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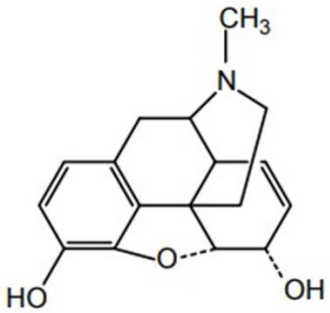
How Does The Chemical Structure Of Morphine Affect Its Analgesic Properties?



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I. Introduction

Analgesics, or more commonly known as painkillers, are a class of medication that are used for pain management and relief. An analgesic relieves pain by altering the way our brain perceives and processes a sensation of pain by blocking calcium channels on nociceptive nerves (nerves which detect painful stimuli) in order to inhibit release of certain neurotransmitters like Substance P, an 11 amino acid neuropeptide (C63H98N18O13S), and glutamate (2-azaniumylpentanedioate) that contribute to nociception.

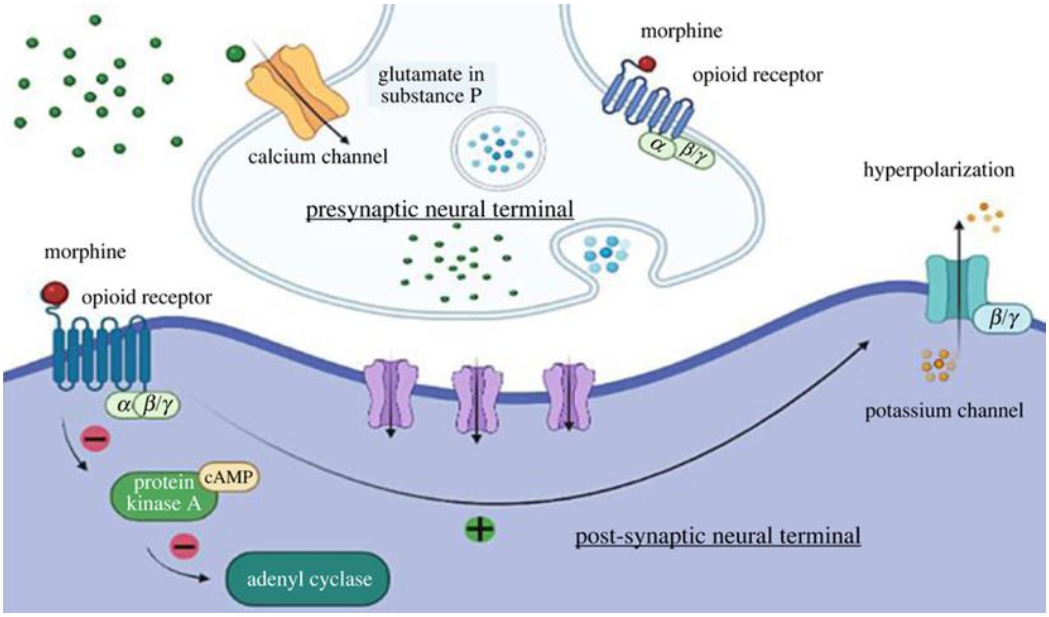
Analgesics can be classified into various subgroups- nonopioid analgesics and opioid analgesics. Nonopioid analgesics include Non Steroidal Anti Inflammatory Drugs (NSAIDs), Acetaminophen, commonly known as Paracetamol [*N*-(4-hydroxyphenyl)acetamide], Antidepressants and Antiepileptic medications. This classification of analgesics do not contain opioids and are used commonly for mild to moderate acute pain.

Opioid analgesics are derived from the opium poppy plant *Papaver somniferum*. Opioids are a classification of drugs that contain naturally occurring plant alkaloids which are referred to as "opiates". These opiates cause a feeling of profound pain relief, for example, morphine ($C_{17}H_{19}NO_3$) and codeine ($C_{18}H_{21}NO_3$). Both morphine and codeine are Benzylisoquinoline alkaloids, which are naturally occurring plant secondary metabolites derived from *Ranunculales* plants and have extensive pharmaceutical uses. In this case, specifically from the opium poppy. Alkaloids are heterocyclic compounds containing nitrogen and have different positions the nitrogen atom in various types.

