LEC.4 4 STAGE

Chemistry II Organic Pharmaceutical

2020-2019

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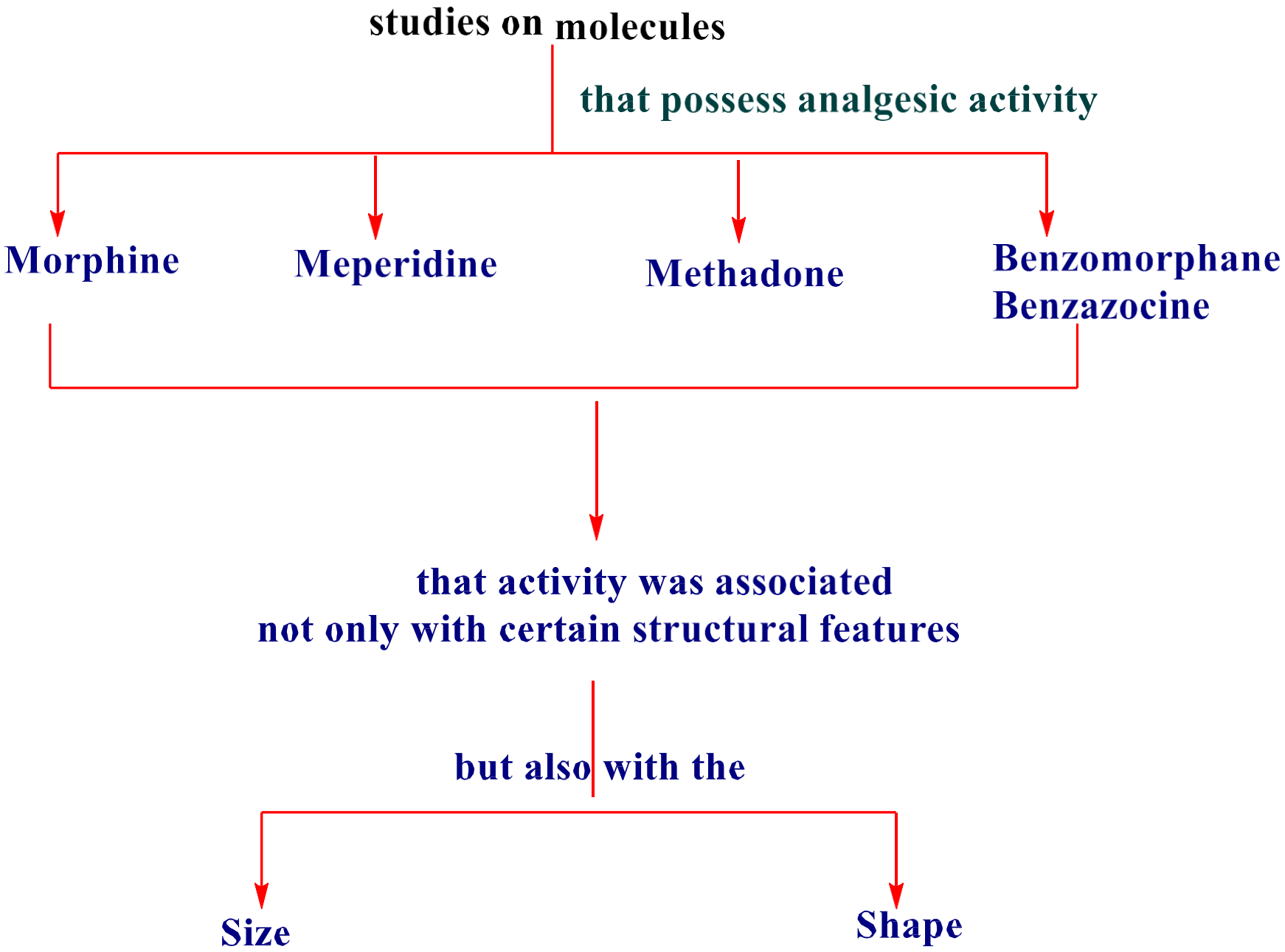
studies on molecules
that possess analgesic activity
Morphine
Meperidine
Methadone
Benzomorphane
Benzazocine
that activity was associated
not only with certain structural features
but also with the
Size
Shape

Beckett and Casy hypothesis

They initially noted that the more active enantiomers of the methadone-and thiambutene-type analgesics were related configurationally to (R)-alanine. This suggested to them that a stereoselective fit at a receptor could be involved in analgesic activity.

