# (+)-cis-N-(Para-, Meta-, and Ortho-substituted benzyl)-N-normetazocines: Synthesis and Binding Affinity at the [<sup>3</sup>H]-(+)-Pentazocine-Labeled ( $\sigma$ 1) Site and Quantitative Structure-Affinity Relationship Studies

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 $\sigma 1$  receptor ligands have potential pharmacological significance as antipsychotic drugs, as tools in the study of drug-induced motor function disorders, and as radiopharmaceutical imaging agents for the noninvasive imaging of malignant tumors in human subjects. A series of substituted N-benzyl-N-normetazocines were synthesized and their binding affinity at the  $\sigma 1$ receptor evaluated in order to examine the details of the structure-affinity relationships (SAR) of a previously determined high-affinity lead compound, (+)-cis-N-benzyl-N-normetazocine ( $K_i$ = 0.67 nM). Variation in the benzyl substituents of these compounds produced a 1590-fold range in affinity at the  $\sigma$ 1 receptor from the unsubstituted benzyl analog to the lowest affinity *p-tert*-butylbenzyl analog ( $K_i = 1066$  nM). The nanomolar binding affinity for the  $\sigma 1$  receptor of (+)-cis-N-(4-fluorobenzyl)-N-normetzocine suggests that this analog may be a useful PET imaging agent.

# Introduction

The  $\sigma$  receptor was originally hypothesized by Martin et al. to explain the human psychotomimetic and canine delirium effects of  $(\pm)$ -N-allyl-N-normetazocine (1).<sup>1</sup> However, with the discovery that the (+)-enantiomer of 1 and other benzomorphans bind to the  $\sigma$  receptor and the (-)-isomers to opioid receptors, it was recognized that the  $\sigma$  receptor was distinct from the opioid receptor. Recently,  $\sigma$  receptors have been the subject of investigation both to verify their existence and to establish the possible neurophysiological role of central  $\sigma$  receptors.<sup>2,3</sup> The finding that both classical and atypical antipsychotic drugs bind to  $\sigma$  receptors has prompted studies to identify new high-affinity and specific  $\sigma$  ligands as useful antipsychotic drugs.<sup>4,5</sup>  $\sigma$ ligands are also of pharmacological interest due to the apparent association of  $\sigma$  receptors with both inherited and antipsychotic drug-induced motor function disorders.<sup>2</sup> More recently, the possible involvement of  $\sigma$ receptors in various neurological disorders and the observation that  $\sigma$  receptors are expressed in human and rodent brain tumors<sup>6</sup> have prompted the search for radiolabeled  $\sigma$  ligands suitable as positron emission computerized tomography (PET) or single photon emission computerized tomography (SPECT) radiopharmaceutical diagnostic agents.<sup>7-10</sup> Research into both the nature and pharmacological implications of  $\sigma$  receptors has been hampered by the lack of high-affinity, highspecificity ligands.

Since ligands from several structural classes bind with high affinity to the  $\sigma$  receptor, structural-affinity (SAR) and molecular modeling studies have been difficult.  $\sigma$  pharmacophore models have been proposed based on SAR studies on several individual classes of  $\sigma$ ligands.<sup>11-21</sup> The wide variety of rigid and flexible structural motifs that bind to the  $\sigma$  receptor has

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affinity analog has been used as a starting point for

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receptors, has been shown to require the 2'-hydroxyl substituent.<sup>12,23</sup> Benzomorphan analogs lacking this (+)-1 (+)-2

provided a somewhat ambiguous picture of the possible pharmacophoric requirements at this receptor. An

additional complication is the identification of two  $\sigma$ 

has focused on benzomorphan derivatives. The benzo-

morphan ring system provides a convenient rigid back-

bone for probing the pharmacophoric requirements of

 $\sigma$  receptor sites. For the purposes of such SAR studies

the benzomorphan nucleus can be conceptually divided

into three zones: the aromatic ring (A), the saturated

or morphan segment (B), and the nitrogen substituent

to the size of the nitrogen substituent (zone C) as can

be seen in a comparison of the PCP/ $\sigma$  K<sub>i</sub> ratios of (+)-

N-allyl-N-normetazocine (1), (3.77) and (+)-pentazocine

(2), (1303).<sup>12</sup> Affinity at the other major receptor

binding target of (–)-benzomorphans, the  $\mu$  and  $\kappa$  opioid

In general, PCP receptor binding affinity is sensitive

Our search for high-affinity, specific  $\sigma$  receptor ligands

receptor subtypes,  $\sigma 1$  and  $\sigma 2.^{22}$ 

(C) (Figure 1).



