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A Literature Review for Synthesis of Benzocaine

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ABSTRACT

Benzocaine is a local aneshthetic commonly used to relieve pain and irritation. The project presents of various methods used for the synthesis of benzocaine. The most common route involves the esterification of p-aminobenzoic acid (PABA) with ethanol in the presence of an acid catalyst such as sulfuric acid. Other methods, such as synthesis from nitrobenzene or aniline, are also discussed to compare their efficiency, yield, and purity. The review focuses on reaction mechanisms, reagents, and conditions that influence the quality and yield of benzocaine. The study also highlights the importance of purification and characterization techniques like melting point, pH, Mass spectrometry, determination infrared spectroscopy to confirm product formation.

Keyword: Benzocaine, Local aneshthetic, Esterification reaction, Sulphuric acid catalyst, Reflux method, Melting point determination, infrared Spectroscopy.

1. INTRODUCTION

Local anesthetic agents are drugs that, when given either topically or administered directly into a localized area, produce a state of local anesthesia by reversibly blocking nerve conductances that transmit the sensations of pain from this localized area to the brain. Unlike the anes-thesia produced by general anesthetics, the anesthesia produced by local anesthetics is without loss of conscious-ness or impairment of vital central cardiorespiratory functions. Local anesthetics block nerve conductance by binding to selective sites on the Na+ channels in the excit-able membranes, thereby reducing Na+ passage (i.e., con-ductance) through the pores and, thus, interfere with the generation of action potentials. Although local anes-thetics decrease the excitability of nerve membranes, they do not affect the neuron's resting potential. Local anesthetics, in contrast to analgesic compounds, do not interact with the pain receptors or inhibit the release or the biosynthesis of pain mediators.

1.1.Chemistry of local anesthetics[2]

All local anesthetics drugs except cocaine are synthetic.Traditionally there are two main classes of compounds available as local anesthetics,the Esters and the Amides.

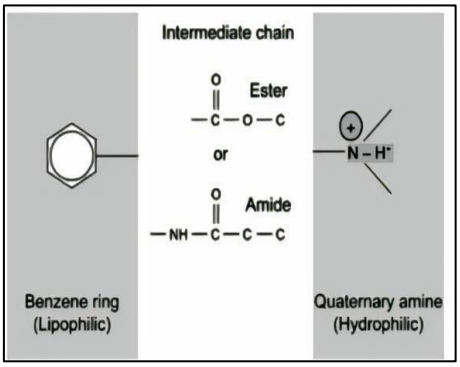

FIG.1.1.General structure for Local anesthetic agents

1.2.CLASSIFICATION[3&4]

Local anesthetics are classified as follows:

(1) Natural agents:Cocaine

(2) Synthetic Nitrogenous compounds:

(I) Derivatives of benzoic acid

(II) Derivatives of para amino benzoic acid

(a) Freely soluble: procaine and Amethocaine

(b) Poorly soluble: ***benzocaine*** and orthocaine

(III) Derivatives of Acetanilide:Lignocaine,Prilocaine and Etidocaine

(IV) Derivatives of Quinoline:Cinchocaine and Dimethisoquin

(3) Synthetic non Nitrogenous Agents :Benzyl alcohol and propanediol.

(4) Miscellaneous Drugs with Local Action:Clove oil,Phenol,Chlorpromazine and Diphenhydramnine.

1.3.INTRODUCTION OF BENZOCAINE[5&6]

Benzocaine is an ethyl ester of 4-aminobenzoic acid discovered as a local anesthetic by the pharmacist Eduard Ritsert in 1903.It was firstly synthesized in 1898 when Limpricht reduced the nitro group of ethyl 4-nitrobenzoate using ammonium sulphide.

Since then, benzocaine became a good target molecule for studies on nitro reduction, amination of aryl halides, and alternative methods to obtain anilines. Some other works were committed specifically in the improvement of benzocaine synthesis, finding more efficient methods, or investing in enabling technologies.

