# The opiate receptor: A model explaining structure-activity relationships of opiate agonists and antagonists

(benzomorphan/morphine/naloxone)

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ABSTRACT     A model of the opiate receptor is proposed which explains structure-activity relationships of opiate drugs, including (i) the unique potency of certain opiates such as etonitazene, fentanyl, phenazocine, and oripavines; (ii) the role of N-allyl substituents in conferring antagonist properties; and (iii) chemical features that afford "pure" antagonists. The model indicates molecular mechanisms for interconversion of the opiate receptor between respective states that bind agonists or antagonists with high affinity.

Unique pharmacological properties of many opiates are not readily explained by their chemical structures. Examples include (i) the great potency of opiates such as etonitazene, fentanyl, phenazocine, and etorphine (Fig. 1); (ii) the dramatic change from agonist to antagonist effects conferred by transforming an opiate N-methyl to an N-allyl or related substituent; and (iii) the chemical features determining that "pure" opiate antagonists such as naloxone lack analgesic and euphoric actions while "mixed" agonist-antagonists possess both.

Studies on opiate receptor binding differentiate agonists and antagonists (1). The opiate receptor appears to exist in two interconvertible forms, one with uniquely high affinity for antagonists and the other with selective affinity for agonists (2). Sodium ions enhance antagonist and depress agonist binding presumably by regulating interconversion of the two opiate receptor states, while manganese selectively facilitates agonist binding (2, 3). These influences may physiologically regulate interactions of the opiate receptor with the naturally occurring, morphine-like peptide, enkephalin (4–7).

Here we suggest possible conformations of opiates at their receptor site which can explain similarities in pharmacological actions of compounds whose chemical structures appear, superficially, quite different. A model of opiate receptor function is proposed specifying conformational changes that underlie the interconversion of the two receptor states and explaining the pharmacological differences of opiate agonists and antagonists.

## Conformational features of certain potent agonists

In homologous series of opiates, some agonists are far more potent than closely related drugs (Fig. 1). Fentanyl, 1000 times more potent an analgesic than meperidine, differs in structure from the latter (among other ways) in having a phenethyl group on the piperidine nitrogen in place of a methyl. The extremely potent benzimidazole opiate etonitazene, like fentanyl, possesses a phenyl group that can be in proximity to the amine nitrogen. The 6,14-endoethenotetrahydrothebaine derivative "PET" (Fig. 1), structurally related to etorphine and of similar high potency (8), also has a phenyl group that can be in an analogous

position. Unlike most other benzomorphan opiates, phenazocine possesses an N-phenethyl group that confers a potency exceeding that of N-methyl benzomorphans of the α-series. The greater potency of these drugs compared to morphine is not adequately explained by pharmacodynamic or metabolic variations (9, 10).

Dreiding and CPK models indicate that the benzene ring associated with the enhanced potencies of phenazocine, fentanyl, etonitazene, and "PET" emerges from different portions of the molecule in each drug. Benzene ring A (Fig. 2) and the amine nitrogen are crucial for all opiate actions. When ring A and the amine nitrogen are set in a fixed location in molecular models of "PET," fentanyl, phenazocine, and etonitazene, only one conformation of benzene ring F can be shared by all four drugs (Fig. 2).

We propose that the uniquely high potency conferred upon etonitazene, phenazocine, fentanyl, and "PET" by ring F is associated with a common conformational localization of ring F for these four drugs, which we refer to as the "agonist" conformation of these drugs. Previously, Bentley and Lewis (8) proposed that ring F of tetrahydrothebaines must interact uniquely with opiate receptors. This model is consistent with a single common orientation in space of rings A and F and the amine nitrogen. We suggest that the interaction of ring F with a specific site of one conformation of the opiate receptor is crucial for the potent agonist activity of these drugs.

Molecular features of other opiates are consistent with this model. Opiate agonists, such as methadone and propoxyphene, which also possess additional benzene rings (also labeled ring F in Fig. 3), are much less potent than etonitazene, phenazocine, "PET," and fentanyl. Despite the presence of the second benzene ring and the well-known flexibility of methadone and propoxyphene, these drugs cannot assume at the same time the critical orientation of both rings A and F and the amine nitrogen that exist in the proposed "agonist" conformation of etonitazene and other potent opiates that contain ring F.

