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Rational design, synthesis and evaluation of (6a*R**,11b*S**)-1-(4-fluorophenyl)-4-{7-[4-(4-fluorophenyl)-4-oxobutyl] 1,2,3,4,6,6a,7,11b,12,12a(RS)-decahydropyrazino[2′,1′:6,1]pyrido [3,4-*b*]indol-2-yl}-butan-1-one as a potential neuroleptic agent☆

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Abstract—In our pursuit to prepare a potent antipsychotic compound, a novel 1,2,3,4,6,6a,7,11b,12,12a-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole derivative was synthesized which incorporates the butyrophenone substructure twice. This molecule has shown D_1, D_2 and 5-HT_{2A} receptor blocking activity where the ratio pK_i (5-HT_{2A}) to pK_i (D_2) is 1.42 better than risperidone (1.15). It blocks amphetamine induced hyperactivity/stereotypy and secondary conditioned avoidance responses in rodents at lower doses than those required for the neuroleptic drugs haloperidol and centbutindole (biriperone).

1. Introduction

About 1% of the general population suffers from schizophrenia, a complex neuropsychiatric illness.[1] The traditional neuroleptics such as haloperidol, chlorpromazine, and fluphenazine, etc. exert their effect primarily through blockade of dopamine (DA) receptors: mesolimbic receptors for the reduction of the positive symptoms of psychosis[2–4] (such as delusion, hallucination, extreme emotions, incoherent thoughts, speech, etc.) and striatal receptors in case of EPS induction. These drugs are less efficacious in attenuating negative symptoms of psychosis[5] (a lack of behaviors, such as emotions, speech, social interaction and action) and are also associated with side effects including involuntary movement disorders or extra pyramidal side effects (EPS). The atypical neuroleptics have different pharmacological profiles which account for their efficacy. The common mechanism of action seen with the available atypical neuroleptics, such as clozapine,[6,7] is the antagonism of serotonin (5-HT_2) receptors in addition to dopamine blockade. The pharmacological effect of serotonin blockade in the nigrostriatal pathway increases dopamine release in this area, thus modulating the effect of dopamine blockade (i.e. decreasing the EPS side effects). Thus an advantage of atypical neuroleptics over traditional neuroleptics is their enhanced efficacy in treating the negative symptoms of schizophrenia and related psychoses, and their decreased liability for causing EPS.

The observation that atypical neuroleptics such as clozapine has higher affinity for 5-HT_{2A} receptor than D_2 receptor has led to the so-called '5-HT_{2A}/D_2 ratio' hypothesis whereby the ratio pK_i 5-HT_{2A}/D_2may be used to discriminate atypical neuroleptics, having a ratio >1.12, from typical neuroleptics.[8] Several atypical antipsychotics with high 5-HT_{2A}/D_2 ratios have now been introduced onto the market, such as risperidone, quetiapine, olanazapine, etc.[9] So, neuroleptic compounds fulfilling the above criteria may be important for treatment of schizophrenia. Earlier we have reported 2-[γ-(4-fluorobenzoylpropyl)]-1,2,3,4,6,7,12,12a-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (centbutindole,

Keywords: Antipsychotic; D_1 receptor; D_2 receptor; 5-HT2A receptor; Decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole; Neuroleptic; NMR; COSY; HMBC.
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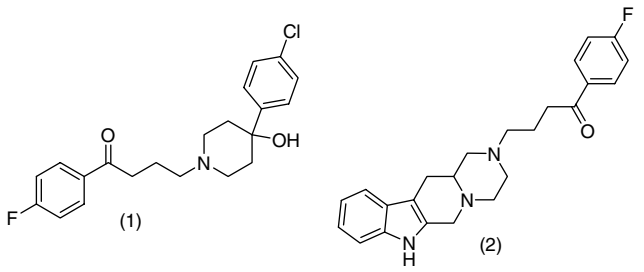


Chart 1.

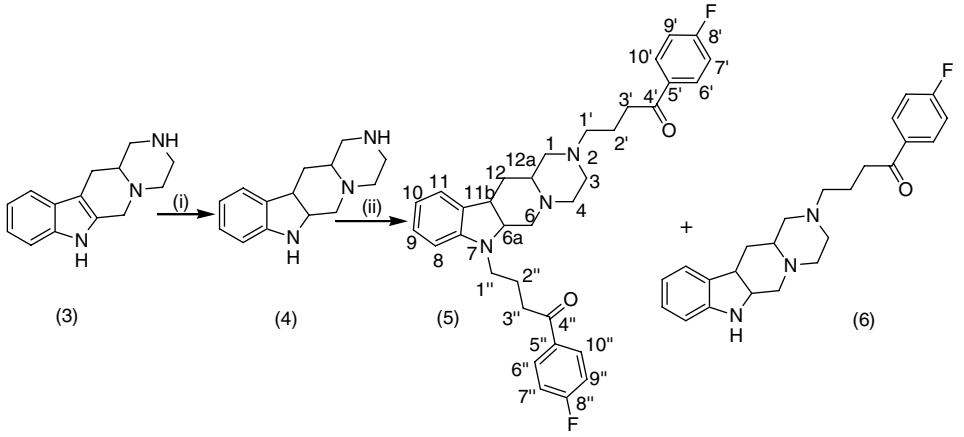
biriperone) as a promising CNS depressant.[10] QSAR studies published earlier by us have established that presence of a substructure in which neuroleptic nitrogen is separated from an aromatic ring by four carbon atoms is essential for neuroleptic activity. One such common substructure was identified as 1-(4-fluorophenyl)-butanone which is present in number of neuroleptics belonging to butyrophenone class, represented by haloperidol (**1**), centbutindole (**2**) (Chart 1), etc.

