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METHODOLOGY TO ACCESS TETRAHYDRODIPYRIDOIMIDAZOLE DERIVATIVES

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Abstract – While the synthesis of β and γ-carboline derivatives were well described in the literature, the preparation of their aza-analogs such as tetrahydrodipyridoimidazole derivatives were less explored. In our laboratory we developed various methods to access to these compounds using Bischler-Napieralski as well as Pictet-Spengler reactions.

INTRODUCTION

The indole derivatives have long been a topic of fundamental interest to organic and medicinal chemists. They display a wide range of biological activities and are frequently found to be active in various classes of pharmacologically important compounds. The indole ring provides an attractive entry to a variety of polycyclic heteroaromatic alkaloids. For example, indoles containing one additional ring fused across the 2,3-positions are widely distributed in nature and used in medicinal chemistry.[1] A lot of work has been done on the synthesis of tricyclic compounds with functionalized pyrido[3,4-*b*]indoles (β-carbolines)[2-6] or the isomeric series of pyrido[4,3-*b*]indoles (γ-carbolines)[7-10] and is well represented in the literature (Figure 1).

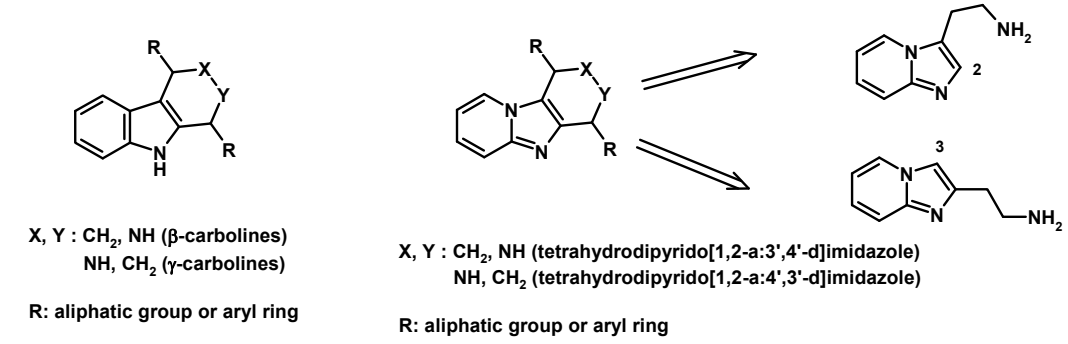


Figure 1. Structures and routes to β, γ-carboline and tetrahydrodipyridoimidazole derivatives

In this paper, we have focused our attention on tetrahydrodipyrido[1,2-*a*:4',3'-*d*]imidazole and tetrahydrodipyrido[1,2-*a*:3',4'-*d*]imidazole compounds, build starting from 2 and 3-ethylaminoimidazopyridine derivatives, which are less well described both pharmacologically and theoretically than their β and γ- carboline analogs (Figure 1).

In our laboratory we synthesized a series of β-carboline compounds and tested for their antioxidant activities (Figure 2).[6] In the course of our extensive studies on the chemistry and pharmacological reactivities, we changed the indole heterocycle to its isoster imidazopyridine, possessing a bridgehead nitrogen atom (Figure 2).

