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Original article

Synthesis, antidepressant and antifungal evaluation of novel 2-chloro-8-methylquinoline amine derivatives

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ABSTRACT

A new series of *N*-[(2-chloro-8-methylquinolin-3-yl)methyl]-(substituted)-aniline/butylamine/cyclohexylamine/benzylamine derivatives (**4a**–**p**) was synthesized by nucleophilic substitution reaction of 2-chloro-3-(chloromethyl)-8-methylquinoline **3** with various aliphatic and aromatic amines in absolute ethanol in the presence of triethylamine (TEA). The newly synthesized secondary amines were characterized by the combined use of IR, ^{1}H NMR, ^{13}C NMR, mass spectral data and microanalyses. The antidepressant activity of the synthesized compounds (**4a**–**p**) was evaluated by Forced swim test in rats and their neurotoxicity was evaluated by the rotarod test. Test compounds and clomipramine were administered intraperitoneally at dose of 100 mg/kg and 20 mg/kg respectively. Preliminary antidepressant screening of compounds (**4a**–**p**) revealed that compounds **4b**, **4c**, **4d**, **4e**, **4i** and **4o** significantly ($P < 0.01$) reduces the duration of immobility time. These compounds were also tested in-vitro for MAO inhibitory effect. All the compounds were also screened for antifungal activity against *Aspergillus niger* MTCC 281, *Aspergillus flavus* MTCC 277, *Monascus purpureus* MTCC 369 and *Penicillium citrinum* NCIM 768 strains.

1. Introduction

Quinoline nucleus is one of the most important and widely exploited heterocyclic ring for the development of bioactive molecules. Recent literature is enriched with progressive findings about the synthesis [1] and pharmacological actions of quinoline and its derivatives. A number of quinoline derivatives are known to possess antibacterial, antifungal, antimycobacterial, antidepressant, antimalarial, anticonvulsant, antiviral, anticancer, hypotensive and antiinflammatory activities [2–13]. The target compounds were designed based on the fact that 2-(1-piperzinyl)quinoline (Quipazine) produces a weak inhibition of monoamine oxidase in both *in-vitro* and *in-vivo* studies is a quinoline derivative [14]. Moreover, the amine function which is frequently present in number of selective and non-selective MAO inhibitors is a structural requirement for the development of MAO inhibitors (Fig. 1) [15,16]. Keeping these facts in mind, it was planned to develop some newer derivatives of 2-chloroquinoline with enhanced and selective MAO inhibitory effect having freely rotatable methylene amine function linked to aromatic or aliphatic group. We report herein the synthesis of a series of *N*-[(2-chloro-8-methylquinolin-3-yl) methyl]-(substituted)-aniline/butylamine/cyclohexylamine/benzylamine derivatives (**4a**–**p**) as antidepressant agent. Since several antidepressant agents like sertraline, fluoxetine and citalopram etc. have also shown to possess potent fungicidal activity against various clinical isolates of *Aspergillus* species [17]. Therefore, it was thought worthwhile to carryout the antifungal activity of these compounds against fungal strains *Aspergillus niger* MTCC 281, *Aspergillus flavus* MTCC 277, *Monascus purpureus* MTCC 369 and *Penicillium citrinum* NCIM 768. Lipophilicity is an important parameter for compounds to manifest central nervous system (CNS) as well as antifungal activity. This thermodynamic property of newly synthesized quinolinyl amine derivatives was calculated by fragment-based algorithm using ACD/CLogP software (12.0 version).

2. Results and discussion

2.1. Chemistry

Target compounds were synthesized according to Fig. 2. The intermediate product 2-chloro-3-(chloromethyl)-8-methylquinoline

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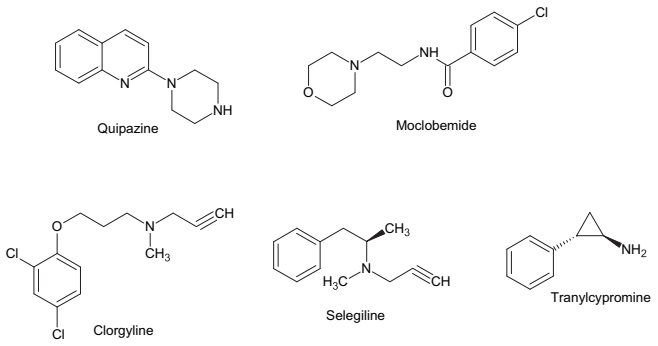


Fig. 1. Structure of Quipazine and various selective and non-selective MAO inhibitors.

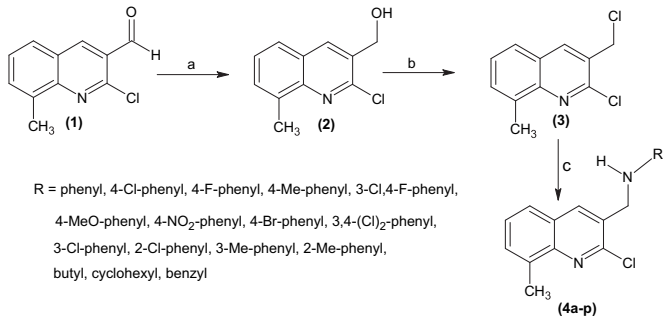


Fig. 2. Synthetic route to (**4a**–**p**). Reagent and conditions: (a) $NaBH_4$, methanol, stirring r.t. (b) $SOCl_2$, dry benzene, reflux. (c) Appropriate primary amine/ethanol, TEA, reflux.

