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ORIGINAL PAPER

Exploring 6-(substituted sulfonyl)imidazopyridines as a potential scaffold for the design of 5-HT_6 ligands

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Abstract Cognitive dysfunction is a characteristic of various forms of dementia such as Alzheimer's disease. We have focused on the 5-HT_6 receptor in order to identify potent ligands. Herein we report the design of a novel series of 6-sulfonylimidazole derivatives substituted with an alkylamino chain at the 2- or 3-position, their synthesis, and their ability to interact with 5-HT_6 receptors as evaluated in radioligand binding assays.

Keywords Bioorganic chemistry · Heterocycles · Receptors · Tin compounds

Introduction

Serotonin 5-HT_6 receptors have attracted considerable interest owing to their high affinity toward a wide range of psychiatric drugs and their specific distribution in the brain regions associated with learning and memory such as the cerebral cortex, hippocampus and striatum [1, 2]. The 5-HT_6 receptor was first cloned in 1993 and is one of the most recently discovered 5-HT receptor subtypes. It is positively coupled to adenylate cyclase and appears to regulate glutaminergic, cholinergic and dopaminergic neuronal activity, together with learning-associated neuronal remodelling [3]. This modulatory activity suggests the potential application for 5-HT_6 receptor antagonists in the treatment of cognitive impairments associated with Alzheimer's disease (AD) and schizophrenia. Thus, research efforts led to the discovery of 5-HT_6 ligands which have already entered clinical trials for anxiety and cognitive impairment associated with these diseases and displayed encouraging results [4]. A great number of agonist and antagonist 5-HT_6 ligands (Fig. 1) have been reported, and many of them are built around an indole scaffold, such as MS-245 [5, 6], E-6837 [7] and WAY-466 [8].

The purpose of our present study was to identify novel, potent 5-HT_6 antagonists for potential use in the treatment of AD. In the course of our extensive studies on the chemistry and pharmacological reactivities, the indole moiety was replaced by its isostere imidazopyridine, possessing a bridgehead nitrogen atom. Imidazopyridine derivates **12–15** were designed (Fig. 1). As described for 5-HT_6 ligands, they were characterized by the presence of some important structural requirements, such as an aminoethyl side chain in position 2 or 3 of the imidazopyridine and an arylsulfonyl moiety on the other side of the scaffold at the 6-position [4]. The affinity of the synthesized compounds for the human recombinant 5-HT_6 receptor was evaluated.

Results and discussion

In order to build the imidazopyridine central core, various conditions have been reported [9]. The reaction was attempted in one step by refluxing commercially available 2-amino-5-bromopyridine (**1**) in ethanol or butanol with the corresponding 1-bromoacetone **2** or 2-bromoaldehyde **3**. Under these conditions, 2-amino-5-bromopyridine was