The judicious incorporation of this substructure was proposed to be very useful in designing new neuroleptics by our group.[11] The inclusion of substructure with high activity frequency (no. of active compounds bearing the substructure/total no. of compounds with the active substructure) more than one time in the molecule may increase the activity due to enhanced possibilities of the molecule to interact with the receptor. Thus in order to use this concept in the molecular modification of centbutindole, the basic tetracyclic structure (octahydropyrazinopyridoindole) was converted into decahydropyrazinopyridoindole so as to impart basic and neuroleptic character to the indole nitrogen and the active butyrophenone substructure was incorporated at N-7 position. This led to design of the highly active title compound[12] incorporating the active substructure twice. This is also substantiated by syntheses and in vitro evaluation of the compounds bearing the active substructure at either N-2 or N-7 of the parent nucleus, where these compounds showed lesser activity than the title compound. The details of these studies are reported in this paper.

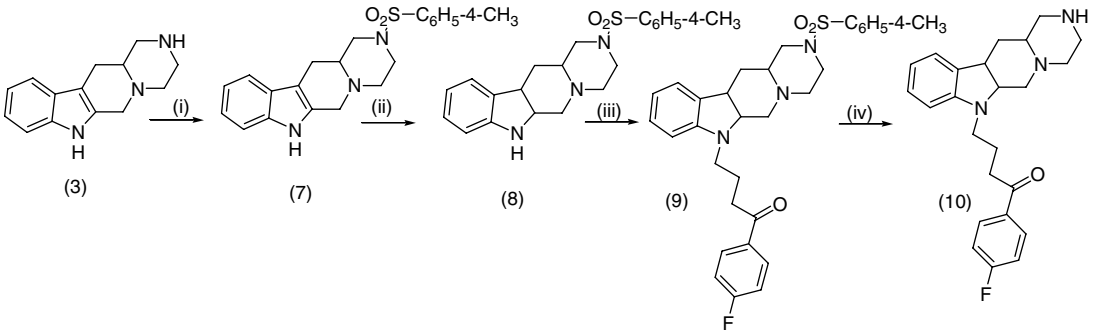
2. Chemistry

The starting material **3** (Scheme 1) was synthesized according to the literature method.[13] This was reduced stereospecifically using borane dimethylsulfide complex[14] yielding (6a*R**,11b*S**)-1,2,3,4,6,6a,7,11b, 12,12a-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (**4**), which was condensed with 4-chloro-4′-fluorobutyrophenone in dry DMF in presence of inorganic base and catalyst. The resulting crude reaction mixture was purified by column chromatography using silica gel as stationary phase and mixture of chloroform and methanol as eluent to obtain (6a*R**,11b*S**)-1-(4-fluorophenyl)-4-{7-[4-(4-fluorophenyl)-4-oxobutyl]-1,2,3,4,6,6a,7,11b,12,12a-decahydropyrazino[2′,1′:6,1] pyrido[3,4-*b*]indol-2-yl}-butan-1-one (**5**) as major and 1-(4-fluorophenyl)-4-{2,3,4,6,6a,7,11b,12,12a(RS)-octahydropyrazino[2′,1′:6,1] pyrido[3,4-*b*]indol-2-yl}-butan-1-one (**6**) as minor products (Scheme 1). The starting material **3** was tosylated in presence of pyridine to yield the compound 2-[(4-methylphenyl)sulfonyl]-1,2,3,4,6,7,12,12a(RS)-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (**7**) which was reduced to (6a*R**,11b*S**)-2-[(4-methylphenyl)sulfonyl]-1,2,3,4,6,6a,7,11b,12,12a(RS)-decahydropyrazino-[2′,1′:6,1]pyrido[3,4-*b*]indole (**8**) using borane dimethylsulfide complex essentially according to our earlier reported procedure.[14] The compound **8** was reacted with 4-chloro-4′-fluorobutyrophenone in dry DMF in presence of inorganic base and catalyst to yield (6a*R**,11b*S**)-1-(4-fluorophenyl)-4-{2-[(4-methylphenyl)sulfonyl]}-1,2,3,4,6,6a,7,11b,12,12a(RS)-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indol-7-yl}-butan-1-one (**9**). The compound **9** was detosylated with trifluoroacetic acid and the crude reaction mixture was purified with column chromatography to give (6a*R**,11b*S**)-1-(4-fluorophenyl)-1,2,3,4,6,6a,7,11b,12,12a(RS)-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indol-7-yl}-butan-1-one (**10**) (Scheme 2).

NMR studies: The proton NMR spectrum of compound **5** was divided into three sets of spectral regions, first (8.05–6.46 ppm), second (3.44–1.81 ppm), and the third set with three protons viz. a triplet at 1.71 ppm and two multiplets at 1.58 and 1.18 ppm. Although the inte-



Scheme 1. Reagents and conditions: (i) $(CH_3)_2SBH_3$, TFA, 0–30 °C, 3 h; (ii) 4-chloro-4′-fluorobutyrophenone, Na_2CO_3, NaI, DMF, 80 °C, 24–26 h.



