A general model of the opiate pharmacophore
1. Regions of the opiate pharmacophore responsible for nonselective affinity for the opiate receptor

N. E. Kuz´mina, E. S. Osipova, V. S. Kuz´min, and V. B. Sitnikov*

State Scientific Research Institute of Organic Chemistry and Technology,
23 sh. Entuziastov, 111024 Moscow, Russian Federation.
Fax: +7 (495) 673 3396. E-mail: arc.sioct@mail.magelan.ru

By superposition of the molecules of opiate receptor ligands of various structural classes, three regions responsible for the nonselective ligand affinity were distinguished in the opiate pharmacophore. Spatial arrangement features, electronic properties, the capability of H-bonding and hydrophobic and electrostatic interactions of these regions were determined. The set of geometric parameters found can be used as a criterion for estimation of the opiate activity in simulation of new types of ligands.

Key words: opiate receptor ligands, nonselective binding to opiate receptors, a model of the opiate pharmacophore, superposition of molecules.

Successful prediction of the "structure—biological activity" relationships should rely on comprehensive information about the pharmacophore, including the set of spatial and electronic features that ensure the supramolecular interactions with the structure of a specific biological target and actuate its biological response. Numerous studies devoted to the structures of opiate pharmacophore (OP) have been carried out. Most often, a set of definite functional groups or typical structural fragments that are distinguished by superposition of opiate-active molecules is proposed as an OP model. The proposed OP models are applicable to either particular structural classes of ligands of opiate receptors (OR)[1—4] or to ligands exhibiting a certain selectivity with respect to OR (see Ref. 5). No general model of OP applicable to all types of OR ligands irrespective of the structural class of the ligand, selectivity of its action on receptors, or the ratio of agonistic/antagonistic properties has been reported.

This study continues the systematic investigation into the structure of OP aimed at the development of a general model of OP not as a set of particular functional groups but a set of some abstractive molecular regions arranged in space in a particular manner and having particular electronic properties. This model will be described by a set of pharmacophore descriptors determining the spatial arrangement of the binding sites of the ligand with the OR, the tendency for H-bonding, hydrophobic and electrostatic interactions, *etc*.

Previously, we have demonstrated that OR ligands can exist as two bioactive conformations (I and II) differing in the mutual orientations of the key structural fragments of OR ligand molecules, namely, the protonated amino group and the phenyl ring.[6] These structural fragments are responsible for the ligand affinity for OR (electrostatic interaction of the protonated nitrogen atom with the anionic group of the complementary OR region supplemented by hydrogen bonding[7—10] and π—π-interaction of the phenyl fragment with a particular complementary section of OR as the electron density donor[11]). The existence of conformations of I and II does not depend on the structural class of the ligand, the selectivity of its action on receptors, or the ratio of agonistic/antagonistic properties. Each conformation is described by its own set of geometric parameters, which vary over very narrow ranges on going from one structural class of ligands to another. The presence of two bioactive conformations indicates that OP includes two regions able to accommodate phenyl fragments. Using the method of superposition of molecules having different bioactive conformations, one can reveal other structural fragments that occupy the same areas in space as the phenyl rings in two bioactive conformations. We introduced the following designations: **A** is the region occupied by the protonated nitrogen atom, **B** is the region of the phenyl fragment in bioactive conformation I, and **C** is the region of the phenyl fragment in bioactive conformation II. The centers of gravity of the phenyl fragments in conformations I and II were taken as the centers of regions **B** and **C**. Figure 1 illustrates the shape, the size, and the mutual positions of regions **B** and **C** with respect to the "cationic head" (the protonated nitrogen atom and its nearest environment)

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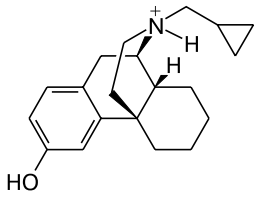
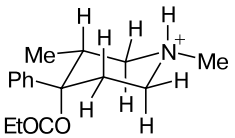
using the molecules of cyclorphan (bioactive conformation I) and β-prodine (bioactive conformation II) as examples.