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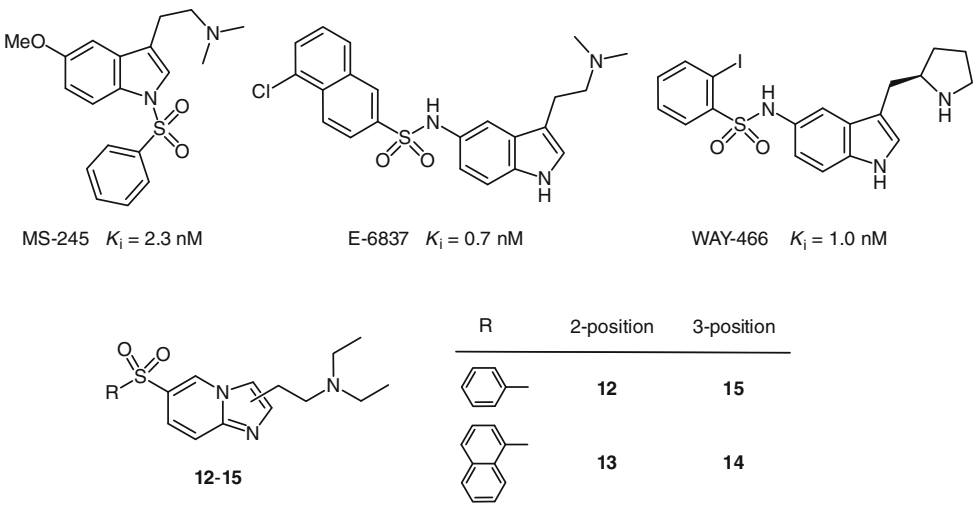
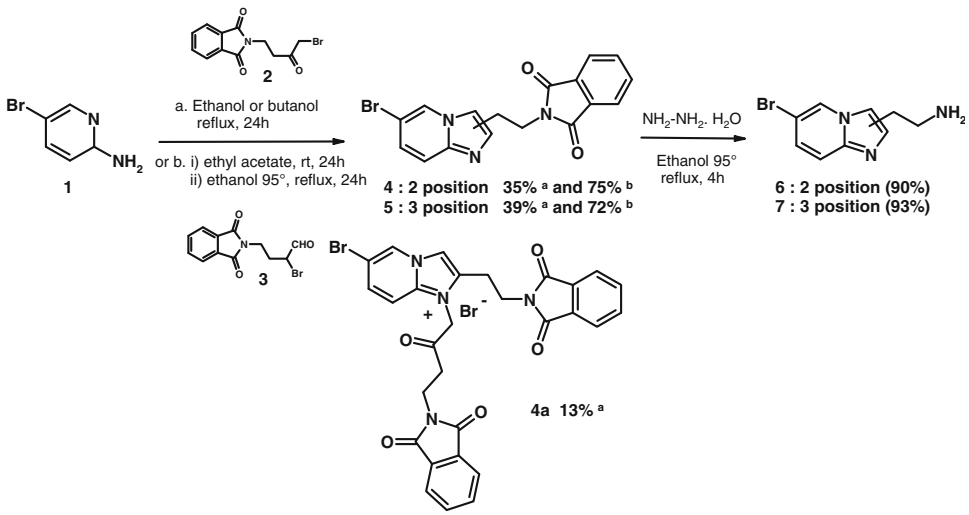


Fig. 1 Structures of some 5-HT_6 ligands and target compounds **12–15**

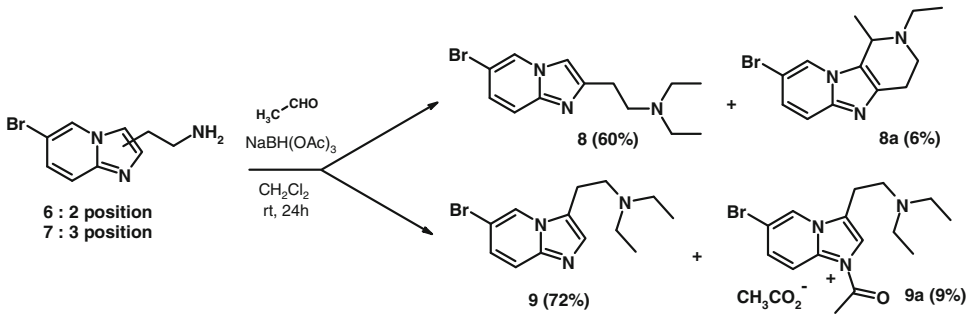
not totally consumed, the purification of reaction media was difficult and the desired compounds **4** and **5** were obtained in low yields of 35 and 39 %, respectively. Furthermore, the formation of side products was observed (Scheme 1). During the synthesis of compound **4**, by-product **4a** was isolated in 13 % yield, owing to a competing *N*-alkylation reaction of substituted imidazopyridine. To overcome this limitation, we turned our attention to the well-known two-step synthesis of imidazopyridine involving the formation and isolation of pyridinium salts. The first step was carried out in ethyl acetate (preferred to the commonly used 1,2-dichloroethane), with 2-amino-5-bromopyridine and the corresponding 1-bromoacetone or 2-bromoaldehyde compounds **2** or **3**. After stirring for 1 day at room temperature, the starting material **1** was totally reacted and the bromide intermediates were filtered, washed with ethyl acetate and then refluxed for the second step in ethanol. This methodology avoided the formation of *N*-alkylated by-products and afforded imidazopyridine compounds **4** and **5** in good yields of 75 and 72 %, respectively (Scheme 1). Deprotection of the phthalimide group was classically performed with hydrazine hydrate in ethanol to give the corresponding ethylamino compounds **6** and **7** [10]. Treatment with ethyl acetate and purification by chromatography on silica gel furnished compounds **6** and **7** in excellent yields of 90 and 93 %, respectively. It is worth emphasising that no water was used in the treatment to eliminate the amine and form phthalhydrazide; indeed we observed that the compounds were partially soluble in water and could not be totally extracted with an organic phase. Under such conditions the yield dropped to 50 and 60 %, respectively.

