Geometric parameters as a criterion for assessment of the bioactive conformations of opiate receptor ligands

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The mutual positions of the phenyl fragment and the protonated amino group in the molecules of opiate receptor ligands of various structural classes were studied. It was concluded that two bioactive ligand conformations exist and their implementation does not depend on the structural class of the ligand, selectivity of its action on receptors, or relationship between the agonistic and antagonistic properties. A set of geometric parameters describing the three-dimensional arrangement of the phenyl fragment and the protonated amino group in bioactive conformations was proposed; this can be used as a criterion for the geometric assessment of the opiate activity.

Key words: opiate receptor ligands, opiate activity, geometric parameters, bioactive conformation.

The interaction of ligand molecules with receptors depends on the structural compatibility of the ligand and the receptor binding site; therefore, the biological activity of the ligands is largely due to their molecular geometry.[1] It is generally accepted that, during interaction, the ligand and the receptor mutually stimulate changes in their spatial structures that are required for their optimum interaction. These spatial changes are called the "induced fitting" effect.[2] The ligand conformation in which interactions with the receptor are maximized is called bioactive. The transition from an inactive conformation of the "free" ligand to the bioactive conformation formed in a complex with the receptor is usually accompanied by energy expenditure, which is equal, on average, to 3—5 kcal mol^{-1} but may reach tens of kcal per mol if the ligand molecule has a large number of rotational degrees of freedom. If these energy expenditure is made up for by the free energy benefit due to hydrophobic, electrostatic, or other type of ligand—receptor interactions, ligand binding to the receptor sites does occur.

In the bioactive conformation, the structural fragments of the ligand molecule that interact with the receptor are oriented in a definite manner with respect to each other. The knowledge of the topology of ligand structural fragments, together with the understanding of the nature of their interaction with the receptor are highly important for elucidation of the reasons for the origin of the ligand affinity for the receptor and the specificity of the ligand action.

This study is concerned with the geometric parameters that describe the mutual arrangement of the key structural fragments of molecules of opiate receptor (OR) ligands in their bioactive conformations. These geometric parameters can be used subsequently as a criterion for assessment of the opiate activity in the targeted search for new opiate-active compounds, while minimizing expensive and labor-consuming experiments.

It was shown in the 1960s that the interaction of narcotic analgesics with receptors involves the protonated form of the ligand,[3,4] the protonated nitrogen atom, like the phenyl group, being the key structural fragment of OR ligands (see Refs 5—7).

It was shown experimentally that the interactions of the protonated N atom and the phenyl group are involved in ligand binding to any type of opiate receptors.[5,8—10] The protonated nitrogen atom is responsible for the ionic interaction with the anionic group of the complementary OR site, which is supplemented by hydrogen binding.[9—12] The phenyl fragment forms a charge-transfer complex with a particular complementary OR site (see Ref. 13).

Numerous studies have been focused on the mutual arrangement of the protonated amino group and the phenyl fragment in the molecules of the OR ligands. The main emphasis was placed on the investigation of the distance "N atom—center of the phenyl ring" and the mutual orientation of the phenyl and piperidine rings in various structural classes of the OR ligands. It was postulated that the distance between the nitrogen atom and the aromatic ring in the opiate pharmacophore does not depend on the structural class of the ligand being equal to 4.5 Å (see Refs 7 and 14), while the mutual orientation of the rings does depend on the ligand class.[15] In mor-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 9, pp. 1462—1468, September, 2006.