Cyclorphan



β-Prodine

Molecules of various structural classes of OR ligands were used as the investigation objects: 4,5-epoxymorphinans, morphinans, morphinan-6-ketones, benzomorphans, 5-arylmorphans, dihydromorphone derivatives, oripavine, buprenorphine, propoxyphene derivatives, 4-phenylpiperidines, diphenylpropylamines, anilidopiperidines, arylcyclohexanolamines, *trans*-4a-phenyldecahydroisoquinolines, arylacetamides, and opioid peptides (Table 1). More than 100 compounds were studied.*

The molecules were subjected to superposition in their bioactive conformations. For conformationally rigid molecules, the bioactive conformation was identified with the existing conformation (X-ray diffraction data for these compounds or their close structural analogs were used). For conformationally flexible molecules, the conformers having the same sets of geometric parameters describing the mutual orientations of the key structural fragments of OP as in "rigid" molecules were considered as bioactive conformers.[6] Superposition of the three-dimensional structures of various molecules was performed by spatial matching the "cationic head" atoms (Figs 2—4).

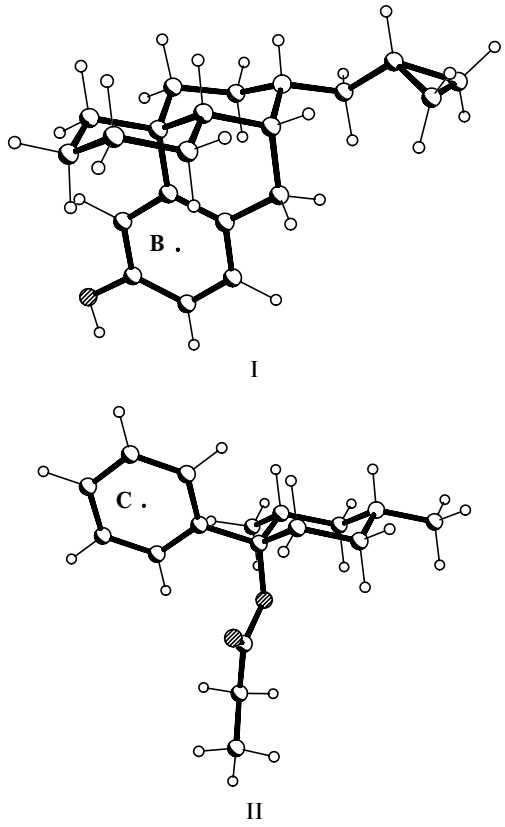


Fig. 1. Bioactive conformations I (cyclorphan molecule, *a*) and II (β-prodine molecule, *b*).

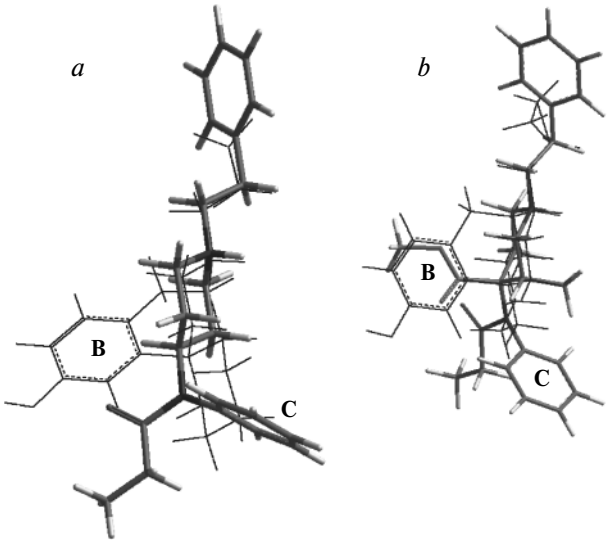
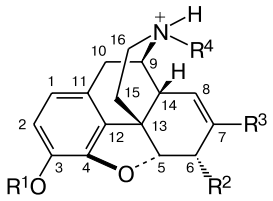
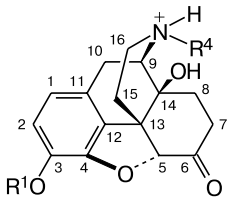


Fig. 2. Different degrees of filling of region **B**: superposition of cyclorphan and fentanil molecules (*a*), cyclorphan and lofentanil molecules (*b*).