3 was prepared in two steps from 2-chloro-3-formyl-8-methylquinoline **1** via its reduction with $NaBH_4$ followed by chlorination with $SOCl_2$. The quinolinyl amines (**4a**–**p**) were prepared by nucleophilic substitution reaction of **3** with various aliphatic and aromatic amines in absolute ethanol in the presence of base triethylamine. The structures of newly synthesized amines were elucidated by combined use of IR, ^1H and ^{13}C NMR and mass spectral data. The NH stretching and C–N stretching vibrations of CH_2NH- were observed in range of 3393–3441 cm^{-1} and 1021–1046 cm^{-1} respectively. In the ^1H NMR spectrum of intermediate **3** a sharp singlet at δ 4.85 arising due to $-CH_2Cl$ function was observed. However, this signal underwent slight upfield shift in compounds (**4a**–**p**) to δ values ranging from 3.98–4.58. This diamagnetic shift may be attributed to weak electron withdrawing effect of N as compared to Cl. Furthermore in ^{13}C NMR spectra, $-CH_2Cl$ carbon resonated at δ 43.11 which underwent slight paramagnetic shift in compounds **4a**, **4b**, **4c** to δ value 45.92, 46.18 and 46.39 respectively. These observations confirmed the successful substitution of chloromethyl group with amines in the final compounds (**4a**–**p**). This fact was further confirmed by the FAB-MS spectrometry of some selected compounds **4a**, **4b**, **4c** and **4d** which registered molecular ion peak at *m/z* 283, 317, 301 and 335 respectively. A fragment peak of $C_{10}H_6ClN^+$ at *m/z* 190 was found to be common in their mass spectra.

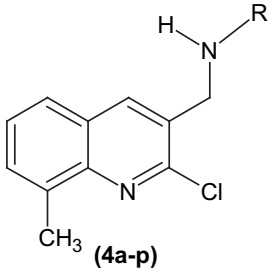
2.2. Antidepressant activity

The quinolinyl amines (**4a**–**p**) were evaluated for antidepressant activity by forced swim test in rats at dose of 100 mg/kg and compared with the standard drug clomipramine (20 mg/kg) and fluoxetine (20 mg/kg). Antidepressant activity was assessed as mean immobility time in seconds and data has been presented as Mean ± S.E.M in Table 2. Results of FST revealed that compounds **4b**, **4c**, **4d**, **4e**, **4i** and **4o** exhibited significant ($P < 0.01$) reduction in the immobility time compared to the control while compounds **4f**, **4j** and **4n** showed moderate antidepressant activity. Compound **4d** and **4e** were found to be the potent derivatives in this series. The preliminary SAR of quinolinyl amines suggested that compound with electron withdrawing groups (F and Cl) showed good antidepressant activity. Replacement of phenyl ring with aliphatic group like butyl causes reduction in antidepressant activity, whereas replacement with cyclohexyl group led to compound **4o** with retention of antidepressant activity. Rotarod test was performed to detect the minimal motor deficit in rats and results are reported in Table 2. Most of the compounds did not induce any significant effect on motor performance at dose of 100 mg/kg, while compound **4c**, **4e** and **4n** exhibited minimal motor deficit in rat as indicated by slight decrease in coordination time (91.33, 90.83 and 92.34 s) respectively. The lipophilicity data obtained within a homologous series of compound **4a**–**p** suggest that quinolinyl amines derivatives were fairly lipophilic in nature and compound **4d** and **4e** were most lipophilic (Clog P 5.77 and 5.86) and showed highest antidepressant activity.

2.3. MAO inhibition activity

The *in vitro* inhibition activities against monoamine oxidase MAO of selected compounds **4b**, **4c**, **4d**, **4e**, **4i** and **4o** was investigated by kynuramine fluorimetric assay method using rat brain homogenate as source of MAO. Results of MAO inhibition study in Table 3 revealed that test compounds **4b**, **4c**, **4d**, **4e**, **4i** and **4o** produces weak to moderate MAO inhibition ranging between (19.58 and 35.05%) at a final concentration of 5×10^{-4} M and maximum inhibition of 35.05 percent was obtained from compound **4e**.

Table 1
Chemical structure and physicochemical data of compounds (**4a**–**p**).



Compound No.	R	Yield[a] (%)	M.P. (°C)	R.f.[c]	Clog P[b]
4a	Phenyl	74	128–129	0.37	4.08 ± 0.25
4b	4-Cl-Phenyl	70	120	0.48	4.86 ± 0.42
4c	4-F-Phenyl	72	87–89	0.39	4.53 ± 0.36
4d	3-Cl,4-F-Phenyl	68	102–103	0.44	5.77 ± 1.17
4e	3,4-$(Cl)_2$-Phenyl	66	141–142	0.45	5.86 ± 1.17
4f	4-CH_3-Phenyl	77	83	0.36	4.54 ± 0.25
4g	4-OCH_3-Phenyl	67	98–100	0.35	3.90 ± 0.27
4h	4-Br-Phenyl	72	130–132	0.38	5.25 ± 0.36
4i	3-Cl-Phenyl	68	92–94	0.40	5.21 ± 1.17
4j	4-NO_2-Phenyl	52	167–169	0.35	4.53 ± 0.28
4k	2-CH_3-Phenyl	63	125	0.35	4.08 ± 0.25
4l	3-CH_3-Phenyl	73	109	0.33	4.08 ± 0.25
4m	2-Cl-Phenyl	70	165–166	0.38	4.59 ± 0.32
4n	Butyl	53	55–56	0.36	4.06 ± 0.26
4o	Cyclohexyl	47	67–68	0.37	4.54 ± 0.26
4p	Benzyl	63	126–127	0.42	4.37 ± 0.28

[a] After recrystallization from ethanol.
[b] Calculated from the ACD lab software 12.0.
[c] Benzene : Acetone (9.5 : 0.5).

