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Synthesis and evaluation of 1-(quinoliloxypropyl)-4-aryl piperazines for atypical antipsychotic effect

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ABSTRACT

A series of 1-(quinoliloxypropyl)-4-aryl-piperazines has been synthesized and the target compounds evaluated for atypical antipsychotic activity in apomorphine induced mesh climbing and stereotypic behaviour in mice. The 8-hydroxyquinoline ether derivative **14** has emerged as an important lead compound showing a potential atypical antipsychotic profile. Employing appropriate physicochemical properties, the similarity of the compounds was assessed with respect to some atypical antipsychotic drugs as clozapine, ketanserine, ziprasidone and risperidone.

Schizophrenia is a complex psychological disorder affecting about 1% of the population worldwide.[1] The use of classical neuroleptics such as chlorpromazine is associated with severe mechanism related side effects including parkinsonism and akathesia (extrapyramidal symptoms), tardive dyskinesia.[2,3] Clozapine, a dibenzodiazepine derivative,[4] prototype of the so called 'atypical antipsychotics' was the first compound to demonstrate a superior profile over conventional neuroleptics, that is, being nearly devoid of extrapyramidal side effects and alleviation of negative symptoms of schizophrenia. Unfortunately, its therapeutic use has been hampered by serious side effects, for example, agranulocytosis and sialorrhoea, attributed to its high affinity for a multitude of CNS receptors.[5,6]

The pertinent approaches for development of atypical antipsychotics include preferential D_4 versus D_2 receptor affinity,[7] preferential D_3 versus D_2 affinity,[8] combined 5-HT_2/D_2 receptor affinity,[9] 5-HT_{1A} agonism,[10] dopamine autoreceptor agonism,[11] sigma (σ) receptor blockade,[12] 5-HT_6 receptor antagonism,[13] 5-HT_3 antagonism,[14] partial glutamate agonists/antagonists, neurotensin agonism[15] or through direct animal studies.[16] In animal models, the atypical antipsychotics are identified by their inhibition of apomorphine induced climbing response (indicative of dopaminergic antagonism in mesocorticolimbic pathway associated with antipsychotic effect) along with weak or no inhibition of apomorphine induced stereotypy (characteristic of antagonism in nigrostriatal system linked to extrapyramidal symptoms).[17]

In this Letter, we report the synthesis and pharmacological evaluation of a new class of CNS active agents with a propoxyquinoline system linked to the 4-chlorobenzyl/benzoyl piperazine ring.

Synthetic scheme for preparation of target compounds **7–14** is summarized in Scheme 1. First step was the conversion of 6-hydroxyquinoline and 8-hydroxyquinoline to their 3-chloropropyl ether derivatives **1** and **2** by refluxing with 1-bromo-3-chloropropane in sodium metal and absolute ethanol. The amidation reaction of benzoyl chloride and 4-chlorobenzoyl chloride with piperazine afforded the compounds **3** and **4** in 80–88% yields**.** Benzyl piperazine and *p*-chlorobenzyl piperazine **5** and **6** were obtained in good yields (80–85%) from reaction of their corresponding aryl chlorides with piperazine. The final target compounds 6-[3-{4-(4-X-aryl)-piperazin-1-yl}-propoxy]quinolines (**7–14**) were prepared by refluxing the chloropropoxyquinolines with the piperazine derivatives in dimethyl formamide. All the reactions were monitored by thin layer chromatography and the products were characterized through spectroscopic data.[18] The target compounds were subjected to preliminary pharmacological evaluation to determine their ability to antagonize apomorphine induced mesh climbing behaviour and apomorphine induced stereotypy in mice. Doses were selected by initial titration at different dose levels. Clozapine group was employed as a standard (positive control).

In apomorphine induced mesh climbing assay, albino lyka mice (six in each group) of either sex (26–38 g) were habituated by individually placing in a circular cage made of wire mesh of diameter 13 cm and height 14 cm. Mice in the test, control and standard groups were injected, respectively, with the test compound, nor-

