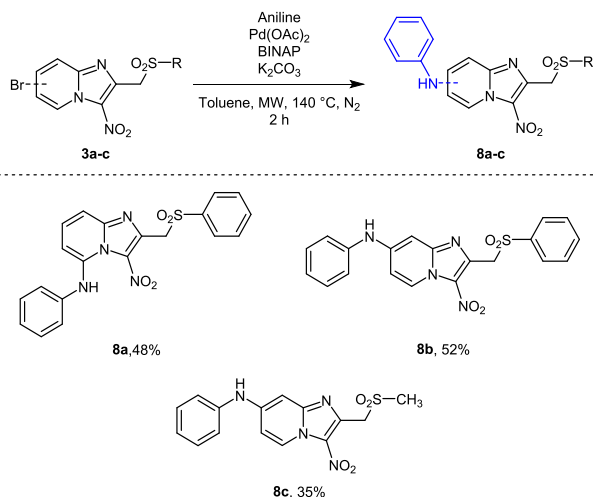


148

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

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

155



156

157 **Scheme 8** Synthesis of compounds 8a-c using Buchwald-Hartwig cross-coupling reaction.
 158 Reagents and conditions: aniline (3 equiv.), Pd(OAc)₂ (0.08 equiv.), BINAP (0.15 equiv.),
 159 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
 164 thirteen compounds 5-substituted and twenty-two 7-substituted. Modulation of the position 5
 165 and the position 7 was performed with nucleophilic aromatic substitution, Suzuki-Miyaura,
 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 μM). This allowed a better definition of the
 170 3-nitroimidazo[1,2-a]pyridine pharmacophore, showing that substitution of the position 5 or 7
 171 was detrimental to the antileishmanial activity. In order to continue the study of the
 172 antikinoplastid structure-activity relationships in 3-nitroimidazo[1,2-a]pyridine series, further
 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
 177 SYNAPT G2 HDMS (Waters) at the Faculté des Sciences de Saint-Jérôme (Marseille). NMR
 178 spectra were recorded on a Bruker Avance NEO 400MHz NanoBay spectrometer at the
 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
 184 ultraviolet light (234 nm). Purity determination of synthesized compounds was checked by
 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
 187 single quadrupole mass spectrometer Thermo MSQ Plus®. The purity of all the synthesized
 188 compounds was > 95%. The RP-HPLC column is a Thermo Hypersil Gold® 50 x 2.1 mm
 189 (C18 bounded), with particles of a diameter of 1.9 mm. The volume of sample injected on the
 190 column was 1 μL. Chromatographic analysis, total duration of 8 min, was on the gradient of

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 (t_R) 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 ^{13}C NMR are available in the Supplementary Materials.

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

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

205 1H NMR (400 MHz, DMSO- d_6) 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 ^{13}C NMR (100 MHz, DMSO- d_6) δ = 145.0, 142.5, 126.0, 116.5, 115.9, 114.1, 112.5, 1C
208 (CH_2Cl) below DMSO- d_6 signal.

209 MS (ESI+): m/z = 245.01/247.04/249.10 $[M+H]^+$.

210 HRMS (ESI+): m/z $[M+H]^+$ calcd for $C_8H_7BrClN_2$: 246.9453; found: 246.9453.

211 7-Bromo-2-chloromethylimidazo[1,2-a]pyridine (1b)

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

217 1H NMR (400 MHz, DMSO- d_6) 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 ^{13}C NMR (100 MHz, DMSO- d_6) 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 $C_8H_7BrClN_2$: 246.9453; found: 246.9450.

222 5-Bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2a)

223 To a solution of 5-bromo-2-chloromethylimidazo[1,2-a]pyridine (1a) (2 g, 8.14 mmol, 1 equiv.)
224 in concentrated sulfuric acid (20 mL) cooled by an ice-water bath, nitric acid 68% (2.2 mL,
225 48.88 mmol, 6 equiv.) was added dropwise. The reaction mixture was stirred for 1 h at room
226 temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated.
227 The solid was collected by filtration and dried under reduced pressure. Compound (2a) was
228 obtained after purification by chromatography on silica gel (eluent: dichloromethane) as a
229 yellow solid in 51% yield (1.2 g). mp 167 °C.