Table 2
Antidepressant and antifungal evaluation data of compounds (**4a**–**p**).

Compound. No	Antidepressant[a] activity	Neurotoxicity	Antifungal activity[b]			
	Duration of immobility in sec. (Mean ± S.E.M)	Coordination time in sec. (Mean ± S.E.M)	*A. niger*	*A. flavus*	*M. purpeurus*	*P. citrinum*
4a	103.2 ± 3.06	100.33 ± 1.80	25 (6.0)	25 (6.5)	100 (7.0)	100 (6.0)
4b	77.2 ± 1.93**	95.17 ± 2.52	12.5 (7.5)	12.5 (6.5)	50 (7.0)	50 (6.0)
4c	80.4 ± 2.76**	91.33 ± 3.27	12.5 (6.0)	12.5 (6.0)	50 (8.0)	50 (7.0)
4d	74.2 ± 2.30**	93.67 ± 2.98	12.5 (8.5)	12.5 (8.5)	25 (5.5)	25 (6.0)
4e	73.6 ± 1.83**	90.83 ± 2.34	12.5 (8.0)	12.5 (9.0)	50 (8.0)	25 (6.5)
4f	96.6 ± 5.51*	96.50 ± 2.67	50 (6.0)	50 (7.0)	100 (7.5)	100 (6.0)
4g	Nt	Nt	50 (6.5)	50 (6.5)	100 (5.5)	100 (6.5)
4h	Nt	Nt	25 (5.5)	25 (6.0)	100 (7.0)	100 (6.5)
4i	76.2 ± 4.24**	97.83 ± 2.26	12.5 (5.5)	12.5 (6.0)	50 (6.5)	25 (5.5)
4j	86.8 ± 3.53**	93.50 ± 3.97	100 (7.0)	100 (6.5)	–	–
4k	Nt	Nt	100 (6.5)	100 (7.0)	–	–
4l	Nt	Nt	100 (6.0)	100 (5.5)	–	–
4m	Nt	Nt	50 (5.5)	50 (6.0)	100 (6.5)	100 (6.0)
4n	97.2 ± 3.56*	92.34 ± 3.09	–	200 (5.0)	–	200 (5.0)
4o	76.6 ± 2.51**	97.17 ± 2.36	200 (5.5)	200 (5.5)	–	200 (5.5)
4p	78.4 ± 3.71*	98.33 ± 2.93	12.5 (5.5)	12.5 (6.0)	100 (7.0)	100 (6.5)
Control	112.4 ± 2.88	116.50 ± 1.18	Nt	Nt	Nt	Nt
Clomipramine	63.4 ± 2.93	110.83 ± 1.49	Nt	Nt	Nt	Nt
Fluoxetine	55.4 ± 3.42	107.20 ± 3.18	6.25 (10.5)	6.25 (11.5)	6.25 (9.0)	6.25 (8.0)
Fluconazole	Nt	Nt	6.25 (13.5)	6.25 (14.5)	6.25 (11.0)	6.25 (12.0)

[a] Data was analyzed by Dunnet's test. $n = 6$; Dose = 100 mg/kg; $^{*}p < 0.05$, $^{**}p < 0.01$, (compared to control).
[b] MIC (Zone of inhibition in mm) and (–) mean no activity Nt-denotes not tested.

Table 3
In vitro inhibition activity of quinolinyl amine derivatives on rat brain mitochondria by kynuramine fluorimetric assay.

S. No.	Compound No.	Monoamine oxidase inhibition[a] (%)
1	4b	23.47 ± 0.96
2	4c	19.58 ± 1.05
3	4d	32.12 ± 0.83
4	4e	35.05 ± 1.20
5	4i	26.80 ± 1.10
6	4o	20.64 ± 1.52
7	Tranylcypromine[b]	91.56 ± 5.81

[a] Each value is the mean from three separate experiments with SE of mean. All compounds were used at a final concentration of 5×10^{-4} M.
[b] Concentration of tranylcypromine used $5.0 \times 10-6$ M.

2.4. Antifungal activity

The synthesized quinolinyl amine derivatives (**4a**–**p**) were also tested for their antifungal activity at conc. range of 6.25, 12.5, 25, 50 and 100 μg/ml. Results of antifungal screening revealed that out of sixteen new derivatives tested, six compounds viz. **4b**, **4c**, **4d**, **4e**, **4i**, and **4p** showed MIC at conc. of 12.5 μg/ml against *A. niger* MTCC 281 and *A. flavus* MTCC 277 as shown in Table 2. While compounds **4a**, **4f**, **4g**, **4h**, and **4m** exhibited MIC in the range of 25–50 μg/ml against *Aspergillus* strain and compound **4n** and **4o** were found to be least active against these fungal strains. In general compounds were more active against *A. niger* MTCC 281 and *A. flavus* MTCC 277 strains whereas less active against *M. purpureus* MTCC 369 and *P. citrinum* NCIM 768 strains. Results of antifungal activity revealed that in compounds **4n** and **4o** replacement of phenyl ring with aliphatic groups like butyl/cyclohexyl led to decrease in antifungal activity. In phenyl substituted compounds, presence of electron withdrawing groups like F, Cl, Br greatly increases the antifungal activity. Moreover, significant increase in antifungal activity was observed for dihalo-substituted derivatives **4d** and **4e** which found to possess maximum Clog *P* value in the present series.

