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Brief Article

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Novel Aza-analogous Ergoline Derived Scaffolds as Potent Serotonin 5-HT$_6$ and Dopamine D$_2$ Receptor Ligands.

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ABSTRACT: By introducing distal substituents on a tetracyclic scaffold resembling the ergoline structure two series of analogues were achieved exhibiting subnanomolar receptor binding affinities for the dopamine D$_2$ and serotonin 5-HT$_6$ receptor subtype respectively. While the 5-HT$_6$ ligands were antagonists, the D$_2$ ligands displayed intrinsic activities ranging from full agonism to partial agonism with low intrinsic activity. These structures could potentially be interesting for treatment of neurological diseases such as schizophrenia, Parkinson's disease and cognitive deficits.

Several of the monoaminergic receptors mediating the effects of dopamine, serotonin, and norepinephrine constitute key targets in the current treatment of a wide range of neurological, psychiatric and cognitive disorders.

In Parkinson's disease (PD) a degeneration of dopamine neurons in the basal ganglia, predominantly the *substantia nigra pars compacta* nuclei, is evident.[1] To reduce the symptoms arising from this progressive neurodegeneration, PD is principally treated with L-DOPA or synthetic dopaminergic agonists. However, the severe drawbacks and temporary effectiveness of this treatment urge the development of therapeutic alternatives.[2]

Schizophrenia (SZ) is a chronic disorder characterized by an array of clinical features resulting in abnormal mental functions and disturbed behaviour.[3] The major treatment paradigm in SZ is the use of dopamine D$_2$ receptor antagonists or partial agonists with low intrinsic activity and all current clinical antipsychotics target this receptor.[4,5]

Finally, the cognitive impairment observed in CNS disorders such as Alzheimers disease (AD) and SZ have in several studies been shown to be addressed by serotonin 5-HT$_6$ receptor antagonists.[6-8]

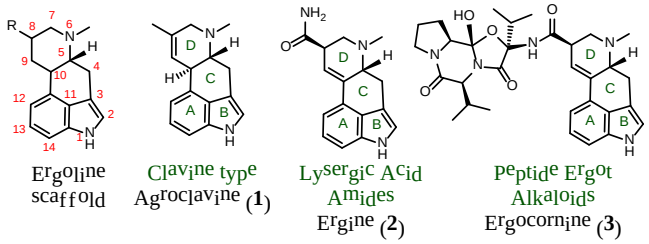


Figure 1: The basic ergoline scaffold and examples of the three types of naturally occurring ergot alkaloids (**1-3**).

