Synthesis of 4,7,8a,9-Tetrahydro-3*H*-diimidazo-[1,5-*a*:4',5'-*d*]pyridine Derivatives

Miguel F. Braña*, Cristina Guisado, Javier Pérez-Castells and Leticia Pérez-Serrano.

Departamento de Química Orgánica y Farmacéutica,
Facultad de Ciencias Experimentales y de la Salud,
Universidad San Pablo CEU, Madrid, Spain.
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The synthesis and evaluation of new ligands for the H_3 receptor of histamine is described. These new compounds are diimidazopyridine derivatives readily prepared by a condensation reaction of spinacine and isocyanates.

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The action of histamine has been characterised pharmacologically as being mediated by three receptors, namely H_1, H_2 and H_3 receptors [1]. The most recently described, the H_3 receptor [2], appears to act as a presynaptic autoreceptor that inhibits histamine synthesis and release from neurones both in the central nervous system and peripherally [3]. The release of other neurotransmitters, such as acetylcholine, noradrenaline, dopamine, serotonin and neuropeptides, is also influenced by histamine H_3 heteroreceptors located on neurons thereof [4].

Considerable advances have been achieved in the medicinal chemical understanding of histamine pharmacology [5]. The therapeutic utility of selective histamine H_3 receptor antagonists has yet to be defined [6], but many applications can be devised for several diseases and conditions of the Central Nervous System (CNS), *e.g.* epilepsy, schizophrenia, arousal and sleep disorders, eating and drinking behaviour, memory and learning deficits and Alzheimer's disease [7].

In this work we describe the synthesis of 4,7,8a,9-tetrahydro-3*H*-diimidazo[1,5-*a*: 4',5'-*d*]pyridine derivatives as new ligands for the H_3 receptor of histamine (Figure 1). We have carried out the design of these new

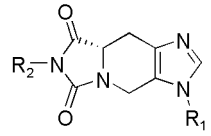


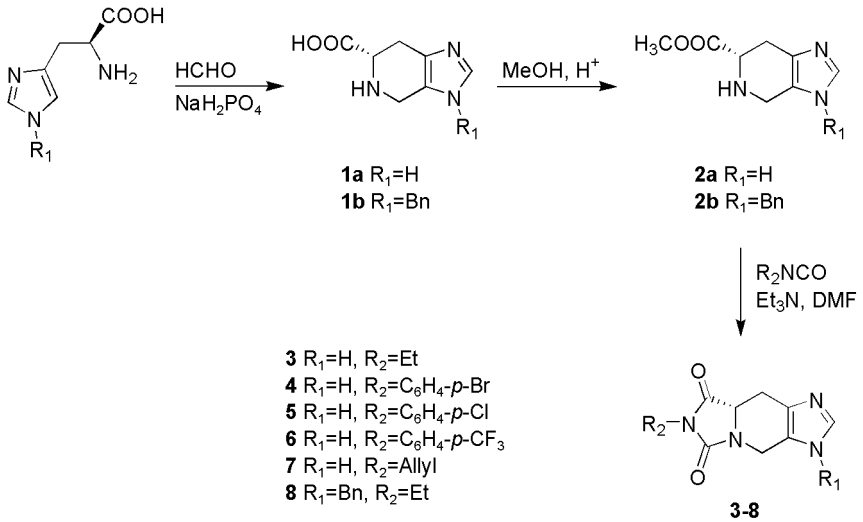
Figure 1

drugs by combining two important pharmacophores: the 4(5)-substitued imidazole, present in many H_3 antagonists, and the hydantoin unit, a moiety that is present in many well known anticonvulsants. This general approach has been used successfully by our group in the search for new drugs with CNS activity [8].

In addition, several substituents that tend to exert electronic, lipophilic and steric influences on these histamine analogs have been introduced on the hydantoin ring. These changes are expected to influence the biological activities of these derivatives.