A reductive amination in dichloromethane with acetaldehyde and $NaBH(OAc)_3$ as the reducing reagent (3 eq) afforded compounds **8** and **9** (Scheme 2). In the series substituted at the 2-position with ethylamino chain (**6**), the reaction gave the desired compound **8** in low yield (30 %) and a by-product **8a** (16 %). When the amount of

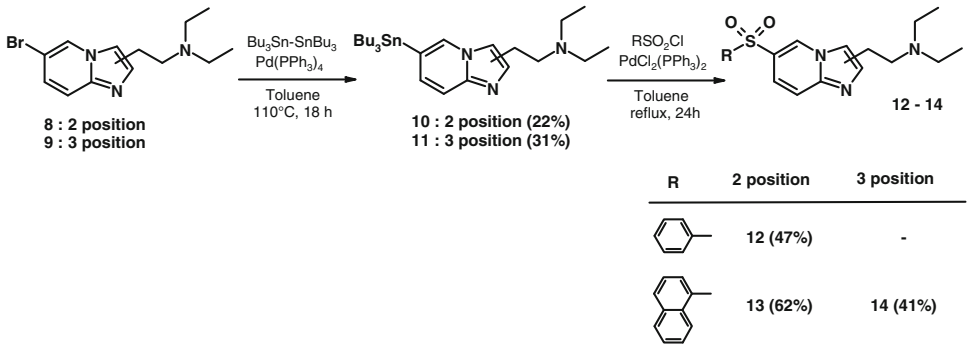
Scheme 1



Scheme 2



Scheme 3



R	2 position	3 position
	12 (47%)	-
	13 (62%)	14 (41%)

$NaBH(OAc)_3$ was increased to 5 eq, the yield of compound **8** increased to 60 % and that of side product **8a** decreased (6 %). The formation of side product **8a** could be explained according to a Pictet–Spengler reaction. Thus, an ethyl group was introduced at the nitrogen atom by reductive amination and a Pictet–Spengler reaction between the intermediate derivative and acetaldehyde occurred at the 3-position of the imidazopyridine. The higher reactivity of the position 3 of imidazopyridine has already been reported [11, 12]. In the second series, with the 3-position substituted by ethylamino chain (**7**), reductive amination in dichloromethane with acetaldehyde and $NaBH(OAc)_3$ (5 eq) afforded the corresponding derivative **9** in 72 % yield and a by-product **9a** (5 %). In these conditions, the 2-position could not react, and this position is slightly reactive [13]. The formation of side product **9a** could be explained by an additional nucleophilic substitution at the 1-position of the imidazopyridine with an acetyl group which could come from the reducing agent $NaBH(OAc)_3$. The structure of compound **9a** was confirmed by full spectral data (^1H, ^{13}C, COSY, HMBC, HSQC).

Starting from derivatives **8** and **9**, the Stille reaction afforded intermediates **10** and **11**. Working in dry toluene under inert atmosphere with tetrakis(triphenylphosphine)palladium and hexabutylditin provided the best results but, unfortunately, only low yields of 22 and 31 %, respectively, were obtained (Scheme 3) [14]. Indeed, we observed degradation of the reaction media and formation of reduced by-products without a bromo atom or tributyltin group at the 6-position. The coupling reaction with 5-tri-*n*-butyltin derivatives **10** and **11** in dry toluene under inert atmosphere with dichloro(diphenylphosphine)palladium and the desired chlorosulfonyl reagent afforded the corresponding products **12–14** [15]. In the series substituted at the 3-position, starting from compound **11**, the final product **15** with a phenylsulfonyl group at the 6-position could never be obtained, and we could only isolate imidazopyridine product without the tributyltin group.

