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# ANTIDEPRESSANTS AND ANTIANXIETY AGENTS BASED ON 9.10-DIHYDROANTHRACENE DERIVATIVES: A MINI REVIEW

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## ABSTRACT

During the last few years, some of the dihydroanthracene have been reported that possess tetracyclic structure and secondary amine side chain can be used as antidepressants and antianxiety agents with some side effects. For that reason, many of the research center and Pharmaceutical companies are still continuous to search about antidepressants and antianxiety agents without the side effects. This review is focuses on the most important of anthracene derivatives which exhibits these activities and revealsthe importance of dihydroanthracene compounds in organic synthesis.

***Keywords***: antidepressants, Diels-Alder, dihydroanthracene, antianxiety, cycloaddition.

## INTRODUCTION:

Depression is the most common psychiatric disorder in the community with significant health and cost implications. [1]Moreover psychiatric illness (depression) is often associated in the worst cases with suicide and there are between 10 and 20 million suicide attempts every year. [2]According to the world health organization report approximately 350 million people suffer from a mental or behavioral disorder. This amounts to 12.3 % of the global burden of disease, and will rise to 15 % by 2020. It is estimated that 1 out of 20 people reported having an episode of depression in the worldwide in 2008, by 2020, depression will be the second leading cause of world disability and by 2030 it is expected to be the largest contributor to disease

burden. [2, 3]There are many factors which play roles in affecting depressive symptoms such as sexual abuse, education, wars, job loss, age, and income. etc. [4, 5]Drugs used for treating mental disorders accompanied by depression are called antidepressants. The era of antidepressants started with isoniazid in 1952, which was accidentally found while being studied as a possible treatment for tuberculosis. It was discovered to have psychoactive properties through euphoric appearance on the tuberculosis patients who were receiving this drug. This discovery was beginning of the road to the synthesis of new generations of antidepressants. Since then, the research centers and pharmaceutical companies have sought to manufacture of antidepressant medication. [6] Recently, the antidepressant medication which used to treat depressive disorders has grown and increased demand for these drugs for curbing depression globally and the number of antidepressant medication has grown dramatically. Therefore it was classified to facilitate deal with them on the basis of their chemical structures and their mechanisms of action to four main classes. The most frequent and widely used drugs for treating endogenous depression are tricyclic and tetracyclic antidepressants. [7]. In this review we will focus on tricyclic and tetracyclic antidepressants which derived from anthracene. Anthracene is planar by virtue of the necessity of maintaining aromaticity, but considering the structure of all tri-cyclic and tetra-cyclic antidepressants which derived from anthracene such as benzoctamine, maprotiline, melitracen, fluotracen, and oxaprotilinefind they take conformation Butterfly is often (**Figure:1**). This contraction in the central ring in the classical tricyclic agents to a dihydroanthracene is often compatible with antidepressant activity for reasons that are not yet understood at the molecular level. [8-10]

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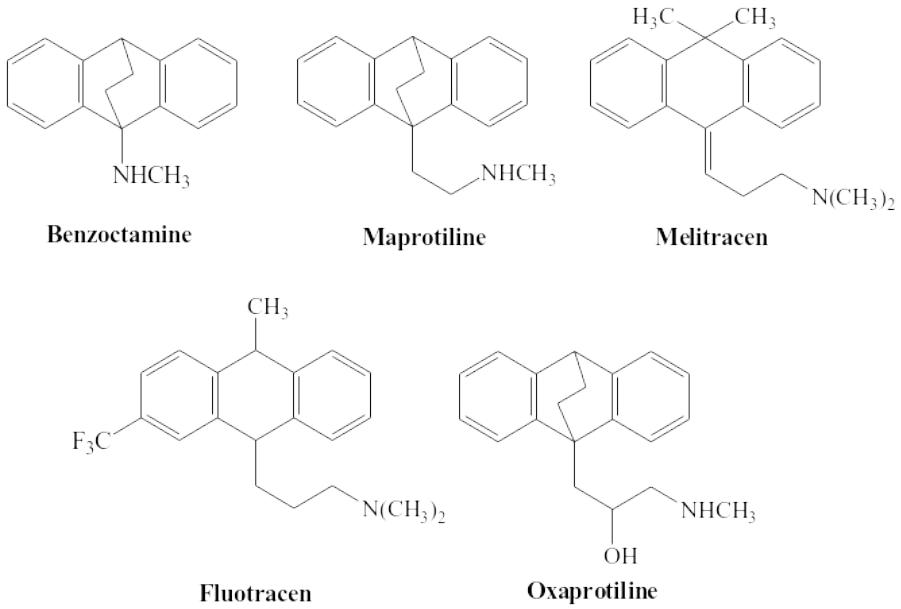