It is found to possess both low potency and low systemic toxicity. It is mostly employed as a local topical anaesthetic in conjunction with other similar agents; though some of these mixtures may give rise to undesired allergic manifestations. Besides, benzocaine is also employed as a possible sulphonamide antagonist.

1.4.MECHANISM OF ACTION [7]

Benzocaine binds to sodium channel and reversibly stabilises the neuronal membrane. This reduce the permeability of sodium channel to Na+ ions. Depolarisation of the neuronal membrane is blocked, and hence the initiation and conduction of nerve impulses is blocked.

1.5.USES[7]

It is used for suppressing gag reflex, as a lubricant and topical anaesthetic on, -oesophagus, mouth, larynx, nasal cavity, rectum, urinary tract, respiratory tract or trachea.

1.6.PHARMACOKINETICS[8]

Absorption: Benzocaine is a weak base with an aromatic ring crucial for lipid solubility, enabling diffusion across nerve cell membranes. The onset of action typically takes 30 seconds with a 20% concentration. However, achieving an adequate depth and intensity may take 2 to 3 minutes.

Distribution: The distribution of local anesthetic tends to align with the tissue/blood partition coefficient and is proportional to the tissue mass and perfusion.

Metabolism: Benzocaine is an ester local anesthetic that follows a metabolic route distinct from amide local anesthetics. Esters experience rapid plasma hydrolysis mediated by pseudocholinesterase, producing para-aminobenzoic acid (PABA).

Elimination: The primary route of elimination of benzocaine is via the kidneys, with the metabolized products excreted in the urine. A minor portion may be eliminated through feces.

1.7.SIDE EFFECT[9]

Table1.1. Side Effect

Common side effect	Serious side effect
Contact dermatitis	hives
stinging	Methemoglobinemia
Skin rash	blistering
burning	Shortness of breath
pruritus	Swelling of the face,lips,tongue
erytherma	oozing

1.8. INTRODUCTION OF INSTRUMENT

1.9. MELTING POINT [10]

The melting point of a substance is the temperature at which the solid melts to become a liquid. pure compounds have a definite melting point. impurities in the solid lower its melting point. The purity of a solid can be estimated by comparing its melting point is characteristic of a substance and may be used to help identify the substance.

The melting point, as a parameter, is used in research, development and quality control, for purity determination or for the identification of different samples. The classical visual observation of a sample in a capillary tube is automated by recording the change of the light transmittance during the melting process. The melting point or the melting range is reported. The experimental method to determine melting point involves heating of a small amount of the sample substance in a capillary tube attached to a thermometer, which is immersed in a suitable bath of liquid. The bath is heated slowly. The temperature at which the compound commences to liquefy and at which it is completely liquid is recorded as the melting range.

Nowadays a number of commercially useful apparatus are available. They require no liquid and heating is done electrically. The unit is provided with a metal block to serve as heating compartment to replace the disagreeable silicone oil. While it determines melting points, melting ranges and boiling points up to 400°C with maximum precision, the new heating system also reduces maintenance and ensures very short cooling-down times, assisted by a fan.

FIG 1.2-Electrically Heated Melting Point Apparatus

1.10. DETERMINATION OF pH VALUES OF SOLUTIONS [11]

The Common methods used to determine the pH of a solution are colorimetric method (using indicators) and electrometric method (using pH meter).

Colorimetric method:

Colorimetric method is based on the use of reagents which alter colour in accordance with the hydrogen ion concentration of solution.These reagents are weak organic acids or bases with undissociated molecules differing in colour from their ions,due to a difference in structure, and are commonly known as acid-base indicators.some useful indicators for determining pH are complex organic compounds such as thymol blue,methyl orange,methyl red,phenol red,bromocresol green,etc.Each of these indicators changes colour over range of about two pH units.Bromocresol green is yellow at a pH 4.0 but changes through various shades of green until it is blue at a pH of 5.6.such an indicator is useful only in this narrow range of pH.At any pH bellow 4.0,it remains yellow,and at any pH above 5.6. it remains blue.Measuring the pH solution outside of this range requires some other indicators.Thymol blue which is sensitive to a pH range from 8.0 to 9.6,can be used in the pH range 8.0-9.6.