## Conformational features determining antagonist activity

Converting the N-methyl substituent of an opiate agonist to an N-allyl or cyclopropylmethyl usually confers antagonist activity. Presumably, the N-allyl or other such group interacts with a portion of the opiate receptor regulating antagonist activity. Some antagonists are "contaminated" with agonist properties while others, such as naloxone, naltrexone, and oxilorphan, are "pure" or "nearly pure" antagonists. For most opiate antagonists, the N-allyl grouping is flexible and can rotate among several conformations (11). Introduction of a 14-hydroxyl group systematically produces pure antagonists like naloxone and oxilorphan. The 14-hydroxyl group will reduce the free rotation of the N-allyl and should also increase the

Abbreviation: PET, 7-[1-phenyl-3-hydroxybutyl-3-]endoethenotetrahydrothebaine.
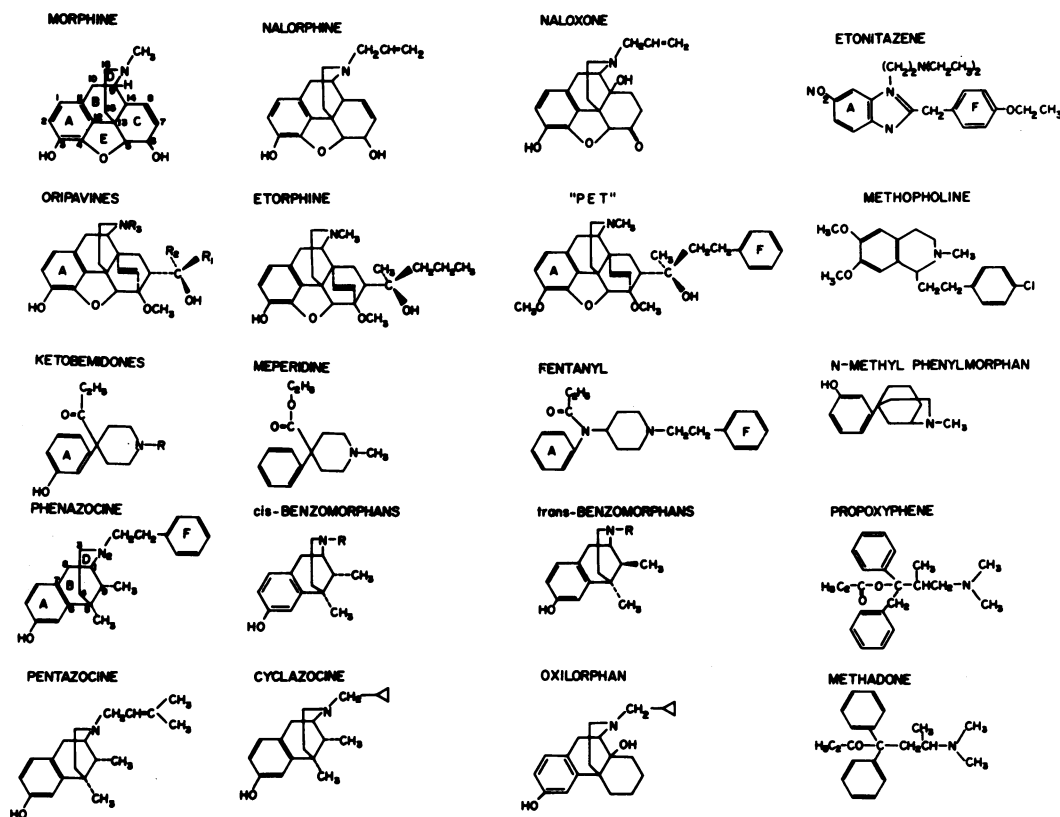* To whom reprint requests should be sent.