The 4,5,6,7-tetrahydro-3*H*-imidazo [4,5-*c*] pyridine-6-carboxilic acids **1a-b** were obtained by Pictet-Spengler condensation between L-histidine or N_{im}-benzyl-L-histidine with formaldehyde at pH 7 according to literature procedures

Scheme 1

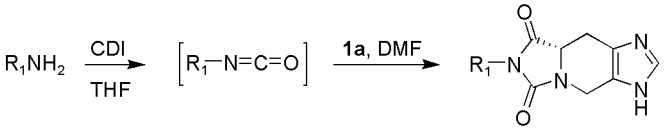


(Scheme 1) [9]. Their methyl esters **2a-b** were prepared by a variation of the reported procedures starting from **1a-b** [9,10]. Thus, treatment of **1a** with methanol and HCl concentrated for 72 hours at reflux temperature afforded **2a** (90%). The same treatment of **1b** afforded **2b** (95%).

Compounds **3-8** were synthesized by reaction of the spinacine methyl ester **2a** or its 3-benzyl derivative **2b** with the appropriate isocyanate and triethylamine in dimethylformamide (DMF) at 60 °C (Scheme 1). We found a slight improvement in yield when using methyl esters **2a-b** as starting material, instead of carboxilic acids **1a-b**. The products were obtained in good yields. All of them showed good water solubility, except compound **8,** which could not be evaluated because of that reason.

The synthesis of compounds **9-11** involved the preparation of suitable isocyanate. These were readily generated *in situ*, from the corresponding amines and carbonyl diimidazole (CDI) in anhydrous tetrahydrofurane (THF), according to a general procedure for similar compounds [11]. The target compounds were prepared by the addition of the isocyanate to a solution of spinacine **1a** in anhydrous dimethylformamide, under an argon atmosphere at reflux temperature (Scheme 2). These products were obtained with lower yields than the former ones, as several byproducts, which are not easy to separate, are formed in the course of the reaction. All of them showed good water solubility.

Scheme 2



9-11

9 R_1=$CH_2CH_2N(CH_3)_2$
10 R_1=$CH_2CH_2CH_2N(CH_3)_2$
11 R_1=$CH_2CH_2N(CH_2CH_3)_2$

The histamine H_3 receptor activity of these compounds was determined on a *in vitro* assay on the basis of the inhibitory effect of histamine H_3 receptor agonists on electrically-evoked contractions (induced by endogenous acetylcholine release) of guinea pig intestine preparations [12]. All the compounds tested did not show either remarkable agonist or antagonist activity on the histamine H_3 receptor (data not shown).

EXPERIMENTAL

Melting points were determined on a Büchi 530 apparatus and were uncorrected. IR spectra were recorded on a Perkin Elmer 1330 infrared spectrophotometer as potassium bromide pellets. NMR spectra were determined on a Bruker AM-300 instrument. Chemical shifts for hydrogen and carbon are reported in ppm (δ) relative to tetramethylsilane, using DMSO-d_6 and $CDCl_3$ as solvents. Merck silica gel (230-400 mesh) was used for flash chromatography. Elemental analyses were performed in the UCM Microanalysis Service (Facultad de Farmacia, Universidad Complutense de Madrid, Spain) and agreed with theoretical values to within ±0.4%. Optical rotations were run on a Belligham Stanley ADP 220 polarimeter.

The following products were prepared according to literature [9,10]: spinacine (4,5,6,7-Tetrahydro-3*H*-imidazo[4,5-*c*]-pyridine-6-carboxylic acid) **1a**, N_{im}-benzyl-spinacine **1b**, spinacine methyl ester **2a** and N_{im}-benzyl-spinacine methyl ester **2b**.

General Procedure for the Preparation of the 7-Alkyl or Aryl-4,7,8a,9-tetrahydro-3*H*-diimidazo [1,5-*a*:4',5'-*d*] pyridine-6,8-dione Derivatives **3-8**.

The appropriate isocyanate (5.5 mmol) was added to a solution of spinacine methyl ester **2a** or **2b** (5.5 mmol) and triethylamine (5.5 mmol) in DMF (15ml). The reaction mixture was heated at 60 °C for 24 hours. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography (eluent, $CHCl_3$:MeOH).

(8a*S*)-7-Ethyl-4,7,8a,9-tetrahydro-3*H*-diimidazo [1,5-*a*:4',5'-*d*] pyridine-6,8-dione (**3**).