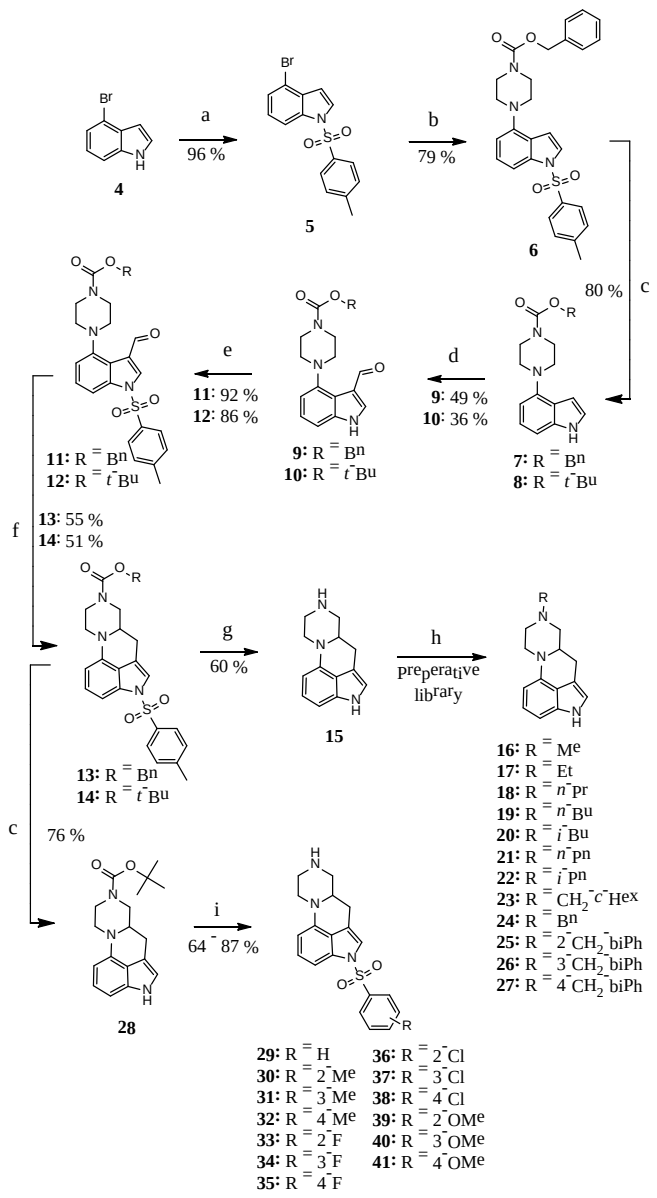
Ergot alkaloids are derivatives of the tetracyclic ergoline scaffold and can be divided in to three main groups (**Figure 1**). The ergot alkaloids display a diverse spectrum of pharmacological properties, including central, peripheral and neurohormonal activities that arise from their activities at various monaminergic receptors.[9] Ergot alkaloids are used in the clinical treatment of PD and have also been pursued as putative therapeutics for treatment of SZ.[10-13] Thus, the basic ergoline structure presents an intriguing scaffold for further modification and development of novel monoaminergic receptor ligands.

In the present study, the potential of a novel ergot analogue scaffold was probed through the design and synthesis of two series of tetracyclic piperazine analogues (**15-27** and **29-41**). These compounds were pharmacologically characterized at either the dopamine D$_2$ or the serotonin 5-HT$_{2C}$ and 5-HT$_6$ receptors. The objective of this preliminary study was to obtain an ergoline analogous scaffold by combining two privileged scaffolds (indole and phenyl piperazine) that upon introduction of distal substitutions on the resulting tetracyclic core scaffold could embrace the different monoaminergic pharmacophore models and target various monoaminergic receptor subtypes.

RESULTS AND DISCUSSION

Chemistry. Carbamate-protected piperazino indoles **7** and **8** are readily available from protection of commercially available 4-piperazinoindole, however, the disbursement of the compound prompted an alternative synthetic route. The chemistry leading from 4-bromoindole **1** to compound **12** and **25** followed a previously developed protocol (**Scheme 1**).[14] Tetracycle **15** was readily alkylated or benzylated selectively at the secondary amine. The syntheses of the derivatives **16-27** were only performed in small scale and purified by preparative LC-MS with the *n*-propyl analogue being the exception for full characterization purposes. Boc-protected tetracycle **28** was sequentially sulphonated at the indole nitrogen and deprotected to complete a small, selected series of phenylsulphone-substituted analogues.

Scheme 1.[a]



[a]Reagents and conditions: (**a**) *p*-TsCl, *n*-Bu_4NHSO_4, NaOH (16 %), PhMe, 60 °C, 2 h; (**b**) Cbz-piperazine, $Pd(dba)_2$, 1-biphenyl-P(*t*-Bu)$_2$, NaO-*t*-Bu, PhMe, reflux, 15 h; (**c**) Mg (dust), MeOH (dry), THF (dry), sonication, rt, 30 min; (**d**) 1) $POCl_3$, DMF, 0 °C, 1.5 h - rt, 2 h; 2) H_2O, rt, 45 min; (**e**) *p*-TsCl, *n*-Bu_4NHSO_4, NaOH (16 %), PhMe, rt, 45 min; (**f**) 1) *p*-$TsNHNH_2$, PhMe, sonication, rt, 3 h, 2) NaH (60 % in mineral oil), PhMe, microwave irradiation, 130 °C, 12 min; (**g**) KOH (20 % in H_2O), DMSO, microwave irradiation, 150 °C, 4 min. (**h**) DIPEA, DMSO, alkyl bromide, 60 °C, 42 h (**16 - 23**); DIPEA, DMSO, benzyl bromide, rt, 18 h (**24 - 27**); (**i**) 1) *p*-TsCl, *n*-Bu_4NHSO_4, NaOH 16 %), PhMe, rt, 2 h; 2) MeOH, Et_2O, 2 M HCl in Et_2O, rt, 18 h.