The test solution is taken in a test tube and the and then added a few drops of the selected indicator.The colour is compared with a series of control test tubes that contain the same indicator in solutions of different but known pH values.such series of control tubes can be purchases for each indicators.The colour of the test solution are matched with that of one of the solutions in the series of test tubes,the pH is read as printed below the matching test tube.

Colorimetric determination of pH can be more conveniently carried out by using paper strips.These paper strips are impregnated with a solution of one of the indicators previously mentioned,and then dried.The paper strip is wetted with a drop of the test solution or immersed in the test solution.The colour developed in this paper strip is then compared with a pH colour chart that comes with the paper strips.The short-range pH papers of this kind are useful for an approximate determination of pH,such as the pH of a lithographic dampening solution.

Accuracy of determination can be improved by the use of so-called universal indicators,which are indicator mixtures changing colour over a wide range of pH.

Electrometric method (using pH Meter): -

The pH of a given solution can be accurately measured using pH meter. The pH meter is associated with a cell for the measurement of pH. The cell consists of two electrodes.one is the glass electrode and the other is the saturated calomel electrode (a reference electrode).in practice, the glass electrode and the reference electrode are assembled into one unit that can be easily immersed into any solution whose pH is to be measured.

A pH meter will read pH very accurately if it is calibrated with a standard buffer solution that has a pH fairly close to the pH readings to be made. For example, if the pH readings are in the range of 3-5,one should use a standard buffers solution that has a pH of4.0,or whatever is available that is close to this value. Assume that a standard buffer solution of pH 4.0 is selected.it is placed in a small beaker, and the combined electrode of pH meter is immersed in it. Using the calibration knob on the pH meter,the pH reading is adjusted until the pH meter reads exactly 4.0.The pH meter is now calibrated.

Once the pH meter is calibrated, determination of the pH of any solution is simple. The combined electrode of the pH meter is immersed in the test solution in a beaker. The meter shows the pH value of the test solution immediately. After each use,the electrode is washed with distilled water.

1.11. INFRARED SPECTROSCOPY [12]

The region of infrared spectrum which is of greatest importance to the organic chemist is that which lies between 4000 and 400 cm $^{(-1)}$. Absorption bands in the spectrum result from energy changes arising as a consequence of molecular vibrations of the bond stretching and bending (deformation) type. The positions of atoms in molecules may be regarded as mean equilibrium positions, and the bonds between atoms may be considered as analogous to springs, subject to stretching and bending. Each atom or group of atoms in a molecule oscillates about a point at which attraction of nuclei for electrons balances the repulsion of nuclei by nuclei, and electrons by electrons. These oscillations have natural periods which depend upon the masses of the atoms and the strengths of the bonds involved. The amplitude of the oscillations, but not the frequency, can be increased by supplying energy by means of electromagnetic radiation. Nuclei and electrons bear electric charges, the force required can be supplied by the oscillating electric vector of an electromagnetic wave of frequency and phase which match those of a particular molecular vibration. Transfer of energy

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in this way is possible if a change in the amplitude of that vibration results in a change of molecular dipole moment (the dipole moment may be regarded as analogous to the coupling mechanism of a spring); radiant energy is then absorbed and the intensity of radiation at this particular wavelength is decreased on passing through the compound. The intensity of absorption bands depends upon the magnitude of the change in oscillating dipole moment of the bonds during the transition, and also is directly proportional to the number of bonds in the molecule responsible for that particular absorption. Thus hydrogen or carbon bonded to oxygen or nitrogen gives rise to strong infrared absorption because of the polarity of these particular bonds. In contrast, no absorption results from stretching vibrations in a homonuclear double bond or triple bond which is symmetrically substituted; such vibrations are termed infrared inactive. The recognition of such bonds is, however, made possible by an examination of the Raman spectra of such molecules (i.e. the vibrations are Raman active).