Scheme 2. Reagents and conditions: (i) TosCl, C_5H_5N, 30 °C, 15 min; (ii) $(CH_3)_2SBH_3$, TFA, 0–30 °C, 3 h; (iii) 4-chloro-4′-fluorobutyrophenone, Na_2CO_3, NaI, DMF, 80 °C, 16–18 h; (iv) TFA, 30 °C, 48 h.

gral value obtained in the ^{1}H NMR spectrum clearly suggested the number of aromatic protons to be 12, it was difficult to evaluate the number of aliphatic protons due to the high overlapping of the signals at 300 MHz. Hence, the complicated pattern of ^{1}H NMR spectrum provided very little preliminary information regarding the structure of compound. The ^{13}C NMR spectrum consisted of 29 carbon signals. The ^{13}C and DEPT spectral edited experiments revealed three aliphatic methine, eight aromatic methines, 11 methylenes, and five quaternary carbons. The complete assignments of **5** were then carried out by a combined use of COSY, DQF COSY, HSQC, and $^3J_{CH}$ optimized HMBC experiments. The assignments of aromatic region protons of the indoline along with the phenyl rings of the side chain substituted at N-2 and N-7 were unambiguous and were deduced clearly from the COSY and HMBC spectrum. The complicated aliphatic protons were initially characterized by COSY spectrum and further reconfirmed through the use of DQF COSY and HMBC spectrum. The most down field quaternary carbon signals at 198.6 and 198.5 ppm were assigned to the two-carbonyl carbon C-4′ and C-4″ of the side chains. A multiplet at 1.91 ppm, having integral value for total five protons included two methylene and one methine protons, based on the HSQC correlation. Hence its corresponding ^{13}C chemical shifts at 21.6 and 20.7 ppm were assigned to C-2″ and C-2′, respectively, as its three-bond correlations with C-4′ and C-4″ were observed in the HMBC spectrum. A methylene triplet at 2.34 ppm with its carbon signal resonating at 57.7 ppm showed two-bond correlation with C-2′ was assigned to H-1′. The three-bond correlation of H-1″ with two methylenes carbon of tetra cyclic ring system at 52.8 and 59.0 ppm clearly depicted the substitution of the side chain at N-2 position. Assignment of H-1′ was further reinstated by the presence of three-bond correlation with a methylene carbon of side chain at 36.3 ppm, assigned to H-3′ inequivocally. Further, another overlapped signal at 3.27 ppm correlated to its methylene carbon signal at 45.2 ppm, provided two-bond correlation with C-2″ and three-bond correlation with a methine carbon at 63.1 ppm confirmed it as H-1″ of the side chain substituted at N-7. While the methine at 63.1, with its corresponding proton signal resonating at 3.44 ppm was automatically assigned to C-6a of the reduced tryptophan nucleus. In the COSY spectrum, it provided cross peaks with signals at 2.97 ppm (H-11b) and 2.25 ppm (H-6) having vicinal couplings of 7.62 and 4.88 Hz, respectively. The H-11b proton showed correlation with the distinct multiplets of the adjacent methylene proton at 1.18 and 1.58 ppm. The methylene proton at 1.18 and 1.58 ppm was assigned as H-12 (ax) and H-12 (eq), respectively, as it also correlated with another overlapped methine multiplet at 1.95 ppm. The multiplet at 1.95 ppm further provided a long-range correlation with the triplet at 1.75 ppm suggested it to be H-12a methine proton. The signal resonating at 2.25 ppm was assigned as H-6 (ax) and signal at 3.13 ppm was confirmed as H-6 (eq) proton. Both the H-6 methylene protons provided geminal coupling of 14.0 Hz as evaluated from the DQF COSY spectrum. These observations were consistent with the structure **5** and subsequently confirmed by the HSQC and HMBC spectrum. Assignment of H-11b at 2.97 ppm was reconfirmed by a three-bond correlation with C-7a and two-bond correlation with C-11 observed in the HMBC spectrum. In a similar manner, the other ^{1}H and ^{13}C assignments were carried out. The detailed assignments along with the coupling constants calculated by DQF COSY are presented in Table 1.

Stereochemistry: The relative stereochemistry of three aliphatic methine protons viz. H-6a, H-11b, H-12a and the conformation of the two heterocyclic cyclohexane rings present in tetra cyclic ring system was established by the NOESY spectrum. The H-6a proton was taken as a starting point for analysis. A strong NOE cross peak of H-6a at 3.44 ppm with the H-11b and H-12a suggested their relative stereochemistry to be cis in nature. Further, the chair conformations of both the heterocyclic rings were reinstated by the presence of strong NOE cross peaks of H-1 (ax) proton with H-3 (ax) and H-1 (ax) with H-12 (ax) proton revealing the 1–3 di axial relationship of a chair conformer. It was further reinforced by the presence of cross peaks of H-6a proton with H-6 (ax), H-11b with H-12 (eq), and H-12a with H-1 (eq) proton. Since these observations depicted 1–2 axial equatorial relationship of a chair conformer, H-11b and H-12a protons were assigned as axial while H-6a proton was confirmed as equatorial orientation. The stereochemistry of H-1″ methylene proton of the side chain substituted at N-7 was found to be equatorial as it provided cross peak with H-6a (eq). Similarly, H-1′ proton of the other side chain substituted