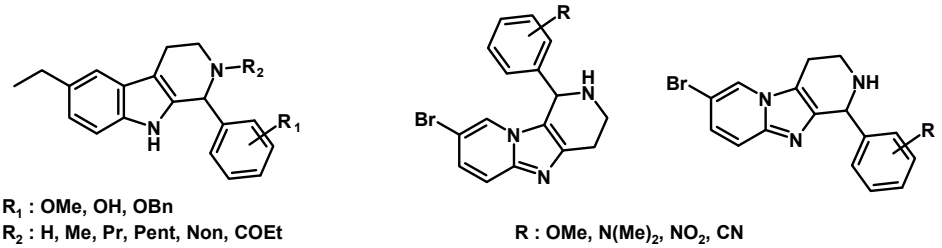


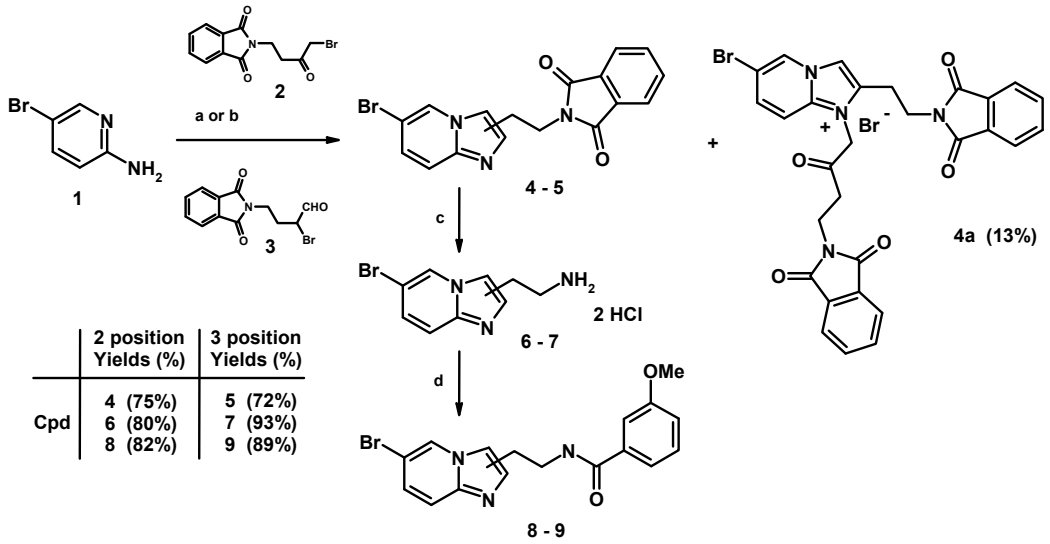
Figure 2. β-Carboline compounds with antioxidant activities and their isoster tetrahydro-dipyridoimidazole derivatives

RESULTS AND DISCUSSION

To build these tetrahydrodipyridoimidazole derivatives, isosters of β-carboline compounds, the synthesis of 8-bromo-1-substituted tetrahydrodipyridoimidazole compounds, as key intermediates, was explored by two routes involving Bischler-Napieralski or Pictet-Spengler ring closures. These intermediates were substituted at the 8 position by a bromo atom to insert alkyl chain, heterocyclic or heterocyclic carbonyl moiety using palladium coupling reaction. Various alkyl or carbonylalkyl chains could be introduced at the nitrogen atom of the tetrahydrodipyridoimidazole compounds by nucleophilic substitution (Figure 2).

In the literature, these tetrahydrodipyridoimidazole compounds were synthesised starting from 2 or 3-ethylaminoimidazopyridine derivatives (Figure 1). The reactivity of imidazo[1,2-*a*]pyridine has been described,[11,12] the 2 position is known to be a less reactive than the 3 position. Indeed, this 2 position is able to react as an electrophile to give the corresponding compound with low yield (4%) as previously described in the reaction between an imidazopyridine compound and phenyl isocyanate in refluxing toluene.[13]

To build tetrahydrodipyrido[1,2-*a*:4',3'-*d*]imidazole and tetrahydrodipyrido[1,2-*a*:3',4'-*d*]imidazole heterocycles, we developed two routes starting from 2 or 3-ethylaminoimidazopyridine and involving Bischler-Napieralski or Pictet-Spengler ring closures.



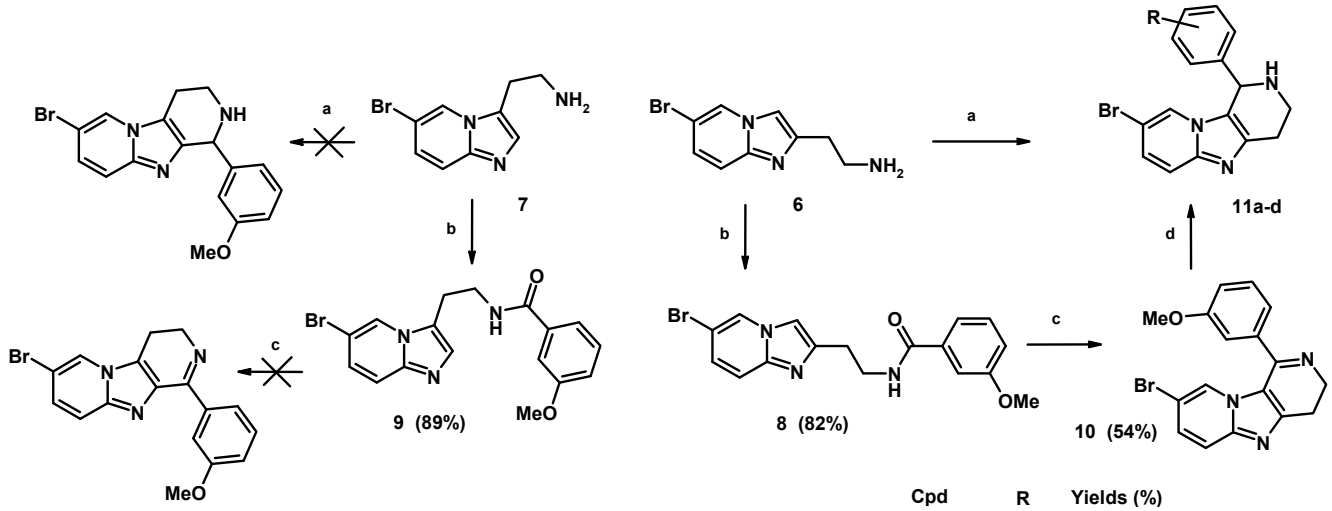
Reagents and conditions: (a): 1-bromoketone compound (**2**), EtOH or BuOH (b): i: 1-bromoketone (**2**) or 2-bromoaldehyde (**3**) compounds, EtOAc; ii: EtOH (c): NH_2-NH_2. H_2O, EtOH (d): 3-methoxybenzoyl chloride, K_2CO_3, H_2O, EtOAc.