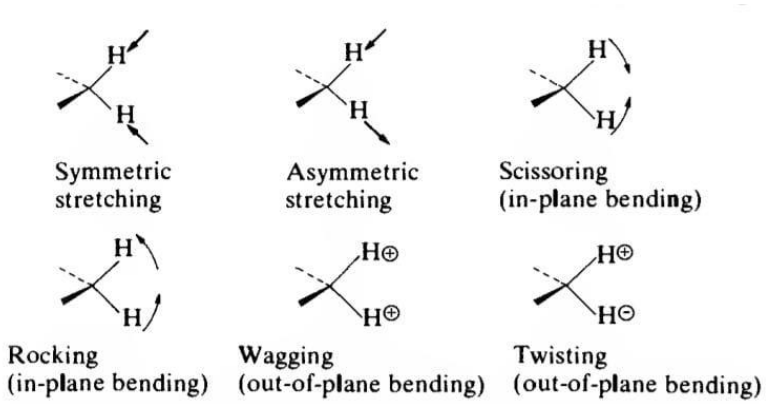
There are two main types of molecular vibrations: stretching and bending. A stretching vibration is a vibration along a bond axis such that the distance between the two atoms is decreased or increased. A bending vibration involves a change in bond angles.

For a diatomic molecule A—B, the only vibration that can occur is a periodic stretching along the A—B bond. The masses of the two atoms and their connecting bond may be treated, to a first approximation, as two masses joined by a spring and Hooke's law may be applied. This leads to the expression for the free quency of vibration v in wavenumbers (cm^{-1}):

$$\bar{\nu} = \frac{1}{2\pi c}\left(\frac{f}{m_A m_B/m_A + m_B}\right)^{\frac{1}{2}}$$

where c is the velocity of light (ms^{-1}), /is the force constant of the bonds (Nm^{-1}) and mA and mB the masses (in g) of the atoms A and B respectively. The value of/is c. 500Nm^{-1} for single bonds and about two or three times this value for double and triple bonds /respectively: it is a measure of the resistance of the bond to stretching and is roughly proportional to the energy of the bond. Application of this equation to the case of the stretching of a C—H bond, and using 19.9 x 10^{-24}g and 1.67 x 10^{-24}g as the mass values for carbon and hydrogen respectively, together with the accepted values for c and/ gives a frequency of 3020 cm^{-1}. The stretching of a carbon-hydrogen bond in a methyl or a methylene group is actually observed in the regions about 2975 and 2860 cm^{-1} respectively; the slight deviation from the calculated value is a reflection of the fact that modifications to the frequency of vibration arise from the strengths and polarities of the bonds associated with the carbon atom, and these have been ignored in this calculation.

With polyatomic molecules many more fundamental vibrational modes are possible. A qualitative illustration of the stretching and bending modes for the methylene group is shown in Arrows indicate periodic oscillations in the directions shown; the (+) and (-) signs represent, respectively, relative movement at right angles to the surface of the page. A symmetrical stretching mode, where the hydrogens are vibrating in phase towards and away from the carbon nucleus, requires less energy than the corresponding asymmetric stretching mode and therefore absorbs at a slightly lower wavenumber. Bending vibrations, which are descriptively termed scissoring, rocking, twisting or waging modes, absorb at considerably lower wavenumbers since the energy associated with these deformations is much less.