230 1H NMR (400 MHz, DMSO- d_6) δ : 8.00 (dd, J = 8.6, 1.0 Hz, 1H), 7.88 – 7.67 (m, 2H), 5.01 (s,
231 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 C₈H₆BrClN₃O₂: 291.9304; found: 291.9304.

235 7-Bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2b)

236 To a solution of 7-bromo-2-chloromethylimidazo[1,2-a]pyridine (1b) (2 g, 8.14 mmol, 1 equiv.)
237 in concentrated sulfuric acid (20 mL) cooled by an ice-water bath, nitric acid 36% (2.2 mL,
238 48.88 mmol, 6 equiv.) was added dropwise. The reaction mixture was stirred for 3 h at room
239 temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated.
240 The solid was collected by filtration and dried under reduced pressure. Compound (2b) was
241 obtained after purification by chromatography on silica gel (eluent: cyclohexane-
242 dichloromethane 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 C₈H₆BrClN₃O₂: 291.9304; found: 291.9301.

248 5-Bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3a)

249 To a solution of 5-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2a) (0.5 g, 1.72 mmol,
250 1 equiv.) in dimethylsulfoxide (20 mL), sodium benzenesulfinate (0.42 g, 2.58 mmol, 1.5
251 equiv.) was added. The reaction mixture was stirred for 15 h at room temperature. Then, the
252 mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected
253 by filtration and dried under reduced pressure. Compound (3a) was obtained after
254 purification by chromatography on silica gel (eluent: dichloromethane) as a yellow solid in
255 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).

258 ¹³C NMR (100 MHz, DMSO-d₆) δ: 147.0, 139.0, 138.5, 134.3, 132.8, 132.2, 129.4 (2C),
259 128.0 (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)

263 To a solution of 7-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2b) (0.5 g, 1.72 mmol,
264 1 equiv.) in dimethylsulfoxide (20 mL), sodium benzenesulfinate (0.42 g, 2.58 mmol, 1.5
265 equiv.) was added. The reaction mixture was stirred for 15 h at room temperature. Then, the
266 mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected
267 by filtration and dried under reduced pressure. Compound (3b) was obtained after
268 purification by chromatography on silica gel (eluent: dichloromethane) as a yellow solid in
269 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)

277 To a solution of 7-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2b) (0.5 g, 1.72 mmol,
278 1 equiv.) in dimethylsulfoxide (20 mL), sodium methanesulfinate (0.27 g, 2.58 mmol, 1.5
279 equiv.) was added. The reaction mixture was stirred for 15 h at room temperature. Then, the
280 mixture was slowly poured into an ice-water mixture and precipitated. The solid was collected
281 by filtration and dried under reduced pressure. Compound (3c) was obtained after purification
282 by chromatography on silica gel (eluent: dichloromethane) as a beige solid in 61% yield (0.35
283 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)

291 To a solution of 5-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2a) (0.5 g, 1.72 mmol,
292 1 equiv.) in dimethylsulfoxide (20 mL), sodium benzenesulfinate (0.85 g, 5.16 mmol, 3 equiv.)
293 was added. The reaction mixture was stirred for 3 h at room temperature. Then, the mixture
294 was slowly poured into an ice-water mixture and precipitated. The solid was collected by
295 filtration and dried under reduced pressure. Compound (4a) was obtained after purification
296 by chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as a yellow solid
297 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)

305 To a solution of 5-bromo-2-chloromethyl-3-nitroimidazo[1,2-a]pyridine (2a) (0.5 g, 1.72 mmol,
306 1 equiv.) in dimethylsulfoxide (20 mL), sodium methanesulfinate (0.53 g, 5.16 mmol, 3 equiv.)
307 was added. The reaction mixture was stirred for 3 h at room temperature. Then, the mixture
308 was slowly poured into an ice-water mixture and precipitated. The solid was collected by
309 filtration and dried under reduced pressure. Compound (4b) was obtained after purification
310 by chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as a yellow solid
311 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),
313 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,
320 1.00 mmol, 2 equiv.) in dimethylsulfoxide (3 mL), 4-chlorobenzenethiol (145 mg, 1.00 mmol,
321 2 equiv.) was added under N₂ atmosphere. The reaction mixture was stirred at room
322 temperature for 30 min. Then a 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
324 dimethylsulfoxide (6 mL) was injected. The reaction mixture was stirred for 15 h at room
325 temperature. Then, the mixture was slowly poured into an ice-water mixture and precipitated.
326 Compound (5a) was obtained after purification by chromatography on silica (eluent:
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 C₂₀H₁₅ClN₃O₄S₂: 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,
336 1.00 mmol, 2 equiv.) in dimethylsulfoxide (3 mL), 4-chlorobenzenethiol (145 mg, 1.00 mmol,
337 2 equiv.) was added under N₂ atmosphere. The reaction mixture was stirred at room
338 temperature for 30 min. Then a 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:
343 dichloromethane) as a yellow solid in 82% yield (0.19 g). mp 238 °C.