To depict the dimensions of an analgesic receptor, they selected morphine (because of its semirigidityand high activity) to give them information about the receptor

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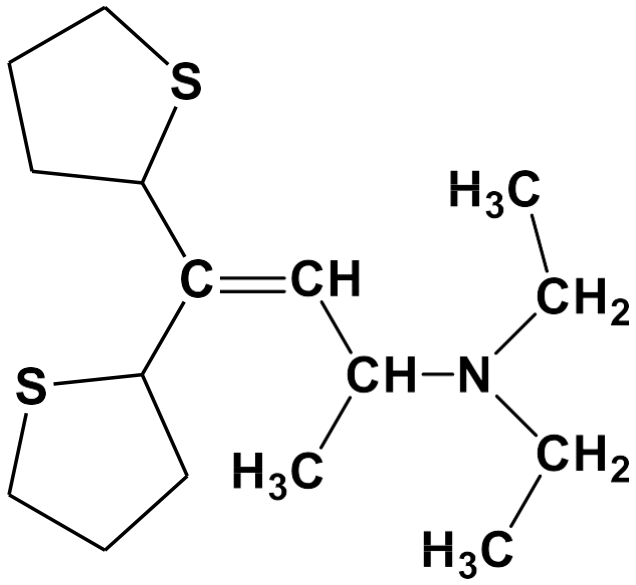

