Roles of Two Basic Nitrogen Atoms in 1-Substituted
4-(1,2-Diphenylethyl)piperazine Derivatives in Production of Opioid
Agonist and Antagonist Activities

Kagayaki Natsuka,* Yoshinori Nishikawa, and Hideo Nakamura


Received May 10, 1999; accepted August 23, 1999

To ascertain roles of the two basic nitrogen atoms in 1-substituted 4-[2-(3-hydroxyphenyl)-1-phenylethyl]-
piperazine derivatives (1) in the expression of opioid agonist and antagonist activities, a methine group (CH) was
isosterically substituted for nitrogen atom at the 1-position (N-1) in compound 1 to obtain 4-substituted 1-[2-(3-
hydroxyphenyl)-1-phenylethyl]piperidine derivatives (2). Their analgesic action and ability to produce physical
dependence (jump-producing activity) as the μ-opioid receptor specific in vivo actions, and narcotic antagonist
action in mice were compared with those of compound 1. Results of this study showed that, in cases of the race-
mate and the (S)-(+) enantiomer, opioid agonist activities (analgesic and jump-producing activities) were not
greatly affected by the methine-substitution for N-1 in compound 1, but that the narcotic antagonist activity of
the (R)-(−) enantiomer was abolished by this substitution. It thus appears that N-1 in compound 1 contributes to
the expression of narcotic antagonist activity, whereas the nitrogen atom at the 4-position corresponds to the
tyramine moiety necessary for the expression of μ-opioid agonist activity.

Key words μ-opioid agonist; opioid antagonist; diphenylethylpiperazine; role of two basic nitrogen atoms

Morphine is known to produce its specific pharmacologi-
cal activities of analgesic action and physical dependence liabil-
ity through the μ-opioid receptor binding. A morphine
molecule has a 2-(4-hydroxyphenyl)ethylamine (tyramine)
moiety possibly essential for opioid receptor binding. The
tyramine moiety is also found in most opioids thought to
bind specifically with μ-opioid receptor. Morphine-type
analogues are known to acquire narcotic antagonist activity
when a group such as an allyl or a cyclopropylmethyl group
is introduced onto the nitrogen atom of the tyramine moiety.
Kolb considers this to be due to a substitution-induced change in
the N-lone pair (electron lobe). Thus, the nitrogen
atom of the tyramine moiety may be essential for the expres-
sion of the agonist and antagonist activities of morphine-
type analogues. Unlike these opioids, however, a group of
strong analogues, 1-substituted 4-[2-(3-hydroxyphenyl)-1-
phenylethyl]piperazine derivatives (1), contain two nitrogen
atoms in the molecule (Fig. 1). The nitrogen atom at the 4-
position (N-4) in compound 1 may correspond to the
narcotic atom of the tyramine moiety included in a morphine
molecule. However, there is also a possibility that the nitrogen
atom of the 1-position (N-1) in compound 1 pharmacologi-
cally corresponds to the nitrogen atom of the tyramine
moiety, since narcotic antagonist activity was induced by in-
troduction of a narcotic antagonist group (e. g., a cyclobutyl-
methyl group and a 3-methyl-2-butenyl group) onto N-1. Thus,
these role of these two nitrogen atoms in the expres-
sion of opioid agonist and antagonist activities, 4-substi-
tuted 1-[2-(3-hydroxyphenyl)-1-phenylethyl]piperidine deriv-
atives (2) were synthesized by isosteric substitution of
N-1 with a methine (CH) group, and their analgesic action
and ability to produce physical dependence as the μ-opioid
receptor specific in vivo actions, and narcotic antagonist
action in mice were investigated and compared with those of
compound 1.