The infrared spectrum therefore consists of a number of absorption bands arising from infrared active fundamental vibrations; however, even a cursory inspection of an i.r. spectrum reveals a greater number of absorptions than can be accounted for on this basis. This is because of the presence of combination bands, overtone bands and difference bands. The first arises when absorption by a molecule results in the excitation of two vibrations simultaneously, say vl and v2, and the combination band appears at a frequency of v1 + v2; an overtone band corresponds to a multiple (2v, 3v, etc.) of the frequency of a particular absorption band. A difference band arises when absorption of radiation converts a first excited state into a second excited state. These bands are

frequently of lower intensity than the fundamental absorption bands but their presence, particularly the overtone bands, can be of diagnostic value for confirming the presence of a particular bonding system.

1.12. MASS SPECTROMETRY [13]

It is unlikely that the laboratory organic chemistry will be required to record mass spectra of compounds produced in the laboratory as they will normally be obtained through a centralised service. This section therefore concentrates on the interpretation of spectra rather than on the techniques for obtaining the spectra. For further information on this aspect of mass spectrometry the reader should consult the sources listed in the references at the end of this chapter [4].

Probably the most common use of mass spectrometry by the organic chemistry is for the accurate determination of molecular weight. A second important use is to provide information about the structure of compounds by an examination of the fragmentation pattern.

1.13.THE MASS SPECTRUM

In a typical mass spectrometer, an organic compound under high vacuum is bombarded with electrons (of about 70 eV energy). Loss of an electron from the molecule followed by various fission processes gives rise to ions and neutral fragments. The positive ions are expelled from the ionisation chamber and resolved by means of a magnetic or an electric field.

The mass spectrum is a record of the current produced by these ions as they arrive at a detector. The intensity of a peak in the spectrum is thus an indication of the relative number of ions; the larger the peak the more abundant the ion producing it. Many mass spectrometers produce up to five traces simultaneously of differing sensitivity to allow weaker peaks to be studied, while also allowing intense peaks to be recorded on the chart.

low resolution spectrum and a number of features should be noted. The most intense peak in the spectrum is known as the base peak. Ions produced in the fragmentation of the organic compound are separated according to their mass: charge ratio (m/z) (formerly mje). Since the majority of ions are singly charged the scale is often thought of as a mass scale; however, doubly charged ions are not Uncommon and these appear at half their mass value on the m/z scale. Many compounds give rise to an ion which corresponds to the removal of a single electron from the molecule; this is known as the molecular ion (M) and usually has the highest m/z value in the spectrum, with the exception of a characteristic group of peaks at m/z values of M + 1, M + 2, M + 3, etc. The latter are isotope peaks which arise from the fact that many of the elements normally present in organic molecules are not monoisotopic. Peaks in the mass spectrum are usually sharp and appear at integral mass values (with the exception of those arising from some doubly charged ions). Occasionally peaks are observed which are broad, spread over several mass units and of low intensity; these are called 'metastable peaks' and give valuable information about the mode of fragmentation.

Spectra produced by most spectrometers are not in a suitable form for reproduction and cannot easily be compared with spectra from other instruments. Magnetic focusing instruments give spectra with non-linear m/z scales whereas those from quadrupole or time-of-flight instruments are linear. It is common practice to represent spectra in the form of a bar with a linear m/z scale. The base peak is given the arbritrary value of 100 per cent and the height of each other peak is measured relative to that value. An alternative method of representation is to tabulate the intensity of the current arising from each ion relative to the total ion current. The output from many mass spectrometers can now be handled by computers which allow considerable flexibility in the form of presentation of the spectra. Bar graphs can be produced directly and a large reference collection has been produced in this way[6h].

Instruments vary considerably in the extent to which they can separate ions of closely related m/z values. In the vast majority of routine uses the organic chemist requires only the separation of ions having nominal unit masses of up to molecular weights of about 500-600, which can be achieved using an instrument of low resolution. Occasionally, however, it is of value to determine the precise mass of particular ions accurately (up to six places of decimals) and for this purpose an instrument of high resolution is required.