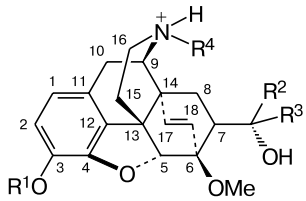
* The list of compounds studied (apart from those discussed in the paper): anileridine, allylnormetazocine, allylprodine, azidomorphine, alletorphine, butorphanol, bremazocine, buprenorphine, benzethidine, bemidone, codeine, cyclazocine, cyanoethylnormetazocine, cyanopropylnormetazocine, cyanobutylnormetazocine, cyprenorfin, cyprodim, dihydromorphine, diprenorphine, dezocine, dextromoramide, dipipanone, diampromide, diamorphine, etorphine, etoxyridin, ethylketocyclazocine, hydrocodone, hydrocodeine, 3-hydroxy-6-ketomorphinan, isomorphine, ketocyclazocine, ketobemidone, ketamine, levalorfan, levorfanol, lofentanil, morphine, methorphan, metazocine, metopon, meptazinol, methadone, metofoline, methohexital, 3-methylfentanil, 4-methylfentanil, normorphine, nalorphine, nalbuphine, nalbuphone, nalmefene, naloxone, naltrexone, nalmexon, normepyridine, β-naltrexamine, naltrindole, *N*-cyclopropylmethylnoretorphine, oxymorphone, oxycodone, OH-methylfentanil, phenopyridine, phenapromid, phenazocine, proxidol, α-prodine, α-promedol, β-promedol, γ-promedol, pentazocine, piminodine, profadol, propiophenone, picenadrol, prodilidine, petidin, remifentanil, trifluadom, tramadol, thiopental, furanylate, β-CNA, COA, β-FNA, FOA, MCL 101, LY255582, Ly246736, Mr2266, U50,488, ICI204448, SB-205588, SB-235863, PD-117302, 2,9β-dimethyl-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonane, 2-(1-methyl-2-phenethyl)-5-(3-hydroxyphenyl)-2-azabicyclo[3.3.1]nonane.