Papaver Somniferum

Benzylisoquinoline ($C_{16}H_{13}N$) is an isoquinoline with a benzyl group. It is formed in plants through a biosynthetic pathway including the initial formation of the central intermediate (S)-Norcoclaurine (C16H17NO3) which is later subjected to enzymatic reactions such as methylation, oxidative coupling, hydroxylation to finally form different benzylisoquinoline alkaloids. Some opiates are synthetic derivatives, for example, fentanyl [N-(1-(2-phenethyl)-4-piperidinyl-N-phenyl-propanamide] and heroin [(5α,6α)-7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol acetate]. These are created in laboratories.

The usage of opioids for treatment of pain has been dated as early as 3400 BC in Mesopotamia. "Opiates" is a term for a mixture of alkaloids from poppy seeds and "Opioid" is a term used to describe all compounds that bind to the opioid receptors Mu (μ), Kappa (κ), Delta (δ) in the Central Nervous System. The opioid receptors in our CNS are stimulated by endogenous opioid peptides like α-endorphins which are sequences of 16 amino acids (C77H120N18O26S) that are produced in response to the presence of noxious stimuli.



Mechanism of opioid binding to mu-opioid receptor

Medical usage of opioid analgesics include relief for post surgical pain or severe pain due to trauma or diseases, prescribed by a doctor. They may be given orally, through a skin patch, or intravenously.

My project focuses on the opioid analgesic Morphine and how its chemical properties affect its analgesic properties. I have gathered secondary data from links such as PubMed, PubChem and Google Scholar. I read various articles written by biomedical professionals, doctors and chemists and watched videos on YouTube to gather information. I have researched and collated the data and information I came across on my chosen topic and have analyzed it in my project. I have used this method of research as I was unable to gather primary data regarding my topic.

Morphine

Morphine, (4*R*,4*aR*,7*S*,7*aR*,12*bS*)-3-methyl-2,4,4*a*,7,7*a*,13-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol), is a major alkaloid opiate derived from the opium poppy. It is an extremely potent psychoactive drug and acts directly on the Central Nervous System to relieve pain by binding to the Mu (μ) receptor in the brainstem and medial thalamus in the brain. It is a heteropentacyclic compound, alkaloid and tertiary amino compound.

It was discovered and isolated by the German pharmacist Freidrich Wilhelm Adam Serturner in 1804 and he coined the name after "Morpheus", the Greek god of sleep.

During the 1800s, synthesis and development of new drugs from plant extracts started emerging. Out of the various herbal remedies, opium remained a vital medication.

Scientists and pharmacologists had been researching throughout the years from 1803 to 1817 on how to isolate morphine in its purest form. In 1817, Freidrich Wilhelm Adam Serturner successfully obtained and isolated pure morphine. He prepared the same by extracting opium using hot water and precipitating morphine using ammonia. Colourless crystals were formed which were poorly soluble in water- but soluble in acids and alcohol.

Freidrich Wilhelm Adam Serturner

Physical Properties:

It can be in the form of a white crystalline alkaloid, prism or small rhombic prisms or needles from dilute alcohol as the monohydrate. It is odourless and has a bitter taste. Its boiling point is 190ºC and melting point is 255°C. It is basic in nature, having a pH of 8.5.

On prolonged exposure to air, morphine sulphate salt (C17H21NO7S) slowly loses its water of hydration and darkens in colour when exposed to light.