344 1H NMR (400 MHz, DMSO-d6) δ : 9.16 (d, J = 7.4 Hz, 1H), 7.73 (m, 3H), 7.69 – 7.55 (m, 6H),
345 7.44 (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 C₂₀H₁₅ClN₃O₄S₂: 460.0187; found: 460.0189.

350 7-[(4-Chlorophenyl)thio]-2-[(methylsulfonyl)methyl]-3-nitroimidazo[1,2-a]pyridine (5c)

351 To a sealed 20 mL flask containing sodium hydride (60% dispersion in mineral oil) (48 mg,
352 1.20 mmol, 2 equiv.) in dimethylsulfoxide (3 mL), 4-chlorobenzenethiol (173 mg, 1.20 mmol,

353 2 equiv.) was added under N₂ atmosphere. The reaction mixture was stirred at room
354 temperature for 30 min. Then a solution of 7-bromo-2-[(methylsulfonyl)methyl]-3-
355 nitroimidazo[1,2-a]pyridine (3c) (0.2 g, 0.60 mmol, 1 equiv.) in dimethylsulfoxide (6 mL) was
356 injected. The reaction mixture was stirred for 15 h at room temperature. Then, the mixture
357 was slowly poured into an ice-water mixture and precipitated. Compound (5c) was obtained
358 after purification by chromatography on silica (eluent: dichloromethane-ethyl acetate 9:1) as
359 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 C₁₅H₁₃N₃O₄S₂: 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,
373 dried over anhydrous Na₂SO₄, filtered and evaporated. The crude residue was purified by
374 column chromatography.

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

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

378 ¹H NMR (400 MHz, DMSO-d₆) δ: 7.90 (d, J = 4.1 Hz, 2H), 7.79-7.74 (m, 3H), 7.61 (t, J = 7.8
379 Hz, 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)

385 Compound (6b) was obtained after purification by chromatography on silica gel (eluent:
386 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)

394 Compound (6c) was obtained after purification by chromatography on silica gel (eluent:
395 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,
397 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) δ: 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
411 (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)

417 The reaction mixture was stirred and heated at 75 °C for 48 h. Compound (6e) was obtained
418 after purification by chromatography on silica gel (eluent: dichloromethane) as a yellow solid
419 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)

428 A mixture of 7-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3b) (200 mg,
429 0.5 mmol, 1 equiv.), tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.05 mmol, 0.1 equiv.),
430 potassium carbonate (348 mg, 2.52 mmol, 5 equiv.), and appropriate boronic acid (1.5 equiv.)
431 in THF (7 mL) under N₂ atmosphere was heated at 120 °C under microwave irradiation for 2
432 h (except for compound 6j). Water was then added and the mixture was extracted three

433 times with dichloromethane. The organic layer was washed three times with water, dried over
434 anhydrous Na₂SO₄, filtered and evaporated. The crude residue was purified by column
435 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 C₂₀H₁₅N₃O₄S: 412.0762; found: 412.0763.

476 3-Nitro-2-[(phenylsulfonyl)methyl]-7-(pyridin-4-yl)imidazo[1,2-a]pyridine (6j)

477 [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (37 mg, 0.05 mmol, 0.1 equiv.)
478 was used instead of tetrakis(triphenylphosphine)palladium(0). The reaction mixture was
479 heated at 120 °C under microwave irradiation for 4 h. Compound (6j) was obtained after
480 purification by chromatography on neutral alumina gel (eluent: dichloromethane-ethyl acetate
481 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
496 times with dichloromethane. The organic layer was washed three times with water, dried over
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.