Scheme 1. Synthesis of substituted imidazopyridine compounds (**4-9**)

For the construction of imidazopyridine compounds, various conditions have been used in the literature. We attempted this reaction in one step by refluxing 2-amino-5-bromopyridine (**1**) in ethanol or butanol[14] with the corresponding 1-bromoketone or 2-bromoaldehyde compounds (**2**,**3**). In these conditions the desired compounds (**4**,**5**) were obtained with low yields (35-39%) together with the formation of side products (Scheme 1). Furthermore, the purification of the expected products (**4**,**5**) was difficult and the 2-amino-5-bromopyridine (**1**) was not totally consumed. One explanation is the presence of a competing side reaction such as *N*1-alkylation of substituted imidazopyridine as observed during the synthesis of compound **4** (yield 35%) leading to the by product **4a** (yield 13%).

To overcome this limitation, we turned our attention to the well known two-step synthesis of imidazopyridine involving first the formation and isolation of pyridinium salts. The first step was carried out in ethyl acetate (prefered to commonly used 1,2-dichloroethane), with 2-amino-5-bromopyridine (**1**) and the corresponding 1-bromoketone or 2-bromoaldehyde compounds (**2**,**3**). After one day of stirring at room temperature, the primary material (**1**) was totaly consumed and the intermediate bromide products were filtered, washed with ethyl acetate and then refluxed for the second step in ethanol. Using this methodology avoiding the formation of *N*-alkylated by products, final compounds (**4**,**5**) were obtained in good yields (72-75%) (Scheme 1). The deprotection of phthalimide group of compounds **4**,**5** was performed with hydrazine hydrate in ethanol to give the corresponding ethylamino compounds **6**,**7**.[15] It is worth emphasizing that water was not used in the treatment to eliminate the formation of phthalhydrazide, indeed we observed that the compounds were partially solubilised in water and could not be totally

extracted with an organic phase, under these conditions the yield was only 50-60%. Treatment with ethyl acetate and purification by chromatography on silica gel furnished compounds **6**,**7** with excellent yields (90-93%).



Cpd	R	Yields (%)
11a	3-OMe	74
11b	4-N(Me)$_2$	78
11c	4-NO$_2$	65
11d	4-CN	69

Reagents and conditions: (a): substituted benzaldehyde, TFA, MeOH (b): 3-methoxybenzoyl chloride, K_2CO_3, H_2O, EtOAc (c): $POCl_3$ (d): $NaBH_4$, MeOH.

Scheme 2. Synthesis of tetrahydrodipyridoimidazole compounds **11a-d** starting from compound **6**

The cyclization of imidazopyridine compounds to tetrahydrodipyridoimidazole was described in the literature with low yields (20-25%) in methanol at room temperature and with the presence of magnesium sulfate.[16,17] In order to improve the reaction yields, the use of Bischler-Napieralski or Pictet-Spengler reactions starting from ethylamino derivatives (**6-7**) was evaluated. The Bischler-Napieralski cyclization was achieved in three steps from amino compounds (**8**,**9**).[18] For the first step, amidation reaction of ethylamino compounds (**6-7**) and 3-methoxybenzoyl chloride in a biphasic solution containing aqueous 5% potassium carbonate and ethyl acetate solutions gave compounds (**8**,**9**) (Scheme 1). The cyclization step was performed in refluxing $POCl_3$, used as solvent and reagent, and the amido products (**8**,**9**). In the series substituted at the 3 position of the imidazopyridine derivative (**9**) the cyclization was not realised and we only recovered starting material and degradation products, probably due to the lack of reactivity of the 2 position of the imidazo[1,2-*a*]pyridine. For the second series, substituted at the 2 position (**8**), the cyclization in $POCl_3$ afforded compound **10** with 54% yield (Scheme 2). The next step was a reduction with sodium borohydride of the imine group (**10**) which gave the cyclized compound **11a**. The overall yield of the Bischler-Napieralski pathway was 37%. The second route was accomplished starting from