Pharmacology. Naturally occurring ergot structures are almost exclusively methylated at the amine in the 6-position. However, different small alkyl substituents are accommodated by dopamine agonists such as 3-(3-hydroxyphenyl)-*N*-propylpiperidine (3-PPP) and pergolide (**42**), which is most likely due to a well-defined pocket in the monoamine receptor fitting the *n*-propyl substituent.[15] Thus, it was decided to include small straight or branched alkyl substituents up to the length of the pentyl chain in the analogues. Moreover, the dopamine D_2 affinity of bifeprunox (**43**) indicates a very efficient interaction between the receptor and the aromatic biphenyl group of the ligand.[16] Due to the size of the *N*-substituent it will have to protrude into a different and much more spacious cavity of the binding site as it is seen in the case of bromocriptine (**44**).[17] In view of this, analogues with benzyl or different methylene biphenyl substituents in this position were also included in this series.

In the evaluation of the pharmacological properties of the synthesized analogues described *vide infra*, it is important to keep in mind that the compounds were tested as racemic mixtures and that the conclusions concerning the spacious cavity is based on the crystal structure of 5-HT_{1B} co-crystallised with ergotamine as a model for the D_2 receptor binding site, which is in correlation with existing literature.[17-19]

As can be seen from **Table 1**, a pronounced correlation ranging over more than a 1000 fold difference in binding affinities exists between the size of the substituent and the binding affinities of the compounds at the human D_{2L} receptor. Interestingly, the *n*-Pr analogue **18** displays relatively low binding affinity, which could indicate that the alkyl substituent in this position is not able to accommodate the restriction of the alkyl binding cavity and therefore will have protrude the larger cavity of the binding site.[15] The spacious orientation of the biphenyl moiety also seems to be of great importance despite protruding into a different and much larger cavity of the D_2 receptor pocket, resulting in a 700-fold difference in D_2 binding affinity.[17]

Compound **26** stands out as the most potent D_2 receptor ligand and to come from the series displaying an interesting D_2 receptor profile compared to the structurally related compounds pergolide (**42**), bifeprunox (**43**), bromocriptine (**44**), and lisuride (**45**).[16,20-22] The binding affinity of compound **26** was comparable to that of lisuride (**45**), the classical anti-parkinson ergot, while the compound exhibited a significantly higher D_2 affinity than pergolide (**42**) and bromocriptine (**44**) also used in the treatment of PD.[18] However, being a partial D_2 agonist with an intrinsic activity comparable to that of bifeprunox (**43**), compound **26** resembles a potential antipsychotic more than an anti-Parkinson therapeutic by shifting the D_2 profile towards those of typical antipsychotics such as chlorpromazine (**46**) and haloperidol (**47**), which display antagonism and inverse agonism at the D_2 receptor, respectively (**Figure 2**).[23] Interestingly, an inverse correlation between the dopamine D_2 efficacy and the size of the amine substituent can be observed for the compounds in this series characterized functionally. Thus, compounds **22** and **23** which comprise smaller alkyl substituents are full agonists of the D_2 receptor and could be speculated to hold more potential as putative PD therapeutics than compound **26**.