Chemistry Compounds 2a and 2b were synthesized by
the routes shown in Chart 1. Racemic 2b was first prepared
as follows. Benzaldehyde and potassium cyanide were re-
acted with 4-cyclohexylpiperidine (6) according to the
method of Goodson and Christopher to give a phencyl-
benzotriazole derivative (7). Then, compound 5b was prepared by
the Grignard reaction from compound 7 and m-methoxyben-
ylbenzylmagnesium chloride, and was converted to (±)-2b by
demethylation with 47% hydrobromic acid. Compounds (−)
2a, (+)-2a, (−)-2b, and (−)-2b were prepared as follows.
The intermediate, 1,5-dichloro-3-cyclohexylpentane (4b),
was prepared by catalytic reduction of 1,5-dihydroxy-3-
phenylpentane in the presence of a platinum oxide catalyst
followed by chlorination with thionyl chloride. Compounds
(−)-5a and (−)-5b were obtained by reactions of (R)-(−)-2-
(3-methoxyphenyl)-1-phenylethylamine [(R)-(−)-3] with
1,5-dihalopentanes (4a and 4b), respectively, in the presence of
sodium hydrogen carbonate. Compounds (−)-2a and (−)-2b
were then heated with 47% hydrobromic acid to give (−)
2a and (−)-2b, respectively. Compounds (−)-2a and (−)-2b
were derived from (R)-(−)-3, hence they each had the R-con-
figuration. Compounds (S)-(+)2a and (S)-(+)2b were also derived from (S)-(+)3 by the above two step reactions. The
compounds thus synthesized are listed in Tables 1 and 2.

Pharmacological Results and Discussion

Each synthesized compound was subcutaneously injected
into mice, and its analgesic activity was examined by the tail
flick method. Narcotic antagonist activity was assessed by
the tail flick method using antagonist action to morphine as

![Fig. 1](image_url)
an index. The ability to produce physical dependence in mice was assessed by the jumping test[15,16] (Table 3).

As reported previously, among the (R)-(−)-enantiomers of 1-substituted 4-[2-(3-hydroxyphenyl)-1-phenylethyl]-piperazine derivatives (I), some compounds with relatively strong analgesic activity and weak jump-producing activity were antagonistic to opioids. Unlike analgesic activity, antagonist activity toward opioids was observed only for the (R)-(−) enantiomers, whereas the (S)-(+) enantiomers failed to show such antagonist activity.5 Analytic ED50-values of (S)-(−)-1b, (S)-(+)−1b and (R)-(−)-1b have been reported to be 0.126, 0.054 and 4.24 mg/kg, s.c.,8 and both (S)-(+)−1a and (R)-(−)−1a to be more than 80 mg/kg, s.c.9

The analgesic potency of (z)−2b was 0.39 times that of (z)−1b and 10.4 times that of morphine hydrochloride for the molar basis. The analgesic potency of (S)-(+)−2b was 0.19 times that of (S)-(+)−1b, whereas (R)-(−)-2b was 5.34 times more potent than the corresponding (R)-(−)−1b (Table 3). The potency ratios of the (S)-(+)−enantiomers to the racemates were 1.94 for (S)-(+)−1b and 0.95 for (S)-(+)−2b. Similarly, the ratios of the (S)-(+)−enantiomers to the (R)-(−)-enantiomers were 78.6 and 2.81 for 1b and 2b, respectively. Thus, the substitution of N-1 with a methine group caused somewhat of a decrease in analgesic activity and an recognizable decrease in enantioselectivity. At a maintenance dose of 1 mg/kg (3.99 mg/kg/2 d), both (z)−2b and (S)-(+)−2b produced jumping in all mice tested (jumping incidence = 100%). Thus, this may show that jumping possibly has parallel analgesic activity, as noted for (z)−1b and (S)-(+)−1b (jump-producing ED50-value: 1.16 and 0.24 mg/kg, s.c., respectively).6 However, (R)-(−)-2b showed certain jump-producing activity (Table 3) as did also (S)-(−)-2b, in contrast to the finding5 that the maximum jump rate among doses up to 20 mg/kg tested for (R)-(−)-1b was only 40%. Namely, the jump-producing activity of the racemate and the (S)-(+)−enantiomer was only slightly affected by the methine-substitution for N-1, whereas that of the (R)-(−)-enantiomer was potentiated by this substitution. Neither (z)−2b nor (S)-(+)−2b showed antagonist action toward opioids, as true in the case of (z)−1b and (S)-(+)−1b. Compound (R)-(−)-1b was antagonistic to opioids, with maximum reversal rate of 50% at a dose of 2 mg/kg, s.c.,10 but not (R)-(−)-2b. Compound (R)-(−)-1a was clearly antagonistic to opioids, with antagonistic ED50-value of 86.8 mg/kg, s.c.,8 whereas (R)-(−)-2a was not (Table 3). Thus, the methine-substitution of N-1 abolished the antagonist activity of the (R)-(−)-enantiomers.