The affinity of the synthesized compounds for the human 5-HT_6 receptor was determined using [^{3}H]-lysergic acid diethylamide (LSD) as the radioligand (Table 1). Indeed, compounds **12** and **13**, with a diethylaminoethyl chain at the 2-position, inhibited 5 and 14 % of specific binding at 1 μM (relative to control), respectively. Derivative **14** presented higher activity with 38 % inhibition. The presence of the diethylamino chain at the 3-position of the imidazopyridine (**10**) seemed to be favourable,

Table 1 5-HT_6 receptor binding assays of synthesized compounds (**12–14**)

Compound	Inhibition of control specific binding/%[a]
12	5
13	14
14	38

[a] Competition binding assay at 1 μM giving the displacement (%) of compounds (radioligand, [^{3}H]-LSD; $n = 3$)

compared with compounds **12** and **13** with a diethylamino chain at the 2-position. Nevertheless, these new compounds exhibited much lower affinities than many known ligands which have nanomolar activities.

Conclusion

Novel imidazopyridine compounds were designed according to a 5-HT_6 pharmacophore model, synthesized and evaluated. These derivatives (**12–14**) have an aminoethyl side chain in position 2 or 3 of the imidazopyridine and an aryl sulfonyl moiety on the other side of the scaffold at the 6-position. Unfortunately, this novel series presented only low affinities for the 5-HT_6 receptor. Other work in our laboratory will involve the variation of the position of the arylsulfonyl moiety on the imidazopyridine, together with the reversion of the sulfonyl function. Taking into account the results of this study, the synthesis of compounds substituted with an aminoethyl side chain in position 3 of the imidazopyridine will be favoured.

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 on a Büchi 510 capillary apparatus. ^{1}H 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*.

6-Bromo-2-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-ethyl]-1-[4-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-2-oxobutyl]imidazo[1,2-a]pyridinium bromide
(**4a**, $C_{29}H_{22}Br_2N_4O_5$)
2-Amino-5-bromopyridine (2.3 g, 13.2 mmol) and 3.3 g 2-(4-bromo-3-oxobutyl)-1*H*-isoindole-1,3(2*H*)-dione (11.0 mmol) were added to 100 cm^3 ethanol or butanol. The mixture was refluxed for 24 h. The solution was evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel (40–63 mesh), eluting with dichloromethane/methanol (95:5, v/v). Yield 13 %; m.p.: 176–177 °C; $R_f = 0.2$ (dichloromethane/methanol 90:10, v/v); ^{1}H NMR (DMSO-d_6): $\delta = 3.15$ (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, 1.8 Hz), 8.29 (s, 1H, H_3), 9.35 (d, 1H, H_5, $J = 1.8$ Hz) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 23.0, 33.0, 36.0, 38.0, 54.0, 112.0, 113.5, 114.0, 123.7, 124.0, 130.3, 132.4, 132.6, 135.3, 135.6, 137.0, 137.3, 139.6, 170.0, 201.0$ ppm; MS (APCI+): $m/z = 585.2, 587.3$ ($[M + H]^+$).

*General procedure for the synthesis of compounds **4** and **5***

2-Amino-5-bromopyridine (6.9 g, 39.7 mmol) and 9.8 g 2-bromo-4-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)butyraldehyde or 2-(4-bromo-3-oxobutyl)-1*H*-isoindole-1,3(2*H*)-dione (33.1 mmol) were added to 100 cm^3 ethyl acetate. The mixture was stirred for 1 day at room temperature. The precipitate was filtered and washed with 200 cm^3 ethyl acetate. The product was solubilised in 150 cm^3 95 % ethanol and refluxed for 24 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The residue obtained was dissolved in 100 cm^3 of an aqueous solution of 5 % potassium carbonate and extracted with dichloromethane (2 × 100 cm^3). 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]-1H-isoindole-1,3(2H)-dione (**4**, $C_{17}H_{12}BrN_3O_2$)
Yield 75 %; m.p.: 195–196 °C; $R_f = 0.3$ (dichloromethane/methanol 94:6, v/v); ^{1}H NMR (DMSO-d_6): $\delta = 3.00$ (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, 2.0 Hz), 7.40 (dd, 1H, H_8, $J = 9.6$ Hz, 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, 0.8 Hz) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 24.6, 36.9, 110.7, 113.5, 113.6, 123.6, 129.4, 132.0, 134.9, 135.9, 140.0, 138.6, 168.2$ ppm; MS (APCI+): $m/z = 370.2, 372.3$ ($[M + H]^+$).