3. Conclusion

The results of the study demonstrate that out of sixteen synthesized quinolinyl amine derivatives, six compounds showed antidepressant activity by forced swim test in rats and weak monoamine oxidase (MAO) inhibitory activity. Compounds with 4-chloro, 4-fluoro, 3-chloro-4-fluoro, 3,4-dichloro, 3-chloro and benzyl group exhibited both antifungal and antidepressant activities. Moreover in neurotoxicity study by rota rod method, most of the compounds were devoid of potential motor deficit in rats. Though the compound (3-chloro-*N*-[(2-chloro-8-methylquinolin-3-yl)methyl]-4-fluoro aniline) **4d** and (3,4-dichloro-*N*-[(2-chloro-8-methylquinolin-3-yl)methyl]aniline) **4e** emerged as most potential antifungal and antidepressant agents but the purposeful modification of compounds did not produce any significant enhancement in MAO inhibitory activity as expected. These finding suggest a different mechanism of action of these compounds beside inhibition of MAO.

4. Experimental

4.1. Chemistry

Melting points were determined by the open capillary method with electrical melting point apparatus and are uncorrected. IR spectra were recorded as KBr (pellet) on Bio Rad FT-IR spectrophotometer and ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 300 MHz spectrophotometer using DMSO-d_6 or $CDCl_3$ as an NMR solvent. Mass spectra were recorded on JEOL SX102/DA-6000 mass spectrometer using m-nitrobenzylalcohol as a matrix and elemental analysis on Vario-EL III CHNOS-Elemantar analyzer. Thin Layer Chromatography (TLC) was performed to monitor progress of the reaction and purity of the compounds, spot being located under iodine vapors or UV-light.

The starting material, 2-chloro-3-formyl-8-methylquinoline **1** was prepared according to the literature method [18].

4.1.1. Synthesis of 2-chloro-3-(hydroxymethyl)-8-methylquinoline *2*

To a solution of **1** (2.05 g, 0.01 mol) in absolute methanol (50 ml), solid $NaBH_4$ (0.46 g, 0.012 mol) was added portion wise over a period of 30 min with constant stirring at room temperature. The solvent was evaporated under reduced pressure and the residue was triturated with water (25 ml), when the crystalline solid separated out which was filtered, washed with water and

dried. The product was recrystallized from methanol to give colourless to cream colored crystals.

Yield: 82%; m.p.: 167–168 °C; IR (KBr) cm^{-1}; 3617 (OH), 1623 (C═C), 1599 (C═N), 758 (C–Cl). ^1H NMR (300 MHz, DMSO-d_6) δ; 2.74 (s, 3H, CH_3), 4.68 (s, 2H, CH_2), 5.66 (s, 1H, OH, D_2O-exchangeble), 7.46–7.51 (t, 1H, H-6, J = 7.5 Hz), 7.60–7.62 (d, 1H, H-7, J = 7.1 Hz), 7.84–7.86 (d, 1H, H-5, J = 7.8 Hz), 8.37 (s, 1H, H-4). ^{13}C NMR (75 MHz, DMSO-d_6) δ; 17.39 (CH_3), 59.88 (CH_2), 125.71, 126.91, 127.19, 130.01, 133.60, 135.22, 136.15, 145.10, 147.45. FAB-MS; m/z 208 (M^+), 210 (M+2). Anal. Calcd. for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.52; H, 4.83; N, 6.78%.

4.1.2. Synthesis of 2-chloro-3-(chloromethyl)-8-methylquinoline ***3***

To a solution of compound **2** (2.07 g, 0.01 mol) in dry benzene (30 ml), $SOCl_2$ (1.54 g, 0.013 mol) was added and the mixture was refluxed for 4–6 h. Solvent was evaporated under reduced pressure and the residue was dissolved in ether, washed with 10% $NaHCO_3$ and twice with water. It was then dried over Na_2SO_4 and concentrated in vacuo to give a residue which was crystallized from methanol as brown to light brown crystals.

Yield: 89%; m.p.: 80–81 °C; IR (KBr) cm^{-1}; 1624 (C═C), 1599 (C═N), 763 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.74 (s, 3H, CH_3), 4.85 (s, 2H, CH_2), 7.47–7.53 (t, 1H, H-6, J = 7.4 Hz), 7.61–7.63 (d, 1H, H-7, J = 7.2 Hz), 7.84–7.87 (d, 1H, H-5, J = 7.7 Hz), 8.24 (s,1H, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz) δ; 17.64 (CH_3), 43.11 (CH_2), 125.29, 127.04, 128.47, 130.85, 136.34, 138.72, 146.33, 148.37. FAB-MS; m/z 226 (M^+), 228 (M+2), 190 ($C_{11}H_9ClN^+$). Anal. Calcd. for $C_{11}H_9Cl_2N$: C, 58.43; H, 4.01; N, 6.19. Found: C, 58.63; H, 4.03; N, 6.23%.