This compound was obtained in 40% yield, mp 120-122 °C (hexane). IR υ cm^{-1}: 3450, 1760, 1700. ^{1}H-NMR (DMSO-d_6): δ 1.04 (t, 3H, *J* = 7.0 Hz.), 2.71 (dd, 1H, *J* = 14.6 Hz., *J* = 6.0 Hz.), 2.99 (dd, 1H, *J* = 14.6 Hz., *J* = 6.0 Hz.), 3.44 (q, 2H, *J* = 7.0 Hz.), 4.14 (d, 1H, *J* = 15.2 Hz.), 4.38 (dd, 1H, *J* = 11.0 Hz., *J* = 6.0 Hz.), 4.64 (d, 1H, *J* = 15.2 Hz.), 7.59 (s, 1H). ^{13}C-NMR (DMSO-d_6): δ 15.7, 23.5, 32.9, 34.0, 54.5, 135.2, 154.5, 172.1. α_D = -100° (c 0.20, H_2O).

Anal. Calcd. for $C_{10}H_{12}N_4O_2 \cdot 3H_2O$: C, 43.79; H, 6.56; N, 20.43. Found: C, 43.40; H, 6.64; N, 20.69.

(8a*S*)-7-(4'-Bromophenyl)- 4,7,8a,9-tetrahydro-3*H*-diimidazo [1,5-*a*:4',5'-*d*]pyridine-6,8 dione (**4**).

This compound was obtained in 42% yield, mp 135-140 °C (toluene/hexane). IR υ cm^{-1}: 3110, 1770, 1710. ^{1}H-NMR ($CDCl_3$): δ 2.94 (dd, 1H, *J* = 15.1 Hz., *J* = 10.7 Hz.), 3.31 (dd, 1H, *J* = 15.1 Hz., *J* = 5.5 Hz.), 4.35 (d, 1H, *J* = 14.6 Hz.), 4.41 (dd, 1H, *J* = 10.7 Hz., *J* = 5.5 Hz.), 5.05 (d, 1H, *J* = 14.6 Hz.), 7.36 (d, 2H, *J* = 8.8 Hz.), 7.60 (d, 2H, *J* = 8.8 Hz.), 7.63 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 22.9, 37.5, 53.7, 120.0, 124.0, 126.6, 127.7, 129.8, 130.7, 134.1, 152.2, 169.9. α_D = -80.9° (c 0.21, $CHCl_3$).

Anal. Calcd. for $C_{14}H_{11}N_4O_2Br \cdot 1.5H_2O$: C, 45.04; H, 3.75; N, 15.01. Found: C, 45.36; H, 3.21; N, 14.65.

(8a*S*)-7-(4'-Chlorophenyl)-4,7,8a,9-tetrahydro-3*H*-diimidazo-[1,5-*a*:4',5'-*d*]pyridine-6,8-dione (**5**).

This compound was obtained in 36% yield, mp 150 °C (dc.) (toluene/hexane). IR υ cm^{-1}: 3115, 1775, 1710. ^{1}H-NMR ($CDCl_3$): δ 2.91 (dd, 1H, *J* = 15.1 Hz., *J* = 11.0 Hz.), 3.27 (dd, 1H, *J* = 15.1 Hz., *J* = 5.5 Hz.), 4.32 (d, 1H, *J* = 15.4 Hz.), 4.40 (dd, 1H, *J* = 11.0 Hz., *J* = 5.5 Hz.), 5.00 (d, 1H, *J* = 15.4 Hz.), 7.38 (d, 2H, *J* = 9.3 Hz.), 7.43 (d, 2H, *J* = 8.8 Hz.), 7.60 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 24.4, 38.7, 54.9, 127.2, 128.2, 129.0, 129.3, 129.9, 134.0, 135.4, 153.7, 170.7. α_D = -24.5° (c 0.20, $CHCl_3$).

Anal. Calcd. for $C_{14}H_{11}N_4O_2Cl \cdot 1.4H_2O$: C, 51.27; H, 4.21; N, 17.09. Found: C, 51.68; H, 3.99; N, 16.52.

(8a*S*)-7-(4'-Trifluoromethylphenyl)-4,7,8a,9-tetrahydro-3*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8-dione (**6**).