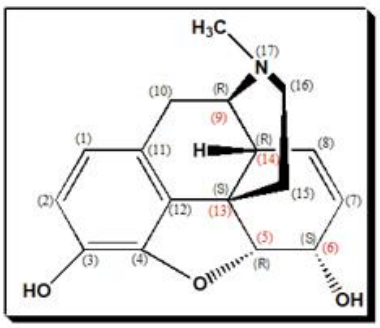
On heating, morphine decomposes and emits toxic fumes of nitrogen oxide.

It is alkaline to litmus and produces a blue colour on the litmus paper.

It is a weak Bronsted base with a pKa 7.9

Natural morphine is optically active and is levorotatory. It has five chiral centres on carbon atoms 5, 6, 9, 13 and 14.

Morphine crystals

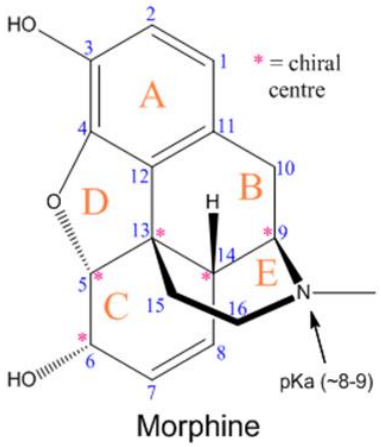


Chiral Centres of Morphine

Structure:

Morphine is made up of a benzene ring entailing a phenolic hydroxyl group at position 3 and an alcohol hydroxyl group at position 6, attached to the Nitrogen atom. It has 5 rings:

1. A: Benzene ring (aromatic ring).
2. **B**: Cyclohexane ring (saturated ring).
3. **C**: Cyclohexene ring (unsaturated ring with a double bond).
4. **D**: Piperidine ring (a six-membered ring containing nitrogen).
5. **E**: Tetrahydrofuran ring (an oxygen-containing ring).



Morphine

The nitrogen-containing ring and remaining ring are at right angles to the other three rings. It has a perhydrophenanthrene skeleton and is a hydrophilic phenanthrene derivative. A non linear polycyclic aromatic hydrocarbon, phenanthrene's structure consists of three fused benzene rings. It is an ortho-fused polycyclic arene and ortho-fused tricyclic hydrocarbon. Morphine is a part of the 4,5-epoxymorphinan class of phenanthrene alkaloids that alters immune functions.

Both the phenolic hydroxyl and alcoholic hydroxyl group can be converted into esters or ethers- examples of this would be codeine and heroin. Codeine has the same structure as morphine but is O-methylated at position 3 whereas heroin having the same structure as morphine is O-acetylated at position 3 and 6. Some moieties of morphine include phenanthrene and, phenyl- and diphenyl-ethylamines. More about them will be touched upon soon.

Functional groups of morphine such as the C3 phenolic and C6 secondary alcoholic group render it to be chemically reactive. Due to the presence of the hydrophilic -OH groups at C3 and C6, it is soluble in water and poorly soluble in lipids.

Bonds

Single Bonds (Σ-Bonds):

Carbon-Carbon (C-C) Single bonds: Found all over the molecule's carbon skeleton, these serve as the structural foundation for the phenanthrene ring system and other components.

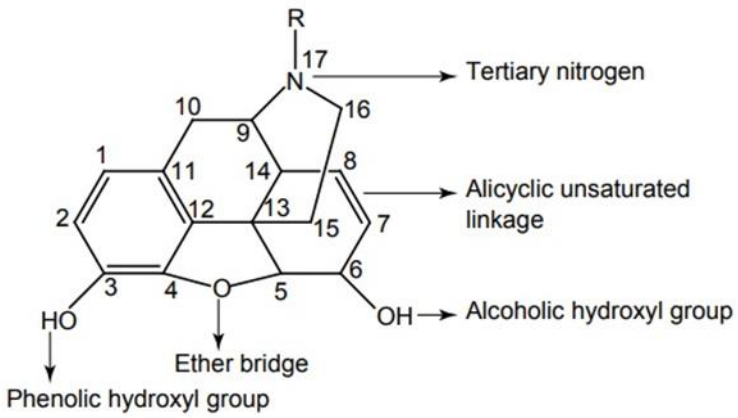
Hydrogen-Carbon (C-H) Single Bonds: Every carbon atom is connected to a hydrogen atom, with the exception of those in double bonds or particular functional groups.