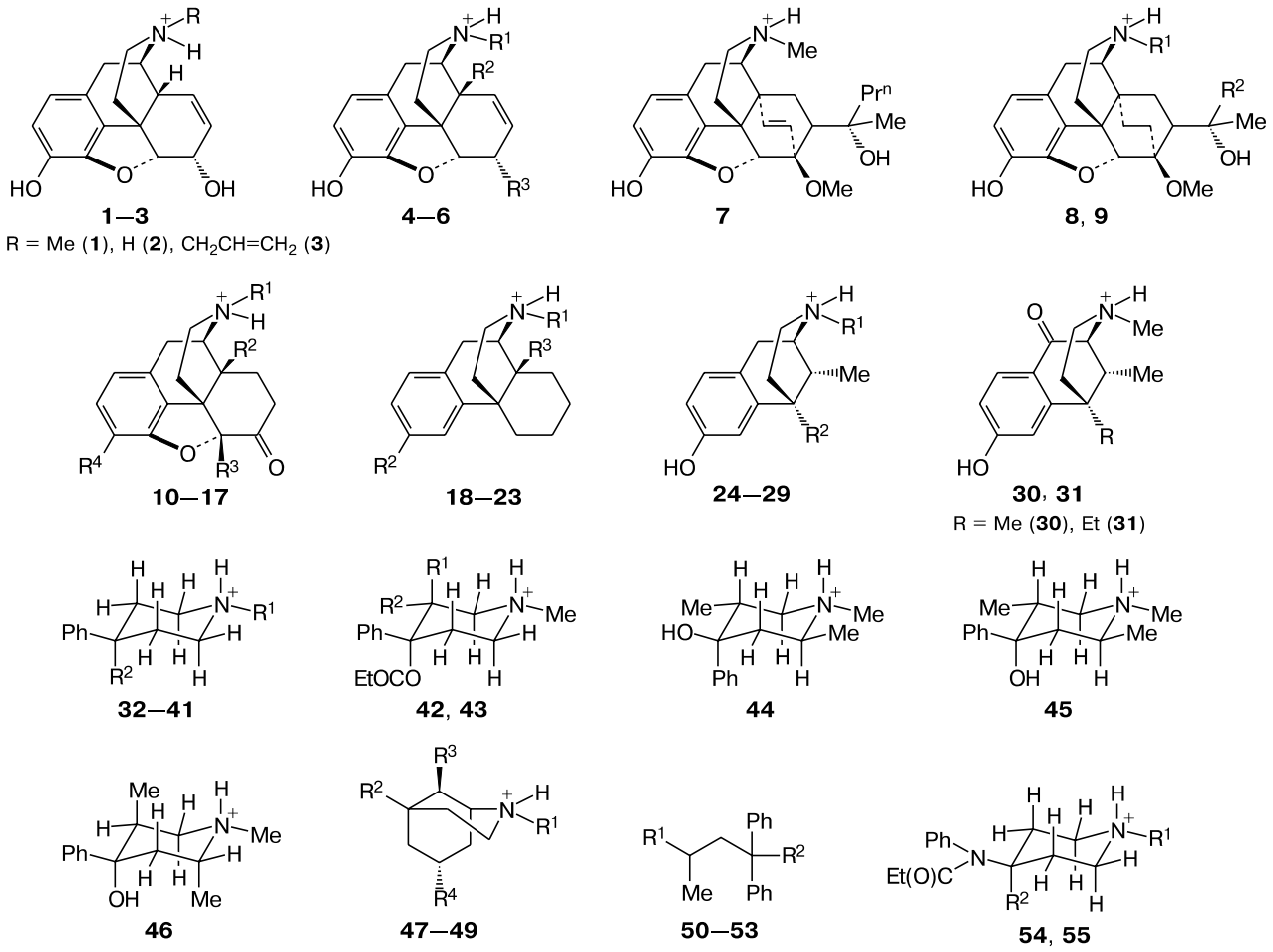
1066-5285/06/5509-1516

phine analogs, the phenyl substituent is located in the axial position with respect to the piperidine ring, while in the molecules of 4-phenylpiperidine derivatives, it occupies the equatorial position. The dihedral angles between the mean planes of the rings in the molecules of these structural classes have opposite signs.[16] Thus, studies on

Table 1. Subjects of investigation

Compound	Receptor type	Type of activity	Ref.
Morphine (**1**)	μ	Agonist	18
Normorphine (**2**)	μ	Agonist	18
Nalorphine (**3**)	μ, κ	Mixed agonist-antagonist	18
Dihydromorphine (**4**)	μ	Agonist	19
Nalbuphine (**5**)	μ, κ	Mixed agonist-antagonist	18
Nalmefene (**6**)	μ	Antagonist	20
Etorphine (**7**)	μ	Agonist	18
Diprenorphine (**8**)	μ, δ, κ	Antagonist	14
Buprenorphine (**9**)	μ, κ	Mixed agonist-antagonist	18
Naloxone (**10**)	μ, κ	Antagonist	20
Naltrexone (**11**)	μ, δ, κ	Antagonist	20
Nalmexone (**12**)	—[a]	Antagonist	[b]
Dihydromorphone (**13**)	μ	Agonist	18
Metopon (**14**)	μ	Agonist	[b]
Hydrocodone (**15**)	μ	Agonist	[b]
Nalbuphone (**16**)		Antagonist	21
Oxymorphone (**17**)	μ	Agonist	[b]
Cyclorphan (**18**)	μ, δ, κ	Mixed agonist-antagonist	22
MCL 101 (**19**)	μ, δ, κ	Mixed agonist-antagonist	22
Levalorphan (**20**)	—[a]	Mixed agonist-antagonist	15
Butorphanol (**21**)	μ, κ	Mixed agonist-antagonist	7
Levorphanol (**22**)	μ	Agonist	18
Methorphan (**23**)	—[a]	Agonist	15
Metazocine (**24**)	μ, κ	Mixed agonist-antagonist	7
Cyclazocine (**25**)	μ, δ, κ	Mixed agonist-antagonist	22
Bremazocine (**26**)	μ, κ	Mixed agonist-antagonist	23
Pentazocine (**27**)	μ, δ, κ	Agonist	22
Allylnor-metazocine (**28**)	μ, κ	Antagonist	24
Cyanoethylnor-metazocine (**29**)	μ, κ	Agonist	24
Ketocyclazocine (**30**)	κ	Agonist	15
Ethylketo-cyclazocine (**31**)	μ	Agonist	15
Normeperidine (**32**)	—[a]	Agonist	15
Meperidine (**33**)	μ	Agonist	18
Propiophenone-normeperidine (**34**)	—[a]	Agonist	25
Aceperone (**35**)	—[a]	Agonist	25
Benzethidine (**36**)	—[a]	Agonist	25
Furanylate (**37**)	—[a]	Agonist	25
Aniliridine (**38**)	—[a]	Agonist	25
Ethoxyridine (**39**)	—[a]	Agonist	25
Proxidol (**40**)	—[a]	Agonist	25
Phenopyridine (**41**)	—[a]	Agonist	25
α-Prodine (**42**)	—[a]	Agonist	25
β-Prodine (**43**)	—[a]	Agonist	25
α-Promedol (**44**)	—[a]	Agonist	25
γ-Promedol (**45**)	—[a]	Agonist	25
β-Promedol (**46**)	—[a]	Agonist	25
47[c]	μ	Mixed agonist-antagonist	26
48[d]	μ	Mixed agonist-antagonist	27
49[e]	κ	Agonist	28
Metadone (**50**)	μ	Agonist	18
Acetylmetadol (**51**)	μ	Agonist	18
Dipipanone (**52**)	—[a]	Agonist	26
Phenadoxone (**53**)	—[a]	Agonist	26
Fentanyl (**54**)	μ	Agonist	18
Sufentanyl (**55**)	μ	Agonist	18
Dezocine (**56**)	μ, δ	Mixed agonist-antagonist	18
Tramadol (**57**)	μ	Agonist	18
Propoxyphene (**58**)	μ	Agonist	18