(zone A) hydroxyl lack opioid but retain  $\sigma$  receptor

affinity.<sup>14</sup> In a previously published study of zone C

analogs, (+)-N-benzyl-N-normetazocine (3) was found to have the highest  $\sigma$  receptor affinity (0.67 nM) of any

benzomorphan analog examined to date.<sup>12</sup> This high-

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Figure 1. Structure-activity relationship zones for the benzomorphan structure.

further SAR studies into the details of the influence of N-substituents (zone C) on  $\sigma$  receptor binding affinity. In this paper we describe the synthesis,  $\sigma$ 1 receptor binding affinity, and structure-affinity relationship results for a series of 2-, 3-, and 4-substituted benzyl-N-normetazocines.

**Chemistry.** (+)-(1S,5S,9S)-*cis-N*-Normetazocine (4) was the starting material for the entire series of *N*-(substituted benzyl)normetazocines **5**-**22**. Alkylation of (+)-*N*-normetazocine with the appropriate benzyl halide and sodium hydrogen carbonate in ethanol gave compounds **5**, **7**-**13**, **16**, **21**, and **22** indicated in Table 1. Compounds **6**, **14**, and **17**-**20** were prepared by reductive amination using the appropriate substituted benzaldehyde, sodium cyanoborohydride, and acetic acid in methanol. Reduction of the nitro analog **9** with nickel boride afforded the 4-aminobenzyl derivative **15**.

## **Results and Discussion**

The  $\sigma 1$  receptor binding affinity of the (+)-cis-N-(substituted benzyl)normetazocines expressed as  $K_i$  are listed in Table 1. Of the 19 compounds in this series tested, the unsubstituted benzyl analog remains the highest affinity ligand for the  $\sigma 1$  receptor. Variation in functional group type and position on N-benzyl substituents produces significant differences in the affinity of normetazocines for the  $\sigma$ 1 receptor. This SAR trend of N-(substituted benzvl)-N-normetazocines contrasts with observations by other workers of the relative insensitivity of  $\sigma$  binding affinity to aromatic substitution in certain other classes of  $\sigma$  ligands. ^{16,7,24} Binding affinities ranged by a factor of 1590, spanning the highest (benzyl, compound **3**) to lowest (4-tert-butylbenzyl, compound **22**) affinity compounds. It is interesting to note that substitution with electron-withdrawing (p-F, p-CN, p-NO<sub>2</sub>, p-Cl; compounds 5, 7, 9, 10), electrondonating  $(p-OCH_3, \text{ compound } 11)$  and neutral  $(p-CH_3, p-CH_3)$ compound 8) substituents all showed high-affinity for the  $\sigma$ 1 site. Substituent volume at the benzyl para position has a clear effect on binding potency as observed in the rank order of potency  $H \ge F \ge Cl \ge Br$ > I > t-Bu (3 > 5 > 10 > 12 > 14 > 22). Another trend is apparent in the influence of substituent position on binding potency. For a given substituent, the rank order of binding potency of positional isomers is para > meta > ortho. Substituent volume appears to play a role in this trend also, as binding potency is uniformly more sensitive to substituent volume at positions in the order ortho > meta > para. For example, increasing the size of the para substituent from F (compound 5) to I (compound 14) decreases binding potency by a factor of 17 while the same increase in substituent volume at the ortho position decreases binding potency by a factor of 641 (compounds 6 and 21).

These results suggested that a quantitative structure– affinity relationship (QSAR) analysis based only on the volume of the para, meta, and ortho substituents (measured in Å<sup>3</sup>) might lead to a good correlation. An analysis of the entire set of compounds correlating binding affinity  $(K_i)$  with volume (in Å<sup>3</sup>) of the substituents gave eq 1. A similar analysis using only the parasubstituted compounds gave eq 2. The increasingly

$$log(1/K_i) = 0.05(para volume) - 0.07$$
(meta volume) -0.11(ortho volume) + 0.22 (1)

$$n = 19, s = 0.34, F = 45.11, r^2 = 0.90$$

$$log(1/K_i) = 0.05(para volume) + 0.19$$
 (2)