Single bonds between carbon and nitrogen (C-N): Found in the piperidine ring where carbon atoms are joined by nitrogen.

Oxygen and carbon (C-O) Single bonds: Found in the hydroxyl groups (-OH) that are joined to the structure's carbon atoms.

Double Bonds (Π-Bonds):

Carbon-Carbon (C=C) Double Bonds: These are a component of the phenanthrene system's aromatic benzene rings. Conjugated π-bond systems, or alternating double and single bonds, are the distinguishing features of benzene rings.



Bonds and structure of morphine

Ether Linkage:

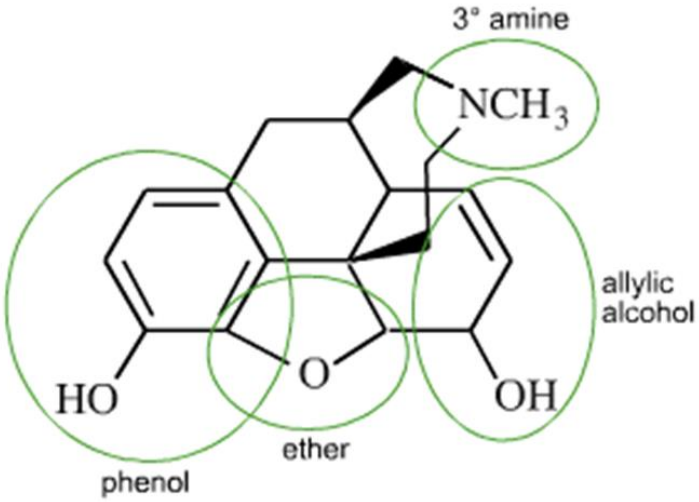
Oxygen, Carbon, and Carbon (C-O-C) Ether Linkage: This bond joins a carbon in the piperidine ring to one of the benzene rings in the morphine structure as part of the ether bridge (epoxide).

Hydroxyl Group:

Alcohol (–OH) Groups: Two hydroxyl groups are present in morphine. The phenolic property of one is attributed to its attachment to a benzene ring, whereas the alcohol character is attributed to its attachment to a carbon atom in the non-aromatic portion of the structure.

Tertiary Amine (-N(Ch_3))

At position 17, the nitrogen atom is part of the piperidine ring and is bonded to a methyl group.



Structure and Functional groups present

Moieties Of Morphine

Moieties are a special group of atoms within a molecule which are responsible for the molecule's characteristic chemical properties. Morphine includes 2 such moieties which are, Phenanthrene and, Phenyl- and Diphenyl- ethylamines.

Phenanthrene:

Phenanthrene, C14H10, is a non-linear polycyclic aromatic hydrocarbon which is composed of 3 fused benzene rings. It is planar due to the aromaticity of the molecule, enabling delocalization of π-electrons. All the Carbon Carbon bonds are highly conjugated and follow the typical nature of alternating single and double bonds of aromatic compounds.

Morphine may be considered as a partially hydrogenated phenanthrene as its molecular structure consists of a phenanthrene core which is embedded within a more complicated framework. As mentioned above, phenanthrene consists of three fused benzene rings out of which two of these are directly present in morphine, and the third one slightly modified but a part of the overall structure. The phenanthrene skeletal structure of morphine classifies morphine as an opioid and the presence of additional functional groups and rings makes morphine a more complex molecule, allowing it to perform various other chemical and biological activities.