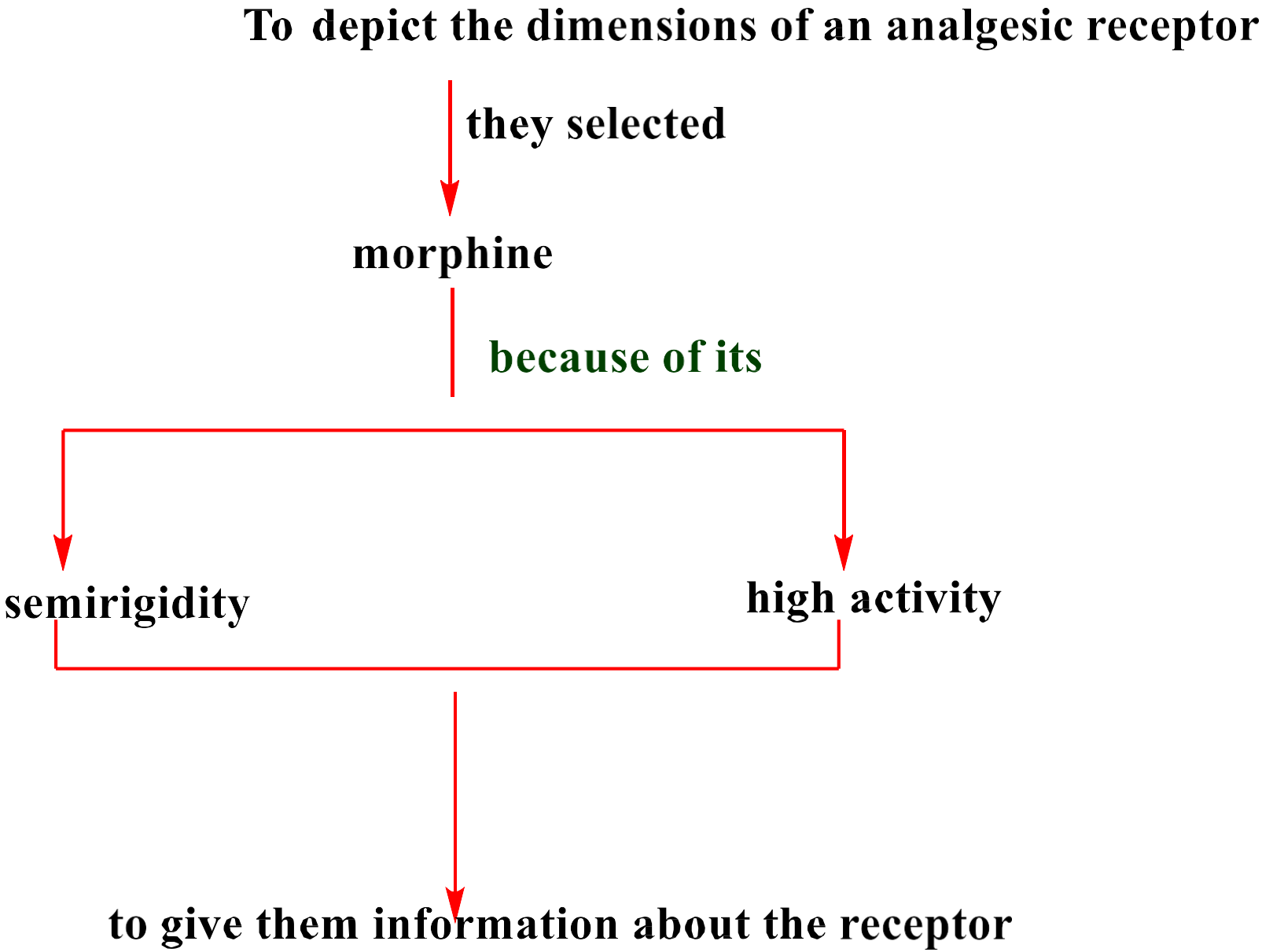
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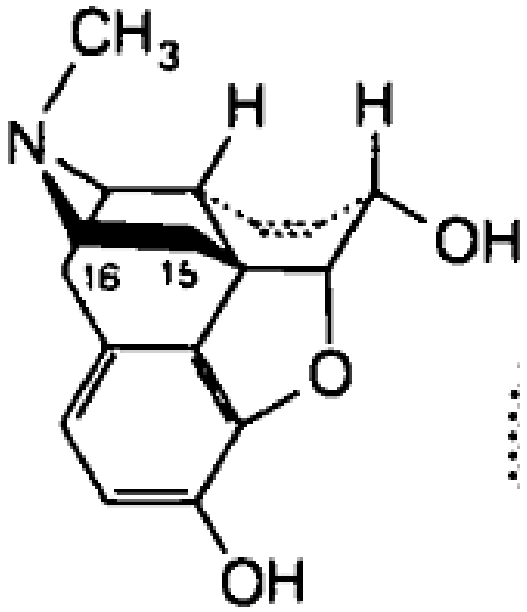
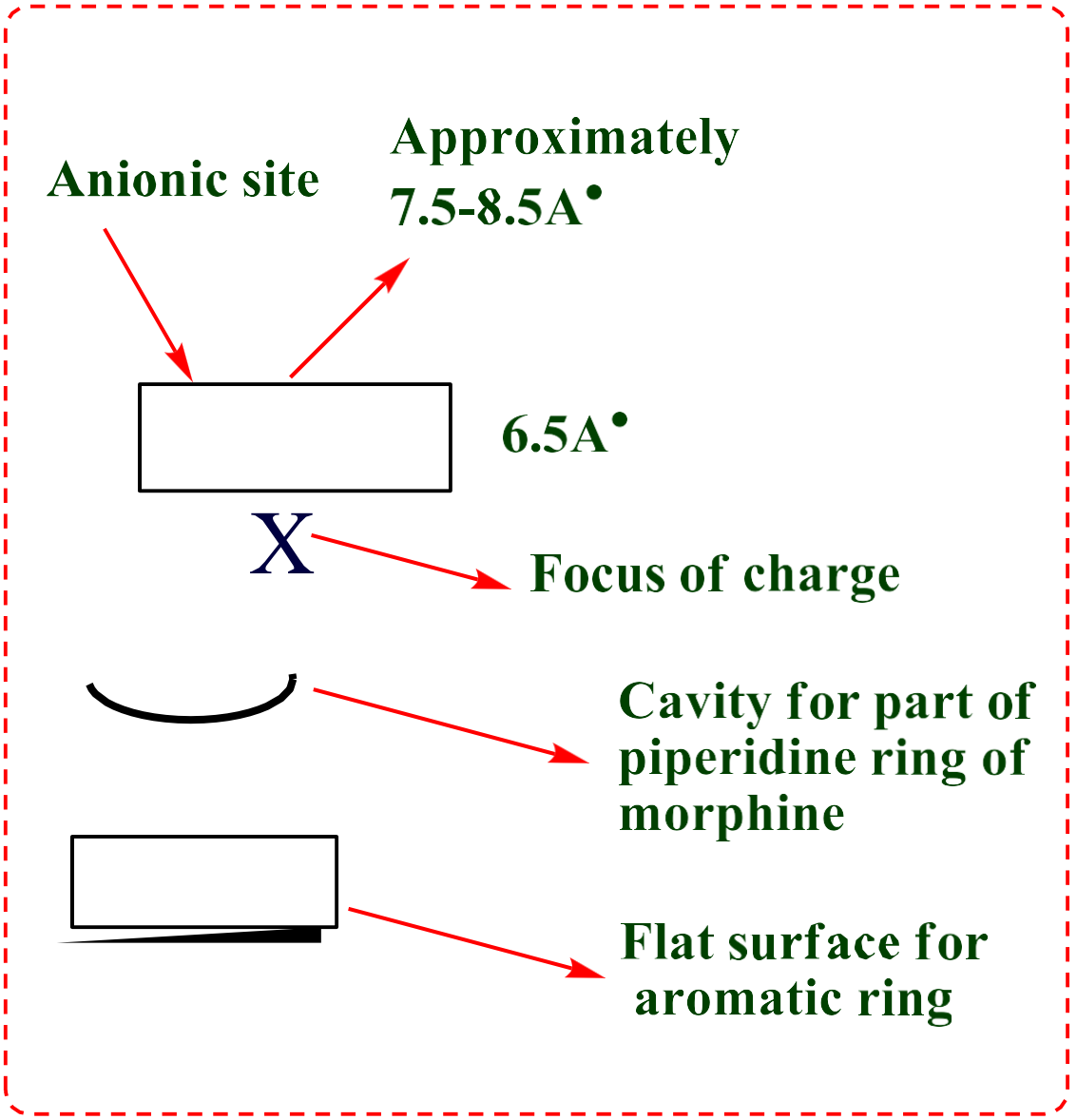