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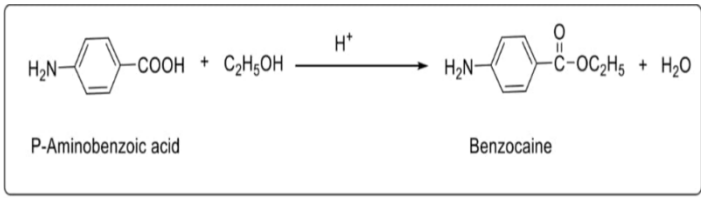
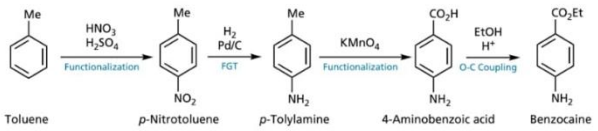
2. REVIEW OF LITERATURE

Sr no.	Title	Description	Ref. no.
1.	Synthesis of benzocaine from p-amino benzoic acid	 the synthesis of benzocaine from p-aminobenzoic acid. P-aminobenzoic acid is reacted with ethanol in the presence of hydrochloric acid via an esterification reaction to form ethyl p-aminobenzoate (benzocaine). The percentage yield of benzocaine obtained was 93.3%, close to the theoretical yield, and it has a melting point of 91°C. Benzocaine is used as a local anesthetic to relieve minor mouth pain.	14
2.	Synthesis of benzocaine from Toluene	 synthesis of benzocaine through a four-step process starting from toluene. The steps involve: - Functionalization of toluene to p-nitrotoluene - Reduction to p-tolylamine - Oxidation to 4-aminobenzoic acid - Esterification to benzocaine	15
3.	Evaluation of Fischer Esterification Method: Synthesis and Modification of Benzocaine; A Local Anaestatic	- ***Synthesis method:*** Fischer esterification method. - Product: Benzocaine (local anesthetic) and N-acetylbenzocaine. - Yield: - Benzocaine: 78% - N-acetylbenzocaine: 96% - Characterization techniques: - Infrared spectroscopy (FTIR) - Melting point determination (89-91°C for benzocaine, 103-105°C for N-acetylbenzocaine) - Thin Layer Chromatography (TLC)	16
4.	Synthesis of Benzocaine Analogues via Esterification Reaction in the Presence of Sustainable Natural Deep Eutectic Solvents/Catalyst	- Uses Natural Deep Eutectic Solvents (NADES) as reaction media. - Employs urea choline chloride as a catalyst. -Involves esterification of carboxylic acids (like p-aminobenzoic acid) in NADES. -Benzocaine is synthesized from p-amino benzoic acid via acid-catalyzed esterification with ethanol. - Yield of benzocaine (ethyl p-aminobenzoate) is 69%, m.p. 91 °C.	17
5.	Synthesis and microbiological evaluation of several benzocaine derivatives	- Synthesis method: Fischer esterification - Starting material: p-Aminobenzoic acid - Product: Benzocaine (ethyl p-aminobenzoate) - Characterization: IR, melting point, TLC - Yield: 78%	18