$$n = 14, s = 0.34, F = 76.53, r^2 = 0.86$$

greater sensitivity of binding affinity to the volume occupied by substituents in the ortho, meta, and para positions noted above is reflected quantitatively in eq 1 by the relative magnitude of the volume coefficients (ortho 0.11 > meta 0.07 > para 0.05). A graph of binding affinity (expressed as  $log(1/K_i)$ ) calculated by eq 1 compared to the actual values is shown in Figure 2. The 4-aminobenzyl analog (15) is an outlier, with its binding affinity significantly overestimated by the QSAR equation. Assuming the amino analog binds to the  $\sigma$ 1 receptor in the same mode as the other compounds, this deviation from the size—affinity relationship may be an indication that solvation of the primary amine may create a molecular aggregate occupying a larger effective substituent volume.

In order to determine the relative importance of lipophilicity  $(\pi)$  to the binding potency within the series of substituted N-benzylnormetazocines an analysis of the 14 para-substituted analogs correlating binding potency with  $\pi$  and molar refractivity (MR) was conducted and gave eq 3. Although this correlation of lipophilicity to  $\sigma 1$  binding affinity gave a somewhat

$$\log(1/K_{\rm i}) = 0.12\pi - 0.33\pi^2 - 0.11\rm{MR} + 0.27 \quad (3)$$
  
n = 14, s = 0.42, F = 16.54, r<sup>2</sup> = 0.83

poorer performance than the QSAR equations based only on substituent volume, it did suggest that lipophilicity might play a role in the binding of ligands to the  $\sigma 1$  receptor.

This possibility was explored by conducting a series of 3D-QSAR studies using the Sybyl CoMFA<sup>26</sup> module in combination with Sybyl steric/electrostatic CoMFA fields and Hint<sup>27</sup> hydrophobic/polar fields. An initial CoMFA/PLS analysis of compounds 3 and 5-22 was performed using the Sybyl steric/electrostatic CoMFA fields. As substituent volume had been found to correlate well with binding affinity, the steric field contribution was expected to be significant. However, the low value (+0.39) of the cross-validated  $r^2$  ( $q^2$ ), the correlation of the CoMFA fields and binding affinity is not sufficient to provide a valid predictive model. A second PLS analysis using both the Sybyl CoMFA steric/ electrostatic and Hint hydrophobic/polar fields also did not produce a predictively valid model ( $q^2 = +0.27$ ). Although weak, the correlations produced by the 3D-QSAR studies based on either steric/electrostatic fields or a combination of steric/electrostatic and hydrophobic/