2-[2-(6-Bromoimidazo[1,2-a]pyridin-3-yl)ethyl]-1H-isoindole-1,3(2H)-dione (**5**, $C_{17}H_{12}BrN_3O_2$)
Yield 72 %; m.p.: 172–173 °C; $R_f = 0.4$ (dichloromethane/methanol 94:6, v/v); ^{1}H NMR (DMSO-d_6): $\delta = 3.35$ (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, 1.8 Hz), 9.40 (d, 1H, H_4, $J = 1.8$ Hz) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 22.7, 34.8, 111.4, 114.1, 122.1, 123.6, 125.0, 127.7, 131.9, 135.0, 136.0, 138.9, 168.0$ ppm; MS (APCI+): $m/z = 369.9, 371.9$ ($[M + H]^+$).

*General procedure for the synthesis of compounds **6** and **7***

2-[2-(6-Bromoimidazo[1,2-*a*]pyridin-2-yl or -3-yl)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (1.41 g, 3.81 mmol) and 0.95 g hydrazine monohydrate (19 mmol) were added to 50 cm^3

95 % ethanol. The solution was refluxed for 4 h. After cooling to room temperature, the reaction mixture was evaporated under reduced pressure. The precipitate obtained was triturated with ethyl acetate (2 × 100 cm^3) and filtered. The filtrate was evaporated under reduced pressure and the oily residue was washed with ethyl ether (3 × 50 cm^3). The resulting crude product was purified by chromatography on silica gel (40–63 mesh), eluting with dichloromethane/methanol (95:5, v/v). The products were solubilized in dry ethyl acetate and treated with 20 cm^3 gaseous hydrochloric acid in diethyl ether. The obtained precipitate was filtered and washed with ethyl acetate (2 × 20 cm^3) to afford the desired compounds.

2-(6-Bromoimidazo[1,2-a]pyridin-2-yl)ethanamine dihydrochloride (**6**, $C_9H_{12}BrCl_2N_3$)
Yield 90 %; m.p.: 192–193 °C; $R_f = 0.2$ (dichloromethane/methanol 85:15, v/v); ^{1}H NMR (DMSO-d_6): $\delta = 3.14$ (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, 1.6 Hz), 8.17 (s, 1H, H_2), 8.35 (brs, 3H, NH^+, NH_2), 9.38 (s, 1H, H_5) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 23.7$, 37.9, 110.1, 113.8, 113.9, 129.1, 135.0, 135.3, 139.3 ppm; MS (APCI+): $m/z = 240.0$, 242.0 ($[M + H]^+$).

2-(6-Bromoimidazo[1,2-a]pyridin-3-yl)ethanamine dihydrochloride (**7**, $C_9H_{12}BrCl_2N_3$)
Yield 93 %; m.p.: 95–96 °C; $R_f = 0.2$ (dichloromethane/methanol 85:15, v/v); ^{1}H NMR (DMSO-d_6): $\delta = 2.85$ (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, 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) ppm; ^{13}C NMR (DMSO-d_6): $\delta = 21.2$, 36.4, 111.1, 114.1, 122.9, 123.5, 127.8, 135.6, 139.2 ppm; MS (APCI+): $m/z = 240.0$, 242.0 ($[M + H]^+$).

*General procedure for the preparation of products **8** and **9***

In 15 cm^3 dichloromethane 1.5 g 2-(6-bromoimidazo[1,2-*a*]-pyridin-2-yl or -3-yl)ethanamine (6.2 mmol), 1.4 g acetaldehyde (31 mmol) and 6.6 g $NaBH(OAc)_3$ (31 mmol) were stirred at room temperature under inert atmosphere for 24 h. The reaction mixture was quenched by adding 20 cm^3 aqueous 1 M NaOH and the product was extracted with dichloromethane. The product was purified by chromatography on silica gel using dichloromethane/methanol (95:5, v/v) to afford oily products.