Table 1. ^{1}H and ^{13}C NMR data (300/75 MHz) of **5** in $CDCl_3$

Position	δ_C	δ_H	J [Hz]
1	59.0	2.69 (m) eq, 1.75 (t) ax	$J_{(gem)} = 11.2$, $J_{(gem)} = 11.2$
3	52.9	2.05 (m) eq, 2.69 (m) ax	$J_{(gem)} = 10.5$, $J_{(gem)} = 10.5$
4	55.0	2.58 (t) eq, 2.17 (o) ax	$J_{(gem)} = 10.7$, $J_{(gem)} = 10.7$
6	54.1	3.13 (m) eq, 2.25 (m) ax	$J_{(gem)} = 14.0$, $J_{(gem)} = 14.0$, $J_{6(ax),6a(eq)} = 4.4$
6a	63.1	3.44 (d) eq	$J_{6a(eq),11b(ax)} = 7.6$, $J_{(6a),6(ax)} = 4.8$
7a	151.6	—	—
8	108.3	6.55 (d)	$J_{(8,9)} = 7.5$
9	123.2	7.05 (m)	Overlapped
10	118.0	6.66 (t)	$J_{(10,9)} = 7.4$
11	127.8	7.05 (m)	Overlapped
11a	134.3	—	—
11b	38.6	2.97 (m) ax	Overlapped
12	34.6	1.58 (q) eq 1.18 (q) ax	$J_{12(eq)11b(ax)} = 9.8$, $J_{(gem)} = 13.9$, $J_{12(eq),12a(ax)} = 9.3$, $J_{(gem)} = 13.9$
12a	58.3	1.95 (m) ax	Overlapped
1′	57.7	2.34 (t)	$J_{1',2'} = 7.14$
2′	21.6	1.91 (m)	Overlapped
3′	36.3	2.95 (m)	Overlapped
4′, 4″	198.5	—	—
5′, 5″	134.2	—	—
6′, 10′	130.8	7.99 (m)	Overlapped
7′, 9′	115.8	7.07 (m)	Overlapped
8′, 8″	165.8	—	—
1″	45.2	3.27 (m)	Overlapped
2″	20.7	1.90 (m)	Overlapped
3″	35.6	2.94 (m)	Overlapped
6″, 10″	130.9	7.98 (m)	Overlapped
7″, 9″	115.7	7.07 (m)	Overlapped

at N-2 was found to be axial as NOE cross peak was observed with H-1 (ax), respectively.

3. Results and discussion

The binding affinities for D_2, 5-HT_{2A}, D_1 receptors and the ratio of pK_is (D_2/5-HT_{2A}) of compounds **5**, **6**, and **10** with centbutindole (2) and haloperidol (1) tested under similar experimental conditions are summarized in Table 2. The affinity of compound **5** for D_2 (pK_i = 5.647) was lesser than that of **6** (pK_i = 7.028), **2** (pK_i = 7.881), and **1** (pK_i = 9.33). The new compound **5** showed 5-HT_{2A} receptor affinity (pK_i = 8.029) far ahead from the three compounds **6** (pK_i = 7.034), **2** (pK_i = 7.619) and **1** (pK_i = 7.460). The value of the ratio pK_i (5-HT_{2A}) to pK_i (D_2) considered as an important criterion for atypical neuroleptics is 1.42 for the new compound **5** which is far above the threshold value (1.12) for atypical antipsychotic activity. Hence the compound **5** is better than the standard neuroleptics **2** [pK_i (5-HT_{2A})/pK_i (D_2) = 0.96], **1** [pK_i (5-HT_{2A})/pK_i (D_2) = 0.80], and risperidone [pK_i (5-HT_{2A})/pK_i (D_2) = 1.15]. The compound **6** having the active substructure once into the decahydropyrazinopyridoindole nucleus at N-2 showed almost equal affinity to the D_2 (pK_i = 7.028) and 5-HT_{2A} (pK_i = 7.034) receptors but of lesser order than the compounds **1**, **2**, and **5**. The compound **10** having the active substructure only at N-7 did not show significant affinity (pK_i < 4.0) toward D_2 or 5-HT_{2A}receptors. The lesser activity of the compound **10** as compared to **6** may be due to the lesser basicity of N-7 as compared to N-2. In view of above, that is, the higher ratio of pK_i (5-HT_{2A})/pK_i (D_2), the compound **5** should have lesser extrapyramidal side effects (EPS) than the standard neuroleptics **1**, **2** and risperidone. This compound (**5**) with higher affinity toward 5HT_{2A} receptor should also better ameliorate the negative symptoms of schizophrenia as compared to the above-mentioned standard neuroleptics (**1**, **2** and risperidone). Further the high affinity of the compound **5** for D_1 receptor (pK_i = 9.192) as compared to compound **2** (pK_i = 6.372) and **1** (pK_i = 7.236) indi-

Table 2. pK_i values for D_1, D_2, and 5-HT_{2A} receptors from rat brain

Compound	D_1 [^{3}H]SCH23390	D_2 [^{3}H]Spiperone	5-HT_{2A} [^{3}H]Ketansarin	pK_i ratio (5-HT_{2A}/D_2)
5	9.192 ± 0.09	5.647 ± 0.15	8.029 ± 0.21	1.42
2	6.372 ± 0.15	7.88 ± 0.18	7.619 ± 0.14	0.96
1	7.236 ± 0.11	9.30 ± 0.20	7.46 ± 0.19	0.80
6	—	7.028 ± 0.13	7.034 ± 0.20	1.00
10	—	<4.0	<4.0	—
Risperidone	—	8.508 ± 0.19	9.795 ± 0.22	1.15

cates that the compound **5** may have less adverse neurological effects based on the earlier studies.[15,16]