(-) Morphine



Receptor

The essential features for the proper receptor fit are:-

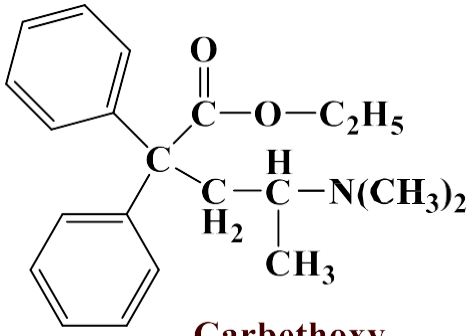
1.A basic center able to associate with an anionic site on the receptor surface.

2.A flat aromatic structure, coplanar with the basic center, allowing van der Waals bonding to a flat surface on the receptor site to reinforce the ionic bond.

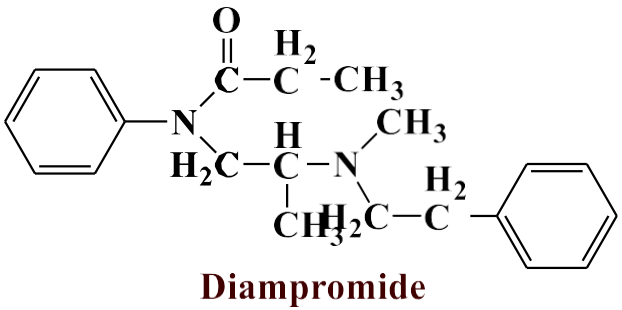
3.A suitably positioned projecting hydrocarbon moiety forming a three-dimensional geometric pattern with the basic center and the flat aromatic

Difficulties of accepting Beckett and Casy hypothesis:-

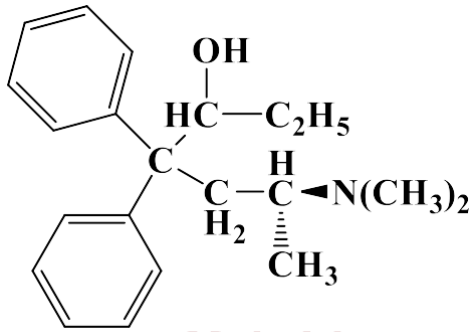
- **The more active enantiomer of α-methadol is not related configurationally to (R) alanine, in contrast with the methadone and thiambutene series. This is also true for the carbethoxy analogue of methadone and for diampromide and its analogues.**