**(Figure: 1)**

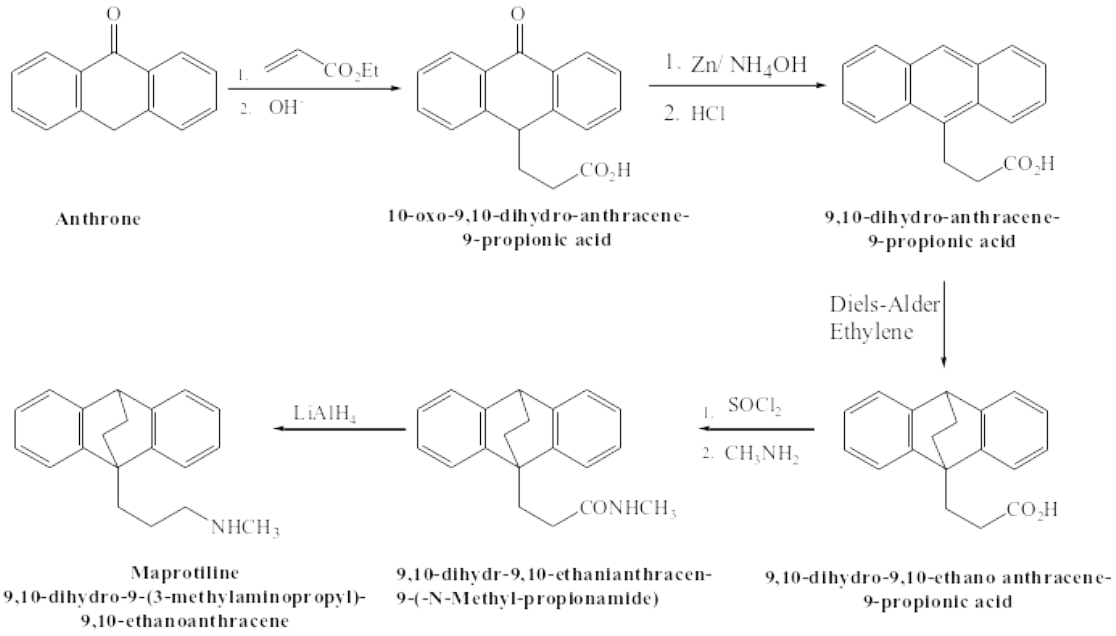
Maprotiline and benzoctamine, drugs derived from anthracene, present anxiolytic and antidepressants activity. [11]

Maprotiline[9,10-dihydro-9-(3-methylaminopropyl)-9,10-ethanoanthracene], the first tetracyclic antidepressant was synthesized and developed in Ciba-Geigy research group in Switzerland by Wilhelm and Schmidt in 1967. [12]

The clinical studies conducted by Kuhn found it to be a clinically useful for the treatment of depressant, and launched in 1975 for the treatment of depression by Novartis. [13]

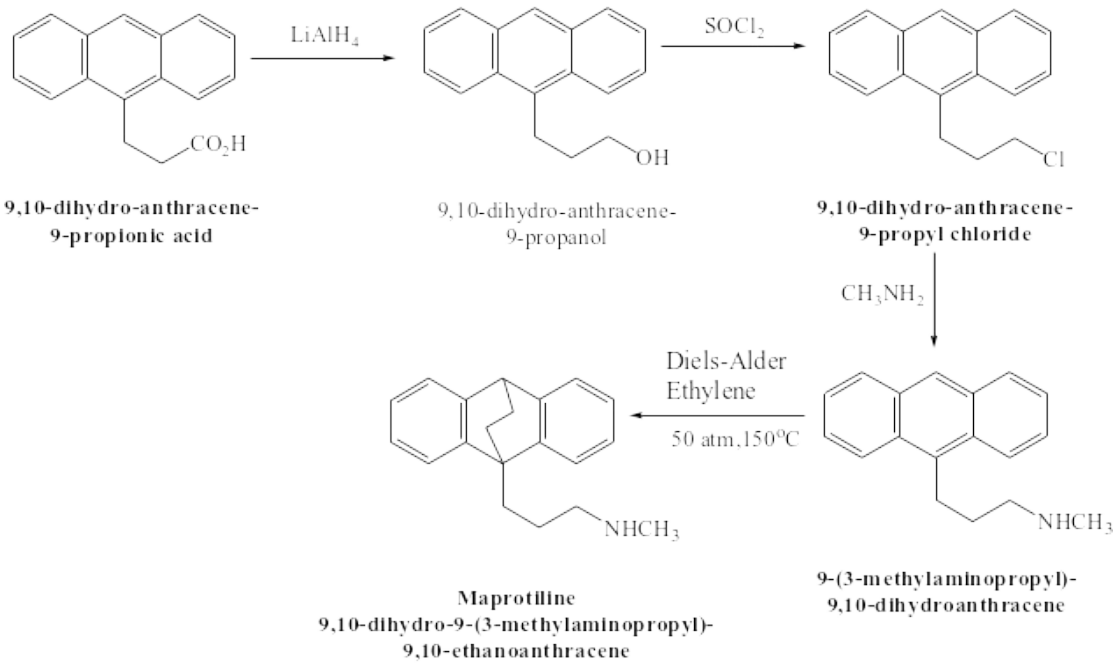
Maprotiline is an atypical antidepressant compound and pharmacologically clinically can be used to treatment of various forms of depression which accompanied by a feeling of fear and irritability and possesses moderate tranquilizing and cholinergic activity. It improves mood significantly and relieves of fear by disabling neuronal reuptake of monoamines in the central nervous system. Ludiomil is a synonym of maprotiline. [14]The key step to synthesized of maprotiline[9,10-dihydro-9-(3-methylaminopropyl)-9,10-ethanoanthracene] was Diels–Alder addition of ethylene to