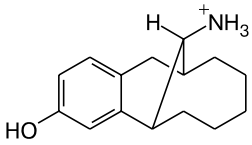
[a] No data on the selectivity of ligand action on opiate receptors was found.
[b] http://www.drugs.com.
[c] 2,9β-Dimethyl-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonane (**47**).
[d] 2-(1-Methyl-2-phenetyl)-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonane (**48**).
[e] *N*-[4β-Methyl-5-(3-hydroxyphenyl)-2-(3-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(piperidino)propanamide (**49**).



the structures and pharmacological activities of morphine-like compounds and 4-phenylpiperidine derivatives provided the following conclusion: the phenyl fragments in these two classes of molecules are bound to different receptor sites.[16,17] This conclusion implies the existence of at least two bioactive conformations in which the protonated N atom and the phenyl fragment interacting with the OR are oriented differently with respect to each other. It would be pertinent to compare the bioactive conformations of the OR ligand molecules of various structural classes including open-chain compounds containing no piperidine fragment: 4,5-epoxymorphinans, dihydromorphones, morphinans, benzomorphans, oripavines, arylmorphans, 4-phenylpiperidines, 4-anilidopiperidines, diphenylpropylamines, aminotetralins, and arylcyclohexanolamines (Table 1).

In our opinion, the geometric parameters used in the literature (the distance "N—the center of the phenyl ring," the torsion angle describing the position of the substituent with respect to the piperidine ring, the dihedral angle between the planes of the phenyl and piperidine rings) do not suffice for describing the mutual arrangement of the phenyl fragment and the protonated amino group. The opiate activity is known to depend on the orientation of the N—H bond, *i.e.*, only one of the two diastereomers of the protonated ligand molecule is active.[29] It was proven experimentally that bioactivity is manifested for the diastereomer with the axial N—H bond. The introduction of a hydroxy group into position 11β of benzomorphans or into position 3 of the piperidine ring in phenylpiperidines hampers the inversion of nitrogen and decreases the fraction of the diastereomer with equatorial N—H bond; as a result, the analgesic activity sharply increases.[30] In addition, X-ray diffraction data indicate that the N—H bonds in all bioactive molecules of the opiate receptor ligands are axial.[15,25]

When choosing the geometric parameters that would describe unambiguously the bioactive conformation of the protonated ligand, we were guided by the method of description of the mutual positions of points in the three-dimensional space by means of intrinsic coordinates (Z-matrix). We considered the following geometric parameters: (i) the distance "center of gravity of the phenyl ring—nitrogen atom" (R_{Cent-N}); (ii) the distance "center of gravity of the phenyl ring—ammonium hydrogen atom" (R_{Cent-H}); (iii) the angle "nitrogen atom—center of grav-



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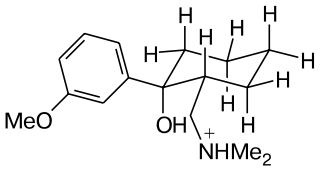

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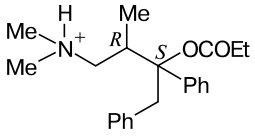