Carbethoxy

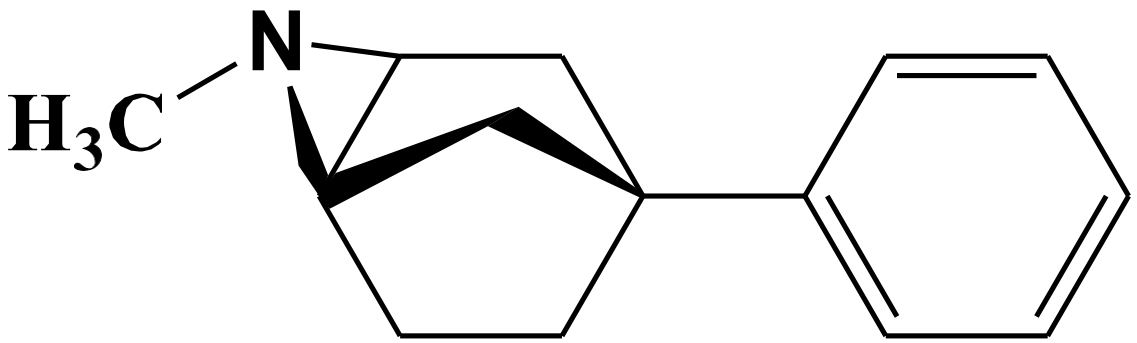


Diampromide



α-Methadol

The phenyl ring at the 4 position of the piperidine moiety should be in the axial orientation for maximum activity according to this hypothesis, but compound with equatorial phenyl group, also possesses activity equal to that of morphine, so that the axial orientation is not necessary for receptor fit requirement, like the following compound.

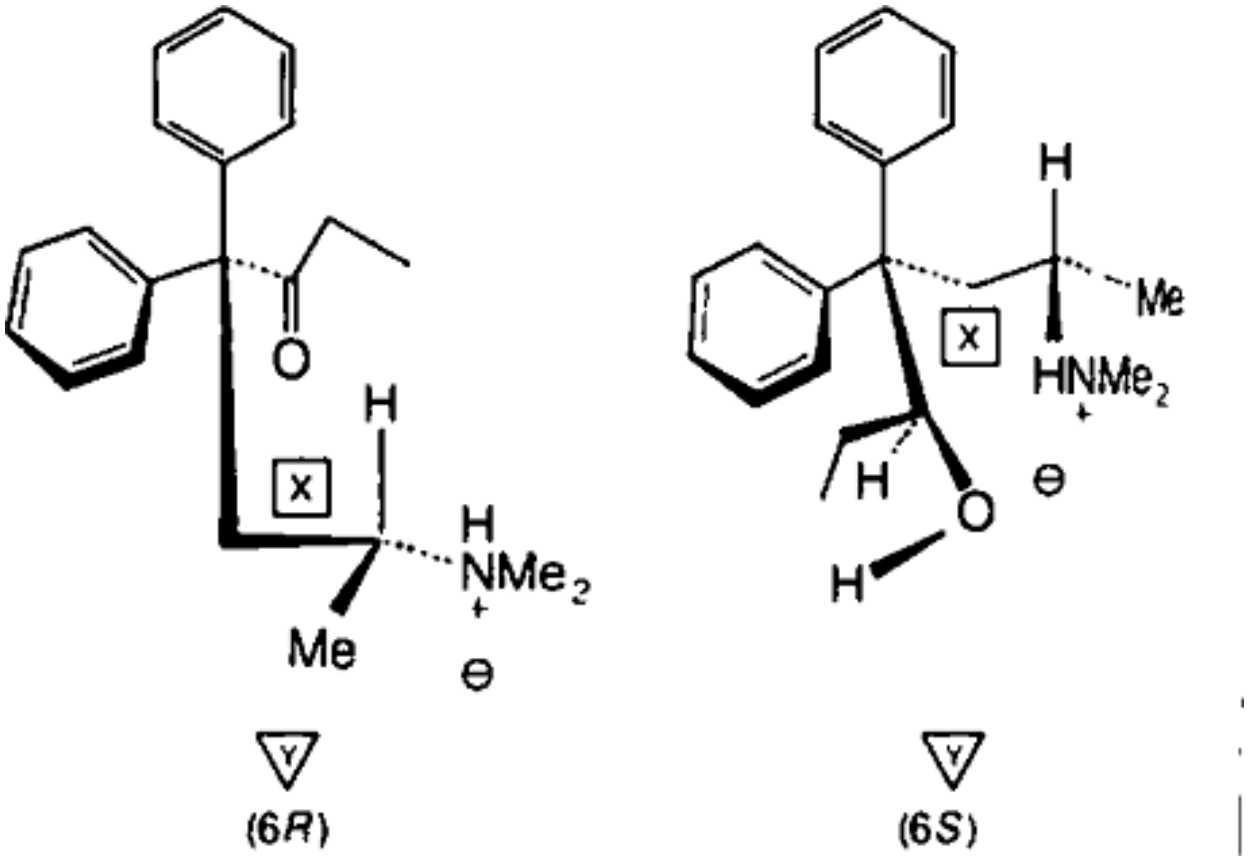


Portoghese hypothesis

This hypothesis is based on the established ability of enzymes and other types of macromolecules to undergo conformational change on interaction with small molecules (substrates or drugs). The fact that configurationally unrelated analgesics can bind and exert activity, meaning that more than one mode of binding may be possible at the same receptor. Such different modes of binding may be due to differences in positional or conformational interactions with the receptor.