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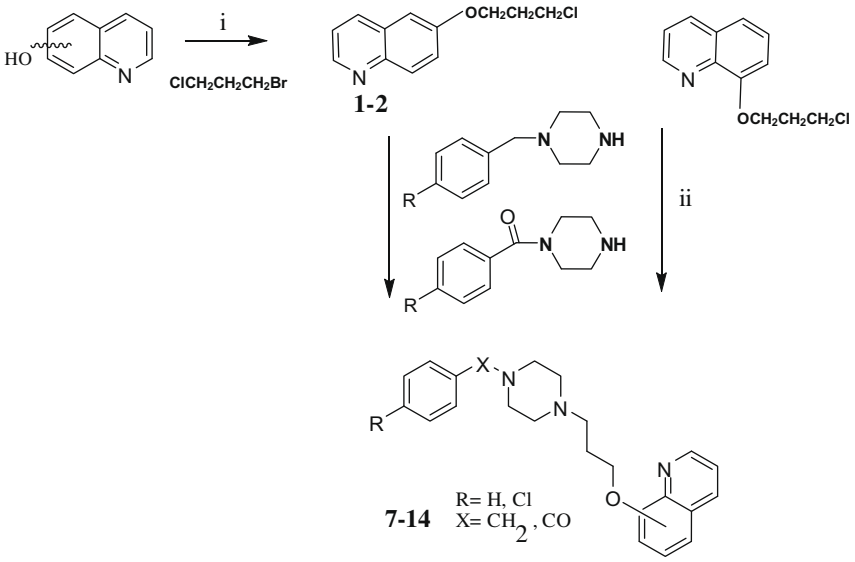


Scheme 1. Reagents and conditions: (i) Na, EtOH, 20–24 h; (ii) DMF, 18–20 h reflux.

mal saline and clozapine intraperitoneally and returned to the home cage. After a gap of 10 min, apomorphine (2.5 mg/kg) was injected intraperitoneally. Mesh climbing behaviour was noted at 10, 15, 20, 25 and 30 min after the apomorphine injection by placing the mice in the mesh cage for 60 s. Severity of the climbing behaviour was scored as 1 (one, two or three paws on the mesh) and 2 (all four paws on the mesh).

Apomorphine induced stereotypy assay was carried out with the same albino lyka mice employed in the mesh climbing assay. Stereotypy was noted at 10, 15, 20, 25 and 30 min after apomorphine injection by placing the animal in an inverted 500 ml beaker for 60 s. Scoring of stereotypy was done as 1 (rearing, sniffing, grooming) and 2 (licking, biting).

The final mean score results obtained in the both the assays are given in Tables 1 and 2 and graphically depicted in Figures 1 and 2. The test results were compared with the control group and statistical analysis was carried out employing non parametric Kruskal Wallis test or one way ANOVA. Level of significance was fixed at $p < 0.05$. Summary of results along with chemical structures of target compounds are given in Table 3.

Best amongst the series were 8-quinoline ether derivatives **10** and **14** (120 and 80 mg kg^{-1} ip, respectively). In the given test dose, both produced a statistically significant reduction in apomorphine induced mesh climbing behaviour (*H* values for **10** and **14 =** 9 and 68, respectively; >tabulated values) and **14** showed higher potency. However, both the compounds did not reverse apomorphine induced stereotypy at all (H values for **10** and **14 =** 0.098 and 29, respectively; <tabulated values). The 6-quinoline analogs of compounds **10** and **14** (compounds **8** and **12**; 25 and 5 mg kg^{-1}, respectively**)** did not produce statistically significant decrease in either of the assays. The benzoyl derivatives **7**, **9** and **11** (25, 20 and 1 mg kg^{-1} ip, respectively) reversed the apomorphine induced stereotypy behaviour significantly (*H* values for **7, 9** and **11 =** 5.77, 9 and 70, respectively; >tabulated values). The results show that

Table 1
Mean score of compounds in apomorphine induced mesh climbing assay

Time (min)	Mean score in compounds[a]									
	Control	7	8	9	10	11	12	13	14	Clozapine
10	3.3	2.2	3.0	3.1	0.6	1.2	2.6	3.1	0.2	2.2
15	1.8	3.5	2.6	3.6	1.2	3.6	1.8	3.2	0.6	2.2
20	2.3	2.5	2.4	3.0	0.8	1.6	1.6	3.2	0.4	3.0
25	1.5	1.6	2.8	2.5	1.4	1.1	1.6	2.9	0.8	2.8
30	2.1	1.2	2.0	2.0	1.0	1.1	0.8	2.7	0.0	2.4

[a] All values are expressed as mean SEM ($n = 5$).

Table 2
Mean score of compounds in apomorphine induced stereotypy assay

Time (min)	Mean score in compounds[a]									
	Control	7	8	9	10	11	12	13	14	Clozapine
10	3.8	1.3	4.0	0.8	3.4	0.6	3.6	1.2	2.2	4.0
15	4.8	1.5	3.6	1.5	4.4	0.8	3.8	1.1	4.6	4.6
20	3.5	1.1	4.2	0.7	3.6	0.1	4.0	0.7	3.2	3.8
25	2.5	1.0	4.4	0.5	2.4	0.1	4.2	0.8	1.8	3.6
30	1.6	1.8	3.4	0.6	1.8	0.5	4.4	0.6	1.4	3.6

[a] All values are expressed as mean SEM ($n = 5$).