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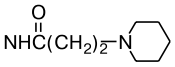
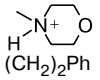
Compound	R^1	R^2	R^3	R^4	Compound	R^1	R^2	R^3	R^4
4	Me	H	OH	—	**28**	$CH_2CH{=}CH_2$	Me	—	—
5	*cyclo*-$C_4H_7CH_2$	OH	OH	—	**29**	$(CH_2)_2CN$	Me	—	—
6	*cyclo*-$C_3H_5CH_2$	OH	$=CH_2$	—	**32**	H	COOEt	—	—
8	*cyclo*-$C_3H_5CH_2$	Me	—	—	**33**	Me	COOEt	—	—
9	*cyclo*-$C_3H_5CH_2$	Bu^t	—	—	**34**	$(CH_2)_2C(O)Ph$	COOEt	—	—
10	$CH_2CH{=}CH_2$	OH	H	OH	**35**	$(CH_2)_3C(O)PhF$-*p*	$CH_2NHCOMe$	—	—
11	*cyclo*-$C_3H_5CH_2$	OH	H	OH	**36**	$(CH_2)_2OCH_2Ph$	COOEt	—	—
12	$CH_2CH{=}CMe_2$	OH	H	OH	**37**	$(CH_2)_4Ph$	COOEt	—	—
13	Me	H	H	OH	**38**	$(CH_2)_2Ph$-NH_2-*p*	COOEt	—	—
14	Me	H	Me	OH	**39**	$(CH_2)_2O(CH_2)_2OH$	COOEt	—	—
15	Me	H	H	OMe	**40**	$(CH_2)_2OEt$	OCOEt	—	—
16	*cyclo*-$C_4H_7CH_2$	OH	H	OH	**41**	$(CH_2)_2CH(OH)Ph$	COOEt	—	—
17	Me	OH	H	OH	**42**	H	Me	—	—
18	*cyclo*-$C_3H_5CH_2$	OH	H	—	**43**	Me	H	—	—
19	*cyclo*-$C_4H_7CH_2$	OH	H	—	**47**	Me	*m*-OH-C_6H_4	Me	H
20	$CH_2CH{=}CH_2$	OH	H	—	**48**	$CH(Me)CH_2Ph$	*m*-OH-C_6H_4	H	H
21	*cyclo*-$C_4H_7CH_2$	OH	OH	—	**49**	$(CH_2)_3Ph$	*m*-OH-C_6H_4	Me	
22	Me	OH	H	—	**50**	N^+HMe_2	COEt	—	—
23	Me	OMe	H	—	**51**	N^+HMe_2	CH(Et)OCOMe	—	—
24	Me	Me	—	—	**52**		COEt	—	—
25	*cyclo*-$C_3H_5CH_2$	Me	—	—	**53**		COEt	—	—
26	*cyclo*-$C_3H_4(OH)CH_2$	CH_2Me	—	—	**54**	$(CH_2)_2Ph$	H	—	—
27	$CH_2CH{=}C(Me)_2$	Me	—	—	**55**		CH_2OMe	—	—

ity of the phenyl ring—ammonium hydrogen atom" (N—Cent—H); (iv) the torsion angle "center of gravity of the phenyl ring—phenyl carbon atom linked to the nitrogen atom through the alkyl bridge—nitrogen atom—ammonium hydrogen atom" (Cent—C_{Ph}—N—H). The alkyl bridge is three single C—C bonds long. An exception is provided by anilidopiperidine molecules in which the chain connecting the phenyl fragment and the protonated nitrogen contains additionally a nitrogen atom.

For cage compounds, one more geometric parameter was measured, namely, the dihedral angle between the plane of the phenyl ring and the plane through three nonhydrogen atoms of the substituent at nitrogen in the cationic "head" (Ph/CCC). This parameter characterizes the mutual orientation of the N—H bond and the π—π interaction. For molecules in which the phenyl fragment freely rotates around the C—C bond (the rotation energy does not exceed 5 kcal mol^{-1}), this parameter was not considered.

X-Ray diffraction data for compounds under consideration or for their close analogs were used as the starting models in the calculation of geometric parameters of the protonated molecules.[31] First, conformationally rigid molecules were considered, in particular, cage molecules and 4-phenylpiperidine molecules with fixed configurations of the chiral centers. We proceeded from the fact that the mutual arrangement of the phenyl ring and the protonated nitrogen atom in conformationally rigid molecules is the same as in the bioactive conformation, because the "conformational adjustment" of such ligands to the receptor is exceptionally limited due to the lack of the rotational degrees of freedom in the molecular core of the ligand. In the case of 4-phenylpiperidine derivatives, the expression "molecular core" was used to mean the piperidine ring with a fixed configuration of the chiral centers and only bioactive diastereomers were considered. In these diastereomers, the Ph group was oriented either axially (as in α-promedol) or equatorially (as in β-promedol). The orientation of the chiral centers in active diastereomers found experimentally (see references in Table 1) is reflected in the structural formulas of the compounds. The results of calculations are presented in Table 2.