[9,10-dihydroanthracene-9-propionic acid]under high pressure leads to the addition across the 9,10 positions and the formation of the central 2,2,2-bicyclooctane moiety **(Scheme: 1)**. [15]



**(Scheme: 1)**

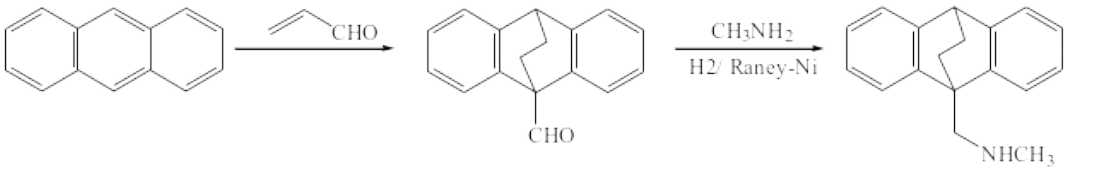
In another process, maprotiline is synthesized by a 4+2 cycloaddition reaction of [9-(3-methylaminopropyl)-9,10-dihydroanthracene]with ethylene **(Scheme: 2)**. [16]




**(Scheme: 2)**

Shorten the side chain in maprotiline produces the benzoctamine [9,10-dihydro-9-(N-methylmethanamine)-9,10-ethanoanthracene]. Benzoctamine was synthesized and developed into a clinically useful drug for the treatment of anxiety, a sedative and muscle relaxant by Ciba-Geigy research group in Switzerland through a series of successive reactions. The key step was [4+2] cycloaddition of ethylene and anthracene-9-carboxylic acid. [16]

In another method for synthesized of benzoctamineused [4+2] cycloaddition of anthracene with acrolein at 170°C, across the 9, 10 positions to give the central 2, 2, 2-bicyclooctyl moiety. Tacitin is a synonym of benzoctamine has anxiolytic properties **(Scheme: 3)**. [8, 17]




Anthracene

(9, 10-Dihydro-9, 10-ethanoanthracene-9-yl) methanal

Benzoctamine
9, 10-dihydro-9-(N-methylaminomethyl) -9, 10-ethanoanthracene

**(Scheme: 3)**

The evidence points to it being as effective as other clinical anxiety drugs but benzoctamine is different from most sedative drugs because in most clinical trials and pharmacological and biochemical studies does not produce respiratory depression but stimulates the respiratory system. [18]

There are some side effects from the use of maprotiline and benzoctamine as an antidepressant and anxiety such as drowsiness, sweating, headache, arrhythmia and memory impairment, Therefore, the research is still ongoing for the synthesis of antidepressants and anxiety more efficient without the side effects. One of these research was the anthracene system in maprotiline or benzoctamine can be linked with another groups to achieve better activity and minimizing of side effects for these drugs. [19, 20]

**CONCLUSIONS**:

Dihydroanthracene are important compounds in synthetic organic chemistry, due to ituse as intermediate for synthesis of biologically active compounds such as antidepressants and antianxiety agents which are prepared by cycloaddition reactions between anthraceneand / or its derivatives with suitable dienophile.

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