Synthesis, CNS and chloroquin resistance reversal activity of benzenepropanamines  

V L Sharma a, b, Kalpana Bhandari a, Girija Shankar b, H K Singh b, Pratima Srivastava a & V C Pandey c  
Division of Chemical Technology a, Pharmacology b and Biochemistry, c  
Central Drug Research Institute, Lucknow-226001, India.  
Received 3 May 2002; accepted (revised) 17 March 2003

Several benzenepropanamines with a benzyl group attached to the 3-amino function are synthesized and evaluated for their CNS and chloroquin resistant reversal activity. The compounds are fully characterized by spectral and elemental analyses. These compounds are tested for their effect on gross behaviour and for antidepressant, anticonvulsant and anorexigenic activity. No effect is observed on gross behaviour where as most of them show fluoxetine like anantipside and anorexigenic activity. Since this class of compounds have been reported to modulate the chloroquin resistance in P. falciparum, therefore these compounds are tested for chloroquin resistance reversal activity in vitro. Five compounds selectively inhibit P. falciparum heme oxygenase like fluoxetine.

The development of antidepressant drugs having unique and novel properties, such as reduced side effects, enhanced clinical efficacy and the potential for a rapid onset of action is a viable and realistic research objective since it is the major area which would remain one of the unmet medical needs to year 2005 (ref. 2). Phenylpropamines class of antidepressants, fluoxetine and paroxetine (SSRI) has been top selling products in last many years 3, 4. It suggests their efficacy, specificity of action and acceptibility but these are not devoid of side-effects 5 such as delayed onset of action 6, slow elimination 7 specially in liver 8 and renal impairments 9 and suicide ideation 10, 11.

In view of above observations, it was thought worthwhile to work upon benzenepropanamines (10-18) (Scheme 1) with a benzyl group attached to the 3-amino function along with the required methyl group as in fluoxetine skeleton were prepared. It was hoped that this additional benzyl group in fluoxetine nucleus may enhance lipophilicity 12 of the molecule and thus in turn availability in the brain. The N-demethylation of these compounds may give rise to the metabolites which may not accumulate in the body tissues as in case of desmethyl fluoxetine. The phenyl ring of 3-N-benzylamine function was substituted with 4-methoxy and N,N-dimethylamino groups with a view to further enhance the lipophilicity 13. The methoxy group may provide additional advantage of not being accumulated after demethylation during metabolism. The metabolite hydroxy derivative might be excreted in the form of a water-soluble glucuronide 14. These compounds (10-18) were supposed to act via 5 HT-mechanism like fluoxetine 15, therefore, evaluated for biological activities related to serotonin 16 such as antidepressant, anorexigenic and anticonvulsant activity.

These compounds also fulfill some important characteristics 17 of drug resistance reversal modulators e.g., lipid solubility, two planer aromatic rings and a tertiary nitrogen atom. Fluoxetine has also been reported to posses in vitro chloroquin resistance reversal activity 18, 19. Therefore, these compounds (10-18) may exhibit chloroquin resistance reversal activity as well as antidepressant activity with least side effects. Results of various activities may help in understanding the structure activity relationship.

Chemistry

The compounds (10-18) were synthesized according to Scheme 1. N-Methyl benzylidines (4-6) were synthesized by appropriate benzaldehyde (1-3) and methyamine. These benzylidines were reduced to corresponding benzylmethyl amines (7-9) by catalytic hydrogenation at room temperature. 3-Substituted benzylmethyl aminopropionophenones (10-12) were synthesized by mannich reaction of acetophenone and benzylmethyl amines (7-9). These keto compounds were reduced by sodium borohydride to corresponding alcohol (13-15). The reactions of these alcohol (13-15) with p-chlorobenzotri fluoride in presence of sodium hydride in dimethyl acetamide gave N-methyl-N-substituted benzyl-3-(4-triluoromethyl)phenoxybenzenepropanamines (16-18). The compounds (10-18) were converted into their hydrochloride salts and characterized by 1H NMR, mass spectra and elemental analyses (Table 1).

Pharmacology

The study was carried out in albino mice (weighing between 16-20g) of either sex. Each group comprises of 5 animals. All the compounds were administered in
a dose of 75 μmol/kg i.p. as aqueous solution or aqueous suspension in gum acacia. Gross behavioural effects\(^{19}\), anticonvulsant\(^{20}\), antidepressant\(^{21}\), anorexigenic\(^{22}\) and anxiolytic activity\(^{23}\) were carried out by standard methods. Saline treated controls were run concurrently. Chloroquin resistance reversal activity was assayed by inhibition of heme oxygenase at 10μg/mL concentration\(^{24}\). The results are given in Table II.