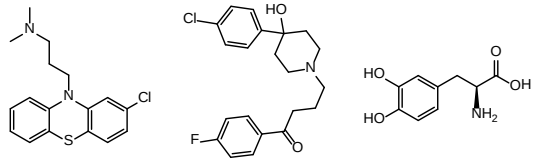


Figure 2: The chemical structures of chlorpromazine (**46**), haloperidol (**47**) and L-DOPA (**48**).

A pronounced consequence of neurodegenerative diseases such as AD and SZ is cognitive dysfunction.[6,7] Due to its CNS distribution and its ability to modulate multiple neurotransmitter systems involved in cognition, the serotonin 5-HT_6 receptor has emerged as an interesting target through which this core feature of AD and SZ can be addressed.[6-8] The serotonin 5-HT_{2C} receptor subtype has also been identified as a potential pharmacological target in relations to cognitive deficits and SZ.[4,24,25]

While both receptor subtypes have been included in this preliminary study focus will *vide infra* be upon the pharmacological interactions of the tetracyclic derivatives and the 5-HT_6 receptor.

In order to introduce 5-HT_6 receptor activity in the tetracyclic ergot analogous scaffold, a phenylsulphonylate substituent was introduced at the indole nitrogen of compound **15**, as this would address the receptor interacting elements defined in the classical 5-HT_6 pharmacophore model.[6,26] A small selection of substituents with a limited size and different electronical properties were introduced into this series of compounds in order to probe their potential as 5-HT_6 ligands.[6,27]

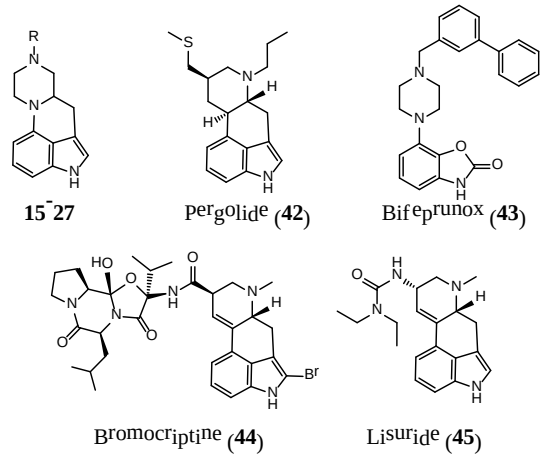
As can be seen from the 5-HT_6 receptor binding affinities exhibited by the sulphonamide analogues outlined in **Table 2**, substituents in the 4-position of the scaffold appear to be unfavorable compared to substituents in the 2- and 3-positions, whereas the receptor does not seem to discriminate between the latter two positions. It is not possible to derive any SAR conclusions about the size and electronic properties of the substituents chosen except that introduction of fluorine in these positions seem to be favored by the receptor. Compound **34** displayed the highest binding affinity (0.75 nM) at the 5-HT_6 receptor and a 250-fold selectivity for this receptor over the 5-HT_{2C} receptor. Moreover, the compound was found to be an antagonist at the 5-HT_6 receptor (CEREP).[28]

While the subnanomolar 5-HT_6 binding affinity displayed by compound **34** was lower than that exhibited by the structurally similar 5-HT_6 antagonist SB-742457 (**49**), it was either higher or comparable to those exhibited by other sulphonyl-containing compounds such as Ro 63-0563 (**50**) and SB-271046 (**51**) and also by LU AE58054 (**52**).[29,30] Interestingly, despite distinct structural differences these three compounds display similar 5-HT_6/5-HT_{2C} binding selectivity ratios as compound **34**. Mesulergine (**53**), which also contains the ergot scaffold, but with the sulphonamide attached to the piperidine moiety, displays the opposite 5-HT_6/5-HT_{2C} selectivity.