2-(6-Bromo-1H-imidazo[1,2-a]pyridin-2-yl)-N,N-diethylethanamine (**8**, $C_{13}H_{18}BrN_3$)
Yield 60 %; $R_f = 0.4$ (dichloromethane/methanol 90:10, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 1.06$ (t, 6H, CH_3, $J = 7.2$ Hz), 2.65 (q, 4H, NCH_2, $J = 7.2$ Hz), 2.95 (m, 4H, CH_2, NCH_2), 7.13 (dd, 1H, H_7, $J = 9.6$ Hz, 1.8 Hz), 7.36 (d, 1H, H_8, $J = 9.6$ Hz), 7.39 (s, 1H, H_3), 8.16 (dd, 1H, H_5, $J = 1.8$ Hz, 0.7 Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.4$, 26.1, 46.8, 52.3, 106.4, 109.8, 117.4, 125.4, 127.4, 143.3, 146.7 ppm; MS (APCI+): $m/z = 296.0$, 298.0 ($[M + H]^+$).

8-Bromo-2-ethyl-1,2,3,4-tetrahydro-1-methyldipyrido[1,2-a:4′,3′-d]imidazole (**8a**, $C_{13}H_{16}BrN_3$)
Yield 6 %; $R_f = 0.6$ (dichloromethane/methanol 90:10, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 1.11$ (t, 3H, CH_3, $J = 7.1$ Hz), 1.32 (d, 3H, CH_3, $J = 6.7$ Hz), 2.62 (m, 3H, CH_2), 2.96 (m, 2H, CH_2), 3.09 (m, 1H, CH_2), 4.05 (q, 1H, CH, $J = 6.7$ Hz), 7.10 (dd, 1H, H_7, $J = 9.5$ Hz, 1.8 Hz), 7.37 (d, 1H, H_8, $J = 9.5$ Hz), 7.86 (d, 1H, H_5, $J = 1.1$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.3$, 15.4, 22.8, 43.2, 46.9, 49.7, 106.3, 117.1, 122.6, 123.1, 126.4, 104.7, 142.9 ppm; MS (APCI+): $m/z = 294.2$, 296.2 ($[M + H]^+$).

2-(6-Bromo-1H-imidazo[1,2-a]pyridin-3-yl)-N,N-diethylethanamine (**9**, $C_{13}H_{18}BrN_3$)
Yield 72 %; $R_f = 0.5$ (dichloromethane/methanol 85:15, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 1.00$ (t, 6H, CH_3, $J = 7.1$ Hz), 2.60 (q, 4H, NCH_2, $J = 7.1$ Hz), 2.76 (t, 2H, CH_2, $J = 6.6$ Hz), 2.95 (t, 2H, NCH_2, $J = 6.9$ Hz), 7.13 (dd, 1H, H_7, $J = 9.6$ Hz, 1.8 Hz), 7.37 (s, 1H, H_2), 7.43 (d, 1H, H_8, $J = 9.6$ Hz), 8.18 (d, 1H, H_5, $J = 1.6$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 11.6$, 22.3, 46.8, 51.0, 106.7, 118.3, 123.6, 123.7, 126.7, 131.7, 143.7 ppm; MS (APCI+): $m/z = 296.0$, 298.0 ($[M + H]^+$).

1-Acetyl-6-bromo-3-[2-(diethylamino)ethyl]imidazo[1,2-a]-pyridinium acetate (**9a**, $C_{17}H_{24}BrN_3O_3$)
Yield 9 %; $R_f = 0.6$ (dichloromethane/methanol 85:15, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 1.10$ (t, 6H, CH_3, $J = 7.1$ Hz), 2.02 (s, 3H, CH_3), 2.75 (q, 4H, NCH_2, $J = 7.2$ Hz), 2.92 (m, 2H, CH_2), 3.10 (m, 2H, CH_2), 7.21 (dd, 1H, H_7, $J = 9.5$ Hz, 1.7 Hz), 7.42 (s, 1H, H_2), 7.51 (d, 1H, H_8, $J = 9.5$ Hz), 8.06 (d, 1H, H_5, $J = 1.0$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 10.3$, 21.3, 22.5, 46.9, 50.3, 107.2, 118.3, 122.4, 123.8, 127.2, 131.5, 135.1, 143.8, 176.1 ppm.

*General procedure for the preparation of products **10** and **11***

In 30 cm^3 dry toluene 1.0 g 2-(6-bromo-1*H*-imidazo[1,2-*a*]-pyridin-2-yl or -3-yl)-*N*,*N*-diethylethanamine (3.6 mmol), 0.4 g tetrakis(triphenylphospine)palladium (0.36 mmol) and 3.1 g hexa-*n*-butylditin (5.4 mmol) were stirred at 110 °C under inert atmosphere for 18 h. The solution was evaporated under reduced pressure. The product was purified by chromatography on silica gel using dichloromethane/methanol (97:3, v/v) to afford oily products.

