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Research on:- Synthesis and evaluation of phenothiazine derivative for Antidepressant Activity

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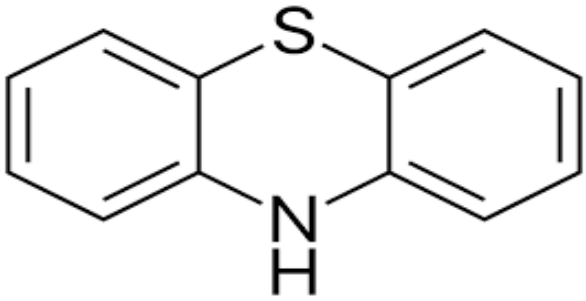
ABSTRACT

Phenothiazines are widely used in various medical fields, particularly in psychopharmacology. These substances have the ability to effectively block dopamine, histamine, serotonin, acetylcholine, and a-adrenergic receptors, resulting in a wide range of effects and side effects. In addition to their antipsychotic properties, phenothiazines also exhibit significant antimicrobial effects by enhancing the bactericidal function of macrophages and inhibiting efflux pumps. They can also eliminate bacterial resistance plasmids and disrupt bacteria through their membrane-destabilising effect. Furthermore, they have been found to have antiviral, antiprotozoal, antifungal, and antiprion activities. Clinical trials have also shown that phenothiazines can destroy cancer cells and make them more susceptible to chemotherapy. Additionally, they have been reported to have anti-angiogenesis and anti-cancer stem cell activities, suggesting potential applications as adjuvants in the treatment of infections and tumours. Finally, phenothiazines may also be effective in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's.

Keywords:- Phenothiazine, derivative, compounds, agonist, antagonist, synthesis, evaluation, Antidepressant, Activity.

Phenothiazine:-



Phenothiazine (PTZ) is a heterocyclic organic compound represented by the formula S(C6H4)(2NH). It falls under the category of thiazine-like molecules. While the parent compound itself does not have any practical applications, its derivatives have proven to be highly bioactive, widely utilised, and possess a rich history. One such derivative, chlorpromazine, has brought about a revolution in the field of psychiatry and allergic treatment. Another earlier derivative, ethylene blue, stands as one of the pioneering anti-malaria drugs. Ongoing investigations are exploring the potential of derivatives as anti-infective agents. Phenothiazine serves as the fundamental structure in medicinal chemistry for pharmaceutical development. (1)

Depression affects an estimated 350 million individuals worldwide. The World Mental Health Survey, conducted across 17 countries, revealed that on average, approximately 1 in 20 people reported experiencing a depressive episode within the previous year. Depression disorders often manifest at a young age, impairing individuals' functioning and frequently recurring. Consequently, depression stands as the leading cause of disability globally, measured by the total number of years lost due to disability. The global demand to address depression and mental health conditions is steadily rising. In 2012, the World Health Assembly called upon the World Health Organization (WHO) and its member states to prioritise this issue.

In its most severe form, depression can lead to suicide. Tragically, nearly 1 million lives are lost each year due to suicide, equating to 3000 suicide deaths daily. For every person who completes suicide, there may be 20 or more individuals who attempt to end their own lives. Depressants, also known as central depressants, refer to drugs or endogenous compounds that diminish neurotransmission levels, resulting in a decrease in arousal or stimulation within various regions of the brain. Psychosis is a condition marked by a distorted connection with reality, often seen in severe mental illnesses. Individuals in a psychotic state may exhibit hallucinations or delusions. Hallucinations involve sensory perceptions without any external stimuli. For instance, a person might hear their mother scolding them even

though she is not present, or see a figure that is not actually there. Delusions, on the other hand, are false beliefs that contradict factual evidence. In addition to these symptoms, individuals experiencing psychosis may also display a lack of motivation and withdraw from social interactions. Common signs of psychosis include trouble focusing, feelings of sadness, changes in sleep patterns, anxiety, distrustfulness, isolation from loved ones, disorganised speech, like abruptly changing topics, feelings of despair, and thoughts of self-harm.

Normal stage:-
Brief hallucinations are not uncommon in individuals without any psychiatric disease. There are several causes or triggers for these hallucinations. One cause is falling asleep and waking, which can result in hypnagogic and hypnopompic hallucinations. These types of hallucinations are completely normal and not a cause for concern. Another trigger is bereavement, where hallucinations of a deceased loved one are common. Severe sleep deprivation and stress can also lead to brief hallucinations.

Trauma:-
Traumatic life events have been associated with an increased risk of developing psychotic symptoms. Specifically, childhood trauma has been shown to predict the onset of psychosis in adolescents and adults. It is estimated that around 65% of individuals with psychotic symptoms have experienced childhood trauma, such as physical or sexual abuse, as well as physical or emotional neglect. This highlights the importance of trauma prevention and early intervention in reducing the occurrence of psychotic disorders and mitigating their effects.