4.1.3. General procedure for the synthesis of compounds ***4a–p***

Compound **3** (1.13 g, 0.005 mol) was dissolved in 20 ml of absolute ethanol and to this solution equimolar amount of substituted aniline/butyl/cyclohexyl/benzylamine (0.005 mol) along with 1 ml of triethylamine was added and the mixture was refluxed for 12–16 h. After completion of the reaction (monitored by TLC), the contents of the flask were reduced to one third of its volume and left overnight. The solid mass obtained was filtered, washed with water, dried and recrystallized from ethanol. The physical data of compounds **4a–p** is presented in the Table 1

4.1.3.1. N-[(2-chloro-8-methylquinolin-3-yl)methyl]aniline ***4a***. IR (KBr) cm^{-1}; 3418 (N-H), 1632 (C═C), 1591 (C═N), 1025 (C–N), 746 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.77 (s, 3H, CH_3), 4.33 (s,1H, NH), 4.56 (s, 2H, CH_2), 6.61–6.64 (d, 2H, H-2′ and 6′, J = 7.5 Hz), 6.71–6.76 (t, 1H, H-4′ J = 6.9 Hz), 7.14–7.19 (t, 2H, H-3′ and 5′, J = 7.0 Hz), 7.37–7.42 (t, 1H, H-6, J = 7.3 Hz), 7.51–7.58 (m, 2H, H-5 and 7), 8.10 (s,1H, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz) δ; 17.64 (CH_3), 45.92 (CH_2), 112.86, 116.36, 126.13, 127.24, 129.10, 131.64, 135.98, 140.07, 145.79 148.05, 149.87. FAB-MS; m/z 283 (M^+), 285 (M+2), 190 ($C_{11}H_9ClN^+$). Anal. Calcd. for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.39; H, 5.34; N, 9.95%.

4.1.3.2. 4-Chloro-N-[(2-chloro-8-methylquinolin-3-yl)methyl]aniline ***4b***. IR (KBr) cm^{-1}; 3392 (N–H), 1622 (C═C), 1581 (C═N), 1032 (C–N), 752 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.77 (s, 3H, CH_3), 4.37 (s,1H, NH), 4.54 (s, 2H, CH_2), 6.53–6.56 (d, 2H, H-2′ and 6′, J = 8.0 Hz), 7.09–7.12 (d, 2H, H-3′ and 5′, J = 7.7 Hz), 7.39–7.43 (t, 1H, H-6, J = 7.2 Hz), 7.52–7.59 (m, 2H, H-5 and 7), 8.05 (s,1H, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz) δ; 18.21 (CH_3), 46.18 (CH_2), 114.58, 123.87, 125.91, 126.76, 129.10, 131.64, 135.98, 140.07, 145.79 148.05, 149.87. FAB-MS; m/z 317 (M^+), 319 (M+2), 190 ($C_{11}H_9ClN^+$). Anal. Calcd. for $C_{17}H_{14}Cl_2N_2$: C,. 64.37; H, 4.45; N, 8.83. Found: C, 64.24; H, 4.46; N, 8.87%.

4.1.3.3. N-[(2-chloro-8-methylquinolin-3-yl)-methyl]-4-fluoroaniline ***4c***. IR (KBr) cm^{-1}; 3410 (N–H), 1629 (C═C), 1590 (C═N), 1023 (C–N), 765 (C–Cl).^1H NMR (300 MHz, $CDCl_3$) δ; 2.74 (s, 3H, CH_3), 4.36 (s,1H, NH), 4.55 (s, 2H, CH_2), 6.54–6.57 (d, 2H, H-2′ and 6′, J = 8.0 Hz), 7.13–7.16 (d, 2H, H-3′ and 5′, J = 7.7 Hz), 7.38–7.4 (t, 1H, H-6, J = 7.2 Hz), 7.54–7.61 (m, 2H, H-5 and 7), 8.09 (s,1H, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz) δ; 17.63 (CH_3), 46.39 (CH_2), 113.93, 121.82, 125.96, 127.42, 129.17, 130.98, 133.98, 136.08, 141.51, 146.96, 149.87, 153.47. FAB-MS; m/z 301 (M^+), 303 (M+2), 190 ($C_{11}H_9ClN^+$). Anal. Calcd. for $C_{17}H_{14}ClFN_2$: C, 67.89; H, 4.69; N, 9.31. Found: C, 67.70; H, 4.65; N, 9.35%.

4.1.3.4. 3-Chloro-N-[(2-chloro-8-methylquinolin-3-yl)methyl]-4-fluoroaniline ***4d***. IR (KBr) cm^{-1}; 3428 (N–H), 1636 (C═C), 1597 (C═N), 1036 (C–N), 749 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.75 (s, 3H, CH_3), 4.37 (s,1H, NH), 4.57 (s, 2H, CH_2), 6.55–6.57 (d, 1H, H-6′, J = 7.7 Hz), 6.71 (s, 1H, H-2′), 7.19–7.21 (d, 1H, H-5′, J = 7.7 Hz), 7.40–7.44 (t, 1H, H-6, J = 7.5 Hz), 7.52–7.60 (m, 2H, H-5 and 7), 8.10 (s,1H, H-4). FAB-MS; m/z 335 (M^+), 337 (M+2), 190 ($C_{11}H_9ClN^+$). Anal. Calcd. for $C_{17}H_{13}Cl_2FN_2$: C, 60.91; H, 3.91; N, 8.36. Found: C, 61.11; H, 3.92; N, 8.38%.