As described above, the isoteric substitution of N-1 with a methine group had no significant effect on the analgesic or

### Table 1. 4-Substituted 1-(1,2-Diphenylethyl)piperidine Derivatives

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-2a</td>
<td>OH</td>
<td>H</td>
<td>HCl</td>
<td>A</td>
<td>220−221</td>
<td>iso-PrOH 79</td>
<td>C18H24NO2HCl</td>
</tr>
<tr>
<td>(+)-2a</td>
<td>OH</td>
<td>H</td>
<td>HCl</td>
<td>A</td>
<td>220−221</td>
<td>iso-PrOH 76</td>
<td>C18H24NO2HCl</td>
</tr>
<tr>
<td>(+)-5a</td>
<td>OMe</td>
<td>H</td>
<td>HCl</td>
<td>B</td>
<td>254−255</td>
<td>EtOH 54</td>
<td>C18H24NO2HCl</td>
</tr>
<tr>
<td>(+)-5a</td>
<td>OMe</td>
<td>H</td>
<td>HCl</td>
<td>B</td>
<td>254−255</td>
<td>EtOH 54</td>
<td>C18H24NO2HCl</td>
</tr>
<tr>
<td>(+)-5a</td>
<td>OMe</td>
<td>H</td>
<td>HCl</td>
<td>C</td>
<td>217−222</td>
<td>EtOH 60</td>
<td>C18H24NO2HCl</td>
</tr>
<tr>
<td>(+)-5a</td>
<td>OMe</td>
<td>C6H11</td>
<td>Maleate</td>
<td>B</td>
<td>140−142</td>
<td>EtOH 56</td>
<td>C18H24NO2-C6H5O5</td>
</tr>
<tr>
<td>(+)-5a</td>
<td>OMe</td>
<td>C6H11</td>
<td>Maleate</td>
<td>B</td>
<td>140−142</td>
<td>EtOH 46</td>
<td>C18H24NO2-C6H5O5</td>
</tr>
<tr>
<td>(+)-5a</td>
<td>OMe</td>
<td>C6H11</td>
<td>Maleate</td>
<td>A</td>
<td>160−163</td>
<td>EtOH 86</td>
<td>C18H24NO2</td>
</tr>
<tr>
<td>(+)-5a</td>
<td>OMe</td>
<td>C6H11</td>
<td>Maleate</td>
<td>A</td>
<td>196−198</td>
<td>EtOH 83</td>
<td>C18H24NO2-0.5C6H5O5</td>
</tr>
<tr>
<td>(+)-5a</td>
<td>OMe</td>
<td>C6H11</td>
<td>Maleate</td>
<td>A</td>
<td>196−198</td>
<td>EtOH 83</td>
<td>C18H24NO2-0.5C6H5O5</td>
</tr>
</tbody>
</table>

a) Capital letters refer to the procedures in the Experimental Section. b) All compounds were analyzed for C, H, N, and, where present, CI; analytical results were within ± 0.4% of the theoretical values.