N,N-Diethyl-2-[6-(tributylstannyl)imidazo[1,2-a]-pyridin-2-yl]ethanamine (**10**, $C_{25}H_{45}N_3Sn$)
Yield 22 %; $R_f = 0.4$ (dichloromethane/methanol 85:15, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 0.89$ (t, 15H, CH_3, $J = 7.2$ Hz), 1.09 (m, 6H, CH_2, $J = 7.3$ Hz), 1.31 (m, 6H, CH_2), 1.53 (m, 6H, $SnCH_2$), 3.02 (q, 4H, NCH_2, $J = 7.2$ Hz), 3.28 (d, 4H, CH_2, NCH_2, $J = 2.4$ Hz), 7.13 (d, 1H, H_7, $J = 8.9$ Hz), 7.47 (m, 1H, H_3, H_8), 7.92 (s, 1H, H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 9.8, 11.2, 13.9, 26.3, 27.7, 29.4, 46.6, 51.9, 106.9, 111.2, 118.3, 126.1, 128.7, 142.9, 147.3$ ppm; MS (APCI+): $m/z = 506.5$ ($[M + H]^+$).

N,N-Diethyl-2-[6-(tributylstannyl)imidazo[1,2-a]-pyridin-3-yl]ethanamine (**11**, $C_{25}H_{45}N_3Sn$)
Yield 31 %; $R_f = 0.4$ (dichloromethane/methanol 85:15, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 0.90$ (t, 15H, CH_3, $J = 7.2$ Hz), 1.11 (q, 6H, CH_2, $J = 7.1$ Hz), 1.35 (m, 6H, CH_2), 1.55 (m, 6H, $SnCH_2$), 2.65 (q, 4H, NCH_2, $J = 7.1$ Hz), 2.85 (t, 2H, CH_2, $J = 6.5$ Hz), 3.05 (t, 2H, NCH_2, $J = 7.0$ Hz), 7.13 (d, 1H, H_7, $J = 8.8$ Hz), 7.40 (s, 1H, H_2), 7.57 (d, 1H, H_8, $J = 8.8$ Hz), 7.88 (s, 1H, H_5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 9.7, 11.5, 13.7, 24.5, 27.4, 29.2, 46.3, 52.4, 106.2, 119.9, 122.2, 124.2, 127.8, 134.5, 142.7$ ppm; MS (APCI+): $m/z = 506.5$ ($[M + H]^+$).

General procedure for the preparation of products ***12–14***

Compound **10** or **11** (0.2 g, 0.39 mmol) in 30 cm^3 dry toluene was placed under inert atmosphere and 0.03 g $PdCl_2(PPh_3)_2$ (0.04 mmol) and the desired aryl chloride (0.59 mmol) were added. The reaction was refluxed for 24 h. The solution was evaporated under reduced pressure and the product was purified by chromatography on silica gel using dichloromethane/methanol (85:15, v/v) to afford oily products.

N,N-Diethyl-2-[6-(phenylsulfonyl)imidazo[1,2-a]-pyridin-2-yl]ethanamine (**12**, $C_{19}H_{23}N_3O_2S$)
Yield 47 %; $R_f = 0.5$ (dichloromethane/methanol 85:15, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 1.34$ (t, 6H, CH_3, $J = 7.3$ Hz), 3.17 (q, 4H, NCH_2, $J = 7.3$ Hz), 3.31 (m, 2H, CH_2), 3.45 (m, 2H, NCH_2), 6.75 (td, 1H, H_{Ar}, $J = 1.0$ Hz, 6.8 Hz), 7.14 (m, 1H, H_{Ar}), 7.27 (s, 1H, H_{Ar}), 7.38 (m, 2H, H_7, H_{Ar}), 7.46 (d, 1H, H_{Ar}, $J = 9.1$ Hz), 7.56 (s, 1H, H_5), 7.88 (m, 1H, H_8), 8.08 (d, 1H, H_{Ar}, $J = 6.8$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.8, 23.9, 46.9, 51.6, 110.8, 112.4, 116.8, 124.9, 125.0, 125.9, 126.3, 128.2, 129.9, 141.7, 145.0$ ppm; MS (APCI+): $m/z = 357.1$ ($[M + H]^+$).