ethylamino compounds (**6-7**) using Pictet-Spengler reaction. A first attempt using 1.25% TFA/dichloromethane solution and benzaldehyde reagent under various temperature conditions did not give the corresponding cyclized compounds.[19,20] The solvent was then replaced by methanol. In these conditions and under reflux in the presence of 3-methoxybenzaldehyde, compound (**6**) bearing the ethylamino chain at the 2 position of the imidazo[1,2-*a*]pyridine was converted in good yield (74%) into compound **11a**. (Scheme 2). This cyclization has already been described in one step, but with low yield (20-25%).[16,17] As observed previously for the Bischler-Napieralski pathway, our attempts failed to perform cyclization at the 2 position *via* Pictet-Spengler reaction starting from compound **7**.

In a second time, various electron donating or withdrawing groups ($N(Me)_2$, NO_2, CN) were introduced into the phenyl ring using the more efficient Pictet-Spengler method (Scheme 2). As expected phenyl ring bearing electron-donating groups (**11a-b**) gave the highest yields (74-78%) and shortest time reactions (24 h) compared to derivatives (**11c-d**) with electron-withdrawing groups (65-69%; 48 h respectively).

These compounds (**11a-d**) could be used as intermediates in medicinal chemistry. Indeed, various reactions at the nitrogen atom of the tetrahydrodipyridoimidazole with nucleophilic substitution and also palladium coupling reaction with the bromo atom at the 8 position of the tetrahydrodipyridoimidazole with Stille, Suzuki, Heck reactions.

CONCLUSION

Tetrahydrodipyridoimidazole coupounds **11a-d**, bearing various substituents were synthesized using two methods, Bischler-Napieralski and Pictet-Spengler reactions. The best yields were obtained by the Pictet-Spengler pathway. These compounds could be used in medicinal chemistry with nucleophilic substitution or palladium coupling reaction.

EXPERIMENTAL

TLC and column chromatography were carried out on silica gel 60 F_{254} plates and on glass column silica gel 60 (40-63 mesh). All of the reagents and solvents were AR grade. Melting points were determined by a Büchi 510 capillary apparatus and are uncorrected. Infrared spectra were recorded on a BECKMAN ACCULAB IV spectrometer in KBr. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 spectrometer and chemical shifts are expressed in ppm using tetramethylsilane as internal standard. Mass spectra were recorded on a Thermofinnigan Surveyor MSQ Single Quadrupole Mass Spectrometer operating in electrospray, positive single ion mode to monitor m/z. The purity of final compounds was verified by two types of high pressure liquid chromatography (HPLC) columns: C18 Deltapak (C18N) and C4 Interchrom UP5WC4-25QS (C4).

2-[2-(6-Bromo-1-(2-oxo-4-isoindole-1,3-dionebutyl)imidazo[1,2-*a*]pyridin-2-yl)ethyl]isoindole-1,3-dione bromide (4a)

In EtOH or BuOH (100 mL), 2-amino-5-bromopyridine (2.3 g, 13.2 mmol) and 2-(4-bromo-3-oxobutyl)isoindole-1,3-dione (3.3 g, 11.0 mmol) were added. The mixture was refluxed for 1 day. The solution was evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (40-63 mesh), eluting with CH_2Cl_2 / MeOH (95/5, v/v). Yield 13%, mp 176-177 °C, HPLC (C18, 35 min) PHPLC 90%, tR 13.8 min; HPLC (C4, 35 min) PHPLC 90%, tR 22.1 min. IR 1775 (CO), 1709 (CO), 1643 (CN). ^{1}H NMR (DMSO-d_6) δ 3.15 (m, 4H, CH_2), 3.87 (m, 4H, NCH_2), 5.70 (s, 2H, $COCH_2$), 7.80 (m, 8H, H_{Ar}), 8.18 (d, 1H, H_8, J = 9.7 Hz), 8.26 (dd, 1H, H_7, J = 9.7 Hz, J = 1.8 Hz), 8.29 (s, 1H, H_3), 9.35 (d, 1H, H_5, J = 1.8 Hz). ^{13}C NMR (DMSO-d_6) δ 23.0, 33.0, 36.0, 38.0, 54.0, 112.0, 113.5, 114.0, 123.7, 124.0, 130.3, 132.4, 132.6, 135.3, 135.6, 137.0, 137.3, 139.6, 170.0, 201.0. *MS (APCI+): m/z* 585.2, 587.3.