502 ¹H NMR (400 MHz, DMSO-d₆) δ: 9.40 (dd, J = 7.3, 0.6 Hz, 1H), 8.35 (d, J = 1.1 Hz, 1H),
503 8.01 – 7.95 (m, 2H), 7.92 (dd, J = 7.4, 1.9 Hz, 1H), 7.65 – 7.48 (m, 3H), 5.12 (s, 2H), 3.17 (s,
504 3H).

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 –
513 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,
524 126.3, 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 (6o)

538 [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (44 mg, 0.06 mmol, 0.1 equiv.)
539 was used instead of tetrakis(triphenylphosphine)palladium(0). The reaction mixture was
540 heated at 120 °C under microwave irradiation for 4 h. Compound (6o) was obtained after
541 purification by chromatography on neutral alumina gel (eluent: dichloromethane-ethyl acetate
542 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,
544 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,
546 121.4 (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
552 equiv.), copper iodide (9.5 mg, 0.05 mmol, 0.1 equiv.), diisopropylamine (850 μ L, 6.05 mmol,
553 12 equiv.) and phenylacetylene (83 μ L, 0.76 mmol, 1.5 equiv.) in THF (7 mL) was stirred
554 under N₂ at room temperature for 24 h. Then, the mixture was slowly poured into an ice-
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,
561 130.5, 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,
566 0.50 mmol, 1 equiv.), tetrakis(triphenylphosphine) palladium(0) (58 mg, 0.05 mmol, 0.1
567 equiv.), copper iodide (9.5 mg, 0.05 mmol, 0.1 equiv.), diisopropylamine (850 μ L, 6.05 mmol,
568 12 equiv.) and phenylacetylene (83 μ L, 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,
574 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
576 (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
582 equiv.), copper iodide (9.5 mg, 0.05 mmol, 0.1 equiv.), diisopropylamine (850 μ L, 6.05 mmol,
583 12 equiv.) and but-3-yn-1-ol (58 μ L, 0.76 mmol, 1.5 equiv.) in THF (7 mL) was stirred under
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
592 (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
598 equiv.), copper iodide (11.4 mg, 0.06 mmol, 0.1 equiv.), diisopropylamine (1 mL, 7.18 mmol,
599 12 equiv.) and phenylacetylene (99 μ L, 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 ice-
601 water mixture and precipitated. Compound (7d) was obtained after purification by
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),
607 128.2, 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,
614 12 equiv.) and but-3-yn-1-ol (68 μ L, 0.90 mmol, 1.5 equiv.) in THF (7 mL) was stirred under
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% yield (0.105 g). 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)

626 A mixture of 5-bromo-3-nitro-2-[(phenylsulfonyl)methyl]imidazo[1,2-a]pyridine (3a) (0.2 g,
627 0.50 mmol, 1 equiv.), palladium(II) acetate (9 mg, 0.04 mmol, 0.08 equiv.), rac-BINAP (47
628 mg, 0.075 mmol, 0.15 equiv.), potassium carbonate (138 mg, 1.00 mmol, 2 equiv.) and

629 aniline (140 μ L, 1.50 mmol, 3 equiv.) in toluene (7 mL) was stirred under N₂ atmosphere and
630 heated at 140 °C under microwave irradiation for 2 h. Then, the mixture was slowly poured
631 into an ice-water mixture, extracted three times with dichloromethane, dried over anhydrous
632 Na₂SO₄, filtered and evaporated. Compound (8a) was obtained after purification by
633 chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as a red solid in
634 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).

638 ¹³C NMR (100 MHz, DMSO-d₆) δ : 147.8, 142.3, 142.2, 139.3, 139.0, 134.4, 134.2, 131.9,
639 129.6 (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 μ L, 1.50 mmol, 3 equiv.) in toluene (7 mL) was stirred under N₂ atmosphere and
647 heated at 140 °C under microwave irradiation for 2 h. Then, the mixture was slowly poured
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 μ L, 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
666 Na₂SO₄, filtered and evaporated. Compound (8c) was obtained after purification by
667 chromatography on silica gel (eluent: dichloromethane-ethyl acetate 9:1) as an orange solid
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,
670 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.

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