6.	Benzocaine can be synthesized in number of ways	- Methods of synthesis: - Esterification of p-nitrobenzoic acid followed by reduction with metallic tin and hydrochloric acid or hydrogen in the presence of platinum oxide.- - Esterification of p-aminobenzoic acid. - Reduction of ethyl p-nitrobenzoate with ammonium sulfide. - Spectral analysis: - Infrared spectrum obtained using a Perkin-Elmer 257 spectrophotometer. - Nuclear magnetic resonance spectrum obtained on a Varian T-60 NMR spectrometer.	19
7.	Spectroscopic Analysis of Benzocaine Using 1^{H} NMR, 13^{C} NMR, MS, and IR Spectroscopy	-starting materials and reagents: Identification of precursors like p-aminobenzoic acid and ethanol. - Reaction pathways: Common methods involve esterification of p-aminobenzoic acid with ethanol. - Purification methods: Techniques like recrystallization to obtain pure benzocaine. - Characterization techniques: Methods like NMR, IR, MS to confirm structure and purity.	20
8.	Determination of Benzocaine in Pharmaceutical Formulations by indirect SERRS Assay Combined with azo coupling	- Starting materials: benzocaine is synthesized from p-aminobenzoic acid (PABA). - Synthesis methods: Common methods involve esterification of PABA with ethanol. - Reaction conditions: Conditions like temperature, catalysts, and reaction time are crucial for yield and purity. - Purification techniques: Methods like recrystallization are used to purify benzocaine. - Analytical techniques: Methods like chromatography or spectroscopy (e.g., SERRS surface-enhanced resonance raman scattering) can be used for detection and quantification	21
9.	Microwave Assisted Synthesis of Benzocaine	Esterification reaction: Benzocaine is synthesized through the reaction of p-aminobenzoic acid with ethanol. Characterization methods: Techniques like UV spectrum, FTIR, and spectroscopic methods verify the authenticity and purity of synthesized benzocaine. Antibacterial activity evaluation: The synthesized benzocaine was tested against Escherichia coli and Staphylococcus aureus.	22
10.	Chemical oxidative polymerization of benzocaine	- Oxidation of 4-carbethoxyaniline: Synthesis of novel electroactive paramagnetic ortho-coupled aniline oligomers functionalized with ethyl ester groups. - Characterization methods: Elemental analysis, gel-permeation chromatography, conductivity measurements, FTIR, Raman and EPR spectroscopies, and scanning electron microscopy were used to characterize oligobenzocaines. - Theoretical study of benzocaine oxidation mechanism: Based on AM1 and RM1 semi-empirical quantum chemical computations of heat of formation and ionization energy. - Influence of pH and solvation effects: Considered in the study of benzocaine, protonated benzocaine, generated reactive species, and reaction intermediates.	23
11.	Synthesis, characterization, antibacterial evaluation,2D-QSAR modelling and molecular docking	- Incorporation of cyanoacetamide function: To get a powerful synthon ethyl 4-cyanoacetamido benzoate. - Synthesis of heterocyclic scaffolds: Like triazine, pyridone, thiazolidinone, thiazole, and thiophene containing the benzocaine core. - Use of reactions like coupling, Michael addition, condensation, and nucleophilic attack: For synthesizing target compounds.	24

	studies for benzocaine derivatives	- Characterization of synthesized compounds: Using IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. - Evaluation of antibacterial activity: Against Gram-positive and Gram-negative bacteria. - Molecular docking studies: To understand interactions with S. aureus proteins	
12.	Two step continuous – flow synthesis of benzocaine	- Method of synthesis: a two-step continuous-flow synthesis of benzocaine. - Starting material: The synthesis involves the reduction and esterification of p-nitrobenzoic acid. - Conversion and selectivity: The model applied in a continuous flow system achieved high conversion (>99%) and selectivity (>99%). - Residence times: The synthesis achieved these results with residence times as low as a minimum of 12 seconds.	25
13.	Green Approach towards synthesis and Structural analysis of benzocaine based compound and it's co crystal	- Pharmaceutical cocrystals: Improving physicochemical properties like water solubility. - Synthesis method: Mechanochemical solvent-assisted grinding for obtaining benzocaine-based cocrystals. - Characterization techniques: - P-XRD (Powder X-Ray Diffraction) for confirming cocrystal formation and phase differences. - FTIR (Fourier Transform Infrared) spectroscopy for confirming cocrystal formation through IR peak shifts. - Melting point analysis: To support cocrystal formation by showing a different melting point compared to pure components. - Structural analysis: Using Cambridge Structural Database (CSD) surveys and mercury software for analyzing benzocaine's structure and bond interactions.	26
14.	A Quick and Easy Simplification of Benzocaine's NMR Spectrum	- Starting materials and reagents: benzocaine is synthesized from p-aminobenzoic acid (PABA) via esterification. - Reaction conditions: Esterification of PABA with ethanol in the presence of an acid catalyst like sulfuric acid or hydrochloric acid is common. - Purification methods: Crystallization or recrystallization are often used to purify benzocaine. - Characterization techniques: NMR spectroscopy (as mentioned in the text) and other methods like IR spectroscopy and melting point determination are used to confirm the product.	27
15.	Synthesising Benzocaine via Reflux with a Condenser	- Mechanism of Action: Benzocaine works by preventing nerve conduction when applied locally to nerve tissues. - Benefits of Local Anaesthetics: Doesn't cause unconsciousness, reversible action, and complete tissue recovery with no permanent damage. - Synthesis Method: Synthesis via reflux with a condenser - Application of Benzocaine: Commonly used as a topical pain reliever.	28
16.	Spectrophotometric Determination of Benzocaine by AzoDye Formation Reaction	- Starting Materials: Benzocaine is synthesized from p-aminobenzoic acid (PABA). - Synthesis Route: Common methods involve esterification of PABA with ethanol in the presence of an acid catalyst like sulfuric acid or hydrochloric acid. - Reaction Conditions: Control of reaction conditions like temperature, catalyst concentration, and reaction time is crucial for yield and purity. - Purification: Crystallization or recrystallization is often used to purify benzocaine.	29