The above in vitro results put compound **5** forward as a good candidate for atypical antipsychotic with less cataleptogenic activity. In order to evaluate the compound **5** in detail, it was tested in vivo in rodents and the results were compared with the standard neuroleptics **1** and **2** for its possible antipsychotic activity and induction of EPS. The antipsychotic potential of this compound was estimated in terms of its effects seen on spontaneous motor activity (SMA), amphetamine induced toxicity and hyperactivity, blockade of conditioned, secondary conditioned, and unconditioned avoidance responses (CAR, SCR, and UR), and forced locomotor activity (results in Table 3). These reproducible experimental models based on quantal responses recorded in a group of animals are sensitive to D_2 receptor antagonists and predict therapeutic efficacy of the test compound. The SMA was reduced significantly by the compound **5** with ED_{50} = 5.15 mg/kg. The behavior of compound **5** in the spontaneous activity tests correlates with its affinity for D_1, D_2, and D_4 but without further evidence it may not necessarily be attributable to action at these receptors; although D_1 and D_2 are known to be involved in the rapidity of initiation of movement and speed,[17] a reduction in spontaneous motor activity can be caused by many substances that are not DA antagonists including, for example, H1-blockers, α 1-blockers, and reserpine (by induction of DA depletion), and is therefore indicative of only general CNS depressant action.

The amphetamine induced hyperactivity reduced by the compound **5** (ED_{50} = 1.70 mg/kg) is less than the compound **2** (ED_{50} = 0.75 mg/kg). The amphetamine induced hyper-activity is attributed to the activation of D_2 receptors in the nucleus accumbens by DA released due to the amphetamine induced reversal of the DA reuptake system.[18,19] The results obtained with the *d*-amphetamine dosage used in this work (5 mg/kg) is a more specific sign of in vivo D_2-blocking activity as the effects on behavior are dose-dependent. While dose in the range 4.5–5 mg/kg induced maximum increase in hyperactivity, higher doses caused a predominance of stereotyped activity by inducing the release of DA in other pathways. Use of 50 mg/kg of *d*-amphetamine produced 100% mortality among mice within 24 h. Compound **5** shows antagonism of amphetamine toxicity (ED_{50} = 5.57 mg/kg) better than **2** (ED_{50} = 7.5 mg/kg). These results support toward the more atypical character of neuroleptic activity of compound **5** as compared to **2**. Detection of motor deficit in mice was done by rota rod test and ED_{50} for motor in coordination was found to be 4.33 mg/kg for compound **5** as compared to 2.55 mg/kg ip for compound **2**. The antipsychotic potential of compound **5** was further evaluated by studying blockade of CAR, SCR, and UR in mice (Table 3) where it compares well with compound **2** and haloperidol for its in vivo DA antagonism leading to the establishment of its antipsychotic activity. The atypical character or the risk of the extra pyramidal symptoms (EPS) which is of major concern with typical neuroleptics was evaluated by the ratio of the neuroleptic activity and the degree of catalepsy induced. The compound **5** showed a comparable cataleptogenic potential with ED_{50} = 0.88 mg/kg administered ip, comparable to **2** (ED_{50} = 0.86 mg/kg) with the ratio of the value for ED_{50} catalepsy/ED_{50} CAR ratio (in rats) being 12.6 for **5**, than 9.5 for **2**. Thus the new compound **5** has a higher threshold for inducing catalepsy and which may, by analogy, translate into lower clinical EPS liability. The compound **5** meets the Meltzer criterion for atypical antipsychotic activity and has a high ED_{50} catalepsy/ED_{50} CAR ratio. All the above observations indicate toward the potential of the molecule **5** to be developed as an atypical antipsychotic agent. The observed results also corroborate the concept of judicious incorporation of active substructures into the prototype molecule for enhancement of biological activity.

4. Experimental

4.1. Chemistry

All the reactions were monitored by thin layer chromatography over silica gel coated TLC plates, the spots were visualized by exposing them to Iodine vapors or spraying the plates with Dragendorff reagent. Melting points were determined on an electrically heated apparatus (JSGW). The IR spectra were taken (KBr or neat) on a Perkin-Elmer 881 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance DRX 300 spectrometer using tetramethylsilane as an internal standard. Mass spectra viz., FAB, ESI, and HR were recorded on JEOL SX 102, Quatro II, and JEOL JMS-600H instruments, respectively. Elementary analyses were carried

Table 3. In vivo assays performed in rodents

Tests	5	2	1
Amphetamine hyperactivity (mice) ip (ED_{50} mg/kg)	1.71 (1.41–2.08)	0.75	—
Amphetamine toxicity (mice) ip (ED_{50} mg/kg)	5.75 (5.01–6.60)	1.00	—
Block SCR (rat) ip (ED_{50} mg/kg)	0.01 (0.01–0.03)	0.04 (0.03–0.05)	0.04 (0.03–0.05)
Block CR (rat) ip (ED_{50} mg/kg)	0.07 (0.03–0.15)	0.09 (0.07–0.12)	0.1 (0.09–0.11)
Block UR (rat) ip (ED_{50} mg/kg)	5.60 (3.39–9.23)	9.80	—
Rota Rod (mice) ip (ED_{50} mg/kg)	4.33 (3.98–4.71)	2.55 (1.85–3.50)	—
Cataleptic activity (rat) ip (ED_{50} mg/kg)	0.88 (0.79–0.98)	0.86 (0.54–1.26)	—
CAT/CAR	12.6	9.5	—

Values shown in parentheses are the 95% confidence limits.

out on Carlo ERBA-1108 analyzer. Silica gel 60–120 mesh was used for column chromatography.