The manner in which the hypothesis can be adapted to the methadoncan be illustrated as follows:-

Different polar grp.s in analgesic molecule may cause inversion in the configurational selectivity of an analgesic receptor..

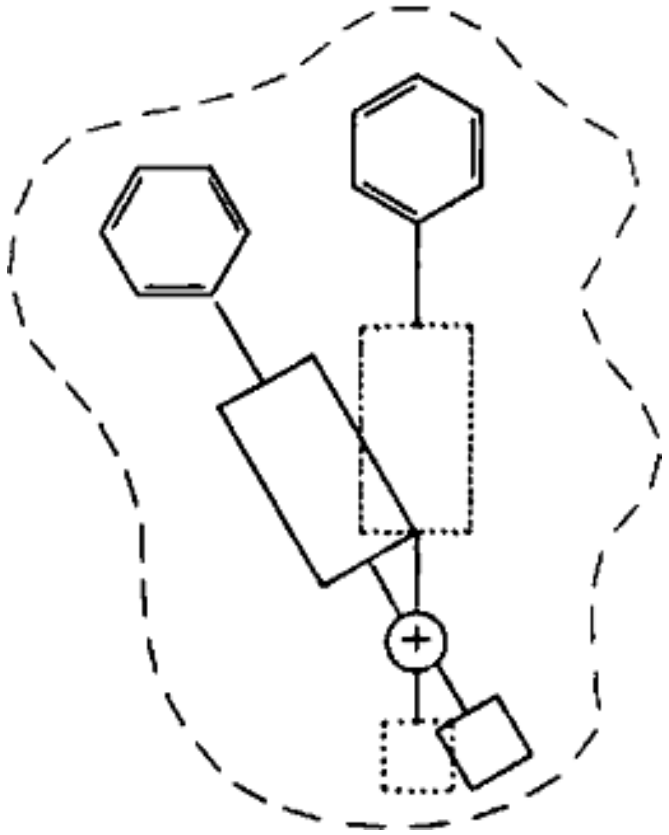


Illustrationof how different polar group of analgesic molecules may cause inversionin in the configuration selectivity of an analgesic receptor.
A hydrogen-bonding moiety, denoted by X and Y, represents a site that is capabe of being hydrogen bonded.

Portoghese noted that in certain series, there was parallelism in the direction of activity when identical changes in N-substituents were made. In others there appeared to be a nonparallelism. The parallelism and nonparallelismoccur due to similar and dissimilar modes of binding.

This hypothesis liberalizes the concept of binding in that a response may be obtained by two different molecules binding stereoselectively in 2 different precise modes at the same receptor.

A schematic representation of such different possible binding modes is shown bellow



Schematic illustration of two different molecular modes of binding to a receptor ⊕ protonated nitrogen. □, an N-substituent, The anionic Sites lie directly beneath the protonated nitrogen

If two different analgesiophores(the analgesic molecule minus the N-substituent. i.e., that portion of the molecule that gives the characteristic analgesic response) bearing identical N-substituents are positioned on the receptor surface such that the N-substituent occupies essentially the same position, a similar pharmacological response is given. Thus, as one proceeds from one N-substituent to another, the response should likewise change, resulting in parallelism of effect.

On the other hand, if two different analgesiophores are bound to the receptor such that the N-substituents are not arranged identically, there will be nonidentical responses to changing the N-substituent (i.e., a nonparallel response).

Considerable evidence now demonstrates that multiple receptors exist.

Martin has characterized and named these by responses to probe molecules: μ (mu) receptors for morphine-specific effects. δ (delta) for cyclazocine, and K(kappa) for ketocyclazocine. Various combinations of these in different tissues could be responsible for the varying effect observed.

Another important SAR study development of highly active analgesics from the N-allyl-type derivatives that were once thought to be only morphine antagonists and devoid of analgesic properties.