The data of Table 2 indicate that protonated ligands of opiate receptors can exist in two bioactive conformations (I and II). Each conformation has its own set of geometric parameters, which vary over narrow ranges. Both con-

Table 2. Geometric parameters of bioactive conformations of the conformationally rigid opiate receptor ligands **1—49**

Compound	Conformation	R_{Cent-N}	R_{Cent-H}	Angle/deg[a]		
		Å		φ	ψ	ω
1	I	4.6	5.3	8	190	82
2	I	5.0	5.3	7	190	84
3	I	4.5	5.3	8	190	83
4	I	4.5	5.3	8	186	82
5	I	4.5	5.2	9	185	100
6	I	4.4	5.2	7	183	94
7	I	4.6	5.3	8	194	107
8	I	4.6	5.1	7	186	101
9	I	4.6	5.3	9	195	102
10	I	4.6	5.3	7	184	86
11	I	4.5	5.3	7	182	94
12	I	4.5	5.3	7	184	87
13	I	4.5	5.3	8	190	83
14	I	4.5	5.3	7	184	87
15	I	4.5	5.2	7	183	86
16	I	4.5	5.3	8	186	95
17	I	4.5	5.3	8	192	86
18	I	4.4	5.2	7	180	88
19	I	4.4	5.2	7	183	89
20	I	4.4	5.2	8	179	81
21	I	4.5	5.2	8	184	93
22	I	4.4	5.2	7	176	93
23	I	4.4	5.2	7	181	94
24	I	4.5	5.3	7	178	91
25	I	4.5	5.2	7	178	90
26	I	4.4	5.2	8	178	90
27	I	4.4	5.3	7	179	90
28	I	4.4	5.2	7	180	90
29	I	4.4	5.2	7	179	90
30	I	4.5	5.3	7	178	88
31	I	4.5	5.3	7	180	86
32	II	5.6	5.6	10	0	—[b]
33	II	5.6	5.4	10	9	—
34	II	5.6	5.6	10	7	—
35	II	5.7	5.5	10	3	—
36	II	5.6	5.5	10	9	—
37	II	5.6	5.5	10	6	—
38	II	5.6	5.6	10	7	—
39	II	5.7	5.6	10	2	—
40	II	5.6	5.5	10	11	—
41	II	5.6	5.5	10	11	—
42	II	5.6	5.6	10	−7	—
43	II	5.5	5.7	10	15	—
44	I	4.9	5.7	8	186	—
45	II	5.6	5.6	10	3	—
46	II	5.6	5.7	7	−8	—
47	II	5.7	5.6	7		—
48	II	5.6	5.5	9	13	—
49	II	5.7	5.6	9	9	—

[a] φ is the N—Cent—H bond angle, ψ is the Cent—C_{Ph}—N—H torsion angle, ω is the Ph/CCC dihedral angle.

[b] The parameter was not calculated for molecules with free rotation of the phenyl fragment about the C_{Ph}—C_{Alk} bond.

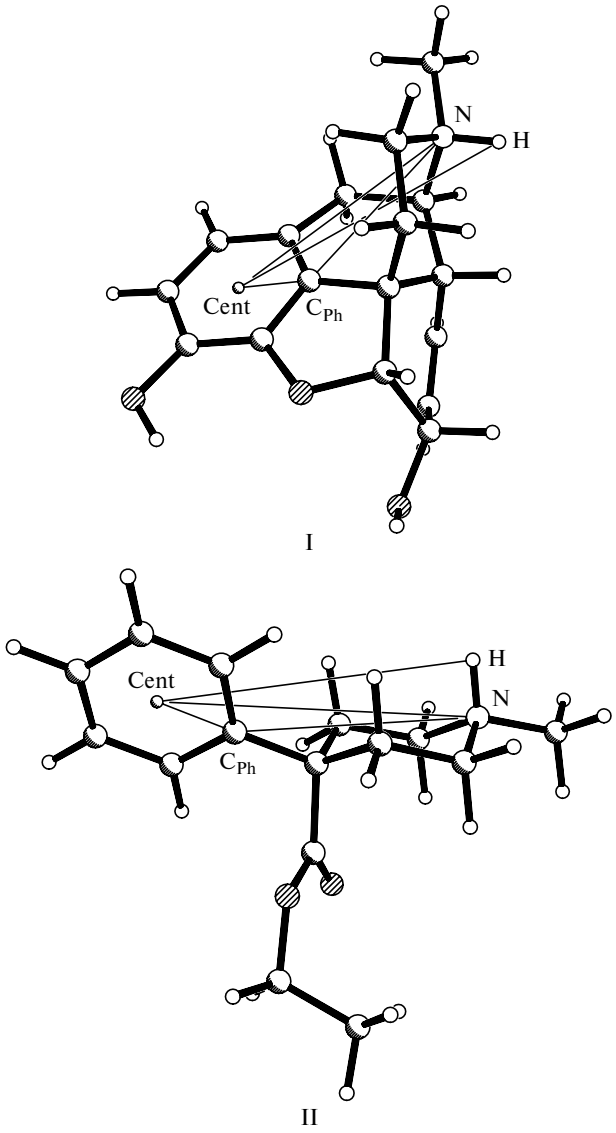


Fig. 1. Bioactive conformations I (morphinan molecule (**1**) and II (meperidine molecule (**33**)): R_{Cent-N} = 4.6 (**1**), 5.6 Å (**33**); R_{Cent-H} = 5.3 (**1**), 5.4 Å (**33**); φ(N—Cent—H) = 8.0 (**1**), 10.0° (**33**); ψ(Cent—C_{Ph}—N—H) = 190 (**1**), 9° (**33**).