Tetrahydrophenanthrene (C14H14) has been found to perform slight analgesic function in a large dosage. Addition of substituents increase analgesic rates, the greatest ones being an amine or an amino alcohol. It has been found that when a diethylaminoethanol is added to position 3 of tetrahydrophenanthrene, it becomes the most active compound showing analgesic action proving to be only 1/25th as effective as morphine.

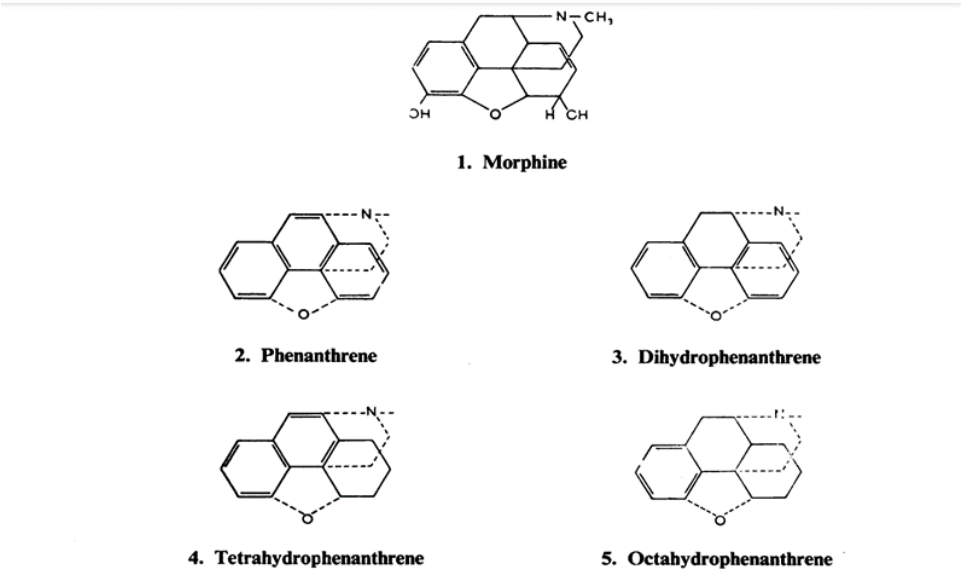


Fig. phenanthrene structures in morphine

Phenyl- And Diphenyl-Ethylamines

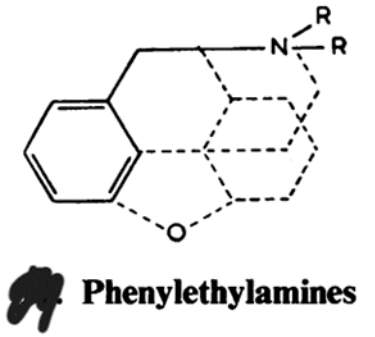
A basic aromatic ring (C_6H_5) attached to a molecule is called a phenyl group.

An aromatic ring is present in morphine, but it is a part of a structure that is more intricate. Particularly, the pentacyclic structure of morphine includes a benzene ring. This ring resembles a phenyl group, but instead of existing as a free moiety, it is included into the larger structure.

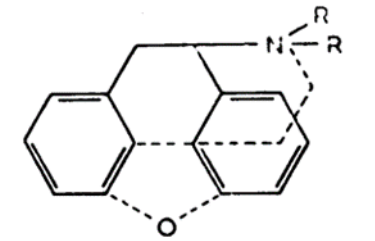
A diphenyl-ethylamine structure is defined as two phenyl rings joined to an amine group-attached ethyl chain ($-CH_2-CH_2-$). Its morphinan backbone does include an ethylamine-like group. It is a nitrogen containing molecule linked to a two-carbon chain. A nitrogen atom (an amine) and a two-carbon chain make up the morphinan core of morphine, but the structure is fused into the broader ring system, making it distinct from a free diphenyl-ethylamine moiety.