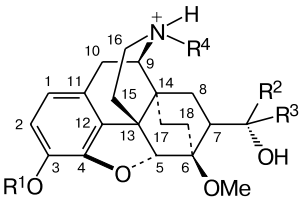
4,5-Epoxymorphinans



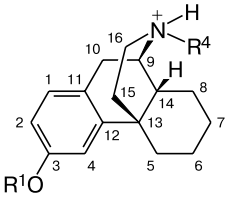
Dihydromorphone derivatives



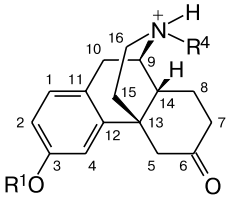
Oripavine derivatives



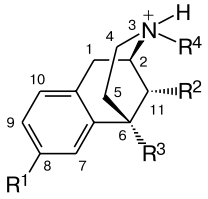
Buprenorphine derivatives



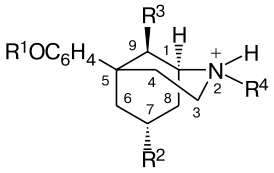
Morphinans



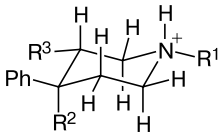
Morphinan-6-ketones



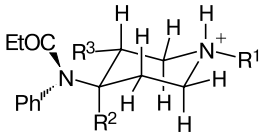
Benzomorphans



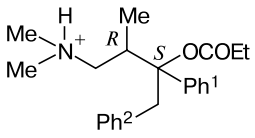
5-Arylmorphans



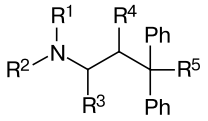
4-Phenylpiperidines



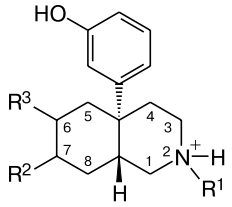
Anilidopiperidines



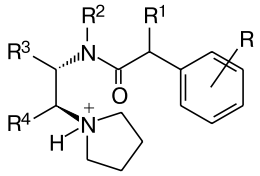
Propoxyphene



Diphenylpropylamines



trans-4a-Phenyldecahydroisoquinolines



Arylacetamides

Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln

Dynorphin A

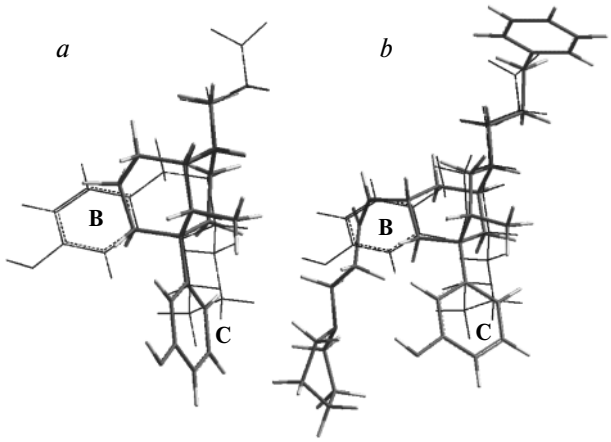


Fig. 3. Different degrees of filling of region **B**: superposition of cyclorphan and 5-(3-hydroxyphenyl)-2-methylmorphan molecules (*a*), cyclorphan and *N*-[4β-methyl-5-(3-hydroxyphenyl)-2-(3´-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-(1-piperidinyl)propanamide molecules (*b*).

Table 1 presents the compounds whose structural fragments coincide with the phenolic fragment of morphine-like molecules (region **B**) and with the phenyl fragment of a 4-phenylpiperidine molecule (region **C**). It can be seen that, apart from the phenolic fragment of cage molecules, region **B** contains also the carboxy group in propoxyphene derivatives, the carbonyl group in arylacetamides, the amide group in peptides, and the aryl fragment in diphenylpropylamines and *trans*-4a-phenyldecahydroisoquinolines. In these structural classes of OR ligands, the centers of gravity of these fragments coincide with the center of region **B**.

For most 4-phenylpiperidine molecules in which the phenyl fragment occupies an equatorial position in the piperidine ring, the 4-substituent in the piperidine rings gets in region **B**, in particular, the carboxy group in meperidine and prodine, the carbonyl group in ketobemidone, the hydroxy group in β- and γ-promedol, and the alkyl substituent in 4-alkyl-4-phenylpiperidines. Note

Table 1. Structural fragments that occupy regions **B** and **C** in various classes of opiate receptor ligands

Ligand class	Region **B**	Region **C**
4,5-Epoxy-morphinans	Ph—OR^1	OC(5)C(6)O, OC(5)C(6)N (O, N—α-atom R^2)
Oripavine derivatives	Ph—OR^1	OC(5)C(6)O
Morphinans	Ph—OR^1	C(5)C(6)
Benzomorphans	Ph—R^1	R^3 (α, β-atoms)
4-Phenyl-piperidines	Ph, R^2 (OCO, COO, CO, OH, Alk)	Ph, R^2 (OH)
Propoxyphene	OCO	Ph^1
trans-4a-Phenyl-decahydroiso-quinolines	Ph—OH	C(5)C(6)R^3 (α-atom)
Dynorphin A	CON	Ph—OMe
Dihydromorphone derivatives	Ph—OR^1	OC(5)C(6)O
Buprenorphine derivatives	Ph—OR^1	OC(5)C(6)O
Morphinan-6-ketones	Ph—OR^1	C(5)C(6)O
5-Arylmorphans	C(6)C(7)R^2 (α, β, γ-atoms)	Ph—OR^1
Diphenylpropyl-amines	Ph	Ph
Anilidopiperidines	R^2 (α, β-atoms) + + CO	Ph
Arylacetamides	CO	R^3

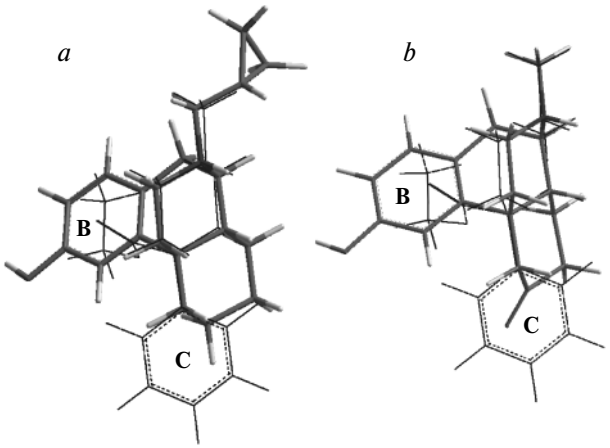
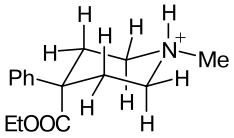


Fig. 4. Different degrees of filling of region **C**: superposition of meperidine and cyclorphan molecules (*a*), meperidine and 3-hydroxy-6-ketomorphinan molecules (*b*).