This compound was obtained in 40% yield, mp 130 °C (dc.)(toluene/hexane). IR υ cm^{-1}: 3110, 1780, 1710. ^{1}H-NMR ($CDCl_3$): δ 2.97 (dd, 1H, *J* = 14.8 Hz., *J* = 11.0 Hz.), 3.34 (dd, 1H, *J* = 14.8 Hz., *J* = 4.9 Hz.), 4.38 (d, 1H, *J* = 15.4 Hz.), 4.44 (dd, 1H, *J* = 11.0 Hz., *J* = 4.9 Hz.), 5.07 (d, 1H, *J* = 15.4 Hz.), 7.64 (s, 1H), 7.65 (d, 2H, *J* = 8.5 Hz.), 7.75 (d, 2H, *J* = 8.5 Hz.). ^{13}C-NMR ($CDCl_3$): δ 24.4, 38.8, 54.8, 122.9, 123.6 (q, *J* = 270.9 Hz.), 125.9, 126.2 (q, *J* = 3.7 Hz.), 128.3, 130.0 (q, *J* = 32.9 Hz.), 134.5, 135.4, 153.4, 170.5. α_D = -21.05° (c 0.19, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{11}N_4O_2F_3 \cdot 1.5H_2O$: C, 49.58; H, 3.86; N, 15.42. Found: C, 49.57; H, 3.86; N, 15.46.

(8a*S*)-7-Allyl- 4,7,8a,9-tetrahydro-3*H*-diimidazo[1,5-*a*:4',5'-*d*]-pyridine-6,8-dione (**7**).

This compound was obtained in 53% yield, mp 48-50 °C (toluene). IR υ cm^{-1}: 3110, 1780, 1710. ^{1}H-NMR ($CDCl_3$): δ 2.79 (dd, 1H, *J* = 14.8 Hz., *J* = 11.2 Hz.), 3.23 (dd, 1H, *J* = 14.8 Hz., *J* = 5.2 Hz.), 4.16 (d, 1H, *J* = 5.5 Hz.), 4.23-4.30 (m, 2H), 4.96 (d, 1H, *J* = 15.4 Hz.), 5.21 (d, 1H, *J* = 7.7 Hz.), 5.26 (d, 1H, *J* = 14.3 Hz.), 5.80-5.89 (m, 1H), 7.62 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 24.3, 38.4, 40.8, 55.0, 118.1, 123.2, 128.2, 131.0, 135.3, 154.8, 171.8. α_D = -121.4° (c 0.21, $CHCl_3$).

Anal. Calcd. for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 57.22; H, 5.55; N, 23.73.

(8a*S*)-3-Bencyl-7-ethyl-4,7,8a,9-tetrahydro-3*H*-diimidazo-[1,5-*a*:4',5'-*d*]pyridine-6,8-dione (**8**).

This compound was obtained in 40% yield, mp 188-190 °C (hexane). IR υ cm^{-1}: 3080, 1760, 1700. ^{1}H-NMR (DMSO-d_6): δ 1.07 (t, 3H, *J* = 5.5 Hz.), 2.57 (dd, 1H, *J* = 10.4 Hz., *J* = 5.5 Hz.), 2.89 (dd, 1H, *J* = 10.4 Hz., *J* = 5.5 Hz.), 3.40 (q, 2H, *J* = 6.7 Hz.), 3.97 (d, 1H, *J* = 15.2 Hz.), 4.31 (dd, 1H, *J* = 11.3 Hz., *J* = 5.5 Hz.), 4.60 (d, 1H, *J* = 15.2 Hz.), 5.16 (d, 1H, *J* = 15.8 Hz.), 5.24 (d, 1H, *J* = 15.8 Hz.), 7.22 (d, 2H, *J* = 7.9 Hz.), 7.36-7.39 (m, 3H), 7.78 (s, 1H). ^{13}C-NMR (DMSO-d_6): δ 13.3, 25.5, 32.9, 35.9, 47.8, 54.7, 121.3, 127.4, 127.8, 128.8, 132.3, 136.7, 137.6, 154.5, 172.1. α_D = -100.0° (c 0.02, MeOH).

Anal. Calcd. for $C_{17}H_{18}N_4O_2 \cdot 1.1H_2O$: C, 61.85; H, 6.12; N, 16.97. Found: C, 61.75; H, 6.07; N, 16.89.

General Procedure for the Preparation of the 4,7,8a,9-Tetrahydro-7-alkyl-3*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8-dione Derivatives **9-11**.