		- Analytical Methods: Techniques like spectrophotometry (as seen in the azo dye formation reaction for determination) can be used for analysis and quantification of benzocaine.	
17.	Diffusion of benzocaine in poly(ethylene-vinyl acetate) membranes: Effects of vehicle ethanol concentration and membrane vinyl acetate content	- Starting materials: Benzocaine is synthesized from p-aminobenzoic acid (PABA). - Synthesis route: Common methods involve esterification of PABA with ethanol. - Reaction conditions: Conditions like temperature, catalysts, and reaction time can impact yield and purity. - Purification methods: Techniques like recrystallization are often used to purify benzocaine. - Safety and handling: Handling chemicals like PABA and benzocaine requires proper safety measures.	30
18.	Benzocaine as precursor of promising derivatives: synthesis, reactions, andbiological activity	-Electrophilic and nucleophilic reaction of benzocaine are the most common procedure to construct a library of benzocaine derivatives. - Benzocaine derivatives show promise with antimicrobial, anti-inflammatory, anticancer activities due to inhibition of enzymes like acetylcholine esterase, cyclooxygenase, fatty acid transport protein, and human immunodeficiency virus.	31
19.	Benzocaine synthesis from toluene and p-xylene	- Starting materials: Toluene and p-xylene are used as petrochemical building blocks. - Drug class: Benzocaine belongs to the amino ester class of drugs. - Chemical structure: Benzocaine has a simple structure with the IUPAC name ethyl 4-aminobenzoate Use of benzocaine: It's a local anesthetic useful as a topical anesthetic and painkiller.	32
20.	Synthesis, characterization and analytical study of new azo ligand driven from benzocaine and its metal complexes	- Starting Materials: Benzocaine is synthesized from p-nitrobenzoic acid or p-aminobenzoic acid. - Synthesis Pathway: Common methods involve esterification of p-aminobenzoic acid with ethanol, or reduction of p-nitrobenzoic acid to p-aminobenzoic acid followed by esterification. - Reaction Conditions: Esterification is often carried out using acid catalysts like sulfuric acid or HCl. - Purification: Crystallization or recrystallization are common methods for purifying benzocaine. - Characterization: Techniques like NMR, IR, and MS are used to confirm the structure of synthesized benzocaine.	33

3.CONCLUSION

The synthesis of benzocaine was successfully performed by esterification of p-aminobenzoic acid. The product obtained showed appropriate physical characteristics, confirming its purity and identify. This experiment demonstrated important organic synthesis techniques and their pharmaceutical significance.

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