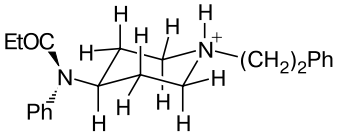
that upon superposition of morphine-like molecules and 4-phenylpiperidine molecules, the carboxy group of the propionyloxy substituent in prodine derivatives is better matched to the phenyl ring of morphine-like molecules than the carboxy group of the ethoxycarbonyl substituent in meperidine derivatives: the distances "center of gravity of the carboxy group—nitrogen atom" in meperidine and prodine derivatives are 4.03 and 4.30 Å, respectively, whereas the distance "center of gravity of the phenyl group—nitrogen atom" in the morphine molecule is 4.5 Å. Apparently, this is responsible for the higher opiate activity of compounds of the prodine family compared with the meperidine analogs.



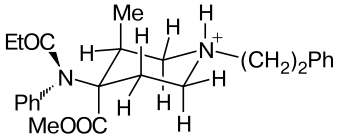
Meperidine

In those cases where the phenyl fragment in 4-phenylpiperidine molecules is oriented axially with respect to the piperidine ring (for example, in the α-promedol molecule), it is this fragment that gets into region **B**.

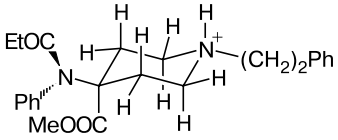
It is noteworthy that region **B** is not always fully occupied. For example, in the molecules of 4-anilidopiperidine derivatives, the carbonyl group of the 4-*N*-phenylpropanamide substituent is located in the peripheral part of region **B** (see Fig. 2, *a*). If the molecule contains one more substituent in position 4 of the piperidine ring, region **B** becomes more fully occupied and, as a consequence, the opiate activity of compounds markedly increases. For example, the introduction of a methoxycarbonyl group to position 4 of the piperidine ring in lofentanil (see Fig. 2, *b*) and carfentanil molecules or a methoxymethyl group in the sufentanil molecule induces a 10—30-fold increase in the agonistic activity with respect to that of fentanil.[3]



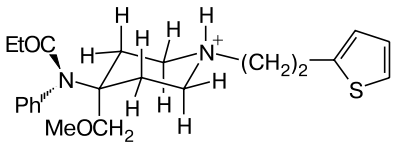
Fentanil



Lofentanil

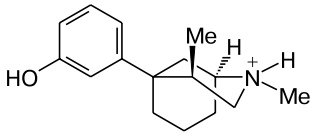


Carfentanil

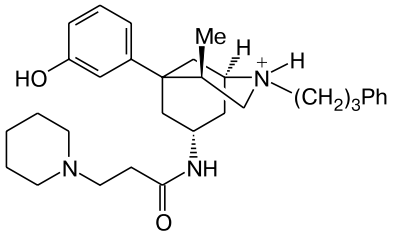


Sufentanil

A similar situation is observed for the molecules of 5-arylmorphan derivatives.



5-(3-Hydroxyphenyl)-2,4β-dimethylmorphan

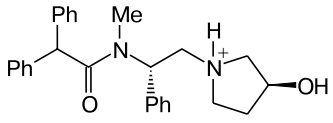


N-[4β-Methyl-5-(3-hydroxyphenyl)-2-(3´-phenylpropyl)-2-azabicyclo[3.3.1]non-7-yl]-3-piperidinopropanamide

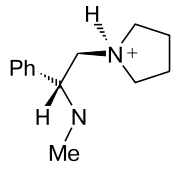
The C(6) and C(7) atoms of the morphan nucleus (see Fig. 3, *a*) get into region **B** (its peripheral part). The introduction of a substituent containing an amide group in position 7 of the nucleus increases the ligand affinity for OR (see Ref. 12). The increase in the affinity is apparently due to more complete filling of region **B**. The center of gravity of the combined C(6)C(7)+NCO fragment coincides with the center of region **B** (see Fig. 3, *b*).

Analysis of the structural fragments that get into region **C** indicates that in many classes of OR ligands (4-phenylpiperidines, diphenylpropylamines, 4-anilidopiperidines, 5-arylmorphans, peptides, and propoxyphene), this region contains an aryl fragment. In the molecules of morphine, dihydromorphone, oripavine, and buprenorphine derivatives, region **C** accommodates the OC(5)C(6)O or OC(5)C(6)N fragment. In the molecules of benzomorphan derivatives, region **C** contains the α- and β-atoms of the 6-substituent, while in molecules of the arylacetamide class, this is the R^3 substituent (for example, the phenyl ring in the ICI199,441 and asimadilin molecules or the phenolic ring in DuP747).