General procedure for the synthesis of compounds 4-5

In EtOAc (100 mL), 2-amino-5-bromopyridine (6.9 g, 39.7 mmol) and 2-bromo-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butyraldehyde or 2-(4-bromo-3-oxobutyl)isoindole-1,3-dione (9.8 g, 33.1 mmol) were added. The mixture was stirred for 1 day at room temperature. The precipitate was filtred and washed with EtOAc (200 mL). The product was dissolved in EtOH (150 mL) and refluxed for 1 day. After cooling to room temperature, the solvent was evaporated under vacuum. The residue obtained was taken up with an aqueous solution of 5% potassium carbonate (100 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The organic phase was dried over $MgSO_4$ filtered and evaporated under reduced pressure. The products were recrystallised in acetonitrile.

2-[2-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)ethyl]isoindole-1,3-dione (4)

Yield 75%, mp 195-196 °C, HPLC (C18, 35 min) PHPLC 100%, tR 9.8 min; HPLC (C4, 35 min) PHPLC 100%, tR 7.1 min. IR 1713 (CO), 1769 (CO), 1649 (CN). ^{1}H NMR (DMSO-d_6) δ 3.00 (t, 2H, CH_2, J = 7.6 Hz), 3.95 (t, 2H, NCH_2, J = 7.6 Hz), 7.25 (dd, 1H, H_7, J = 9.6 Hz, J = 2.0 Hz), 7.40 (dd, 1H, H_8, J = 9.6 Hz, J = 0.8 Hz), 7.75 (s, 1H, H_3), 7.85 (m, 4H, H_{Ar}), 8.80 (dd, 1H, H_5, J = 2.0 Hz, J = 0.8 Hz). ^{13}C NMR (DMSO-d_6) δ 24.6, 36.9, 110.7, 113.5, 113.6, 123.6, 129.4, 132.0, 134.9,135.9, 140.0, 138.6, 168.2. *MS (APCI+): m/z* 370.2, 372.3.

2-[2-(6-Bromoimidazo[1,2-*a*]pyridin-3-yl)ethyl]isoindole-1,3-dione (5)

Yield 72%, mp 172-173 °C, HPLC (C18, 35 min) PHPLC 100%, tR 9.3 min; HPLC (C4, 35 min) PHPLC 100%, tR 18.5 min. IR 1707 (CO), 1765 (CO), 1653 (CN). ^{1}H NMR (DMSO-d_6) δ 3.35 (t, 2H, CH_2, J =

6.4 Hz), 3.95 (t, 2H, NCH_2, *J* = 6.4 Hz), 7.80 (m, 4H, H_{Ar}), 7.98 (d, 1H, H_8, *J* = 9.5 Hz), 8.07 (s, 1H, H_2), 8.13 (dd, 1H, H_7, *J* = 9.5 Hz, *J* = 1.8 Hz), 9.40 (d, 1H, H_4, *J* = 1.8 Hz). ^{13}C NMR (DMSO-d_6) δ 22.7, 34.8, 111.4, 114.1, 122.1, 123.6, 125.0, 127.7, 131.9, 135.0, 136.0, 138.9, 168.0. *MS (APCI+): m/z* 369.9, 371.9 $[M+H]^+$.

General procedure for the synthesis of compounds 6-7

In 95% EtOH (50 mL), 2-[2-(6-bromoimidazo[1,2-*a*]pyridin-2 or 3-yl)ethyl]isoindole-1,3-dione (1.41 g, 3.81 mmol) and hydrazine monohydrate (0.95 g, 19 mmol) were added. The solution was refluxed for 4 h. After cooling to room temperature, the reaction mixture was evaporated under vacuum. The precipitate obtained was tritured with EtOAc (2 x 100 mL) and filtered. The filtrate was evaporated under reduced pressure and the oily residue was washed with Et_2O (3 x 50 mL). The resulting crude product was purified by chromatography on silica gel (40-63 mesh), eluting with CH_2Cl_2 / MeOH (95/5, v/v). The products were solubilized in dry EtOAc and treated with gazeous hydrochloric acid in diethyl ether (20 mL). The obtained precipitate was filtered and washed with EtOAc (2 x 20 mL) to afford desired compounds.