Diphenylethylamines, whose structures can be overlaid on morphine molecules if degree of unsaturation is not accounted for, have also been demonstrated to exhibit slight analgesic effect. A hydroxyl is added to the ethyl linkage in diphenylethylamines to increase analgesic activity.

When a cyclohexyloxy group is added to para- or meta-ethylamine in phenylethylamines, an amount of analgesic effect has been reported. Such a structure can be superimposed on the morphine molecule, regardless of the degree of saturation of the corresponding ring structures. The morphine molecule can only be fitted by a compound where the cyclohexyloxy is in meta-position to the ethylamine; this compound has a lower analgesic effect than one where the substituents are in para-position.



Phenylethylamines



Diphenylethylamines

Fig. phenanthrene structures in morphine

II. Functional Groups And How They Enable Chemical Reactivity

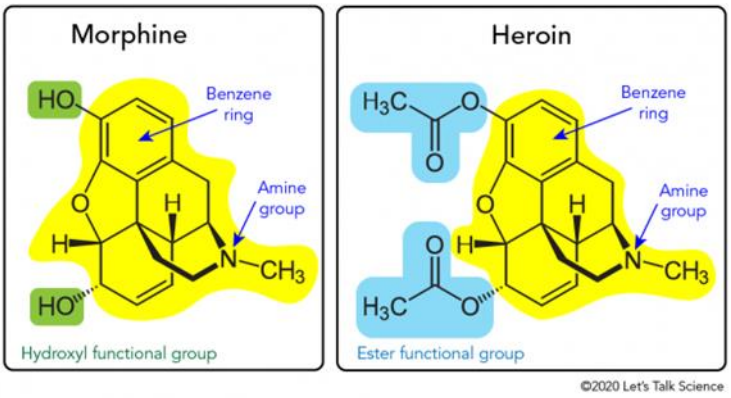
Secondary Alcoholic Group (-Oh)

The secondary alcoholic group positioned on the cyclohexane ring has the ability to be oxidised to form a ketone. The formed ketone which is the hydrogenated ketone of morphine, Hydromorphine, selectively binds to the mu-opioid receptor in the brain. Binding of hydromorphine promotes the G-protein complex's exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP), which inhibits the enzyme adenylate cyclase linked to the plasma membrane and lowers intracellular levels of Cyclic 3',5'-adenosine monophosphate (cAMP). Voltage-gated potassium channels are triggered by a drop in cAMP levels, which cause a significant drop in neuronal excitability. This also disrupts the opening of voltage-gated calcium channels, which halt calcium from entering neuronal cells and lessen the production of nociceptive neurotransmitters.

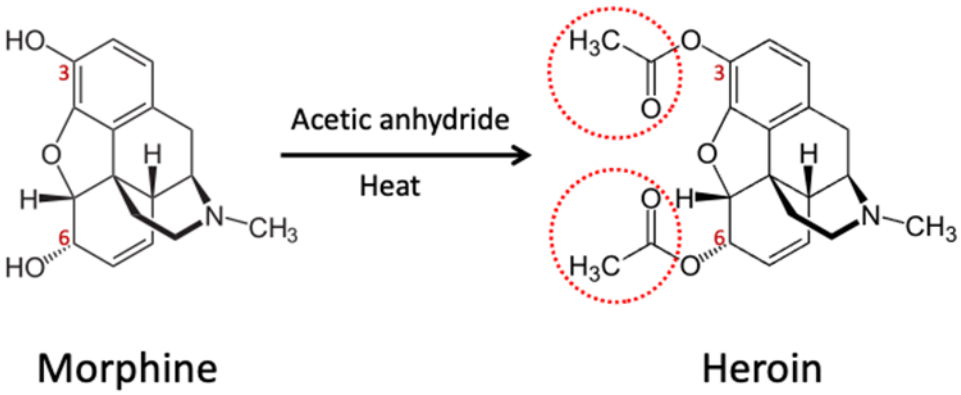
The secondary alcoholic group can also react with carboxylic acids and acid derivatives to form esters.