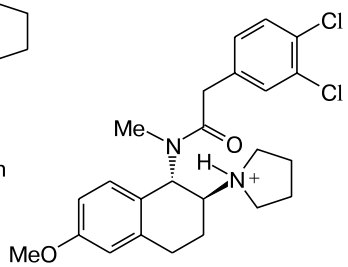
It is noteworthy that the aryl ring of the arylacetamide fragment in arylacetamides occurs outside regions **B** and **C** and probably serves as an additional binding site, ensuring the selectivity of interaction with κ-OR. This conclusion is in good agreement with the results of investigation of the "docking" of arylacetamide and benzomorphan molecules on the 3D model of κ-OR (see Ref. 13). The centers of gravity of these fragments coincide with the center of region **C**.



ICI199,441



Asimadilin



DuP747

Similarly to region **B**, region **C** can be occupied only partially. For example, in morphan type molecules, the C(5) and C(6) atoms get into the peripheral part of region **C** (see Fig. 4, *a*). The introduction of a carbonyl group into position 6 of the morphinan ring increases the degree of filling of region **C** (see Fig. 4, *b*). As a consequence, morphinan-6-ketones are several times more active than morphinans[14] (see Fig. 3).

Table 2 presents the geometric parameters describing the mutual arrangement of regions **A**, **B** and **C** in space:

(1) the distance "center of region **B**—the nitrogen atom of the protonated amine" ($R_{\mathbf{BN}}$);

(2) the distance "center of region **B**—the ammonium hydrogen atom" ($R_{\mathbf{BH}}$);

(3) the distance "center of region **C**—the nitrogen atom of the protonated amine" ($R_{\mathbf{CN}}$);

(4) the distance "center of region **C**—the ammonium hydrogen atom" ($R_{\mathbf{CH}}$);

(5) the distance "center of region **B**—center of region **C**" (R_{BC})

(6) the angle "center of region **B**—nitrogen atom—center of region **C**" (**B**—N—**C**);

(7) the torsional angle "center of region **B**—center of region **C**—the N atom—the ammonium H atom" (**B**—**C**—N—H).

The data of Table 2 indicate that the geometric parameters within the same structural class are similar. The scatter of geometric parameters is somewhat increased on going from one structural class to another; however, it does not exceed 1 Å for distances and 20° for angles. The scatter of geometric parameters can characterize the dimensions of regions **B** and **C**.

Analysis of the structural fragments that occupy regions **B** and **C** in various classes of OR ligands shows their similar features. Most of these fragments are either conju-

Table 2. Geometric parameters of the spatial arrangement of regions **A—C**

OR ligand class	R_{BN}	R_{BH}	R_{CN}	R_{CH}	R_{BC}	**B**—N—**C**	**B**—**C**—N—H
Morphines	4.4—5.0	5.1—5.7	5.1—5.3	5.2—5.4	3.7—3.8	43—46	173—175
Dihydromorphones	4.4—4.5	5.2—5.4	5.1—5.3	5.5—5.6	3.6—3.7	42—45	177—180
Oripavines	4.5—4.6	5.2—5.3	5.1—5.4	5.2—5.3	3.9—4.0	45—47	178—180
Buprenorphines	4.5—4.7	5.1—5.2	5.1—5.3	5.2—5.3	3.9—4.1	46—50	176—178
Morphinans	4.4—4.5	5.1—5.3	5.2—5.3	5.3—5.4	4.1—4.3	50—52	170—173
Pyrrolomorphinans	4.4—4.5	5.2—5.3	5.2—5.3	5.3—5.4	3.7—3.8	43—44	178—180
Morphinan-6-ketones	4.3—4.4	5.2—5.3	5.4—5.5	5.5—5.6	4.0—4.1	48—49	171—175
Benzomorphans	4.4—5.0	5.1—5.7	5.3—5.6	5.2—5.6	4.0—4.8	50—51	175—179
4-Phenylpiperidines	4.0—4.3	4.8—4.9	5.5—5.7	5.4—5.7	4.0—4.3	44—46	178—180
5-Arylmorphans	4.4—4.5	5.1—5.2	5.5—5.8	5.6—5.7	4.9—5.1	53—55	170—176
Diphenylpropylamines	4.6—5.0	5.2—5.8	5.7—5.9	5.6—5.9	4.8—5.1	54—56	173—176
Anilidopiperidines	4.5—4.6	5.1—5.4	5.6—5.7	5.4—5.6	3.9—4.1	53—55	170—175
trans-4a-Aryldecahydro-isoquinolines	4.6—4.7	5.4—5.5	5.4—5.5	5.6—5.7	4.1—4.2	48—50	166—170
Arylacetamides	4.3—4.4	5.3—5.5	5.2—5.3	5.7—5.8	4.7—4.8	57—59	170—180
Peptides	4.5—4.7	5.2—5.4	5.3—5.5	5.6—5.7	4.8—4.9	56—57	176—178