**Table 1.** Physical, Chemical, and  $\sigma$  Binding Data for (+)-cis-N-(Substituted benzyl)-N-normetazocines



compd	R <sub>1</sub>	$R_2$	R <sub>3</sub>	method <sup>a</sup>	% yield	mp, °C	$[\alpha]^{21}$ <sub>D</sub> , deg (c, EtOH)	formula <sup>c</sup>	$K_{i}^{d}$
<b>3</b> <sup>b</sup>	н	Н	н		37				$0.67 \pm 0.10$
5	F	н	н	Α	41	163.2 dec	109.3 (0.075)	C <sub>21</sub> H <sub>25</sub> ClFNO-0.5H <sub>2</sub> O	$0.97 \pm 0.12$
6	н	н	$\mathbf{F}$	В	28	156.1 dec	88.9 (0.09)	C <sub>21</sub> H <sub>25</sub> ClFNO-0.25H <sub>2</sub> O	$1.45\pm0.16$
7	CN	н	н	Α	55	174.2 dec	115.3 (0.085)	C22H25ClN2O-0.25H2O	$1.53\pm0.14$
8	$CH_3$	н	н	Α	26	166.0 dec	106.3 (0.08)	C22H28CINO-0.75H2O	$2.08\pm0.05$
9	$NO_2$	н	н	Α	44	171.5 dec	86.7 (0.075)	$C_{21}H_{25}ClN_2O_30.5H_2O$	$2.19\pm0.10$
10	Cl	н	н	Α	33	172.4 dec	103.2 (0.095)	$C_{21}H_{25}Cl_2NO 0.5H_2O$	$2.37\pm0.80$
11	$OCH_3$	н	н	Α	9	156.2 dec	114.3 (0.07)	$C_{22}H_{28}CINO_{2}0.5H_{2}O$	$2.89\pm0.03$
12	$\mathbf{Br}$	н	н	Α	56	175.0 dec	86.3 (0.95)	C <sub>21</sub> H <sub>25</sub> BrClNO	$3.11\pm0.38$
13	Н	н	$CH_3$	Α	52	160 - 163	69.3 (0.14)	C22H28ClNO-0.25H2O	$12.83\pm0.84$
14	Ι	н	н	В	25	179 - 183	95.2 (1.05)	$C_{21}H_{25}CINO 0.5H_2O$	$16.53 \pm 2.43$
15	$\rm NH_2$	н	н		47	201.0 dec	98.0 (0.1)	$C_{21}H_{28}Cl_2N_2O$ -0.75 $H_2O$	$16.76\pm1.40$
16	$CF_3$	н	н	Α	44	177.0 dec	90.7 (0.075)	$C_{22}H_{25}ClF_3NO$	$20.5\pm2.37$
17	Н	I	н	В	42	168.7 dec	73.0 (0.1)	$C_{21}H_{24}ClNO \cdot 0.5H_2O$	$27.22 \pm 3.43$
18	$NHCOCH_3$	Н	н	В	18	193.7 dec	112.2 (0.09)	$C_{23}H_{29}ClN_2O_2H_2O$	$46.98 \pm 4.83$
19	$N(CH_3)_2$	н	н	В	17	172.6 dec	113.3 (0.09)	$C_{23}H_{32}Cl_2N_2O\cdot H_2O$	$101.7\pm11.86$
20	I	$NO_2$	н	В	87	252.0 dec	89.0 (0.1)	$C_{21}H_{24}ClIN_2O_2$	$386.37 \pm 53.31$
21	Н	Н	I	Α	66	165 - 167	42.0 (0.1)	$C_{21}H_{25}ClINO 0.5H_2O$	$929.72 \pm 75.99$
22	t-Bu	H	H	Α	53	197.4 dec	105.5 (0.11)	$\mathrm{C_{25}H_{34}ClNO}\text{-}0.5\mathrm{H_{2}O}$	$1066 \pm 42$

<sup>a</sup> The general methods are described in the Experimental Section. <sup>b</sup> Previously reported compound (ref 12). <sup>c</sup> All compounds were analyzed for C, H, N. The results agreed to within  $\pm 0.4\%$  of the theoretical values. <sup>d</sup> [<sup>3</sup>H]-(+)-Pentazocine binding assays were carried out using guinea pig brain membranes under the conditions described in the Experimental Section. Twelve concentrations of test ligand were used in one of the following three ranges, depending on an estimated ligand affinity determined by competition with three concentrations: 0.005-1000 nM, 0.05-10000 nM, or 0.5-10000 nM. Data were analyzed using the iterative curve-fitting program GraphPAD InPlot (San Diego, CA). Data were best fit to a one-site model. The  $K_i$  values were calculated from IC<sub>50</sub> values using the Cheng-Prusoff equation (see ref 25) and a  $K_d$  value of 4.8 nM as determined previously.<sup>29</sup> Values are the averages of three to four experiments, each carried out in duplicate.



**Figure 2.** Actual vs calculated  $\sigma 1$  receptor binding affinity based on the para-, meta-, and ortho-substituent volume (eq 1).

polar fields were more significant than the PLS analysis based on the Hint hydrophobic/polar fields alone ( $q^2 = -0.32$ ).

The correlation provided by the very simple substituent volume model suggested that a more sophisticated 3D-QSAR based on related molecular properties (size or lipophilicity in particular) should be effective in providing a more detailed model of the relationship of ligand structure to binding affinity. However, the initial CoMFA/Hint/PLS studies did not find a strong correlation via statistical techniques that also assure predictive usefulness. The basic assumption underlying this 3D-QSAR study was that all of the ligands are locked into identical conformations and that each binds in the same relative orientation or alignment. As alignment and conformation play a crucial role in success of CoMFA studies, the weakness of the correlations described above most likely indicates that freedom in both conformation and alignment between each of the structures should be considered in subsequent calculations.

Although the various published models of the  $\sigma$ pharmacophore include a variety of details drawn from the particular class of ligand studied, an apparent consensus has emerged that the  $\sigma$  receptor pharmacophore consists of three major features: a basic nitrogen flanked by a closely placed ("proximal") aromatic group and a more distant ("distal") lipophilic group without any strict distance constraints between the pharmacophoric groups. Both accessory binding sites appear to tolerate a wide variation in ligand substructure size.<sup>16,17,20</sup> In contrast to these published reports, the present SAR study finds that for the *N*-benzyl-*N*normetazocines, increasing the size of the *N*-substituent uniformly decreases binding potency.