Preliminary clearance and metabolic studies for compound **26** (3.9 L/kg/h(human)) indicated that it would be both metabolized and excreted at a rate unsuitable for a drug. In contrast, compound **34** (0.8 L/kg/h (human)) displayed a more favorable profile in a potential therapeutic context (1.3 L/kg/h (human)). The fast metabolism of compound **26** was not unexpected, since biphenyl moieties are known to be promptly metabolized by 4-hydroxylation.[31] Thus, it is possible that the metabolic and clearance profile of these biphenylic analogues could be improved by introducing a substituent in the 4 position, thereby preventing this elaborate 4-hydroxylation. Interestingly, introduction of small substituents in the 4-position of biphenyl substituted 4-piperazineindole analogues have been found to increase the D_2 receptor binding affinity (data not shown), which suggests that the problematic clearance and metabolism properties of this scaffold could be addressed without compromising the pharmacological properties of the compounds.

In the present study the pharmacological properties of the two series of compounds were characterized on selected monoaminergic receptor subtypes that are well established as potential therapeutic targets in relations to PD, SZ and cognitive dysfunction.[1-8] Considering the rich pharmacology of ergot

Table 1. Dopamine hD_{2L} receptor binding affinities and functional efficacies of compounds **15 – 27** in comparison to benchmark compounds such as pergolide (**42**), bifeprunox (**43**), bromocriptine (**44**), and lisuride (**45**).

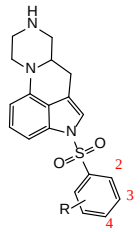


No.	Name (**42-45**) R (**15-27**)	hD_{2L}		
		K_i (nM)	pK_i ± S.E.M.	E_{max}
42	Pergolide	26	7.59 ± 0.06[b]	52
43	Bifeprunox	2.3	8.64 ± 0.02[b]	27
44	Bromocriptine	15	7.83 ± 0.08[b]	28
45	Lisuride	0.66	9.18 ± 0.04[b]	21
15	H	2100	5.68 ± 0.05[a]	n.t.
16	Me	660	6.18 ± 0.02[a]	n.t.
17	Et	140	6.85 ± 0.05[a]	n.t.
18	*n*-Pr	570	6.24 ± 0.01[a]	n.t.
19	*n*-Bu	110	6.96 ± 0.02[a]	n.t.
20	*i*-Bu	310	6.51 ± 0.05[a]	n.t.
21	*n*-Pn	98	7.01 ± 0.13[a]	n.t.
22	*i*-Pn	24	7.62 ± 0.04[a]	96
23	CH_2-*c*-hex	54	7.27 ± 0.13[a]	95
24	Bn	130	6.89 ± 0.06[a]	51
25	2-CH_2-biPh	450	6.70 ± 0.11[b]	n.t.
26	3-CH_2-biPh	0.65	9.64 ± 0.06[a]	35
27	4-CH_2-biPh	140	6.92 ± 0.05[a]	n.t.

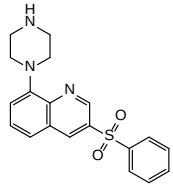
Dopamine D_2 affinity: Displacement of specific [^{3}H]-raclopride binding to membranes of CHO-K1a-hD_{2L} cells (**15-27**), Displacement of specific [^{125}I]iodosulpride at recombinant, human dopamine receptors in CHO cells (**42**, **44**, **45**).[20] Displacement of specific [^{3}H]nemonapride at dopamine D_2 transfected COS-7 cells (**43**).[16] *Dopamine D_2 efficacy:* [^{125}I]-cAMP in CHO cells (**22-24**,**26**). [^{35}S]GTPγS binding to hD_2-like receptors expressed by CHO cells (**42**, **44**, **45**).[21] [^{35}S]-GTPγS binding to membranes of Sf9 cells (**43**).[22] n.t. = not tested, [a](n = 2), [b](n = 3).

structures, it will be important to characterize the pharmacological properties of these compounds at additional monoaminergic receptors such as 5-HT_{2A} (hallucinogenic properties) and 5-HT_{2B} (inadvertent heart effects), just to mention a few, in the future.[37] Embracing the complexity of neurological disorders accentuate the need of therapeutics to display a distinct pharmacological profile rather than being receptor subtype selective. In relation to the pronounced conservation of the orthosteric binding sites in the monoaminergic receptors it would also be interesting to merge the D_2 and 5-HT_6 phamacophores and implement the tetracyclic structure in a hybrid scaffold, since the combination of either D_2 receptor agonism or antagonism with 5-HT_6 antagonism could hold great therapeutic potential.