A solution of carbonyl diimidazole (18.54 mmol) in dry THF (50 ml) was added drop wise to the appropriate amine (18.54 mmol) and the reaction mixture was stirred at room temperature for 4-10 hours (TLC analysis). Then, it was added to a solution of spinacine (18.54 mmol) in dry DMF (100 ml). The reaction mixture was refluxed for 72 hours. After removal of the solvent, the residue was purified by flash chromatography (eluent, AcOEt: MeOH).

(8a*S*)-7-(2-Dimethylaminoethyl)-4,7,8a,9-tetrahydro-3*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8-dione (**9**).

This compound was obtained in 30% yield, mp 125-127 °C (ethyl acetate/hexane). IR υ cm^{-1}: 3300, 1770, 1710. ^{1}H-NMR ($CDCl_3$): δ 2.31 (s, 6H), 2.60-2.69 (m, 3H), 3.14 (dd, 1H, *J* = 14.8 Hz., *J* = 5.5 Hz.), 3.69 (t, 2H, *J* = 6.0 Hz.), 4.13-4.30 (m, 3H), 4.87 (d, 1H, *J* = 15.4 Hz.), 7.57 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 24.1, 36.3, 38.2, 45.1, 54.8, 56.4, 123.3, 127.6, 135.5, 154.9, 172.3. α_D = +10.10° (c 0.20, $CHCl_3$).

Anal. Calcd. for $C_{12}H_{17}N_5O_2 \cdot 1.2H_2O$: C, 50.59; H, 6.81; N, 24.59. Found: C, 50.55; H, 6.70; N, 24.62.

(8a*S*)-7-(3-Dimethylaminopropyl)-4,7,8a,9-tetrahydro-3*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8-dione (**10**).

This compound was obtained in 13% yield, mp 132-134 °C (ethyl acetate/chloroform). IR υ cm^{-1}: 3250, 1770, 1710. ^{1}H-NMR ($CDCl_3$): δ 1.80-1.85 (m, 2H), 2.24 (s, 6H), 2.37 (t, 2H, *J* = 7.1 Hz.), 2.76 (dd, 1H, *J* = 15.4 Hz., *J* = 10.5 Hz.), 3.19 (dd, 1H, *J* = 15.4 Hz., *J* = 6.0 Hz.), 3.60 (t, 2H, *J* = 7.1 Hz.), 4.20-4.28 (m, 2H), 4.93 (d, 1H, *J* = 13.3 Hz.), 7.59 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 24.1, 25.8, 36.8, 38.2, 44.9, 54.8, 56.4, 123.2, 127.6, 135.3, 154.9, 172.2. α_D = +94.7° (c 0.11, $CHCl_3$).

Anal. Calcd. for $C_{13}H_{19}N_5O_2 \cdot 1.7H_2O$: C, 50.71; H, 7.28; N, 22.75. Found: C, 50.87; H, 7.13; N, 22.29.

(8a*S*)-7-(3-Diethylaminoethyl)-4,7,8a,9-tetrahydro-3*H*-diimidazo[1,5-*a*:4',5'-*d*]pyridine-6,8-dione (**11**).

This compound was obtained in 20% yield, mp 107-110 °C (ethyl acetate/hexane). IR υ cm^{-1}: 3280, 1760, 1700. ^{1}H-NMR ($CDCl_3$): δ 1.10 (t, 6H, *J* = 7.1 Hz.), 2.75 (q, 4H, *J* = 7.1 Hz.), 2.83-2.85 (m, 3H), 3.20 (dd, 1H, *J* = 14.8 Hz., *J* = 5.5 Hz.), 3.72 (t, 2H, *J* = 6.6 Hz.), 4.23-4.29 (m, 2H), 4.92 (d, 1H, *J* = 15.4 Hz.), 7.60 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ 11.5, 24.2, 36.5, 38.4, 46.9, 49.7, 55.0, 123.2, 128.4, 135.3, 155.1, 172.4. α_D = +16.5° (c 0.18, $CHCl_3$).

Anal. Calcd. for $C_{14}H_{21}N_5O_2 \cdot 0.4H_2O$: C, 56.34; H, 7.31; N, 23.47. Found: C, 56.51; H, 7.09; N, 23.72.

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