4.2. 1,2,3,4,6,7,12,12a(RS)-Octahydropyrazino[2′,1′:6,1]-pyrido[3,4-*b*]indole (3)

Compound **3** was prepared according to earlier reported method.[13] Mp 232 °C (lit. mp 230–232 °C). IR (KBr): 3400, 3145, 2937, 2810, 1594, 1450, 736 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 3.04 (m, 3H, H-12a, H-12_{ax}, H-4_{ax}), 3.25 (t(o), 1H, H-1_{ax}), 3.34 (m, 1H, H-12_{eq}), 3.48 (t(o), 1H, H-3_{eq}), 3.61 (t(o), 2H, H-3_{ax}, H-4_{eq}), 3.76 (d, ^2J = 11.7 Hz, 1H, H-1_{eq}), 4.05 (d, ^2J = 14.8 Hz, 1H, H-6_{ax}), 4.35 (br s, 1H, NH-2), 4.57 (d, ^2J = 15.0 Hz, 1H, H-6_{eq}), 7.68 (t(o), 1H, H-10), 7.75 (t(o), 1H, H-9), 8.02 (d, ^2J = 7.8 Hz, 1H, H-11), 8.07 (d, ^2J = 7.5 Hz, 1H, H-8), 11.45 (s, 1H, NH-7). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.6 (C-12), 45.6 (C-3), 52.0 (C-6), 52.4 (C-1), 55.7 (C-4), 57.8 (C-12a), 105.3 (C-11b), 110.8 (C-11), 117.2 (C-8), 118.1 (C-10), 120.2 (C-9), 126.5 (C-11a), 131.8 (C-6a), 135.7 (C-7a). ESI-MS: *m*/*z* 228 [M^++1]. Anal. Calcd for ($C_{14}H_{17}N_3$) C, H, N.

4.3. (6a*R**,11b*S**)-1,2,3,4,6,6a,7,11b,12,12a(RS)-Decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (4)

Compound **4** was prepared according to the method reported earlier.[14] Mp 220 °C (lit. mp 220 °C). IR (KBr): 3430, 3291, 2811, 1675, 1600, 1172, 1129, 796 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 0.96 (m, 1H, H-12_{ax}), 1.60 (m, 1H, H-12_{eq}), 2.10 (t(br), 1H, H-12b), 2.27 (t(o), 2H, H-6_{ax}, 4_{ax}), 2.54 (t(o), 1H, H-1_{ax}), 2.84 (m(o), 1H, H-4_{eq}), 2.91 (m(o), 1H, H-11b), 2.98 (m(o), 1H, H-3_{eq}), 3.07 (m(o), 1H, H-6_{eq}), 3.10 (m(o), 1H, H-1_{eq}), 3.28 (m, 1H, H-3_{ax}), 3.65 (br s, 1H, H-6a), 5.61 (br s, 1H, NH-2), 6.54 (t, ^3J = 6.9 Hz, 2H, H-8, H-10), 6.91 (t, ^3J = 7.4 Hz, 1H, H-9), 7.00 (d, ^2J = 7.0 Hz, 1H, H-11), 8.76 (br s, 1H, NH-7). ^{13}C NMR (75 Hz, DMSO-d_6): δ 32.6 (C-12), 37.5 (C-11b), 42.9 (C-3), 46.9 (C-1), 50.6 (C-4), 54.4 (C-12a), 55.3 (C-6), 57.9 (C-6a), 109.0 (C-8), 117.2 (C-10), 123.2(C-11), 127.2 (C-9), 133.9 (C-11a), 151.0 (C-7a). ESI-MS: *m*/*z* 230 [M^++1]. Anal. Calcd for ($C_{14}H_{19}N_3$) C, H, N.

4.4. (6a*R**,11b*S**)-1-(4-Fluorophenyl)-4-{7-[4-(4-fluorophenyl)-4-oxobutyl]-1,2,3,4,6,6a,7,11b,12,12a(RS)-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indol-2-yl}-butan-1-one (5) and 1-(4-fluorophenyl)-4-{2,3,4,6,6a,7,11b,12,12a-(RS)-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indol-2yl}-butan-1-one (6)

A mixture of the compound **4** (0.229 g, 1.0 mmol), 4-chloro-4′-fluorobutyrophenone (0.441 g, 2.2 mmol), baked sodium carbonate (0.233 g, 2.2 mmol), and sodium iodide (0.0075 g, 0.05 mmol) in dry DMF (5 mL) was stirred at 80 °C for 24–26 h. Water (5 mL) was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3× 15 mL), the combined ethyl acetate layer was washed with water, dried over sodium sulphate, and concentrated. The residue thus obtained was subjected to column chromatography using chloroform–methanol as eluent to yield two products **5** and **6**, both as oil.