formations have close R_{Cent-H} distances (5.1—5.7 Å (I) and 5.4—5.7 Å (II)) and N—Cent—H angles (7—9° (I) и 7—10° (II)). The Cent—C_{Ph}—N—H torsion angle in both conformations is close to 180° or to 0°, *i.e.*, the N—H bond is located nearly in the same plane as the center of the phenyl ring and the phenyl carbon atom linked to nitrogen through the alkyl bridge. Figure 1 shows the three-dimensional structures of the morphinan and meperidine molecules, which illustrate bioactive conformations I and II and the corresponding sets of geometric parameters. In cage molecules, the Ph/CCC dihedral angle is close to 90°, indicating that the π—π interaction and the N—H bond are perpendicular to each other. Pre-

sumably, the feature revealed is also valid for those molecules in which the phenyl fragment freely rotates about the C—C bond, because the energy required for realization of a conformation with the dihedral angle Ph/CCC = 90° does not exceed 5 kcal mol^{-1}, *i.e.*, in both bioactive conformations, the N—H bond is directed at right angle to the phenyl π-bond.

The key difference between conformations I and II is the orientation of the N—H bond (the value of the Cent—C_{Ph}—N—H torsion angle). In conformation I, the hydrogen atom is directed away from the phenyl ring, while in conformation II, it is directed toward the phenyl ring, and the R_{Cent-N} distances differ by about 1 Å. Thus, the distance "N—center of the phenyl ring" in the OR ligand molecules is not invariable, as has previously been postulated in the literature. Note that the geometric parameters of bioactive conformation I vary over a broader range than those of conformation II. This is due to the fact that conformation II is formed for a narrower range of structural classes of conformationally rigid OR ligands than conformation I. Presumably, on passing to conformationally flexible ligands, the range of variation of geometric parameters of bioactive conformation II would be somewhat extended.

In the second stage, we verified whether the bioactive conformations we identified can occur for conformationally flexible molecules (4-anilidopiperidines, diphenylpropylamines, aminotetralins, arylcyclohexanolamines). It is generally accepted that the energy expenditure for realization of bioactive conformations does not exceed 20 kcal mol^{-1} (see Ref. 32). We compared the free energies of the molecules in the bioactive conformation and in the conformation corresponding to the energy minimum. Of the two bioactive conformations, we chose the one requiring less energy expenditure. For example, in the case of tramadol, the formation of bioactive conformation I requires 9.0 kcal mol^{-1}, while conformation II, 40.6 kcal mol^{-1}; therefore, conformation I was chosen as the bioactive conformation for this molecule. Table 3 presents the free energies and the geometric parameters of conformationally flexible OR ligands in their bioactive

Table 3. The feasibility of bioactive conformations I and II in conformationally flexible opiate receptor ligands **50—58**

Compound	Conformation	$-\Delta G^{310}$ [a] /kcal mol^{-1}	R_{Cent-N} / Å	R_{Cent-H} / Å	Angle/deg[b] φ	ψ
50	min[c]	31.81	5.9	5.6	9	−25
	II	29.91	5.5	5.6	10	11
51	min	36.01	6.2	7.0	4	141
	II	35.50	5.5	5.7	9	−1
52	min	36.64	4.8	5.2	8	−59
	I	33.24	4.9	5.5	7	195
53	min	33.82	5.6	6.2	8	43
	I	33.01	4.9	5.7	7	184
54	min	35.37	4.9	5.8	5	−166
	II	36.30	5.7	5.4	10	12
55	min	36.79	4.8	4.7	11	−24
	II	35.49	5.7	5.4	10	−7
56	II[d]	26.50	5.2	5.6	10	−6
57	min	27.06	3.5	2.9	7	−30
	I	17.96	5.0	5.7	7	185
58	min	33.82	5.2	5.7	9	−72
	I	33.80	5.0	5.6	9	195

[a] ΔG^{310} is the free energy of the molecule at 37 °C.
[b] φ is the N—Cent—H angle, ψ is the Cent—C_{Ph}—N—H torsion angle.
[c] Conformation of the molecule in the energy minimum (min).
[d] The dezocine molecule in the energy minimum corresponds to the second bioactive conformation.