The compounds tested have no effect on gross behaviour, however fluoxetine had shown the sign of stimulation. In antireserpine tests all the compounds except 13 showed weak to moderate activity (25-50%), whereas fluoxetine showed 100% reversal of reserpine induced ptosis and sedation. None of the compounds had any remarkable effect on reserpine induced hypothermia like fluoxetine\(^{25}\). Compounds 13 and 18 exhibited significant anorexia (>40 - 50%), like fluoxetine which caused high degree of anorexia (80%). No effect was observed in anticonvulsant activity with compounds in MES and antimetrazole tests whereas fluoxetine showed 20% activity in MES test as reported\(^{26}\). In the antihypoxia test, all the compounds including fluoxetine showed enhancement in survival time as compared to control but it was far too less than diazepam.

Results and Discussion

The results indicate that in fluoxetine skeleton, on N-benzylation at 3-methylamino group and also on replacement of trifluoromethoxy moiety by keto or hydroxy grouping at position-1 the antireserpine
### Table I — Physical data of the compounds 10-18

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>m.p./ b.p. (°C)</th>
<th>Yield (%)</th>
<th>Mass, Mol. formula</th>
<th>IR (µ)</th>
<th>IH NMR (δ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>H</td>
<td>187-88</td>
<td>92</td>
<td>C₁₁H₁₂NO.HCl</td>
<td>3035, 2902</td>
<td>3.17-3.21(t, 2H, 2-CH₃), 3.56(s, 2H, CH₂-Benzyl), 7.22-7.30(m, 5H, ArH, Benzyl), 7.42-7.48(m, 2H, 3, 5' ArH), 7.53-7.58(m, 1H, 4', ArH), 7.92-7.95(m, 2H, 2' &amp; 6' ArH) (free base)</td>
</tr>
<tr>
<td>11</td>
<td>OCH₃</td>
<td>62-66</td>
<td>63</td>
<td>C₁₀H₁₅NO₂.HCl</td>
<td>3332, 2900</td>
<td>2.67-2.69(m, 2H, 2-CH₂), 3.34-3.38(m, 2H, 3-CH₂), 3.81(s, 6H, N-CH₃ &amp; OCH₃), 4.07-4.28(m, 2H, CH₂-Benzyl), 6.95-6.97(m, 2H, ArH adjacent to OCH₃), 7.45-7.62(m, 5H, ArH), 7.98-8.01(d, 2H), 3.81(s, 2H, ArH adjacent to keto, J=9.0 Hz), 12.46(bs, 1H, NH)</td>
</tr>
<tr>
<td>12</td>
<td>N(CH₃)₂</td>
<td>182-85</td>
<td>84</td>
<td>C₁₉H₂₆N₂O.HCl</td>
<td>3409, 2900</td>
<td>2.24(s, 3H, N-CH₃), 2.81-2.88(m, 2H, 3-CH₂), 2.89(s, 6H, NCH₂), 3.13-3.20(m, 2H, 2-CH₂), 3.46(s, 2H, CH₂-Benzyl), 6.65-6.69(d, 2H, ArH adjacent to N(CH₃), J=8.6Hz), 7.12-7.16(d, 2H, ArH adjacent to CH₃, J=8.6Hz), 7.38-7.53(m, 3H, ArH), 7.89-7.94(m, 2H, ArH adjacent to keto) (free base)</td>
</tr>
<tr>
<td>13</td>
<td>H</td>
<td>121-22</td>
<td>82</td>
<td>C₂₁H₂₄F₃N₂O.HCl</td>
<td>3250, 3078</td>
<td>1.86-2.05(m, 2H, 2-CH₂), 2.27(s, 3H, N-CH₃), 2.57-2.87(m, 2H, 3-CH₂), 3.46-3.68(q, 2H, CH₂-Benzyl Jₐ=12.9Hz, Jₐ=12.6Hz), 4.90-4.94(m, 1H, 1-CH), 7.21-7.38(m, 10H, ArH)</td>
</tr>
<tr>
<td>14</td>
<td>OCH₃</td>
<td>108-10</td>
<td>77</td>
<td>C₁₉H₁₄N₂O₂.HCl</td>
<td>3338, 3030</td>
<td>2.17-2.27(m, 2H, 2-CH₂), 2.67(s, 3H, N-CH₃), 3.04-3.35(m, 2H, 3-CH₂), 3.81(s, 3H, OCH₃), 4.64-4.72(m, 2H, CH₂-Benzyl), 5.0-5.02(m, 1H, 1-CH), 6.90-6.92(m, 2H, ArH adjacent to OCH₃), 7.24-7.47(m, 7H, ArH), 11.30(bs, 1H, NH)</td>
</tr>
<tr>
<td>15</td>
<td>N(CH₃)₂</td>
<td>184-86</td>
<td>57.7</td>
<td>C₁₆H₁₄N₂O₂.HCl</td>
<td>3440, 2937</td>
<td>1.81-1.91(m, 2H, 2-CH₂), 2.25(s, 3H, NCH₃), 2.56-2.87(m, 2H, 3-CH₂), 2.92(s, 6H, N(CH₃)₂), 3.35-3.60(q, 2H, CH₂-Benzyl, Jₐ=12.63Hz, J₉=12.64Hz, 4.85-4.90(m, 1H, 1-CH), 6.67-6.72(d, 2H, ArH adjacent to N(CH₃), J₀=8.66Hz), 7.17-7.21(d, 2H, ArH adjacent to CH₃, J₀=8.76Hz)</td>
</tr>
<tr>
<td>16</td>
<td>OCH₃</td>
<td>145-47</td>
<td>77</td>
<td>C₁₇H₁₃F₂N₂O.HCl</td>
<td>3440, 2937</td>
<td>2.45-2.58(m, 2H, 2-CH₂), 2.69(s, 3H, N-CH₃), 2.92-3.33(m, 2H, 3-CH₂), 4.10-4.24(m, 2H, CH₂-benzyl), 5.30-5.56(m, 1H, 1-CH), 6.82-6.84(m, 2H, ArH adjacent to O), 7.26-7.43(m, 10H ArH), 7.43-7.55(m, 2H, ArH adjacent to CF₃, J₀=12.35-13.5(bs, 1H, NH)</td>
</tr>
<tr>
<td>17</td>
<td>OCH₃</td>
<td>194-96</td>
<td>89</td>
<td>C₁₇H₁₃F₂N₂O₂.HCl</td>
<td>3440, 2937</td>
<td>2.40-2.74(m, 5H, 2-CH₂ &amp; NCH₃), 3.02-3.39(m, 3H, 3-CH₃), 3.82(s, 3H, OCH₃), 4.03-4.21(q, 2H, CH₂-benzyl), 5.41-5.54(m, 1H, 1-CH), 6.79-6.93(m, 4H, ArH adjacent to O), 7.27-7.39(m, 9H, ArH)</td>
</tr>
<tr>
<td>18</td>
<td>N(CH₃)₂</td>
<td>173-75</td>
<td>69</td>
<td>C₁₇H₁₃F₂N₂O₂.HCl</td>
<td>2928, 2852</td>
<td>1.99-2.07(m, 2H, 2-CH₂), 2.20-2.66(m, 2H, 3-CH₂), 2.86 (s, 6H, NMe₂), 3.37-3.46(m, 2H, CH₂-benzyl), 5.29-5.35(m, 1H, -CH), 6.58-6.62(d, 2H, ArH adjacent to N), 6.84-6.88(d, 2H, ArH adjacent to O), 7.06-7.11(d, 2H, ArH adjacent to CH₃), 7.22-7.30(m, 5H, ArH), 7.38-7.43(d, 2H, ArH adjacent to CF₃)</td>
</tr>
</tbody>
</table>