Most potent antagonist are nalorphine possess psychomimetic properties while weaker antagonist are petazocine and cyclazocine are less potent with less psychomimetic properties so can be used.

Antitussive agents

Cough is a protective, physiological reflex that occurs in health as well as in disease. It is considered as a mild symptom, occurs due to irritation of mucosa exciting the cough center causing bronchoconstriction followed by dilation due to disease and allergy. Among the agents that used in symptomatic control of cough are those that act by depressing the cough center located in the medulla. The more important and widely used ones are morphine, hydromorphone. Codeine, hydrocodone, Methadone, and levorphanol, which are all narcotic agents.

Many of the cough preparations contain various other ingredients in addition to the primary antitussive agent, like:-

1.Antihistamines, useful when the cause of the cough is allergic, (e.g., diphenhydramine) which have also central antitussive action.
2.bronchodilator activity, like ephedrine, methamphetamine. phenylpropanolamine. Isoproterenol, and isooctylamine.
3.parasympatholytics. which help to dry secretions in the upper respiratory tract.

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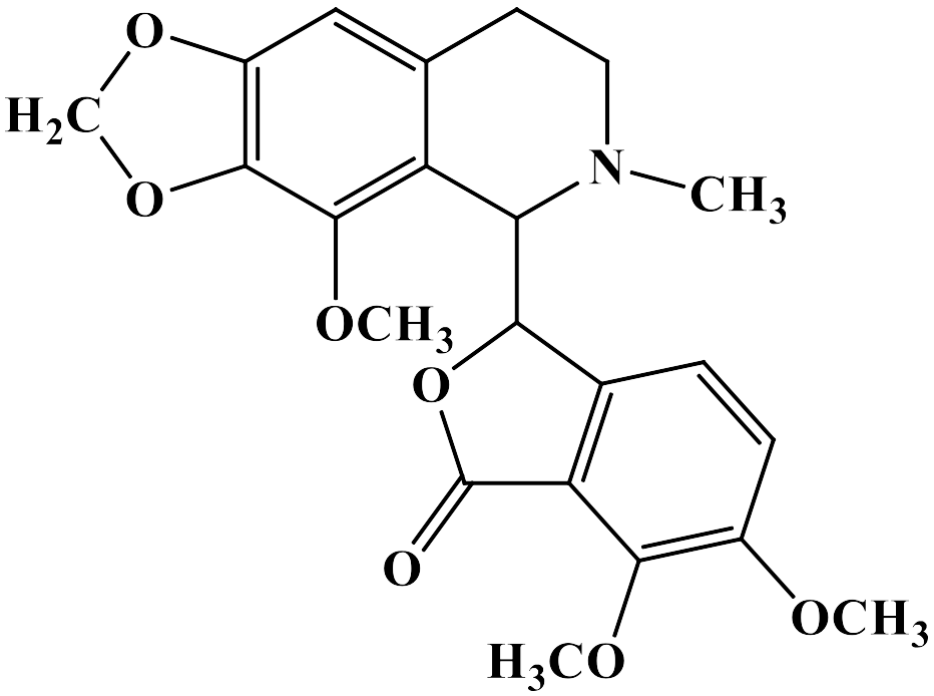
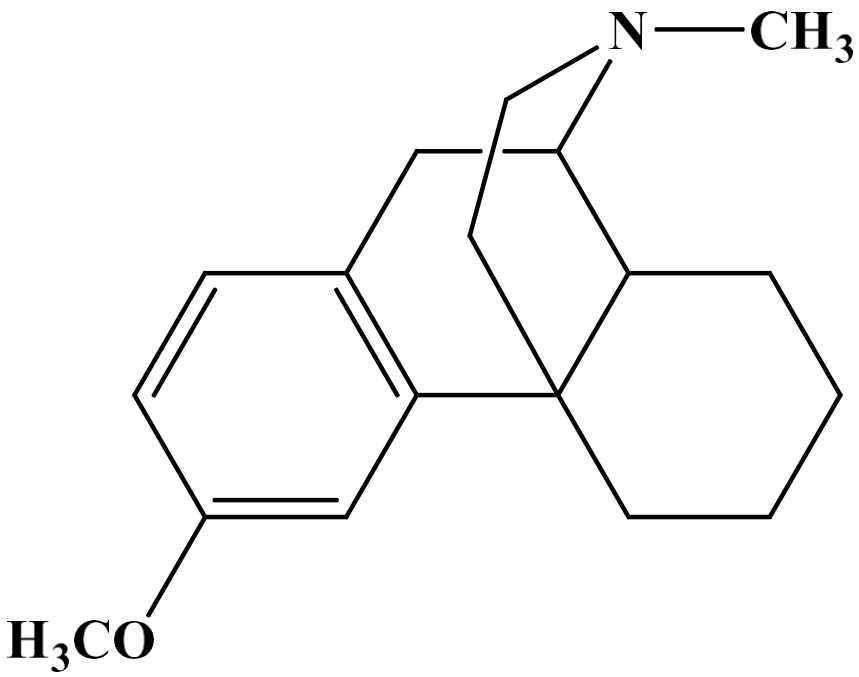
Products