Compound **5**—Yield: 0.31 g, 55.7%. IR (neat): 3416, 3019, 2940, 1681, 1599, 1219, 1157, 763 cm^{-1}. ^1H and ^{13}C NMR data are given in Table 1. FABMS: *m*/*z* 558 [M^++1]. HRMS: *m*/*z* 557.28593 (M^+, Calcd for $C_{34}H_{37}F_2N_3O_2$, 557.28539). Anal. Calcd for $C_{34}H_{37}F_2N_3O_2$ (557): C, 68.92; H, 6.62; N, 7.24. Found: C, 68.74; H, 6.40; N, 7.08. Compound **6**—Yield: 0.05 g, 12.7%. IR (neat): 3362, 2929, 2820, 1683, 1598, 1460, 1360, 1225, 1157, 836, 756, 664 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.19–1.25 (m, 1H), 1.57–1.54 (m, 1H), 1.76–1.96 (m, 5H), 2.18–2.38 (m, 5H), 2.66–2.82 (m, 3H), 2.96–2.99 (m, 3H), 3.11–3.17 (d, ^2J = 13.24, 1H), 6.66–6.75 (m, 2H), 6.99–7.26 (m, 4H), 7.87–8.00 (m, 2H). FABMS: *m*/*z* 394 [M^++1]. Anal. Calcd for $C_{24}H_{28}FN_3O$ (393): C, 73.26; H, 7.17; N, 10.68. Found: C, 73.12; H, 7.23; N, 10.80.

4.5. 2-[(4-Methylphenyl)sulfonyl]-1,2,3,4,6,7,12,12a(RS)-octahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole (7)

Compound **7** was prepared according to the method reported earlier.[14] Mp 206 °C (lit. mp 206 °C). IR (KBr): 3200, 2900, 2400, 1620, 1460, 1420, 1340, 1280, 1230, 1180, 1140, 1100, 1070, 960, 920, 860, 830, 760, 720, 670 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.38 (m, 1H), 2.43 (s, 3H), 2.49–2.77 (m, 5H), 3.03–3.08 (m, 1H), 3.50–3.81 (m, 3H), 3.89 (d, ^2J = 14.8 Hz, 1H), 7.07–7.17 (m, 2H), 7.26–7.66 (m, 4H), 7.66–7.74 (m, 2H). ESI-MS: *m*/*z* 381 [M^+]. Anal. Calcd for $C_{21}H_{23}N_3O_2S$ (381): C, 66.12; H, 6.08; N, 11.01. Found: C, 66.18; H, 6.12; N, 11.03.

4.6. (6a*R**,11b*S**)-2-[(4-Methylphenyl)sulfonyl]-1,2,3,4,6,6a,7,11b,12,12a(RS)-decahydropyrazino-[2′,1′:6,1]pyrido-[3,4-*b*]indole (8)

Compound **8** was prepared according to the method reported earlier.[14] Mp 118 °C. IR (KBr): 3400, 2900, 1620, 1470, 1360, 1300, 1260, 1180, 1120, 1020, 960, 840, 770, 750, 680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (m, 1H, H-12_{ax}), 1.67 (m, 1H, H-12_{eq}), 1.96 (t, ^3J = 10.8 Hz, 1H, H-1_{ax}), 2.12 (m, 1H, H-12a), 2.33 (m, 1H, H-4_{ax}), 2.41 (s, 3H, H-8′), 2.43 (m, 1H, H-6_{ax}), 2.53 (m, 1H, H-3_{eq}), 2.83 (br d, ^2J = 11.1 Hz, 1H, H-4_{eq}), 2.99 (m, 1H, H-11b), 3.11 (d, ^2J = 13.2 Hz, 1H, H-6_{eq}), 3.50 (m, 1H, H-1_{eq}), 3.61–3.64 (m, 1H, H-3_{ax}), 3.82 (br d, ^2J = 6.3 Hz, 1H, 6a), 6.65 (d, ^2J = 7.5 Hz, 1H, H-8), 6.72 (t, ^3J = 7.2 Hz, 1H, H-10), 7.01 (t, ^3J = 7.2 Hz, 1H, H-9), 7.09 (d, ^2J = 6.9 Hz, 2H, 1H, H-11), 7.26 (d, ^2J = 6.9 Hz, 2H, H-3′, H-7′), 7.57 (d, ^2J = 7.8 Hz, 2H, H-4′, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8 (C-13′), 33.9 (C-12), 38.7 (C-11b), 46.1 (C-3), 51.4 (C-1), 54.4 (C-4), 56.4 (C-6), 57.2 (C-12a), 59.2 (C-6a), 111.2 (C-8), 119.7 (C-10), 123.8 (C-11), 128.0 (C-9), 128.3 (C-3′, 7′), 129.9 (C-4′, 7′), 131.9 (C-2′), 134.7 (11b), 144.2 (C-5′), 150.3 (C-7a). ESI-MS: *m*/*z* 383 [M^+]. Anal. Calcd for $C_{21}H_{25}N_3O_2S$ (383): C, 65.77; H, 6.57; N, 10.96. Found: C, 65.62; H, 6.62; N, 10.84.