Psychiatric disorder:-
In terms of psychiatric disorders, subtle physical abnormalities have been observed in conditions that were traditionally considered functional, such as schizophrenia. Primary psychiatric causes of psychosis include schizophrenia and schizophrenic form disorder

Affective disorders, such as major depression and bipolar disorder, can lead to severe mood disturbances. In cases of depression, individuals may experience delusions or hallucinations that involve persecution or self-blame. On the other hand, individuals experiencing a manic episode may develop grandiose delusions. Schizoaffective disorder is characterised by symptoms of both schizophrenia and mood disorders. Brief psychotic disorder, also known as acute or transient psychotic disorder, is another type of mental illness. Delusional disorder, which involves persistent delusions, and chronic hallucinatory psychosis are also recognized conditions. Recent epidemiological studies suggest that mental healthcare priorities should shift from focusing solely on psychotic disorders to addressing common mental disorders. Additionally, there is a need to move away from relying heavily on mental hospitals and instead prioritise mental health services in primary health centres. This shift is crucial due to the increasing prevalence of invisible mental problems, such as suicidal attempts, aggression, substance abuse, marital discord, and divorce rates. It is essential to reevaluate strategies and prioritise the promotion and provision of appropriate mental health services within the community

Combinations:-
The combination of various depressants can pose a significant risk due to the potential exponential increase in depressive effects on the central nervous system, rather than a linear one. This particular trait often leads individuals to choose depressants for intentional overdoses, particularly in cases of suicide. Overdose deaths among opiate addicts are frequently attributed to the concurrent use of alcohol or benzodiazepines with the typical dose of heroin.

Procedure for scheme:-
Step 1: General procedure for the synthesis of 7, 8, or 9 substituted aniline Benzoic acid derivatives involved the addition of an equimolar amount of substituted aniline to a chloro benzoic acid in 5mL of Benzaldehyde and 0.1 percent potassium hydroxide solution. The reaction mixture was then heated under reflux at approximately 80°C for a duration of 2 hours. The completion of the reaction was indicated by TLC. Subsequently, the mixture was cooled by adding a water/ice mixture, and the resulting solid was filtered to obtain an excellent yield.

Step 2: The general procedure for the preparation of 7, 8, or 9 substituted 10H-phenothiazine 1 carboxylic acid derivatives involved adding an equimolar amount of 7, 8, or 9 substituted Anilino Benzoic acid to a solution of sulphur powder and iodine in 5 ml of ethanol. The reaction mixture was then heated under reflux with stirring for approximately 2 hours and subsequently poured into an ice/water mixture. The resulting precipitate was filtered and washed with cold water.

Step 3: The synthesis of derivatives of methyl 10H-phenothiazine-1-carboxylate required refluxing 0.01 mole of 10H-phenothiazine-1-carboxylic acid with concentrated sulfuric acid, using ethanol as the solvent, for a duration of 1 hour in a 250ml round-bottom flask (RBF). The resulting reaction mixture was then cooled in ice-cold water.

Step 4: To synthesise derivatives of 10H-phenothiazine-1-carbohydrazide, 0.01 mole of compound A was refluxed with 3-4 ml of hydrazine hydrate for 1 hour. The resulting reaction mixture was then allowed to cool in an ice bath, and the resulting precipitate was collected and dried.

Step 5: The synthesis of derivatives of N'-benzylidene-10H-phenothiazine-1-carbohydrazide involved refluxing 0.01 mole of compound B with 0.01 mole of substituted aromatic aldehyde for 1 hour. Afterward, the resulting reaction mixture was cooled in an ice bath, and the resulting precipitate was collected, dried, and recrystallized from ethanol.

ANTIDEPRESSANT ACTIVITY

The model proposed by Porsolt et al. (1977, 1978) to test for antidepressant activity involves inducing a state of behavioural despair in mice or rats. These animals are forced to swim in a confined space from which they cannot escape, leading to a characteristic behaviour of immobility. This immobility reflects a state of despair, which can be alleviated by various therapeutic agents that are effective in treating human depression.

Phenothiazine derived drugs:-
In 1876, Heinrich Caro at BASF synthesised methylene blue, a derivative of phenothiazine. The structure of phenothiazine was deduced by Heinrich August Bernthsen in 1885, who had synthesised it in 1883. During the mid-1880s, Paul Ehrlich began using methylene blue in his cell staining experiments, which resulted in significant discoveries about different cell types. His work earned him a Nobel Prize. Ehrlich became particularly interested in using methylene blue to stain bacteria and parasites, such as the malaria pathogen, and found that it was effective for this purpose. He conducted clinical tests and by the 1890s, methylene blue was being used to treat malaria. However, research on derivatives of phenothiazine declined until the introduction of phenothiazine itself as an insecticide and deworming drug. In the 1940s, chemists at Rhone-Poulenc Laboratories in Paris, led by Paul Charpentier, began synthesising derivatives. This led to the development of promethazine, which had no activity against infective organisms but exhibited strong antihistamine activity and a potent sedative effect. It was marketed as a drug for allergies and anaesthesia and remains available as of 2012. Towards the end of the 1940s, the same laboratory produced chlorpromazine, which had an even stronger sedative and calming effect. Jean Delay and Pierre Deniker tested it on their psychiatric patients and published their results in the early 1950s.