FIG. 1. Structures of opiate drugs. "PET" is an abbreviation for 7-[1-phenyl-3-hydroxybutyl-3-]endoethenotetrahydrothebaine.

proportion of molecules with the $N$-allyl in an equatorial (rather than axial) conformation relative to the piperidine ring (Fig. 4). This conclusion, derived from molecular modeling, is supported by data from molecular orbital calculations indicating that introducing a 14-hydroxyl group reduces the potential energy of the equatorial conformation with respect to the axial conformation by about 7–10 kcal/mole (11). The notion that the 14-hydroxyl facilitates "pure" antagonism by spatially fixing the "antagonist" substituent at a specific location relative to ring A and the amine nitrogen, derives support from structure-activity relationships of benzomorphans and related compounds. The 9-methyl substituent of benzomorphans corresponds spatially to the 14-hydroxyl of naloxone when it is in the $\beta$ (*trans*) but not in the $\alpha$ (*cis*) position (Fig. 5). With ethyl

or longer $N$-substituents, *trans*-benzomorphans are purer antagonists than *cis*-benzomorphans (12). Presumably, in a *trans* location the 9-methyl group stabilizes the side chain in an equatorial "antagonist" location as the 14-hydroxyl does in naloxone. Similarly, a 9-hydroxyl group oriented toward the amine nitrogen enhances antagonist properties of benzomorphans, while a 9-hydroxyl directed away from the nitrogen does not affect antagonist potency (13).

We propose that, besides the role played by its chemical nature, this precise spatial localization of the "antagonist" substituent determines the "purity" of the antagonistic pharmacological properties of the drug. Presumably one conformation of the opiate receptor embodies a specific antagonist binding site to which this substituent attaches.

## A model of the opiate receptor

Numerous models assume that the opiate receptor must have a lipophilic site that interacts with ring A and an anionic site that interacts with the amine nitrogen (14), and Portoghese has suggested that separate domains within the receptor may be associated with either agonist or antagonist effects (15). Re-
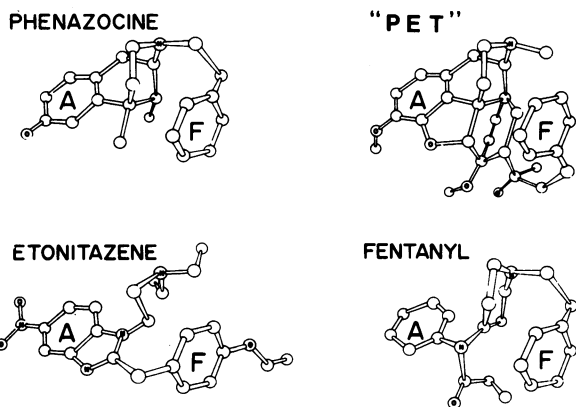


FIG. 2. Molecular models of the potent agonists phenazocine, "PET," etonitazene, and fentanyl. Rings A and F and the amine nitrogen are drawn in common spatial orientation, the hypothetical "agonist conformation" of these drugs.
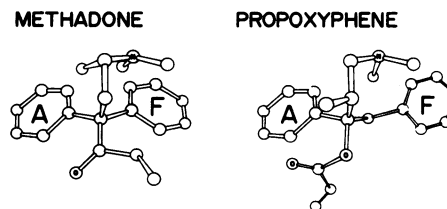


FIG. 3. Molecular models of the weak agonists methadone and propoxyphene. These drugs cannot assume the critical orientation of rings A and F and the amine nitrogen that exist in the conformation proposed for potent agonists.
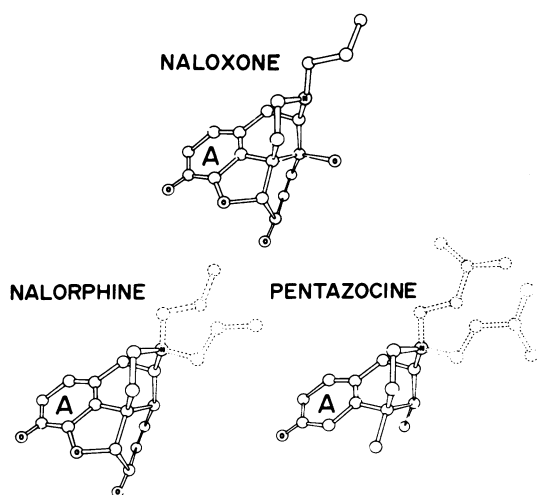
NALOXONE



NALORPHINE        PENTAZOCINE

FIG. 4.   Molecular models of naloxone, nalorphine, and penta-zocine. The "pure" antagonist properties of naloxone may be derived from the capacity of its 14-hydroxyl group to limit free rotation of the *N*-allyl side chain and to stabilize it in the equatorial conformation, the hypothetical "antagonist conformation."

cently, Bentley and Lewis proposed a third lipophilic site to accommodate certain aromatic portions of tetrahydrothebaine and oripavine opiates (8).