N,N-Diethyl-2-[6-(1-naphthalenylsulfonyl)imidazo[1,2-a]-pyridin-2-yl]ethanamine (**13**, $C_{23}H_{25}N_3O_2S$)
Yield 62 %; $R_f = 0.5$ (dichloromethane/methanol 85:15, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 1.36$ (t, 6H, CH_3, $J = 7.3$ Hz), 3.18 (q, 4H, NCH_2, $J = 7.3$ Hz), 3.33 (m, 2H, CH_2), 3.47 (m, 2H, NCH_2), 6.75 (td, 1H, H_{Ar}, $J = 1.1$ Hz, 6.8 Hz), 7.16 (m, 1H, H_{Ar}), 7.50 (m, 4H, H_5, H_{Ar}), 7.58 (m, 1H, H_8), 7.87 (td, 1H, H_{Ar}, $J = 1.4$ Hz, 8.3 Hz), 8.04 (dt, 1H, H_{Ar}, $J = 1.1$ Hz, 2.3 Hz, 6.8 Hz), 8.22 (dd, 1H, H_{Ar}, $J = 1.2$ Hz, 7.2 Hz), 8.98 (d, 1H, H_7, $J = 9.1$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 8.5, 29.7, 47.0, 124.4, 125.7, 126.1, 126.5, 127.0, 128.3, 129.1, 131.3, 134.2, 140.6$ ppm; MS (APCI+): $m/z = 428.9$ ($[M + Na]^+$).

N,N-Diethyl-2-[6-(1-naphthalenylsulfonyl)imidazo[1,2-a]-pyridin-3-yl]ethanamine (**14**, $C_{23}H_{25}N_3O_2S$)
Yield 41 %; $R_f = 0.5$ (dichloromethane/methanol 90:10, v/v); ^{1}H NMR ($CDCl_3$): $\delta = 1.17$ (t, 6H, CH_3, $J = 7.2$ Hz), 2.86 (q, 4H, NCH_2, $J = 7.2$ Hz), 3.02 (m, 2H, CH_2), 3.20 (m, 2H, NCH_2), 6.75 (t, 1H, H_{Ar}, $J = 6.8$ Hz), 7.33 (t, 1H, 1 H_{Ar}, $J = 7.9$ Hz), 7.43 (s, 1H, CH), 7.47 (m, 3H, H_{Ar}), 7.59 (d, 1H, H_8, $J = 9.0$ Hz), 7.83 (d, 1H, H_{Ar}, $J = 7.5$ Hz), 8.13 (d, 1H, H_{Ar}, $J = 6.9$ Hz), 8.18 (d, 1H, 1 H_{Ar}, $J = 7.2$ Hz), 8.98 (d, 1H, H_7, $J = 9.2$ Hz) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 10.5, 29.6, 46.8, 124.2, 125.4, 125.9, 126.7, 126.9, 128.2, 129.2, 130.9, 134.1, 141.6$ ppm; MS (APCI+): $m/z = 428.8$ ($[M + Na]^+$).

Competition binding assay

Stock solutions of the compounds were prepared in DMSO and further diluted with the binding buffer to the desired concentration. Final DMSO concentrations in the assay were less than 0.1 %. The competitive binding experiments were performed as described earlier [16].

Briefly [^{3}H]-LSD (2.5 nM) as radioligand for the human serotonin 5-HT_6 receptor was added to 15 µg of membranes resuspended in 550 mm^3 (final volume) binding buffer (50 mM Tris–HCl pH 7.4, 10 mM $MgCl_2$, 0.5 mM EDTA). After 1 h at 37 °C, the incubation was stopped and the solutions were rapidly filtered over Unifilter-96 GF/C filter (pre-soaked in 0.5 % PEI) on a Filtermate Unifilter 96-Harveste (Perkin Elmer) and washed with 9 × 500 mm^3 of ice-cold wash buffer.

The radioactivity on the filters was measured using a TopCount NXT™ microplate scintillation counter (Perkin Elmer) using 40 mm^3 of MicroScint™ 40 (Perkin Elmer) after 30 min resting. The nonspecific binding was determined in the presence of 5 µM serotonin (Sigma).

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