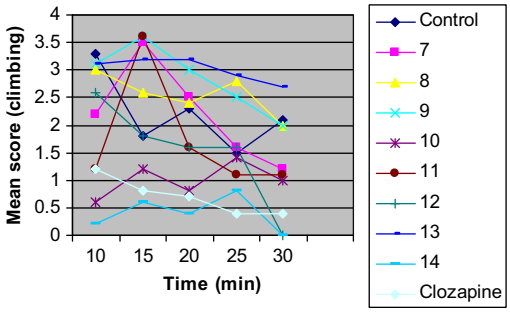


Figure 1. Mean score in apomorphine induced mesh climbing assay.

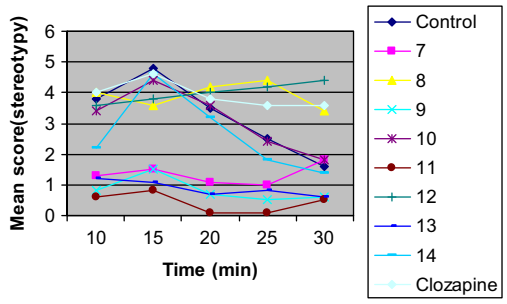
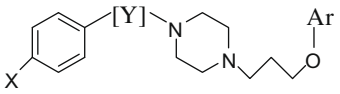


Figure 2. Mean score in apomorphine induced stereotypy assay.

Table 3
Chemical structures and averaged results in pharmacological testing



Compound no.	X	Y	Ar	Dose (mg/kg)	Significant mesh climbing	Reversal in stereotypy
7	H	C=O	6-Quinolyl	25	–	+
8	H	CH_2	6-Quinolyl	25	–	–
9	H	C=O	8-Quinolyl	20	–	+
10	H	CH_2	8-Quinolyl	120	+	–
11	Cl	C=O	6-Quinolyl	1	–	+
12	Cl	CH_2	6-Quinolyl	5	–	–
13	Cl	C=O	8-Quinolyl	5	–	+
14	Cl	CH_2	8-Quinolyl	80	+	–

the *p*-chloro derivatives have an increased potency over non chlorinated analogs. The 8-quinoline ether system is important for binding in mesolimbic areas as **10** and **14** have shown a profile suggesting an atypical antipsychotic potential. In contrast, the 6-quinoline ether system seems to selectively improve the binding affinity in the nigrostriatal region as the 6-quinoline analogs only cause a selective reversal of apomorphine induced stereotypy.

Further, a set of molecular parameters was computed for the target compounds using Chem3D Ultra and their physicochemical and steric similarity assessed with respect to standard drugs clozapine, risperidone, ziprasidone and ketanserine.[19] The steric and molecular surface descriptors include connolly solvent accessible surface area SAS (Å^2), connolly molecular surface area MS (Å^2), connolly solvent excluded volume SEV (Å^3) and Ovality. Global physicochemical properties computed were hydrophobic parameter log *P* and molecular weight MW (atomic mass units). Topological polar surface area, TPSA, important for prediction of drug transport properties including BBB penetration was also determined. Thereby, the distance d_i of a particular target compound *j* to drug molecules, for example, clozapine may be presented by the formula:

$$d_i^2 = \frac{\sum_{j=1}^{n}\left(1 - \frac{X_{i,j}}{X_{i,\mathrm{std}}}\right)}{n}$$

where $X_{i,j}$ is the value of molecular parameter *i* for compound *j*, $X_{i,\mathrm{std}}$ is the value of same molecular parameter for the standard drug, for example, clozapine. Then, the similarity of compound *j* to the standard drug was calculated as

$$\text{Similarity } (\%) = (1 - R) \times 100 \quad \text{where } R = \sqrt{d^2}$$

R is the quadratic mean (root mean square), a measure of central tendency. The calculation results obtained are presented in Table 4 and 5.[20] Average similarity of compounds **10** and **14** to clozapine is quiet less, that is, 56.85%. However, a much higher similarity to other drugs was noted (90.64%; 85.5% and 76.7% with respect to ziprasidone, risperidone and ketanserine, respectively).

In conclusion, a new series of quinolyloxy propyl piperazine derivatives has been investigated and two compounds **10** and **14** have shown promise as potential atypical antipsychotic agents. Their structural similarity to representative drug examples of this class further lends credence to these results.