We propose that the opiate receptor can exist in two con-formations allosterically modulated by sodium ions, the "ago-nist" and "antagonist" conformations (Fig. 6). The lipophilic site that interacts with ring A and the ionic site that interacts with the amine nitrogen are available for binding in either conformation of the opiate receptor. In addition, the receptor has a specific agonist binding site (Fig. 2) at which ring F of potent agonists can bind (Fig. 6). Binding of an agonist to this site stabilizes the agonist conformation of the receptor. This site is not available when the receptor is in the antagonist confor-mation. In the antagonist conformation the receptor uncovers a specific antagonist binding site capable of binding the "an-tagonist" substituents of pure antagonists. Binding to this site (not available in the agonist configuration) stabilizes the an-tagonist conformation of the receptor. The two possible con-formations of the receptor could correspond to a change in the teritary structure of the receptor or to a true "allosteric" tran-sition perhaps mediated by sodium ions between different quaternary conformations. Changes of both kinds are well documented in the binding of $O_2$, 2,5-diphosphoglycerate, and $H^+$ ions to the hemoglobin molecule (16, 17). Normally, the receptor is in the antagonist conformation, corresponding to biological data indicating that under the prevailing sodium concentrations of the brain, the opiate receptor exists pre-dominantly in an antagonist conformation (18).

What about opiate agonists, such as morphine (Fig. 7), that lack an appropriate ring F? Presumably, binding by morphine's ring A and amine nitrogen triggers transformation of the re-ceptor to the "agonist conformation." However, drugs such as morphine are only moderately potent, because they lack a ring F to stabilize the receptor firmly in the "agonist conformation." The stabilization of the "agonist conformation" by the binding · of ring F to the specific agonist binding site accounts for the enhanced potency of etonitazene, "PET," phenazocine, and fentanyl.

In mediating antagonist activity, the specific antagonist binding site of the receptor presumably interacts with the pi-electrons of the *N*-allyl or the atomic configurations of *N*-cyclopropylmethyl or *N*-cyclobutylmethyl groups (19), which
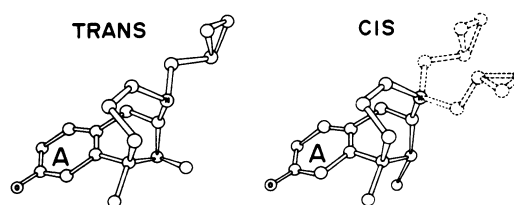
TRANS          CIS



FIG. 5.   Molecular models of a *trans*- and *cis*-homobenzomorphan cyclazozocine homologue, with a seven-member D ring rather than the piperidine ring of cyclazocine. The *trans* isomer is a pure antag-onist, in which the *trans*-9-methyl group mimics the 14-hydroxyl group of naloxone (12).

are required for antagonist pharmacology, thus stabilizing the antagonist receptor conformation. To secure "pure" antagonist properties, the approximation of this substituent to the antag-onist binding site of the receptor must be facilitated by a 14-hydroxyl or 9-$\beta$-methyl substituent as in naloxone or antagonist benzomorphans. Other drugs with *N*-allyl or related groups but lacking this feature, such as nalorphine or pentazocine, will display varying mixtures of agonist and antagonist pharma-cology.

This hypothetical model explains several paradoxical struc-ture-activity relationships. For instance, the tetrahydroiso-quinoline, methopholine, is a codeine-like analgesic yet ap-parently displays no obvious chemical relationship to opiate structures (20). However, its structure can correspond to the three proposed active sites of the potent opiate agonists (Fig. 7). Tetrahydrothebaine and oripavine drugs, whose $R_1$ is a propyl or larger substituent, are analgesic and display no an-tagonist potency even if the $R_3$ substituent is an allyl or cyclo-propylmethyl (Fig. 1). Molecular models indicate that the $R_1$ substituent may interact with the hydrophobic agonist binding site, stabilizing the receptor in the agonist conformation and blocking its transition to the antagonist site.