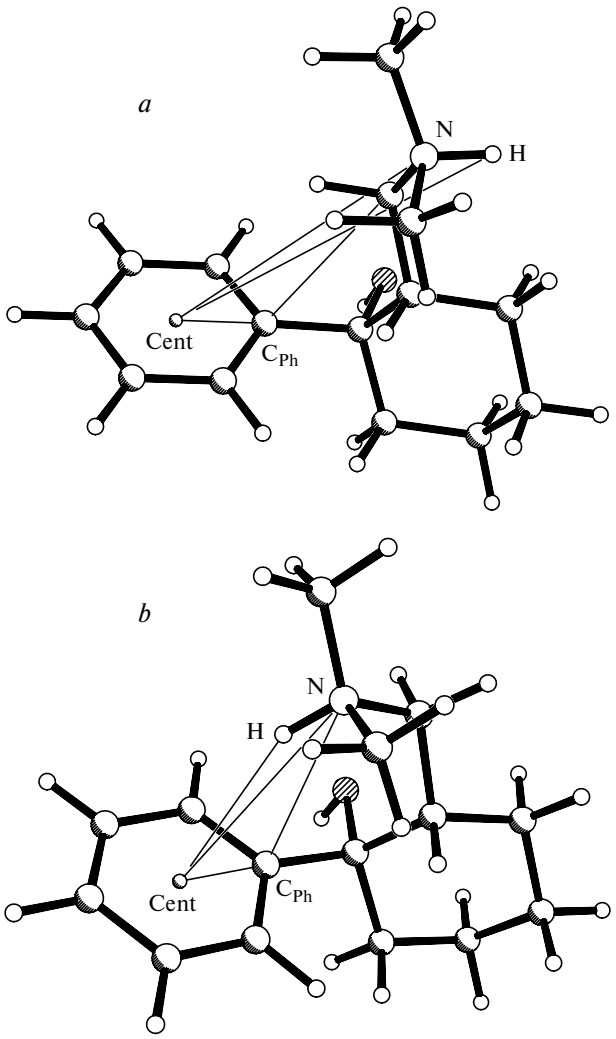


Fig. 2. Tramadol molecule (**57**) in the bioactive conformation (*a*) (R_{Cent-N} = 5.0 Å, R_{Cent-H} = 5.7 Å, φ(N—Cent—H) = 7.0°, ψ(Cent—C_{Ph}—N—H) = 185°) and in the conformation corresponding to the energy minimum (*b*) (R_{Cent-N} = 3.5 Å, R_{Cent-H} = 2.9 Å, φ(N—Cent—H) = 7.0°, ψ(Cent—C_{Ph}—N—H) = −30°).

conformations and in the conformations corresponding to the energy minimum. The tramadol molecule is used as an example to illustrate the difference between the energetically stable and bioactive conformation (Fig. 2). The data of Table 3 indicate that flexible molecules, being adjusted to the receptor, acquire the conformations of rigid structures without substantial energy expenditure.

Thus, study of the mutual arrangement of the phenyl fragment and protonated amine in the OR ligand molecules of various structural classes shows the existence of two bioactive conformations. The existence of a particular conformation does not depend on the structural class of the ligand, the selectivity of its action on receptors, or the ratio of agonistic and antagonistic properties. The bioactive conformations have particular sets of geometric parameters: R_{Cent-N} = 4.4—5.0 and 5.5—5.7 Å, R_{Cent-H} = 5.1—5.7 and 5.4—5.7 Å, φ(N—Cent—H) = 7—9° and 7—10°, and ψ(Cent—C_{Ph}—N—H) = 178—195° and −7—15° for conformations I and II, respectively. A typical feature of the bioactive conformations is the perpendicular orientation of the π—π interaction and the N—H bond. The identified geometric parameters can be used as a criterion for geometric assessment of the opiate activity.

Experimental

Calculations were carried out using the Accelrys program.[33] The geometric parameters were optimized in two stages: first, by molecular mechanics (MM+ parametrization)[34] and then by semiempirical calculations using PM3 parametrization (see Ref. 35). The geometry optimization was considered to be completed when a gradient rate of less than 0.1 kcal (mol Å)$^{-1}$ has been reached. The electronic characteristics were calculated using AM1 parametrization (see Ref. 36).