*Compounds gave satisfactory elemental analyses.

NOTES 209
activity was partly retained. Among the \(N\)-benzyl groups 4-methoxy substituents were found to be more active (11 and 17). In these compounds the major side effect of fluoxetine, i.e., anorexia was minimized. The two compounds 13 and 18 which have shown significant anorexigenic activity were almost devoid of antidepressant activity. Thus it can be concluded that these compounds may lead either to an antidepressant or to an anorexigenic agent.

Five compounds (10-12, 16 and 17) have selectively inhibited the \(P. falciparum\) heme oxygenase at 10 \(\mu g/\) mL concentration, rest of them were either inactive (18) or inhibited (13-15) the heme oxygenase of both the host and \(P. falciparum\). It suggested that the modification carried out at position-1 and 3 in fluoxetine skeleton have no effect on chloroquine resistance reversal activity except the 1-hydroxy compounds (13-15) which were not selective in inhibiting the heme oxygenase of host and parasite both. The results further confirm the structural requirements for drug resistance reversal agents.

**Experimental Section**

Melting points were determined in open capillaries in an electrically heated block and are uncorrected. The progress of the reaction was monitored by TLC. IR spectra (\(v_{\text{max}}\) in cm\(^{-1}\)) were recorded in KBr or neat on a FTIR 8201 PC instrument. \(^1\)H NMR spectra on Brucker DRX 200 MHz instrument using TMS as internal standard (Chemical shifts in \(\delta\) ppm) and mass spectra on a JEOL JMS D300 instrument at 70 eV. The physical data of compounds (10-18) are given in Table I.