4.7. (6a*R**,11b*S**)-1-(4-Fluorophenyl)-4-{2-[(4-methylphenyl)sulfonyl]}-1,2,3,4,6,6a,7,11b,12,12a(RS)-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indol-7-yl}-butan-1-one (9)

A mixture of the compound **8** (0.383 g, 1.0 mmol), 4-chloro-4′-fluorobutyrophenone (0.18 mL, 1.1 mmol), baked sodium carbonate (0.117 g, 1.1 mmol), and sodium iodide (0.0075 g, 0.05 mmol) in dry DMF (5 mL) was stirred at 80 °C for 16–18 h. Water (5 mL) was added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3× 15 mL), the combined ethyl acetate layer was washed with water, dried over sodium sulphate, and concentrated. The residue thus obtained was subjected to column chromatography using chloroform–methanol as eluent to obtain **9** as oil. Yield: 0.40 g, 73.1%. IR (neat): 3430, 3289, 2930, 1690, 1605, 1466, 1370, 1129, 933, 786, 746 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.21–1.46 (m, 2H), 1.58 (s, 3H), 2.01–2.03 (m, 1H), 2.24–2.34 (m, 4H), 2.75–2.85 (m, 2H), 3.10–3.12 (m, 1H), 3.54–3.61 (m, 3H), 3.74–3.76 (m, 1H), 4.44–4.54 (m, 3H), 5.94–6.02 (m, 2H), 6.89–7.13 (m, 5H), 7.36–7.55 (m, 3H), 7.57–7.62 (m, 2H), 8.00–8.05 (m, 2H). ESI-MS: *m*/*z* 548 [M^++1]. Anal. Calcd for $C_{31}H_{34}FN_3O_3S$ (547): C, 67.98; H, 6.26; N, 7.67. Found: C, 68.01; H, 6.33; N, 7.32.

4.8. (6a*R**,11b*S**)-1-(4-Fluorophenyl)-1,2,3,4,6,6a,7,11b,-12,12a(RS)-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indol-7-yl}-butan-1-one (10)

A solution of the compound **9** (0.548 g, 1.0 mmol), in trifluoroacetic acid (1 mL), was stirred for 48 h. Water (5 mL) was added to the reaction mixture and it was extracted with ethyl acetate (3× 15 mL). The combined ethyl acetate layer was washed with water, dried over sodium sulphate, and concentrated. The residue thus obtained was subjected to column chromatography using chloroform–methanol as eluent to **10** as oil. Yield: 0.28 g, 71.2%. IR (neat): 3455, 3278, 2934, 1690, 1605, 1466, 1355, 1229, 933, 777, 747 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.25–1.35 (m, 2H), 1.96–2.15 (m, 5H), 2.18–2.38 (m, 5H), 3.16–3.82 (m, 6H), 3.11–3.17 (d, ^2J = 13.24, 1H), 6.68–6.77 (m, 2H), 6.95–7.36 (m, 4H), 7.90–8.00 (m, 2H). ESI-MS: *m*/*z* 394 [M^++1]. Anal. Calcd for $C_{24}H_{28}FN_3O$ (393): C, 73.26; H, 7.17; N, 10.68. Found: C, 73.53; H, 7.20; N, 10.89.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2007.07.018.

References and notes

1. Work Group on Schizophrenia. *Am. J. Psychiatry* **1997**, *153*, 1.
2. Seeman, P.; Chou-Wong, M.; Tadesco, J.; Wong, K. *Nature* **1976**, *261*, 717.
3. Seeman, P.; Lee, T. *Science* **1975**, *188*, 1217.
4. Peroutka, S. J.; Synder, S. H. *Am. J. Psychiatry* **1980**, *137*, 1518.
5. Fleischhacker, W. W. *Acta Psychiatr. Scand. Suppl.* **1995**, *388*, 24.
6. (a) Filton, A.; Heel, R. C. *Clozapine. Drugs* **1990**, *40*, 722; (b) Meltzer, H. Y. *J. Clin. Psychiatry* **1994**, *55*, 45.
7. Schwarz, J. T.; Brotman, A. W. *Drugs* **1992**, *44*, 981.
8. Meltzer, H. Y.; Matsubara, S.; Lee, J. C. *Psychopharmacol. Bull.* **1989**, *25*, 390.
9. Lowe, J. A. *Curr. Med. Chem.* **1994**, *1*, 50.
10. Drugs of the future **1978**, Vol. III, No. II, 803.
11. Saxena, A. K.; Ram, S.; Saxena, M.; Singh, N.; Prathipati, P.; Jain, P. C.; Singh, H. K.; Anand, N. *Bioorg. Med. Chem.* **2003**, *11*, 2085.
12. Rao, J.; Saxena, A. K.; Dua, P. R.; Shankar, G.; Bhalla, V. N. A process for the synthesis of 2,7-bis-γ-[(4-fluorobenzoyl)propyl]-1,2,3,4,6,6a,7,11b,12,12a-decahydropyrazino[2′,1′:6,1]pyrido[3,4-*b*]indole useful as potential CNS depressant agent. Indian Patent, INXXAP IN 168877, 1991; *Chem. Abstr.*, *118*, 124563.
13. Saxena, A. K.; Jain, P. C.; Anand, N.; Dua, P. R. *J. Med. Chem.* **1973**, *16*, 560.
14. Rao, J.; Chakrabarty, R.; Roy, R.; Mishra, A.; Saxena, A. K. *Arkivoc* **2005**, 20.
15. Waddington, J. L. *Gen. Pharmacol.* **1988**, *19*, 55.
16. Chipkin, R. E.; Iorio, L. C.; Coffin, V. L.; Mcquard, R. D.; Berger, J. G.; Barnett, A. *J. Pharmacol. Exp. Ther.* **1988**, *247*, 1093.
17. Hauber, W. *Neuroscience* **1996**, *73*, 121–130.
18. Sabol, K. E.; Seiden, L. S. *Brain Res.* **1998**, *806*, 69.
19. Pugh, M. T.; O'Boyle, K. M.; Molloy, A. G.; Waddington, J. L. *Psychopharmacology* **1985**, *87*, 308.