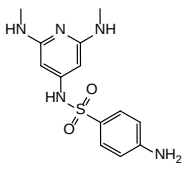
Table 2. Serotonin 5-HT_6 and 5-HT_{2C} receptor binding affinities of compounds **29-41** in comparison to the benchmark compounds **49-53**.



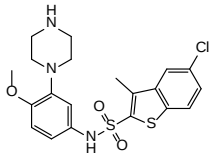
29-41



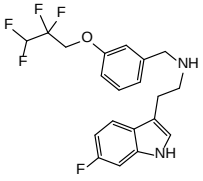
SB-742457 (**49**)



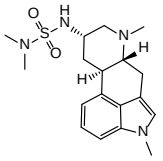
Ro 63-0563 (**50**)



SB-271046 (**51**)



LU AE58054 (**52**)



Mesulergine (**53**)

No.	Name (**49-53**) R (**29-41**)	h5-HT_{2C} K_i (nM)	h5-HT_{2C} pK_i ± S.E.M.	h5-HT_6 K_i (nM)	h5-HT_6 pK_i ± S.E.M.
49	SB-742457	-	-	0.17	9.78 ± 0.14[d]
50	Ro 63-0563	2042	5.69 ± 0.01[e]	12	7.91 ± 0.02[b]
51	SB-271046	770	6.11 ± 0.15[a]	3	8.52 ± 0.09[a]
52	LU AE58054	250	6.60 ± 0.04[c]	0.83	9.08 ± 0.06[c]
53	Mesulergine	1.82	8.74 ± 0.03[b]	776	6.11 ± 0.12[e]
29	H	280	6.55 ± 0.01	9	8.05 ± 0.04[a]
30	2-Me	470	6.33 ± 0.06	21	7.68 ± 0.05[c]
31	3-Me	460	6.34 ± 0.04	24	7.62 ± 0.04[a]
32	4-Me	780	6.11 ± 0.03	96	7.02 ± 0.12[c]
33	2-F	350	6.46 ± 0.02	n.t.	n.t.
34	3-F	240	6.62 ± 0.07	0.75	9.12 ± 0.04[a]
35	4-F	1100	5.96 ± 0.01	29	7.54 ± 0.10[c]
36	2-Cl	460	6.34 ± 0.06	n.t.	n.t.
37	3-Cl	340	6.47 ± 0.07	47	7.33 ± 0.10[c]
38	4-Cl	1200	5.92 ± 0.03	184	6.74 ± 0.14[c]
39	2-OMe	870	6.06 ± 0.04	26	7.59 ± 0.07[c]
40	3-OMe	370	6.43 ± 0.03	24	7.62 ± 0.34[c]
41	4-OMe	2900	5.54 ± 0.07	168	6.77 ± 0.14[c]

Serotonin 5-HT_{2C} affinity: Displacement of specific [^{3}H]mesulergine binding to human 5-HT_{2C} receptors in membranes of tsA-201 cells (**29-41**), displacement of specific [^{3}H]5-HT at human recombinant 3T3 cells (**50**),[32] displacement of specific [^{3}H]5-HT binding to membranes of AV12 cells (**51**, **52**),[33] displacement of specific [^{3}H]5-HT at human recombinant HEK-293 cells (**53**),[34] *Serotonin 5-HT_6 affinity*: Displacement of specific [^{3}H]LSD binding to membranes of BHK-h5HT_6 cells (**29-41**, **51**, **52**),[33] Displacement of specific [^{3}H]LSD binding to membranes of Hela cells (**49**, **50**, **53**).[32,35,36] n.t. = not tested, [a](n = 2), [b](n = 3), [c](n = 4), [d](n = 10), [e](n = multiple).