References

1. A. V. Pogrebnyak, *Moleculeyarnoe modelirovanie i dizain biologicheski aktivnykh veshchestv* [*Molecular Modeling and Design of Biologically Active Compounds*], SKNTs VSh, Moscow, 2003, 28.
2. I. A. Wilson and R. L. Stanfield, *Curr. Opin. Struct. Biol.*, 1993, **3**, 113.
3. A. H. Beckett and A. F. Casy, *J. Pharm. Pharmacol.*, 1954, **6**, 986.
4. D. R. H. Gourley, *Prog. Drug Res.*, 1963, **7**, 36.
5. I. D. Pogozheva, A. L. Lomize, and H. I. Mosberg, *Biophys. J.*, 1998, **75**, 612.
6. S. S. Krylov, *Khim.-Farm. Zhurn.*, 1992, **26**, 122 [*Pharm. Chem. J.*, 1992, **26** (Engl. Transl.)].
7. G. H. Loew, *Modern Drug Discovery*, 1999, **2**, 24.
8. J. V. Aldrich, *Burger´s Medicinal Chemistry and Drug Discovery*, Ed. M. E. Wolf, J. Wiley and Sons, New York, 1996, **3**, p. 321.
9. K. Befort, L. Tabbara, S. Bausch, C. Chavkin, C. Evans, and B. L. Befort, *Mol. Pharm.*, 1996, **49**, 216.
10. A. Mansour, L. P. Taylor, J. L. Fine, R. C. Thompson, M. T. Hoversten, H. I. Mosberg, S. J. Watson, and H. Akil, *J. Neurochem.*, 1997, **68**, 344.
11. J. G. Li, C. Chen, and J. Yin, *Life Sci.*, 1999, **65**, 175.
12. V. M. Kolb and S. Scheiner, *J. Pharm. Sci.*, 1984, **73**, 719.
13. K. Befort, D. Tabbara, D. Kling, B. Maigret and B. L. Kieffer, *J. Biol. Chem.*, 1996, **271**, 10161.
14. V. P. Sergeev and R. L. Shimanovskii, *Retseptory* [*Receptors*], Meditsina, Moscow, 1987, p. 272, p. 275.
15. G. R. Lenz, S. M. Evans, and D. E. Walters, *Opiates*, Acad. Press Inc., New York, 1986, p. 560.
16. P. S. Portoghese, *J. Med. Chem.*, 1992, **35**, 1927.
17. J. B. Thomas, S. W. Mascarella, R. B. Rothman, J. S. Partilla, H. Xu, K. B. McCullough, C. M. Dersch, B. E. Cantrell, D. M. Zimmerman, and F. I. Carroll, *J. Med. Chem.*, 1998, **41**, 1980.
18. P. R. Stout and L. J. Farrell, *Forensic Sci. Rev.*, 2002, **15**, 30.
19. A. K. Gilbert, S. Hosztafi, and L. Mahurter, *Eur. J. Pharmacol.*, 2004, **492**, 123.
20. C. H. Mitch, J. D. Leander, L. G. Mendelsohn, W. N. Shaw, D. V. Wong, B. E. Cantrell, B. G. Johnson, J. K. Rell, J. D. Snobby, A. E. Takemori, and D. M. Zimmerman, *J. Med. Chem.*, 1993, **36**, 2842.
21. G. H Loew and D. S. Berkowitz, *J. Med. Chem.*, 1978, **21**, 101.
22. J. L. Neumeyer, J. M. Bidlack, R. Zong, V. Bakthavachalam, P. Gao, D. J. Cohen, S. S. Negus, and N. K. Mello, *J. Med. Chem.*, 2000, **43**, 114.
23. J. D. Leander, *J. Pharmacol. Exp. Ther.*, 1983, **35**, 227.
24. E. L. May, A. E. Jacobson, M. V. Mattson, J. R. Traynor, J. H. Woods, E. R. Bowman, M. D. Aceto, and L. S. Harris, *J. Med. Chem.*, 2000, **43**, 5030.
25. A. F. Cazy, *Opioid Analgetics*, Plenum Press, New York, 1986, p. 518.
26. H. Awaya, E. L. May, and M. D. Aceto, *J. Med. Chem.*, 1984, **27**, 536.
27. A. Hashimoto, A. E. Jacobson, and R. B. Rothman, *J. Bioorg. Chem.*, 2002, **10**, 1319.
28. J. B. Tomas, R. N. Atkinson, N. Mamdev, R. B. Rothman, K. M. Gigstad, S. E. Fix, S. W. Mascarella, J. B. Burgess, N. A. Vinson, H. Xu, C. M. Dersch, B. E. Cantrell, D. M. Zimmerman, and F. I. Carrol, *J. Med. Chem.*, 2002, **45**, 3524.
29. B. Belleau, T. Conway, F. R. Ahmed, and A. D. Hardy, *J. Med. Chem.*, 1974, **17**, 907.
30. R. J. Kobylecki, A. C. Lane, F. C. Smith, and O. Kennard, *J. Med. Chem.*, 1982, **25**, 1280.
31. *Cambridge Structural Database System, Version 5.17*, 1999.
32. *Pharmacophore. Perception Development and Use in Drug Design*, Ed. O. F. Gunner, International University Line, California, 2002, p. 113.
33. *Accelrys Software Inc.*, *Material Studio, Release 3.2*, San Diego, 2003.
34. U. Burkert and N. L. Allinger, *Molecular Mechanics*, ACS Monograph, 1982, p. 177.
35. J. P. Stewart, *J. Computer-Aided Molecular Design*, 1990, **4**, 1.
36. K. B. Lipkowitz and D. B. Boyd, *Reviews in Computational Chemistry*, VCH Publishers, New York, 1990.

Received December 13, 2005;
in revised form April 26, 2006