Treatment of Antidepressants:-
The aim of the treatment is to prevent harm and to relieve distress or to be prophylactic.
It is important to Differentiate symptoms of the disorder from the premorbid personality.
This means the diagnosis will primarily Influence the way in which these drugs are used rather than the choice of drug per se.

There are several drugs Available in market, which are used as antidepressants.
Standard drugs used in treatment of Depression.
1.Drugs which block both NE and 5-HT reuptake.
2.Imipramine, Clomipramine, Amitriptyline, Doxepin..
3.Drugs which mainly block NE reuptake.
4.Desipramine, Lofepramine.NortriptylineTrazodone, Nefazodone, Bupropion, Mirtazapine, Mianserin, Venlafaxine.
5. MAO Inhibitors.
Non-Selective .Tranylcypromine.
Selective MAO-A inhibitors.Moclobemide.

Experimental method and materials:-
1. The prepared compounds were identified and characterised using various methods to ensure that they were chemically different from the parent compound. These methods included physical constants, thin layer chromatography (TLC), FT-infrared spectroscopy (FT-IR), nuclear magnetic resonance spectroscopy (1H-NMR), and elemental analysis (C,H,N). The melting points of the organic compounds were determined using open capillary in a heavy liquid paraffin bath, and thin layer chromatography was used to identify the formulation of new compounds and determine their purity. Fourier transformer-infrared spectroscopy (FT-IR) was used to identify functional groups and for quality control of raw materials/finished products, while nuclear magnetic resonance spectroscopy (1H-NMR) was used to record H1NMR spectra.

Synthesis of phenothiazine:-
In 1883, the German chemist Benthses published the synthesis of phenothiazine using diphenylamine and sulphur as the reaction substrates under high temperature conditions. This marks the initial documentation of the phenothiazine synthesis method [14]. For many years, this traditional route remained the primary method for synthesizing phenothiazines. However, this method is time-consuming and often results in the production of two positionally isomeric products. These products share similar properties and are difficult to purify. As the exploration of the biological activity of phenothiazine compounds continues, more and more researchers are dedicated to discovering new phenothiazine synthesis methods. Below, we will introduce the phenothiazine synthesis methods. Affarst Vasile et al. utilized iodine as a catalyst for the reaction and employed microwave radiation to heat the reaction between

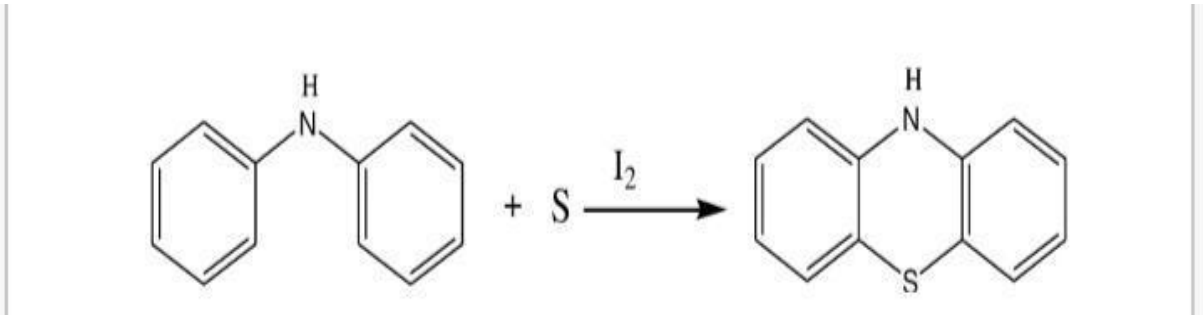
diphenylamine and sulphur. The activation of electrons reduces the reaction time, enhances efficiency, and leads to improved yields.

Side effect:-

The antimuscarinic properties of the TCAs may lead to various side effects, including dry mouth, dry nose, blurry vision, lowered gastrointestinal motility or constipation, urinary retention, cognitive and/or memory impairment, and increased body temperature. Other side effects such as drowsiness, anxiety, emotional blunting (apathy/anhedonia), confusion, restlessness, dizziness, akathisia, and hypersensitivity are also possible.

Overdose:-

TCA overdose is a significant cause of fatal drug poisoning, with documented severe morbidity and mortality due to cardiovascular and neurological toxicity. This is particularly concerning in the paediatric population, where the availability of these drugs in the home, often prescribed for bed wetting and depression, poses a serious problem. In the event of a known or suspected overdose, immediate medical assistance should be sought.



CONCLUSION

The synthesis of 3 derivative compounds, specifically 3 derivatives of substituted phenothiazine, was prepared in scheme 1 from p-chloro benzoic acid aniline derivatives. All compounds were structurally elucidated using physical and analytical methods. In vitro anti-inflammatory activity was evaluated using the protein denaturation method, revealing that some synthesised derivative compounds possess moderate to promising activity compared with the standard, and all showed dose-dependent activity. Future studies of synthesised Phenothiazine derivatives should focus on developing QSAR methods and exploring potential effects.

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