<table>
<thead>
<tr>
<th>Compd (^a)</th>
<th>Antidepressant activity (^b)</th>
<th>Reversal of reserpine induced prossis and sedation</th>
<th>Anorexigenic activity (^c)</th>
<th>Milk left in milk consumption test</th>
<th>Anticonvulsant activity (^d)</th>
<th>MES test</th>
<th>Antijhypoxia activity (^e)</th>
<th>Mean survival time, SEM (% increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10(^f)</td>
<td>+</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>23.4±1.21(24.46)</td>
</tr>
<tr>
<td>11(^f)</td>
<td>++</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22.0±0.17(17.02)</td>
</tr>
<tr>
<td>12(^f)</td>
<td>+</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.2±0.86(7.44)</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24.0±1.52(27.05)</td>
</tr>
<tr>
<td>14</td>
<td>+</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24.8±1.93(31.9)</td>
</tr>
<tr>
<td>15</td>
<td>+</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>21.4±1.50(13.82)</td>
</tr>
<tr>
<td>16(^f)</td>
<td>+</td>
<td>12</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>21.4±1.08(13.32)</td>
</tr>
<tr>
<td>17(^f)</td>
<td>++</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22.4±1.21(19.14)</td>
</tr>
<tr>
<td>18</td>
<td>+</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20.6±1.03(9.57)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>++++</td>
<td>80</td>
<td>20</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>23.2±1.16(23.49)</td>
</tr>
</tbody>
</table>

\(^a\)No effect on gross behaviour. \(^b\)No effect on hypothermia, a change of < 2°C was insignificant, (+) = 25%, (-) = no effect. \(^c\)An anorexia of < 40% was insignificant. \(^d\)No protection in amphetamine test, (+) = no protection. \(^e\)Control value of survival time 18.8 ± 0.98 min; Diazepam showed the mean survival time 33.4 ± 1.21 min with an increase of 77.65%.

Compounds (7-9) were prepared by known procedure. 3-[\(N\)-methyl-\(N\)-(4-substituted benzyl)]aminopropiophenone (10-12). A mixture of amine (0.055 mole) and propanol (25 mL) was cooled in an ice-bath (0-5°C) for 25 min and concd HCl (0.07 mL) was added dropwise with stirring. After 30 min the mixture was allowed to attain room temperature and paraformaldehyde (1/5th of the required 0.075 mole) was added. The flask was heated at 100-110°C for 30 min. Similarly other three portions of paraformaldehyde were added and finally the reaction mixture was heated for 2 hr at 100-110°C. Then it was allowed to cooled to room temperature overnight. Concentration followed by cooling of the reaction mixture gave the compounds (10-12) as hydrochloride salts.

3-[\(N\)-methyl-\(N\)-(4-substituted benzyl)]aminol-phenyl-propanol (13-15). A solution of keto compounds (10-12, free base; 0.013 mole) in methanol (25 mL) was cooled in ice-bath for 30 min and powdered sodium borohydride (0.037 mole) was added in equal portions in 1 hr. The reaction mixture was further stirred in ice-bath for 30 min. The reaction mixture was concentrated under reduced pressure in a rotavapor and the residue was treated with water
(5 mL) and ethyl acetate (30 mL). The ethyl acetate layer was separated, washed with water till neutral washings and dried (anhyd. Na₂SO₄). The resultant free bases were converted into hydrochloride salts (13-15).

N-methyl-N-(4-substituted benzyl)-3-[4-(trifluoromethyl)phenoxy]benzene-propanamines (16-18).

A mixture of sodium hydride (0.0382 mole) and dimethylacetamide (DMAC; 15 mL) was cooled in an ice-bath for 15 min and a solution of hydroxy compounds (13-15; 0.024 mole; free base) in DMAC (10mL) was added dropwise with stirring. After 15 min the reaction mixture was allowed to attain room temperature. The flask was then placed in an oil bath and heated slowly to 80°C in 90 min. The oil bath temperature was maintained 80-90°C for another 2 hr. The colour changed from yellow to brown. This brown solution was cooled to room temperature and p-chlorobenzotrifluoride (0.0382 mole) was added in 15 min with stirring. The mixture was again heated at 100-110°C for 5-6 hr. The r.m. was allowed to attain room temperature and treated with ethyl acetate and water successively. The organic layer was separated and aqueous layer was extracted with ethyl acetate. The combined ethyl acetate layer was washed with water till neutral pH and dried (anhyd. Na₂SO₄). The concentration of the organic layer gave free base (16-18) as oils which were transformed into respective hydrochloride salts (16-18).

Acknowledgement
The authors are thankful to Mrs Tara Rawat for technical assistance.

References
4. Scrip (World pharmaceutical news bulletin), No 2428, April 14th 1999, 8.
5. Scrip (World pharmaceutical news bulletin), No 2549, June 16th 2000, 15.
25. Beil, 12, 1019.