Acknowledgments

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Table 4
Statistics and similarity values of test compounds to selected drug examples

Compd No.	Clozapine ***R***[a]	Ketanserine ***R***	Ziprasidone ***R***	Risperidone ***R***	Similarity[b,c] (%) to			
					Clozapine	Ketanserine	Ziprasidone	Risperidone
7	1.5385	0.1822	0.0906	0.1539	53.85	81.78	90.94	84.61
8	1.202	0.1542	0.0536	0.0515	20.2	84.58	94.64	94.85
9	1.469	0.1053	0.0296	0.1110	46.9	89.47	97.04	88.9
10	1.167	0.1178	0.0719	0.0359	67.0	88.22	92.81	96.4
11	1.848	0.5008	0.2515	0.3191	84.8	49.92	74.85	68.09
12	1.593	0.3574	0.1901	0.1670	59.3	64.26	80.99	83.30
13	1.808	0.3748	0.3128	0.304	80.8	62.52	68.72	69.60
14	1.467	0.3487	0.1153	0.2555	46.7	65.13	88.47	74.50

[a] Quadratic mean (root mean square mean).
[b] $(1 - R) \times 100$.
[c] Calcd from physicochemical properties: molecular weight; molar refractivity; connolly solvent accessible surface area; connolly molecular surface area; connolly solvent excluded volume; topological polar surface area; molecular topological index; Wiener index.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.04.019.

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18. *Data for selected compounds*: *Compound* **7**: IR (KBr, cm^{-1}): 3020, 1640. ^1H NMR (300 MHz, DMSO-d_6): δ 8.60 (d, 1H, J = 9.0 Hz), 8.10 (d, 2H, J = 9.0 Hz); 7.55–7.45 (m, 2H); 7.44–7.38 (m, 5H); 7.10 (s, 1H); 4.30 (t, 2H, J = 6.0 Hz); 2.50 (s, 8H); 2.05–1.98 (m, 4H). MS [EI, *m/z* (relative intensity)]: 375 [M^+], 105 (100) [C_6H_5CO]. Melting point: 185 °C; Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.6; H, 6.7; N, 11.2. Found: C, 73.01; H, 6.24; N, 10.87. Yield 65%.*Compound* **10:** IR (KBr, cm^{-1}): 3000, 1620, 1450. ^1H NMR (300 MHz, $CDCl_3$): δ 8.90 (d, 1H, J = 7.8 Hz), 8.10 (d, 1H, J = 7.8 Hz); 7.55–7.45 (m, 3H), 7.33–7.28 (m, 5H); 7.20 (d, 1H, J = 6.8 Hz); 4.60 (t, 2H, J = 6.0 Hz); 3.80 (s, 2H); 2.81–2.75 (m, 8H); 2.70 (t, 2H, J = 6.5 Hz); 2.23–2.18 (m, 2H). MS [EI, *m/z* (relative intensity)]: 361 [M^+], 91 (100) [$C_6H_5CH_2$]. Melting point: 191°C. Anal. Calcd for $C_{23}H_{27}N_3O$: C, 76.45; H, 7.5; N, 11.6. Found C, 75.98; H, 6.98; N, 11.0.Yield 72.5%.*Compound* **11**: IR (Nujol, cm^{-1}): 3100, 1560, 1450. ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.70 (s, 1H), 7.65 (s, 1H), 7.45–7.39 (m, 7H), 3.52 (t, 6H, J = 6.0 Hz), 3.34 (t, 6H, J = 6.0 Hz), 3.12 (t, 2H, J = 6.0 Hz), 1.80 (quintet, 2H, J = 6.0 Hz); MS [EI, *m/z* (relative intensity)]: 411 (M+2), 409 [M^+], 105 (100) [C_6H_4CHO]. Melting point: 240 °C. Anal. Calcd for $C_{23}H_{24}N_3O_2Cl$: C, 67.1; H, 5.8; N, 10.2. Found: C, 66.61; H, 5.32; N, 10.02. Yield 64.8%.*Compound* (**14**) IR (Nujol, cm^{-1}): 3100, 1450; ^1H NMR (300 MHz, $CDCl_3$): δ 8.80 (d, 1H, J = 6.0 Hz), 8.23–8.17 (m, 1H), 7.50 (s, 2H), 7.35 (d, 3H, J = 8.0 Hz), 7.25 (d, 4H, J = 8.0 Hz), 4.55 (t, 2H, J = 6.0 Hz), 3.53 (s, 2H), 3.23 (t, 4H, J = 6.0 Hz), 2.78–2.72 (m, 6H), 2.90–2.86 (m, 2H); MS[EI, *m/z* (relative intensity)]: 397 (M+2), 395 [M^+], 210, 168, 145, 125 (100) [Cl–$C_6H_4CH_2$], 85. Melting point: 210°C. Anal. Calcd for $C_{23}H_{26}N_3OCl$: C, 69.5; H, 6.5; N, 10.6. Found: C, 69.01; H, 6.32; N, 10.12. Yield 71.8%.
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20. Supplementary data: Table 5 depicting the values of molecular descriptors for the target compounds and standard drugs.