2-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)ethylamine dihydrochloride (6)

Yield 90%, mp 192-193 °C, HPLC (C18, 35 min) PHPLC 100%, tR 2.8 min; HPLC (C4, 35 min) PHPLC 100%, tR 4.9 min. IR 3355, 3286 (NH_2), 1656 (CN). ^{1}H NMR (DMSO-d_6) δ, 3.14 (m, 2H, CH_2), 3.43 (t, 2H, NCH_2, *J* = 6.7 Hz), 7.97 (d, 1H, H_8, *J* = 9.5 Hz), 8.07 (dd, 1H, H_7, *J* = 9.5 Hz, *J* = 1.6 Hz), 8.17 (s, 1H, H_2), 8.35 (brs, 3H, NH^+, NH_2), 9.38 (s, 1H, H_5). ^{13}C NMR (DMSO-d_6) δ 23.7, 37.9, 110.1, 113.8, 113.9, 129.1, 135.0, 135.3, 139.3. *MS (APCI+): m/z* 240.0, 242.0.

2-(6-Bromoimidazo[1,2-*a*]pyridin-3-yl)ethylamine dihydrochloride (7)

Yield 93%, mp 95-96 °C, HPLC (C18, 35 min) PHPLC 99.9%, tR 1.5 min; HPLC (C4, 35 min) PHPLC 100%, tR 5.3 min. IR 3355, 3286 (NH_2), 1656 (CN). ^{1}H NMR (DMSO-d_6) δ 2.85 (t, 2H, CH_2, *J* = 6.7 Hz), 2.95 (t, 2H, CH_2, *J* = 6.7 Hz), 7.25 (dd, 1H, H_7, *J* = 9.5 Hz, *J* = 1.9 Hz), 7.40 (s, 1H, H_2), 7.50 (d, 1H, H_8, *J* = 9.5 Hz), 8.70 (d, 1H, H_5, *J* = 1.9 Hz). ^{13}C NMR (DMSO-d_6) δ 21.2, 36.4, 111.1, 114.1, 122.9, 123.5, 127.8, 135.6, 139.2. *MS (APCI+): m/z* 240.0, 242.0 $[M+H]^+$.

General procedure for the synthesis of compounds 8-9

In an aqueous solution of 5% potassium carbonate (50 mL) and $CHCl_3$ (40 mL), 2-(6-bromoimidazo[1,2-*a*]pyridin-3-yl)ethylamine (1.0 g, 4.16 mmol) and 3-methoxybenzoyl chloride (0.7 mL, 5 mmol) were added. The solution was stirred at room temperature for 2 h. The organic phase was washed with water

(30 mL), dried over $MgSO_4$, filtered and evaporated. The obtained product was recrystallised from MeCN.

_N_-[2-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl)ethyl]-3-methoxybenzamide (8)

Yield 82%, mp 115-116 °C, HPLC (C18, 35 min) PHPLC 99.9%, tR 9.4 min; HPLC (C4, 35 min) PHPLC 100%, tR 7.1 min. IR 3336 (NH), 1668 (CN), 1659 (CO). ^{1}H NMR (DMSO-d_6) δ 2.95 (t, 2H, CH_2, J = 7.3 Hz), 3.60 (t, 2H, CH_2, J = 7.3 Hz), 3.80 (s, 3H, OCH_3), 7.10 (m, 1H, H_{Ar}), 7.29 (dd, 1H, H_7, J = 9.3 Hz, J = 1.7 Hz), 7.38 (m, 3H, H_{Ar}), 7.46 (dd, 1H, H_8, J = 9.3 Hz, J = 0.9 Hz), 7.75 (s, 1H, H_3), 8.60 (bsr, 1H, NH), 8.84 (dd, 1H, H_5, J = 1.7 Hz, J = 0.9 Hz). ^{13}C NMR (DMSO-d_6) δ 29.0, 39.1, 55.7, 105.7, 111.1, 112.8, 117.4, 117.6, 119.8, 127.0, 127.4, 129.9, 136.5, 143.1, 145.8, 159.6, 166.4. *MS (APCI+): m/z* 374.2, 376.2.

_N_-[2-(6-Bromoimidazo[1,2-*a*]pyridin-3-yl)ethyl]-3-methoxybenzamide (9)

Yield 89%, mp 123-124 °C, HPLC (C18, 35 min) PHPLC 100%, tR 9.8 min; HPLC (C4, 35 min) PHPLC 94.8%, tR 7.3 min. IR 3273 (NH), 1661 (CN), 1632 (CO). ^{1}H NMR (DMSO-d_6) δ 3.15 (t, 2H, CH_2, J = 6.7 Hz), 3.55 (t, 2H, CH_2, J = 6.7 Hz), 3.75 (s, 3H, OCH_3), 7.05 (m, 1H, H_{Ar}), 7.30 (m, 2H, H_7, H_{Ar}), 7.36 (m, 2H, H_{Ar}), 7.45 (s, 1H, H_2), 7.52 (dd, 1H, H_8, J = 9.6 Hz, J =0.6 Hz), 8.60 (brs, 1H, NH), 8.75 (dd, 1H, H_5, J = 1.75 Hz, J = 0.6 Hz). ^{13}C NMR (DMSO-d_6) δ 23.8, 37.9, 55.7, 106.5, 112.8, 117.4, 118.6, 119.8, 123.5, 125.0, 126.8, 129.9, 132.6, 136.3, 143.5, 159.6, 166.7. *MS (APCI+): m/z* 374.2, 376.1.