gated systems, or systems with a multiple bond, or systems containing heteroatoms. Hence, regions **B** and **C** are capable of π—π or ρ—π interactions with the receptor binding sites.

The electronic properties of the structural fragments that occupy regions **B** and **C** were estimated by two methods. The donor-acceptor properties in orbitally controlled reactions were estimated using normalized contributions of atoms of the structural fragments to the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO, respectively).[15] It is generally accepted that the HOMO correlates with the ionization potential and measures the electron-donor properties of the molecule and the LUMO correlates with the electron affinity and measures the electron-withdrawing properties of the molecule[15].

The contributions were normalized to the energy of the opposite frontier orbital:[16]

$$F^{HOMO}C(i) = \Sigma(C_{HOMO(n)})^2/|E_{LUMO}|,$$

$$F^{LUMO}C(i) = \Sigma(C_{LUMO(n)})^2/|E_{HOMO}|,$$

where $C_{HOMO(n)}$ is the coefficient for atomic orbital n of atom $C(i)$ in the HOMO, $C_{LUMO(n)}$ is the coefficient in the LUMO.

The donor-acceptor properties for charge-controlled reactions were estimated on the basis of charge distribution on the atoms. In most cases, structural fragments that occupy regions **B** and **C** exhibit electron-donor properties. The atoms of these fragments either give the highest contribution to the HOMO (the aryl fragment (F_{Ar}^{HOMO} = 0.096—0.139 eV) and the furan O atom (F_{O}^{HOMO} = 0.103—0.135 eV)) or bear a substantial negative charge (the O atom of the carboxy and carbonyl groups, heteroatoms of the amide group, or the N atom of the amino group (Table 3)).

Table 3. Charges (in fractions of the electron charge) on the atoms of structural fragments getting into regions **B** and **C**

Group	Charge	Group	Charge
O—C=O	−0.260—−0.265	NH—C=O	−0.313—−0.344
O—C=O	−0.350—−0.354	NH—C=O	−0.358—−0.321
OH	−0.286—−0.292	NH_2	−0.320—−0.323
OMe	−0.260—−0.263	$NAlk_2$	−0.275—−0.278

Unlike regions **B** and **C**, region **A** has electron-withdrawing properties. The atoms of the "cationic head" make the greatest contribution to the LUMO (F_{cat}^{LUMO} = 0.056—0.104 eV) and the H atom bears a substantial positive charge (+0.230—+0.253).

The problem of hydrophobicity of regions **B** and **C** deserves special attention. According to a hypothesis reported in the literature, the phenyl fragment of morphine-like molecules interacts with the hydrophilic reception site, and the phenyl fragment of the 4-phenylpiperidine molecules interacts with the hydrophobic site.[17] This hypothesis was substantiated by the fact that the phenolic prodines and allylprodines are inactive. However, it was found experimentally that in meperidine, 4-alkyl-4-arylpiperidine, and 5-arylmorphan derivatives, the introduction of a hydroxy group into the phenyl ring increases the opiate activity.[14] Thus, the change in the opiate activity caused by the replacement of a phenyl by a phenolic fragment depends on the nature of 4-substituent in the piperidine ring rather than on the hydrophobicity of region **C**. In the case of 4-propionoxy group, an intramolecular hydrogen bond may be formed between the *m*-OH group of the phenyl ring and the carbonyl oxygen atom of

the 4-substituent. This H-bond secures the phenyl ring in a strictly defined position in which the intermolecular π—π interaction with the reception site becomes impossible. In meperidines, no intramolecular H-bond is formed, because the carbonyl group of the 4-ethoxycarbonyl substituent is remote from the *m*-OH group in the phenyl ring.

Analysis of the structural fragments that fall into regions **B** and **C** indicates that most of them contain polar groups capable of hydrogen bonding with the receptor, and, hence, they are hydrophilic.