4.1.3.5. 3,4-Dichloro-N-[(2-chloro-8-methylquinolin-3-yl)methyl]aniline ***4e***. IR (KBr) cm^{-1}; 3420 (N–H), 1643 (C═C), 1602 (C═N), 1021 (C–N), 758 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.77 (s, 3H, CH_3), 4.39 (s,1H, NH), 4.54 (s, 2H, CH_2), 6.55–6.57 (d, 1H, H-6′, J = 7.8 Hz), 6.72 (s, 1H, H-2′), 7.18–7.20 (d, 1H, H-5′, J = 7.8 Hz), 7.40–7.44 (t, 1H, H-6, J = 7.5 Hz), 7.53–7.60 (m, 2H, H-5 and 7), 8.07 (s,1H, H-4). Anal. Calcd. for $C_{17}H_{13}Cl_3N_2$: C, 58.06; H, 3.73; N, 7.97. Found: C, 58.26; H, 3.71; N, 7.99%.

4.1.3.6. N-[(2-chloro-8-methylquinolin-3-yl)methyl]-4-methylaniline ***4f***. IR (KBr) cm^{-1}; 3396 (N–H), 1629 (C═C), 1598 (C═N), 1042 (C–N), 762 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.52 (s, 3H, Ph-CH_3), 2.75 (s, 3H, CH_3), 4.17 (bs,1H, NH), 4.52 (s, 2H, CH_2), 6.50–6.53 (d, 2H, H-2′ and 6′, J = 7.5 Hz), 6.79–6.81 (d, 2H, H-3′ and 5′, J = 7.0 Hz), 7.37–7.42 (t, 1H, H-6, J = 7.3 Hz), 7.53–7.60 (m, 2H, H-5 and 7), 8.11 (s, 1H, H-4). Anal. Calcd. for $C_{18}H_{17}ClN_2$: C, 72.84; H, 5.77; N, 9.44. Found: C, 72.97; H, 5.80; N, 9.48%.

4.1.3.7. N-[(2-chloro-8-methylquinolin-3-yl)methyl]-4-methoxyaniline ***4g***. IR (KBr) cm^{-1}; 3430 (N–H), 1637 (C═C), 1605 (C═N), 1046 (C–N), 758 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.76 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.09 (s,1H, NH), 4.51 (s, 2H, CH_2), 6.57–6.60 (d, 2H, H-2′ and 6′, J = 7.7 Hz), 6.75–6.77 (d, 2H, H-3′ and 5′, J = 6.5 Hz), 7.37–7.42 (t, 1H, H-6, J = 7.3 Hz), 7.53–7.59 (m, 2H, H-5 and 7), 8.10 (s,1H, H-4). Anal. Calcd. for $C_{18}H_{17}ClN_2O$: C, 69.12; H, 5.48; N, 8.96. Found: C, 69.30; H, 5.50; N, 8.98%.

4.1.3.8. 4-Bromo-N-[(2-chloro-8-methylquinolin-3-yl)methyl]aniline ***4h***. IR (KBr) cm^{-1}; 3428 (N–H), 1632 (C═C), 1588 (C═N), 1027 (C–N), 743 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.77 (s, 3H, CH_3), 4.39 (s,1H, NH), 4.54 (s, 2H, CH_2), 6.49–6.52 (d, 2H, H-2′ and 6′, J = 7.5 Hz), 7.23–7.26 (d, 2H, H-3′ and 5′, J = 7.4 Hz), 7.39–7.44 (t, 1H, H-6, J = 7.2 Hz), 7.52–7.59 (m, 2H, H-5 and 7), 8.04 (s,1H, H-4). Anal. Calcd. for $C_{17}H_{14}BrClN_2$: C, 56.46; H, 3.90; N, 7.75. Found: C, 56.33; H, 3.92; N, 7.78%.

4.1.3.9. 3-Chloro-N-[(2-chloro-8-methylquinolin-3-yl)methyl]aniline ***4i***. IR (KBr) cm^{-1}; 3417 (N–H), 1623 (C═C), 1593 (C═N), 1029 (C–N), 768 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.79 (s, 3H, CH_3), 4.46 (bs,1H, NH), 4.58 (s, 2H, CH_2), 6.49–6.52 (d, 1H, H-6′, J = 8.0 Hz), 6.63 (s, 1H, H-2′), 6.71–6.73 (d, 1H, H-4′, J = 7.6), 7.06–7.11 (t, 1H, H-5′, J = 7.9 Hz), 7.41–7.46 (t, 1H, H-6, J = 7.5 Hz), 7.56–7.63 (m, 2H, H-5 and 7), 8.08 (s,1H, H-4). Anal. Calcd. for

$C_{17}H_{14}Cl_2N_2$: C,. 64.37; H, 4.45; N, 8.83. Found: C, 64.51; H, 4.44; N, 8.86%.