The extensive structure-activity data on tetrahydrothebaines and oripavines permit one to draw inferences about detailed interactions of opiates with their receptor. For example, the oripavine in which $R_3$ = cyclopropylmethyl, $R_1$ = methyl, and $R_2$ = *n*-propyl (Fig. 1), is an antagonist with potency compa-rable to that of nalorphine. However, the homologous drug whose $R_1$ is an *n*-propyl group and $R_2$ is a methyl group is an agonist with 1000 times the analgesic potency of morphine (8). This transformation of antagonist to agonist is predicted by our model, because in the latter case the propyl group exerts a hy-drophobic attraction to the agonist binding site moiety of the receptor. Since the group conferring agonist potency (*n*-propyl here, or phenethyl in "PET") lies roughly perpendicular to and slightly below the plane of the A ring in Fig. 2, the agonist site of the receptor molecule also presumably lies perpendicular to and slightly below the plane of the A ring. Localization of the $R_1$ substituent in the plane of the agonist binding site is consis-tent with the capacity of appropriate $R_1$ substituents, such as propyl or phenethyl, to yield opiate agonists, despite the exis-tence of *N*-allyl ($R_3$) substituents. Variations of the $R_2$ substit-uent, not in the plane of the agonist binding site, lack these ef-fects.

We hypothesize that the hydroxyl group on the asymmetric carbon lies along the same plane as the other oxygens in the oripavines, enabling the oxygens to interact with a hydrophilic area of the receptor. Moreover, the hydroxyl on the asymmetric carbon may hydrogen bond to the oxygen of the C-ring me-thoxy substituent, fixing the $R_1$ substituent in the plane of the agonist binding site. The $R_1$ and $R_2$ substituents project into a more hydrophobic receptor environment. Presumably all op-
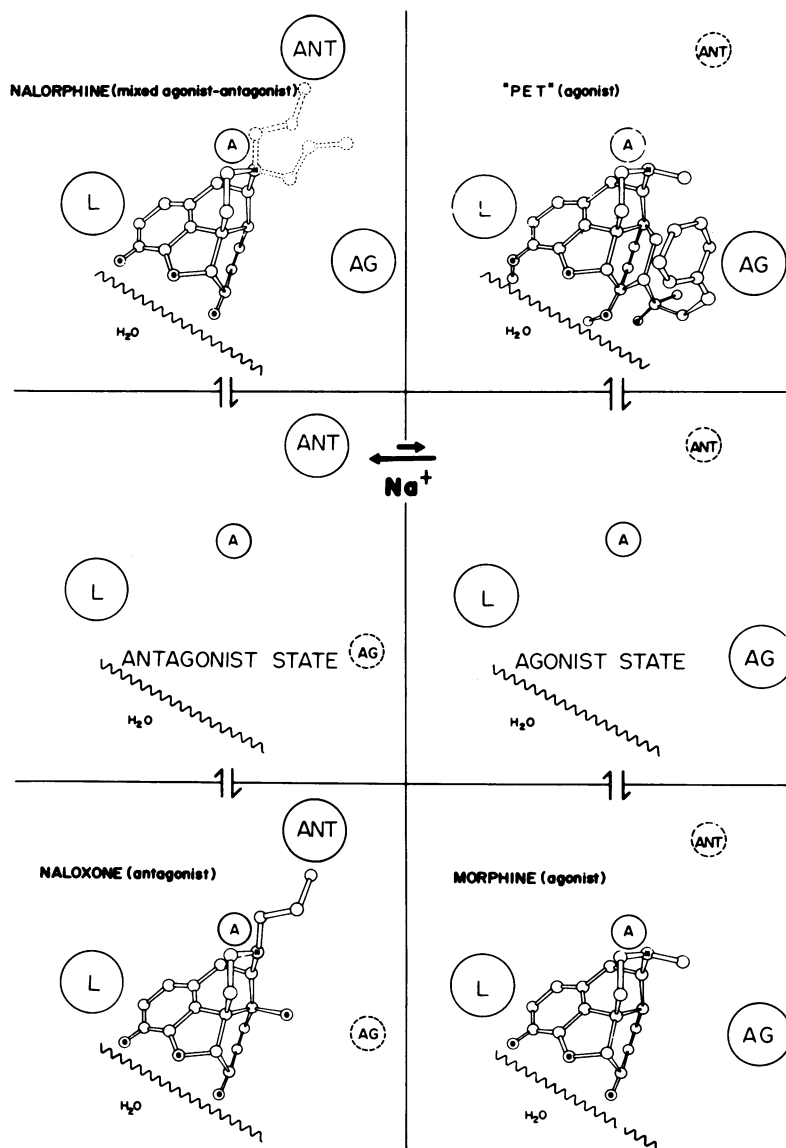
FIG. 6.   Molecular model of the opiate receptor. The receptor exists in two interconvertible states allosterically modulated by sodium, with differential affinity for agonist and antagonist drugs. Binding sites on the receptor are: L, lipophilic site; A, amine binding site; AG, agonist binding site; ANT, specific antagonist binding site.