These results are not necessarily inconsistent. The series of analogs that were used by Glennon and Gilligan to probe the pharmacophoric requirements of both the distal and proximal binding sites consisted of alkyl phenyl and similar relatively long, narrow side chains.<sup>16,17</sup> The current steric effect indicates that there is a steric restriction near the nitrogen atom, i.e., the binding pocket may be relatively narrow at the distance probed by these *N*-benzyl-*N*-normetazocines or alternatively, excessive steric bulk at this distance from the

basic nitrogen may interfere with interaction with hydrogen-bonding residues in the  $\sigma$ 1 receptor site. The rigidity of the benzomorphan may contribute to this effect by holding the N-substituent in a specific location making it less free to avoid unfavorable steric interactions. Another feature of the QSAR described above in eqs 1 and 2 is that, in agreement with previous studies,<sup>11</sup> volume or steric features of the N-(substituted benzyl)-N-normetazocines provide a satisfactory fit to the binding affinity data, no electrostatic or polar terms were found to be necessary.

### Conclusions

We have described the synthesis and  $\sigma$  receptor binding affinity of a series of *N*-(substituted benzyl)-*N*normetazocines. The QSAR correlating the size and location of *N*-benzyl substituents indicates the  $\sigma$  receptor may be narrow in the region occupied by the *N*-benzyl side chain and its substituents. Analogs bearing relatively small substituents retain nanomolar binding affinity, particularly the *p*-fluoro derivative **5**. This suggests that (+)-*N*-(4-[<sup>18</sup>F]fluorobenzyl)-*N*-normetazocine would be a useful radiopharmaceutical agent for PET imaging of tissues, such as human tumors, that express the  $\sigma$ 1 receptor.

#### **Experimental Section**

**Chemical.** Melting points were determined on a Thomas-Hoover capillary tube apparatus. All optical rotations were determined at the sodium D line using a Rudolph Research Autopol III polarimeter (1-dm cell). Thin-layer chromatography (TLC) was performed on 250  $\mu$ m Whatman MK6F silica gel plates. TLC visualization was provided under UV illumination or by exposure in an iodine chamber. Microanalyses were carried out by Atlantic Microlab, Inc.

General Procedure for the Synthesis of (+)-cis-N-(substituted benzyl)-N-normetazocines. Method A. A mixture of 150 mg (0.70 mmol) of (+)-cis-N-normetazocine (4), $^{28}$ 0.77 mmol of the appropriate substituted benzyl halide, and 210 mg (2.5 mmol) of sodium hydrogen carbonate in 8 mL of ethanol was heated to reflux for 4 h. The mixture was concentrated and the residue extracted with diethyl ether. The ethereal extract was concentrated under vacuum to give the crude product which was purified by flash chromatography on silica gel (hexane-ethyl acetate-methanol, 8:1:1). The hydrochloride salts were formed by adding 1 N hydrogen chloride in diethyl ether solution to an ethereal solution of the N-(substituted benzyl)-N-normetazocine free base. The precipitated salts were collected by filtration and thoroughly washed with diethyl ether. The physical data for each compound is listed in Table 1.

General Procedure for the Synthesis of (+)-*cis*-*N*-( Substituted benzyl) normetazocines. Method B. A mixture of 150 mg (0.70 mmol) of (+)-*cis*-normetazocine (4),<sup>28</sup> 1.40 mmol of the appropriately substituted benzaldehyde, 90 mg (1.40 mmol) of sodium cyanoborohydride, and 5 drops of acetic acid in 10 mL of methanol were stirred overnight at room temperature. The reaction mixture was concentrated under vacuum, and the residue was treated with saturated aqueous sodium hydrogen carbonate and extracted with diethyl ether. The ethereal extract was dried over magnesium sulfate and concentrated under vacuum to give the crude product. The free base was isolated and converted to the pure hydrochloride salt as described in method A (*vide supra*).

The purity of the final products was verified to be within acceptable limits by elemental analysis of the hydrochloride salts. Melting points and molecular formula verified by microanalysis are listed in Table 1.