Phenolic Hydroxyl Group (-Oh)

There is a hydroxyl group attached to the aromatic phenolic ring which is slightly acidic, which enables it to react with strong bases and end up forming phenoxide ions. It can also undergo esterification or etherification, reacting with acylating compounds which form esters or ethers. For example, heroin is a diacetyl derivative of morphine formed by the acetylation of the C3 and C6 (-OH) groups with acetic anhydride (C4H6O3) .



Morphine vs. Heroin

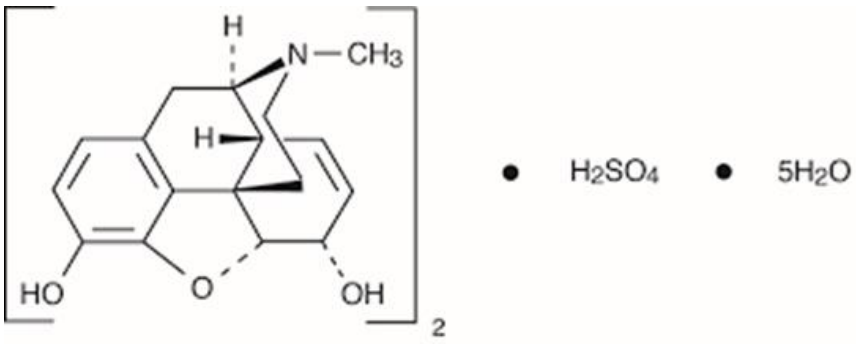


Morphine to Heroin reaction

Tertiary Amine Group (N(Ch3)-)

The tertiary amine group at position 17 attached to a methyl group is basic. In order to create a positively charged ammonium ion, the amine can take up a proton (H^+). The amine group has the ability to do this for the preparation of morphine salts that are more water-soluble and appropriate for injectable or oral usage, such as morphine sulphate (C34H40N2O10S) or morphine hydrochloride (C17H20ClNO3).

To bind with the molecule at the binding site and activate the mu-opioid receptor in the brain which results in analgesic effects, the nitrogen in the tertiary amine engages in hydrogen bonding and ionic interaction with the mu-receptor.



Morphine sulphate

ETHER LINKAGE and ALKENE GROUP do not provide much chemical reactivity. However, the ether linkage could possibly be cleaved by strong acids and the double bond alkene group in the cyclohexane ring can undergo hydrogenation. Hydrogen atoms get added to the double bond.

III. Conclusion

Morphine's strong analgesic effects are closely related to its chemical properties. An important factor in morphine's capacity to interact with opioid receptors in the brain and spinal cord is its distinct pentacyclic structure, which consists of multiple functional groups. Morphine especially the mu-opioid receptor.

- Owing to its basicity, the tertiary amine group has the ability to produce salts that improve the solubility and absorption of morphine while also being necessary for binding to the receptor.
- Vital receptor interactions and metabolism involve the phenolic hydroxyl group at position 3 (C3) and the secondary alcohol group at position 6 (C6). Changes in these locations, such as in the metabolite production of morphine-6-glucuronide (M6G) impact the strength of the drug.
- Morphine's potency and effectiveness as an analgesic is increased by the ether bridge and the rigid T-shaped three-dimensional conformation of the molecule, which provide orientation for receptor binding.
- Morphine's chiral centers also add to its stereospecificity, which makes sure that only the ideal configuration suits opioid receptors, enhancing its potency.

Overall, the precise configuration of morphine's rings, hydroxyl groups, and nitrogen atoms determines how effectively it relieves pain, therefore, the chemical structure of it is crucial to its pharmacological action. Morphine is ranked as one of the most effective medicines and painkillers because of its structural affinity for opioid receptors. Its chemical structure influences how it interacts with biological systems and further studies on morphine are being continued in order for the development of more effective painkillers with fewer adverse effects.

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