iates bind to separate pharmacologically relevant hydrophobic and hydrophilic surfaces of the receptor (Fig. 6). This explains the loss of the activity attendant upon converting the phenolic hydroxyl of morphine's ring A into less hydrophilic groups such as the methoxy of codeine, or upon converting the phenolic hydroxyl of oripavines to the methoxy of tetrahydrothebaines.

A major puzzle of opiate structure-activity analysis is the failure of N-allyl substituents to provide antagonists from N-methylphenylmorphans (21), meperidines (22), and ketobemidones (23). The benzene ring in N-methylphenylmorphan and meperidine or ketobemidone is, respectively, unable and unlikely to assume the axial relationship to the piperidine ring seen in rigid potent opiates when the benzene ring interacts with the ring A binding site of the receptor. We propose instead that the benzene ring interacts with the ring F binding site, which places the piperidine nitrogen in the same position as for most other opiates (Fig. 7). The benzene ring of meperidine, ketobemidone, and N-methylphenylmorphan would therefore bind to the agonist site of the receptor, precluding antagonist prop-

erties even in the presence of N-allyl substituents. Fentanyl, lacking a phenolic hydroxyl, may fit the receptor as drawn in Fig. 2, or with rings A and F reversed. In the latter case, both phenyl piperidine substituents are in the more energetically favorable equatorial position.

The present model also provides a rationale for some puzzling structure-activity relationships of the ketobemidone opiates. For ketobemidones (Fig. 1), and to a lesser extent meperidine, increasing the length of the N-substituent from methyl to ethyl and propyl markedly reduces affinity for the opiate receptor and analgesic potency, while pentyl, hexyl, and heptyl substituents provide potent opiate agonists, but the octyl, nonyl, and decyl substituents result in a marked loss of activity (24). Ethyl and propyl substituents may interfere with the approach of the amine nitrogen to the anionic site of the receptor, accounting for reduced potency. With longer chain length, potency increases, because the chain can now approximate to the position of the ring A of other opiates. With both the ring F and ring A sites occupied, agonist potency increases. Octyl, nonyl, and decyl substituents make for very weak compounds, because
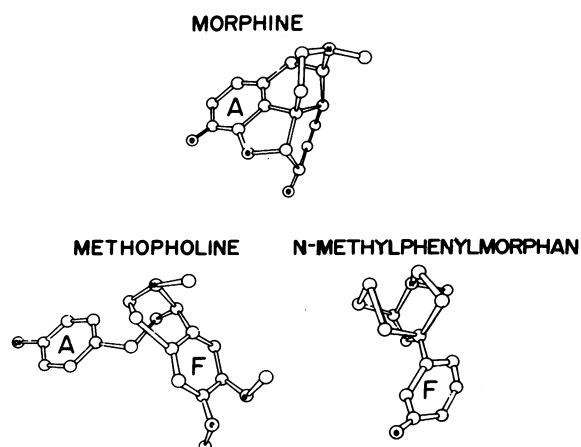
**MORPHINE**

**METHOPHOLINE**     **N-METHYLPHENYLMORPHAN**



FIG. 7. Molecular models of morphine, methopholine, and *N*-methylphenylmorphan. The structure of methopholine corresponds to rings A and F and the amine nitrogen of opiate agonists. The phenyl ring of *N*-methylphenylmorphan corresponds to ring F, accounting for agonist properties.

their sheer bulk and flexibility may impede receptor interactions or may decrease solubility.

Recently Hughes *et al.* (25) have determined that an endogenous morphine-like substance (4–7) is a mixture of two peptides whose amino acid sequences are H-Tyr-Gly-Gly-Phe-Met-OH and H-Tyr-Gly-Gly-Phe-Leu-OH. These peptides could interact as agonists with the opiate receptor in our postulated conformation by the tyrosine and phenylalanine moieties approximating rings A and F, respectively.

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