(+)-cis-N-(4-Aminobenzyl)-N-normetazocine (15). To a solution of 150 mg (0.38 mmol) of (+)-cis-N-(4-nitrobenzyl)-N-normetazocine (9) in 10 mL of ethanol and 2 mL of 1 N aqueous

**Table 2.** Substituent volumes<sup>a</sup> (Å<sup>3</sup>) Used in the Volume/ Binding Potency QSAR Analysis of *N*-(Ortho-, Meta-, and Para-substituted benzyl)-*N*-normetazocines

Н	0	$NO_2$	17.3
F	2.3	OMe	23.3
Cl	11.7	$\mathbf{CF}_3$	23.5
$\mathbf{NH}_2$	11.9	Ι	27.9
CN	14.7	NHCOMe	42.9
Me	16.2	$\mathbf{NMe}_2$	43.7
$\mathbf{Br}$	16.8	t-Bu	65.0

<sup>*a*</sup> Expressed as volume difference from the unsubstituted analog using the Sybyl MVOL command. Note that, for a particular substituent, the volume shown here was used for the analogs with the substituent in the ortho, meta or para positions.

hydrogen chloride was added 300 mg (1.4 mmol) of nickel boride. The mixture was stirred for 5 h at 50 °C, concentrated under vacuum, treated with dilute aqueous ammonium hydroxide, and extracted with diethyl ether. Concentration under vacuum of the ethereal extract gave the crude product which was immediately purified by flash chromatography on silica gel (hexane-ethyl acetate-methanol, 2:1:1) and converted to the hydrochloride salt as described above. The physical data for **15** is listed in Table 1.

**Biochemical.** Ligand binding was carried out using [<sup>3</sup>H]-(+)-pentazocine and guinea pig brain membranes as described in detail previously.<sup>12,29</sup> [<sup>3</sup>H]-(+)-Pentazocine is a highly selective  $\sigma$ 1 receptor probe.<sup>29</sup> Furthermore, being itself an *N*substituted (+)-normetazocine, this radioligand would be expected to interact with the  $\sigma$ 1 receptor in a manner more closely approximating that of the series of benzomorphans under investigation here. Thus, modeling results obtained with [<sup>3</sup>H]-(+)-pentazocine competition should be more reliable than those obtained based on competition with a non-benzomorphan radioligand.

Briefly, 3 nM [<sup>3</sup>H]-(+)-pentazocine was incubated for 120 min with guinea pig brain membranes (0.3–0.4 mg of protein) in 0.5 mL of 50 mM Tris-HCl, pH 8.0 at 25 °C. Nonspecific binding was determined in the presence of 10  $\mu$ M (+)-pentazocine. Assays were terminated by the addition of 0.5 mL of ice-cold 10 mM Tris-HCl, pH 8.0, and vacuum filtration through glass fiber filters. Filters were then washed twice with ice-cold buffer. Filters were soaked in 0.5% polyethyl-enimine for at least 30 min at 25 °C prior to use.

**Molecular Modeling.** Molecular modeling studies were performed with the Tripos Associates Sybyl software package (version 6.03)<sup>30</sup> installed on a Silicon Graphics 4D/310 VGX graphics workstation. Individual substituent volumes were calculated using the Sybyl FIT and MVOL commands by first aligning to and then determining the volume difference between each substituted benzyl fragment and a reference unsubstituted benzyl moiety (Table 2). The lipophilicity ( $\pi$ ) and molar refractivity (MR) molecular descriptors were obtained from published databases<sup>31</sup> or calculated using the Medchem (version 3.53) software package.<sup>31</sup> Multiple linear regressions were performed with the SAS statistics package JMP (version 3.02)<sup>33</sup> running on a Apple Macintosh IIcx microcomputer.

CoMFA studies were performed using Sybyl QSAR and eduSoft Hint<sup>34</sup> modules. The default CoMFA and PLS analysis settings were used throughout the study. A CoMFA alignment rule was defined based on superimposing the corresponding ring atoms of the benzyl fragments of the *N*-substituted-*N*benzomorphans. A CoMFA region was defined automatically to enclose the substituted-benzyl fragments with dimensions of -5.96 to 11.14 Å (x), -7.38 to 6.18 Å (y), and -6.17 to 6.16Å (z). Steric and electrostatic potentials were determined at 2 Å intervals within the CoMFA region using a +1 charged sp<sup>3</sup> carbon probe atom. The Hint CoMFA fields were calculated using the same alignments and region. Cross-validated PLS analyses were performed using 19 cross-validation groups with  $-\log K_i$  as the dependent variable and the appropriate CoMFA fields as the independent variables.

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