Thus, in all types of OR ligand molecules, one can distinguish three OP regions responsible for nonselective affinity for OR: the hydrophilic electron-withdrawing region capable of H-bonding with OR as the proton donor (**A**) and two hydrophilic electron-donor regions capable of π—π or π—ρ interactions and H-bonding with the OR (**B** and **C**).

The spatial arrangement of the regions **A**, **B**, and **C** is described by a particular set of geometric parameters: $R_{\mathbf{BN}}$ = 4.0—5.0 Å, $R_{\mathbf{BH}}$ = 4.8—5.8 Å, $R_{\mathbf{CN}}$ = 4.7—5.7 Å, $R_{\mathbf{CH}}$ = 5.2—5.9 Å, $R_{\mathbf{BC}}$ = 3.6—5.1 Å; **B**—N—**C** = 42—56°, and **B**—**C**—N—H = 166—180°. The geometric parameters depend only slightly on the structural class of the ligand and do not depend on the selectivity of ligand action on the receptors or the relationship between the aginistic and antagonistic properties. The established set of geometric parameters can be used as a criterion for evaluation of the opiate activity in the modeling of new types of OR ligands.

Experimental

The calculations were carried out using the Accelrys program package.[18] The geometric parameters were optimized in two stages: first, by molecular mechanics (MM+ parametrization)[19] and then by a semiempirical method using PM3 parametrization (see Ref. 20). The geometry optimization was considered complete when the gradient norm of less than 0.01 kcal (mol Å)$^{-1}$ was attained. The electronic characteristics were calculated using AM1 parametrization (see Ref. 21).

References

1. A. S. Horn and J. R. Rodgers, *J. Pharm. Pharmacol.*, 1977, **29**, 257.
2. L. I. Wei, J.-I. Hao, Y. Tang, Y. Chen, and Zh. Qiu, *Acta Pharmacogica Sinica*, 2005, **26**, 334.
3. L. Dosen-Micovic, *J. Serb. Soc.*, 2004, **69**, 843.
4. A. Lavecchia, G. Greco, E. Novellino, F. Vittorio, and G. Ronsisvalle, *J. Med. Chem.*, 2000, **43**, 2124.
5. G. H. Loew, *Modern Drug Discovery*, 1999, **2**, 24.
6. N. E. Kuz´mina, E. S. Osipova, V. S. Kuz´min, and V. B. Sitnikov, *Izv. Akad. Nauk. Ser. Khim.*, 2006, 1462 [*Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 1516].
7. K. Befort, L. Tabbara, and S. Bausch, *Mol. Pharm.*, 1996, **49**, 216.
8. J. G. Li, C. Chen, and J. Yin, *Life Sci.*, 1998, **65**, 175.
9. A. Mansour, L. P. Taylor, and J. L. Fine, *J. Neurochem.*, 1997, **68**, 344.
10. V. M. Kolb and S. Scheiner, *J. Pharm. Sci.*, 1984, **73**, 719.
11. N. E. Kuz´mina, E. S. Osipova, V. S. Kuz´min, and V. B. Sitnikov, *Khim.-Farm. Zh.*, 2005, **39**, 24 [*Pharm. Chem. J.*, 2005, **39** (Engl. Transl.)].
12. J. B. Thomas, R. Atkinson, N. Namdev, R. Rothman, K. M. Gistard, 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.
13. A. Lavecchia, G. Greco, E. Novellino, F. Vittorio, and G. Ronsisvalle, *J. Med. Chem.*, 2000, **43**, 2124.
14. G. R. Lenz, S. M. Evans, and D. E. Walters, *Opiates*, Academic Press Inc., New York, 1986, p. 560.
15. *Chemical Reactivity and Reaction Paths*, Ed. G. Klopman, J. Wiley and Sons, 1974, 383.
16. M. Karelson and V. S. Lobanov, *Chem. Rev.*, 1996, **96**, 1027.
17. P. S. Phortogese, *J. Med. Chem.*, 1992, **35**, 1927.
18. *Accelrys Software Inc., Material Studio, Release 3.2*, San Diego, 2003.
19. N. L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127.
20. J. P. Stewart, *J. Computer-Aided Molecular Design*, 1990, **4**, 1.
21. K. B. Lipkowitz and D. B. Boyd, *Reviews in Computational Chemistry*, VCH Publishers, New York, 1990, p. 165.

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