Noscapine



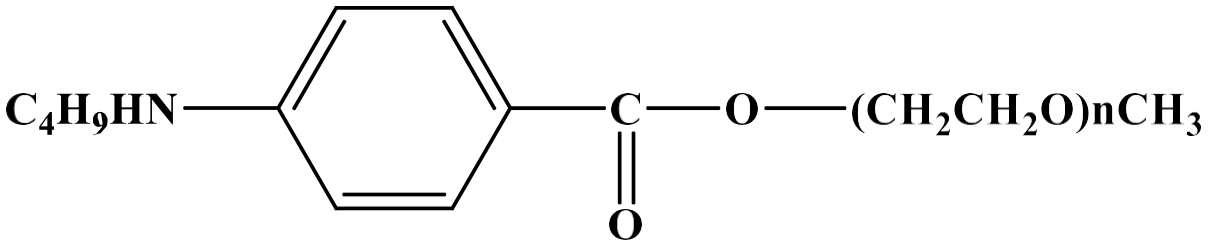
Noscapine [(-)-Narcotine]
central action bronchodilation

Dextromethorphan hydrobromide



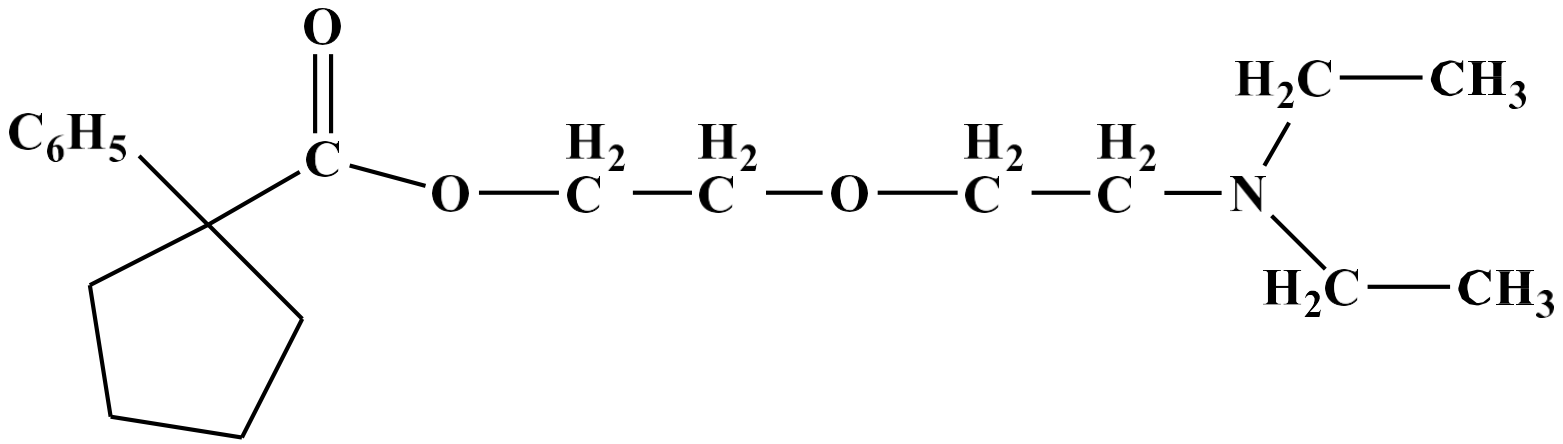
It possesses the antitussive properties of codeine, without the analgesic, addictive, central depressant, and constipating features

Benzonatate



Benzonatate possesses both peripheral and central activity in producing its antitussive effect

Carbetapentane•



2-[2-(diethylamino)-ethoxy]ethyl -1 -phenylcyclopentanecarboxylate

Equivalent to codeine as antitussive and has low S/E