8-Bromo-1-(3-methoxyphenyl)-3,4-dihydrodipyrido[1,2-*a*;4',3'-*d*]imidazole dihydrochloride (10)

In $POCl_3$ (15 mL), *N*-[2-(6-bromoimidazo[1,2-*a*]pyridin-2-yl)ethyl]-3-methoxy-benzamide (1.0 g, 2.8 mmol)was added and the solution was refluxed for 2 days After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue was triturated with EtOAc (50 mL). The precipitate obtained was filtered and recrystallised in MeCN. Yield 54%, mp > 250 °C, HPLC (C18, 35 min) PHPLC 94.8%, tR 11.9 min; HPLC (C4, 35 min) PHPLC 92.5%, tR 6.2 min. IR 3050-2450 (NH^+), 1638 (CN). ^{1}H NMR (DMSO-d_6) δ 2.75 (t, 2H, CH_2, J = 7.0 Hz), 3.15 (t, 2H, CH_2, J = 7.0 Hz), 3.80 (s, 3H, OCH_3), 7.23 (m, 2H, H_{Ar}), 7.31 (d, 1H, H_{Ar}, J = 7.6 Hz), 7.48 (m, 1H, H_{Ar}), 7.82 (dd, 1H, H_{10}, J = 9.3 Hz, J = 0.8 Hz), 7.88 (dd, 1H, H_9, J = 9.3 Hz, J = 1.7 Hz), 8.20 (brs, 2H, NH^+, NH^+), 9.32 (dd, 1H, H_7, J = 1.7 Hz, J = 0.8 Hz). ^{13}C NMR (DMSO-d_6) δ 27.0, 37.6, 55.9, 109.9, 113.7, 117.1, 119.5, 121.6, 121.7, 128.5, 130.6, 134.3, 140.5, 144.0, 148.9, 159.8, 185.8. *MS (APCI+): m/z* 356.2, 358.1 $[M+H]^+$.

Synthesis of compound 11a by reduction of imine 10

8-Bromo-1-(3-methoxyphenyl)-3,4-dihydrodipyrido[1,2-*a*;4',3'-*d*]imidazole dihydrochloride (**10**) (0.50 g, 2.1 mmol) was dissolved in MeOH (2 0 mL). Sodium borohydride (0.15 g, 4.2 mmol) was then added and

the mixture was stirred for 4 h at room temperature. The solvent was then evaporated under reduced pressure. The residue was taken up in water (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The organic phase was washed with water (100 mL), dried over $MgSO_4$, filtered and evaporated. The resulting crude product was purified by chromatography on silica gel (40-63 mesh), eluting with CH_2Cl_2 / MeOH (97/3, v/v) to afford the desired compounds **11a** with 76% yield.

General procedure for the synthesis of compounds 11a-d using Pictet-Spengler methodology

In MeOH (20 mL), 2-(6-bromoimidazo[1,2-*a*]pyridin-2-yl)ethylamine (**6**) (0.5 g, 2.1 mmol), trifluoroacetic acid (0.25 mL, 3.2 mmol) and the desired susbtituted benzaldehyde (4.2 mmol) were added. The solution was refluxed (24 to 48 h). The resulting crude product was purified by chromatography on silica gel (40-63 mesh), eluting with CH_2Cl_2 / MeOH (97/3, v/v) to afford desired compounds **11a-d**.