4.1.3.10. 4-Nitro-N-[(2-chloro-8-methylquinolin-3-yl)methyl]aniline ***4j***. IR (KBr) cm^{-1}; 3422 (N–H), 1643 (C=C), 1598 (C=N), 1025 (C–N), 749 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.76 (s, 3H, CH_3), 4.12 (bs,1H, NH), 4.51 (s, 2H, CH_2), 6.55–6.58 (d, 2H, H-2′ and 6′, $J = 7.7$ Hz), 7.12–7.15 (d, 2H, H-3′ and 5′, $J = 7.5$ Hz), 7.39–7.42 (t, 1H, H-6, $J = 7.5$ Hz), 7.53–7.58 (m, 2H, H-5 and 7), 8.10 (s, 1H, H-4). Anal. Calcd. for $C_{17}H_{14}Cl\,N_3O_2$: C, 62.30; H, 4.31; N, 12.82. Found: C, 62.17; H, 4.29; N, 12.85%.

4.1.3.11. N-[(2-chloro-8-methylquinolin-3-yl)methyl]-2-methylaniline ***4k***. IR (KBr) cm^{-1}; 3441 (N–H), 1612 (C=C), 1590 (C=N), 1024 (C–N), 766 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.51 (s, 3H, Ph-CH_3), 2.77 (s, 3H, CH_3), 4.30 (s, 1H, NH), 4.56 (s, 2H, CH_2), 6.52–6.60 (m, 2H, Ar–H), 6.81–6.97 (m, 2H, Ar–H), 7.40–7.44 (t, 1H, H-6, $J = 7.4$ Hz), 7.59–7.65 (m, 2H, H-5 and 7), 8.03 (s, 1H, H-4). Anal. Calcd. for $C_{18}H_{17}ClN_2$: C, 72.82; H, 5.77; N, 9.44. Found: C, 72.63; H, 5.79; N, 9.47%.

4.1.3.12. N-[(2-chloro-8-methylquinolin-3-yl)methyl]-3-methylaniline ***4l***. IR (KBr) cm^{-1}; 3436 (N–H), 1627 (C=C), 1589 (C=N), 1036 (C–N), 755 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.52 (s, 3H, Ph–CH_3), 2.76 (s, 3H, CH_3), 4.36 (s,1H, NH), 4.57 (s, 2H, CH_2), 6.49–6.52 (d, 1H, H-6′, $J = 7.9$ Hz), 6.63 (s, 1H, H-2′), 6.71–6.73 (d, 1H, H-4′, $J = 7.6$ Hz), 7.06–7.11 (t, 1H, H-5′, $J = 7.9$ Hz), 7.41–7.46 (t, 1H, H-6, $J = 7.5$ Hz), 7.56–7.63 (m, 2H, H-5 and 7), 8.08 (s, 1H, H-4). Anal. Calcd. for $C_{18}H_{17}ClN_2$: C, 72.82; H, 5.77; N, 9.44. Found: C, 72.68; H, 5.75; N, 9.48%.

4.1.3.13. 2-Chloro-N-[(2-chloro-8-methylquinolin-3-yl)methyl]aniline ***4m***. IR (KBr) cm^{-1}; 3429 (N–H), 1618 (C=C), 1587 (C=N), 1036 (C–N), 762 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$) δ; 2.77 (s, 3H, CH_3), 4.33 (bs, 1H, NH), 4.54 (s, 2H, CH_2), 6.53–6.55 (d, 1H, H-6′, $J = 7.3$ Hz), 6.82–7.01 (m, 3H, H-3′,4′ and 5′), 7.43–7.48 (t, 1H, H-6, $J = 7.8$ Hz), 7.54–7.62 (m, 2H, H-5 and 7), 8.09 (s,1H, H-4). Anal. Calcd. for $C_{17}H_{14}Cl_2N_2$: C,. 64.37; H, 4.45; N, 8.83. Found: C, 64.49; H, 4.43; N, 8.80%.

4.1.3.14. N-[(2-chloro-8-methylquinolin-3-yl)methyl]butan-1-amine ***4n***. IR (KBr) cm^{-1}; 3405 (N–H), 1627 (C=C), 1594 (C=N), 1037 (C–N), 761 (C–Cl). ^1H-NMR (300 MHz, $CDCl_3$) δ; 0.98–1.03 (m, 3H, CH_3) 1.26–2.58 (m, 6H, 3 × CH_2), 2.76 (s, 3H, CH_3), 3.63 (s, 1H, NH), 3.98 (s, 2H, CH_2), 7.37–7.42 (t, 1H, H-6, $J = 7.6$ Hz), 7.54–7.60 (m, 2H, H-5 and 7), 8.11 (s, 1H, H-4). Anal. Calcd. for $C_{15}H_{19}ClN_2$: C, 68.56; H, 7.29; N, 10.66; Found : C, 68.71; H, 7.32; N, 10.68%.

4.1.3.15. N-[(2-chloro-8-methylquinolin-3-yl)methyl]cyclohexamine ***4o***. IR (KBr) cm^{-1}; 3416 (N–H), 1629 (C=C), 1588 (C=N), 1027 (C–N), 756 (C–Cl). ^1H-NMR (300 MHz, $CDCl_3$) δ; 1.23–1.44 (m, 4H, cyclohexyl 2 × CH_2) 1.73–1.87 (m, 4H, cyclohexyl 2 × CH_2), 1.96–2.07 (m, 2H, cyclohexyl CH_2), 2.71 (s, 3H, CH_3), 3.57–3.61 (m, 1H, cyclohexyl CH), 4.01 (s, 1H, NH), 4.17 (s, 2H, CH_2), 7.36–7.41 (t, 1H, H-6, $J = 7.4$ Hz), 7.52–7.59 (m, 2H, H-5 and 7), 8.09 (s, 1H, H-4). Anal. Calcd. for $C_{17}H_{21}ClN_2$: C,. 70.70; H, 7.33; N, 9.70. Found: C, 70.58; H, 7.29; N, 9.74%.