CONCLUSION

The present study has identified a novel, pharmacologically interesting and both metabolically and chemically stable scaffold that by distal substitutions potentially can address either the dopaminergic deficits in PD patients or the cognitive impairments of disorders such as SZ and AD. However, despite the intriguing pharmacological properties of the analogues in these series compared to existing tool compounds and compounds in clinical trials or on the market, further pharmacological profiling of these compounds is required in order to evaluate their therapeutic potential. In particular, it will be important to characterize the functional properties of the compounds at other monoaminergic receptors than the D_2, 5-HT_6 and 5-HT_{2c} receptors in this study. Furthermore, it will be interesting to isolate the enantiomers of selected analogs and subjected these to detailed pharmacologically characterization.

EXPERIMENTAL SECTION

Purification performed using prepacked ISOLUTE IST flash columns, ISOLUTE SCX cation exchange columns or preparative LC-MS (See supporting information). All final compounds displayed a purity of ≥95 % (ELS).

General procedure for alkylating compound 15 (16-23): Tetracyclic compound **15** (15 mg, 0.07 mmol, 1.00 eq) was dissolved in DMSO (2 mL) and added DIPEA (20 µL, 0.11 mmol, 1.64 eq.) and alkyl bromide (1.6 eq.). The mixture was heated to 60 °C and stirred over night in a sealed vial under argon. Additional alkyl bromide (0.8 eq.) was added and reaction mixture stirred at 60 °C for 24 h. The mixtures was purified through a SCX cation-exchange column, concentrated *in vacuo* on a centrifuge, dissolved in 180 µL DMSO and purified using preparative LC-MS.

General procedure for benzylating compound 15 (24-27): Tetracyclic compound **15** (15 mg, 0.07 mmol, 1.00 eq) was dissolved in DMSO (2 mL) and added DIPEA (20 µL, 0.11 mmol, 1.64 eq.) and benzyl bromide (1.6 eq.). The reaction mixture was stirred over night at room temperature. The mixtures was purified through a SCX cation-exchange column, concentrated *in vacuo* on a centrifuge, dissolved in 180 µL DMSO and purified using preparative LC-MS.

General procedure for sulphonation and deprotection of compound 28 (29-31 and 33-41): Boc-protected tetracyclic compound **28** (75 mg, 0.24 mmol, 1.00 eq) was weight out in a 4 mL vial, added toluene (1.2 mL) and tetrabutylammonium hydrogensulfate (8 mg, 0.02 mmol, 0.10 eq). The substituted benzenesulfonyl chloride (1.25 eq) and 16 % NaOH (1 mL) was

added sequentially. The vial was sealed and the mixture was stirred vigorously at room temperature for 2 – 3 h. The organic phase was isolated and the aqueous phase was reextracted with toluene (2 x 2 mL). The organic phases were combined, washed with brine (2 mL), dried over $MgSO_4$, filtered, concentrated *in vacuo* and purified by flash chromatography to yield a clear oil.

The oil was dissolved in Et_2O (1.5 mL) and MeOH (1.5 mL) before 2M HCl in Et_2O (1.5 mL) was added. The mixture was stirred at room temperature for 24 h under argon. The mixture was concentrated *in vacuo*, dissolved in water (8 mL), added 2M NaOH (2 mL) and EtOAc (10 mL). After thorough mixing the mixture was filtered, the organic phase isolated and the aqueous phase reextracted with EtOAc (10 mL). The combined organic phases was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

ASSOCIATED CONTENT

Supporting information

Experimental procedures and full characterization of all new compounds including ^{1}H NMR and ^{13}C NMR spectre and pharmacological methods. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

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Notes

The Authors declare no competing financial interest

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ABBREVIATIONS

PD: Parkinson's disease; SZ: Schizophrenia; AD: Alzheimers disease; CNS: Central nervous system.

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TABLE OF CONTENTS GRAPHIC