### Table 2. Data for Optical Rotation

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Salt</th>
<th>Conf.[a]</th>
<th>[α]D°</th>
<th>deg (c, t)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-2a</td>
<td>HCl</td>
<td>S</td>
<td>+89.1</td>
<td>(1.00, 27)</td>
</tr>
<tr>
<td>(+)-2a</td>
<td>HCl</td>
<td>R</td>
<td>−89.1</td>
<td>(1.00, 27)</td>
</tr>
<tr>
<td>(+)-2b</td>
<td>0.5(−)-tartrate</td>
<td>S</td>
<td>+70.0</td>
<td>(0.50, 26)</td>
</tr>
<tr>
<td>(+)-2b</td>
<td>0.5(−)-tartrate</td>
<td>R</td>
<td>−69.7</td>
<td>(0.50, 26)</td>
</tr>
</tbody>
</table>

a) Absolute configuration. b) Solvent: McOH.
jump-producing activity of the racemate and the (S)(+)-enantiomer, whereas it abolished antagonist activity of the (R)(−)-enantiomers toward opioids. Thus, the nitrogen atom at the 1-position in the molecule of 1-substituted 4-[2-(3-hydroxyphenyl)-1-phenylpentyl]piperazine derivatives (1) possibly contributes to the expression of antagonist action to opioids, and the nitrogen atom at the 4-position may correspond to the nitrogen atom of the tyramine moiety essential for analgesic activity. A relationship between the expression of agonist antagonist activity and receptors for morphine-like analogues is satisfactorily demonstrated by the above mentioned model of Kolb6) and the model of Snyder and colleagues.17) The latter17) assert that binding subsites may be present on the opiate receptor comprising agonist and antagonist binding sites in addition to an amine binding site. The relation between the two nitrogen atoms in compound 1 appears to support the hypothetical concept of these researchers.

### Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were obtained with a digital polarimeter (Model DIP-4, Japan Spectroscopic Co., Ltd.). Electron impact mass spectra (EI-MS) were recorded on a Hitachi RMU-6L spectrometer using the direct inlet system at 70-eV ionization potential. 3-(4-Cyclohexylpiperidinyl)phenylacetone (7) This compound was prepared from 4-cyclohexylpiperidine (6) in a manner similar to that described in the literature.25) EI-MS, m/z 282 (M⁺); Yield 99%.

1,5-Dichloro-3-cyclohexylpentane (4b) This compound was prepared by catalytic hydrogenation (4.0 kg/cm²) of 1,5-dihydroxy-3-phenylpentane (11) in the presence of a platinum oxide catalyst followed by chlorination with thionyl chloride: bp 125—127°C (4 mmHg), EI-MS, m/z 222 (M⁺); Yield 82%.

### Table 3. Analgesic, Narcotic Antagonist and Jump-Producing Activities of 4-Substituted 1-(1,2-Diphenylethyl)piperidine Derivatives in Mice

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Salt</th>
<th>Ed₅₀ mg/kg, s.c. (95% confidence limits)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-2a</td>
<td>HCl</td>
<td>&gt;80</td>
</tr>
<tr>
<td>(+)-2b</td>
<td>HCl</td>
<td>&gt;80 Inactive</td>
</tr>
<tr>
<td>(+)-2b</td>
<td>Maleate</td>
<td>0.293 (0.231—0.418) Inactive</td>
</tr>
<tr>
<td>(+)-2b</td>
<td>0.5(+)-tartrate</td>
<td>0.283 (0.192—1.13) Inactive</td>
</tr>
<tr>
<td>(+)-2b</td>
<td>0.5(−)-tartrate</td>
<td>0.796 (0.240—1.24) Inactive</td>
</tr>
<tr>
<td>Morphine</td>
<td>HCl</td>
<td>2.39 (1.78—3.20)</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>HCl</td>
<td>3.79 (1.47—9.74)</td>
</tr>
</tbody>
</table>

### Acknowledgments

We are grateful to Drs. M. Hashimoto and Y. Sekine for valuable discussions and encouragement throughout this work. Thanks are also due to members of our pharmacological section for the biological evaluation and to the staff of our analytical section for elemental analyses and spectral measurements.

### References and Notes

1) Present address: Regulatory Affairs & Pharmacovigilance, Dainippon Pharmaceutical Co., Ltd., Doshomachi 2-6-8, Chuo-ku, Osaka 541-0045, Japan.