4.1.3.16. N-Benzyl-1-(2-chloro-8-methylquinolin-3-yl)methanamine ***4p***. IR (KBr) cm^{-1}; 3393 (N–H), 1637 (C=C), 1598 (C=N), 1031 (C–N), 763 (C–Cl). ^1H NMR (300 MHz, $CDCl_3$): δ 2.78 (s, 3H, CH_3), 3.80 (s, 2H, CH_2-Benzyl), 4.11 (s,1H, NH), 4.43 (s, 2H, CH_2), 6.59–6.62 (d, 2H, H-2′ and 6′, $J = 7.8$ Hz), 6.73–6.78 (t, 1H, H-4′ $J = 7.1$ Hz), 7.11–7.16 (m, 2H, H-3′ and 5′), 7.36–7.41 (t, 1H, H-6, $J = 7.6$ Hz), 7.53–7.61 (m, 2H, H-5 and 7), 8.10 (s, 1H, H-4). Anal. Calcd. for $C_{18}H_{17}ClN_2$: C,. 72.84; H, 5.77; N, 9.44. Found: C, 73.01; H, 5.72; N, 9.48%.

4.2. Antidepressant activity

Behavioral despair or forced swim test (FST) was proposed as a model to test antidepressant activity by Porsolt et al. [19]. It was suggested that mice or rats when forced to swim in restricted space from where they cannot escape are induced to a characteristic behavior of immobility. This behavior reflects a state of despair which can be reduced by several agents which are therapeutically effective in human depression. This behavioral despair test was employed to assess the antidepressant activity of newly synthesized amines. Albino rats of 150–180 g in a group of six each were used and on the first day of the experiment (pretest session), rats were individually placed in a cylindrical recipient (Plexiglass cylinder) of dimensions (diameter 20 cm, height 40 cm) containing 30 cm of water 25 ± 1 °C. The animals were left to swim for 15 min before being removed, dried and returned to their cages. The procedure was repeated 24 h later, in 5 min swim session (test session). The test compounds (100 mg/kg), fluoxetine (20 mg/kg) and clomipramine (20 mg/kg) were administered intraperitoneally (i.p.) as suspension in aqueous Tween 80 (02. % w/v, 0.9% NaCl) in three separate intraperitonel (i.p.) injections, at 1 h, 19 h, and 23 h after the first exposure to swimming a commonly used treatment regimen [20,21]. During 5 min test session, the duration of immobility was recorded. Immobility time is the time spent by rat floating in water without struggling, making only those moment necessary to keep the head above the water. The results of FST have been summarized in Table 2.

4.3. MAO inhibitory activity determination

Spectrophotofluorometric method was used for the determination of MAO activity of rat brain homogenate, using kynuramine as substrate [22,23]. The 4-hydroxy quinoline formed during oxidative deamination of kynuramine was measured fluorometrically using an activating light of 315 nM and measuring fluorescence at a maximum of 380 nM. The reaction mixture, in a total volume of 3 ml, consisted of phosphate buffer (0.5 ml, pH 7.5, 0.2M), 0.1 mM kynuramine and 0.5 ml of rat brain homogenate (equivalent of 10 mg of wet brain weight). Various quinolinyl amines were dissolved in DMSO/H_2O and added to the reaction mixture at a final concentration of 5×10^{-4} M. A control was run for each test and MAO inhibiting activity of compound was expressed as % inhibition of the control and reported in Table 3.

4.4. Neurotoxicity

Minimal motor impairment was measured in rats by the rotorod method [24]. The rats were trained to stay on an accelerating rotorod rotating at 30 rpm over 120 s. The trained animals were injected intraperitoneally with the test compounds **4a**–**p** at doses of 100 mg/kg, 30 min prior to the test session. Neurotoxicity was indicated by the inability of the animal to maintain equilibrilium on the rotating rod and results are reported as duration for which the animal is able to balance on the moving rod (i.e. till the animal falls) is noted as coordination time (mean ± S.E.M).

4.5. Antifungal activity

The newly synthesized compounds (**4a**–**p**) were screened for antifungal activity against *A. niger* MTCC 281, *A. flavus* MTCC 277, *M. purpureus* MTCC 369 and *P. citrinum* NCIM 768 in DMSO by cup-plate method [25]. Potato dextrose agar (Hi-media, Mumbai India)

was used as culture medium. Normal saline with tween 80 (0.01%) was used to make suspension of fungal spore for lawning. 50 ml of PDA medium was poured into each Petri dish (15 cm diameter). 5 ml of the spore suspension was spread over the solid agar medium and plates were dried in incubator at 37° for 1 h. Using an agar punch, wells were made on these seeded agar plates and solutions of test compounds in DMSO at conc. range of 6.25, 12.5, 25.0, 50, 100 and 200 μg/ml were added into each well, labeled previously. A control was also prepared using solvent DMSO. The Petri plates were prepared in duplicate and maintained at 30 ° for 72 h. The petri plates were incubated at 30 ° for 72 h. Antifungal activity was determined by measuring zone of inhibition and the minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. Activity of each compound (**4a**–**p**) was compared with standard fluconazole and results have been summarized as MIC (average zone of inhibition of two reading in ml) in Table 2.

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