8-Bromo-1-(3-methoxyphenyl)-1,2,3,4-tetrahydrodipyrido[1,2-*a*;4',3'-*d*]imidazole (11a)

Yield 74% (24 h), mp 148-149 °C, HPLC (C18, 35 min) PHPLC 98.9%, tR 7.8 min; HPLC (C4, 35 min) PHPLC 100%, tR 6.1 min. IR 3272 (NH), 1595 (CN). ^{1}H NMR ($CDCl_3$) δ 2.00 (brs, 1H, NH), 2.98 (m, 2H, CH_2), 3.15 (m, 1H, NCH_2), 3.30 (m, 1H, NCH_2), 3.78 (s, 3H, OCH_3), 5.20 (s, 1H, CH), 6.75 (m, 2H, H_{Ar}), 6.91 (ddd, 1H, H_{Ar}, J = 7.5 Hz, J = 2.2 Hz, J = 1 Hz), 7.17 (dd, 1H, H_9, J = 9.5 Hz, J = 1.8 Hz), 7.31 (d, 1H, H_{Ar}, J = 7.9 Hz), 7.39 (d, 1H, H_7, J = 1.8 Hz), 7.48 (d, 1H, H_{10}, J = 9.4 Hz). ^{13}C NMR ($CDCl_3$) δ 26.8, 41.5, 55.3, 56.0, 106.3, 113.7, 113.9, 117.6, 119.5, 120.1, 123.5, 126.9, 130.3, 140.9, 143.2, 143.6, 160.3. *MS (APCI+): m/z* 358.1, 360.2.

8-Bromo-1-(4-dimethylaminophenyl)-1,2,3,4-tetrahydrodipyrido[1,2-*a*;4',3'-*d*]imidazole (11b)

Yield 78% (24 h), mp 186-187 °C, HPLC (C18, 35 min) PHPLC 98.3%, tR 6.9 min; HPLC (C4, 35 min) PHPLC 100%, tR 5.6 min. IR 3289 (NH), 1612 (CN). ^{1}H NMR ($CDCl_3$) δ 1.80 (brs, 1H, NH), 2.96 (s, 6H, $N(CH_3)_2$), 3.00 (m, 2H, CH_2), 3.12 (m, 1H, NCH_2), 3.30 (m, 1H, NCH_2), 5.17 (s, 1H, CH), 6.70 (d, 2H, H_{Ar}, J = 8.6 Hz), 7.06 (d, 2H, H_{Ar}, J = 8.6 Hz), 7.16 (dd, 1H, H_9, J = 9.4 Hz, J = 1.6 Hz), 7.42 (s, 1H, H_7), 7.47 (d, 1H, H_{10}, J =9.4 Hz). ^{13}C NMR ($CDCl_3$) δ 26.9, 40.5, 41.5, 55.4, 106.0, 112.8, 117.5, 120.2, 123.7, 126.5, 126.7, 128.7, 143.1, 143.5, 150.6. *MS (APCI+): m/z* 371.2, 373.2.

8-Bromo-1-(4-nitrophenyl)-1,2,3,4-tetrahydrodipyrido[1,2-*a*;4',3'-*d*]imidazole (11c)

Yield 65% (48 h), mp 189-190 °C, HPLC (C18, 35 min) PHPLC 93.2%, tR 7.8 min; HPLC (C4, 35 min) PHPLC 96.1%, tR 5.5 min. IR 3350 (NH), 1602 (CN). ^{1}H NMR ($CDCl_3$) δ 2.10 (brs, 1H, NH), 3.03 (m, 2H, CH_2), 3.20 (m, 2H, NCH_2), 5.33 (s, 1H, CH), 7.15-7.38 (m, 4H, H_{Ar}, H_7, H_9), 7.50 (d, 1H, H_{10}, J = 9.4 Hz), 8.25 (d, 2H, H_{Ar}, J = 8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 26.7, 41.0, 54.9, 106.8, 117.9, 118.3, 122.8,

124.4, 127.5, 128.2, 129.1, 143.4, 144.1, 146.7. *MS (APCI+): m/z* 373.1, 375.

8-Bromo-1-(4-cyanophenyl)-1,2,3,4-tetrahydrodipyrido[1,2-*a*;4',3'-*d*]imidazole (11d)

Yield 69% (48 h), mp 204-205 °C, HPLC (C18, 35 min) PHPLC 100%, tR 6.8 min; HPLC (C4, 35 min) PHPLC 100%, tR 5.4 min. IR 3347 (NH), 1605 (CN). ^{1}H NMR ($CDCl_3$) δ 1.85 (brs, 1H, NH), 2.97 (m, 2H, CH_2), 3.17 (t, 2H, NCH_2, J = 5.6 Hz), 5.29 (s, 1H, CH), 7.22 (dd, 1H, H_9, J = 9.7 Hz, J = 1.5 Hz), 7.28 (m, 3H, H_{Ar}, H_7), 7.51 (d, 1H, H_{10}, J = 9.7 Hz), 7.68 (d, 2H, H_{Ar}, J =8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 26.7, 41.0, 55.2, 106.7, 112.5, 117.9, 118.2, 118.4, 122.9, 127.4, 128.9, 133.0, 143.4, 144.0, 144.8. *MS (APCI+): m/z* 353.2, 355.1.

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