STUDIES IN CHEMISTRY OF THIAZINE CONTAINING BIOACTIVE HETEROCYCLIC COMPOUNDS: A REVIEW

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Abstract

Chemistry is the science of the composition, structure, property and reaction of matter, especially of atomic and molecular systems. Right from the composition of the cell to the whole organism, the presence of chemistry is conspicuous. Like all sciences, chemistry has a unique place in our pattern of understanding of the universe. Organic chemistry often studies life by making new molecules that give information not available from the molecules actually present in living things. Chemistry plays a very significant role in today's society. Without chemistry, modern advances would be nearly impossible.

Key Words: thiazines, Thiadiazines Benzothiazines.

1.1 INTRODUCTION

Chemistry is the science of the composition, structure, property and reaction of matter, especially of atomic and molecular systems. Right from the composition of the cell to the whole organism, the presence of chemistry is conspicuous. Like all sciences, chemistry has a unique place in our pattern of understanding of the universe. Organic chemistry often studies life by making new molecules that give information not available from the molecules actually present in living things. Chemistry plays a very significant role in today's society. Without chemistry, modern advances would be nearly impossible.

Heterocyclic chemistry deals with heterocyclic compounds which constitute about sixty five percent of organic chemistry literature[1]. Heterocyclic compounds are widely distributed in nature and essential to life. They are of very much interest in our life and play a vital role in the metabolism of all living cells. Heterocycles are important constituents of natural compounds[2], synthetic medicines[3] and are known to play a vital role in number of chemical[4] and biochemical processes[5]. For more than a century, heterocycles have constituted one of the largest area of research in organic chemistry and become the prime area of research in the field of synthetic and medicinal chemistry.

1.2 HISTORY OF HETEROCYCLIC CHEMISTRY

The history of heterocyclic chemistry began in the 1800s, in step with the development of organic chemistry. Some noteworthy developments -

1818: Brugnatelli isolates alloxan from uric acid.

1832: Dobereiner produces furfural (a furan) by treating starch with sulfuric acid

1834: Runge obtains pyrrole ("fiery oil") by dry distillation of bones

1906: Friedlander synthesizes indigo dye, allowing synthetic chemistry to displace a large agricultural industry

1936: Treibs isolates chlorophyl derivatives from crude oil, explaining the biological origin of petroleum.

1951: Chargaff's rules are described, highlighting the role of heterocyclic compounds (purines and pyrimidines) in the genetic code.

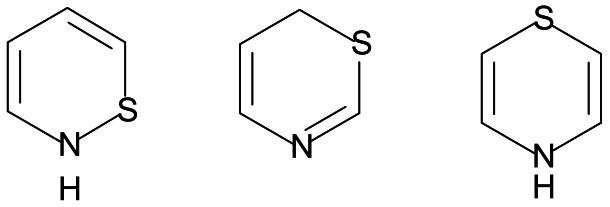
Over millions of years organisms have been under intense evolutionary pressure, and their metabolites may be used to advantage for example, as toxins toward off predators, or as coloring agents to attract mates or pollinating insects. Many heterocycles are being biosynthesized by animals and plants, such as heam derivatives in blood and the chlorophylls essential for photosynthesis. Similarly, the bases found in RNA and DNA are heterocycles, where the sugars that in combination with phosphates provide the backbones and determine the topology of these nucleic acids. Some of the natural products e.g. antibiotics such as penicillin's, cephalosporin; alkaloids such as vinblastine, morphine, reserpine etc. have heterocyclic moieties. The biological properties of heterocycles in general make them one of the prime interests in the pharmaceutical and biotechnology industries.

Heterocyclic compounds are also finding an increasing use as intermediate in organic synthesis. Very often this is because a relatively stable ring system can be carried through a number of synthetic steps and then cleaved at the required stage in a synthesis to reveal other functional groups. They also find applications as sanitizers, developers, antioxidants, corrosion inhibitors, copolymers, dye stuff. They are used as vehicles in the synthesis of other organic compunds.

1.3 THIAZINES AND THIADIAZINES

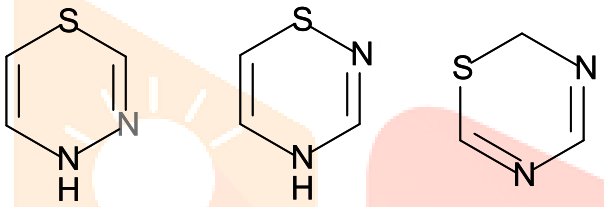
In general biological active compounds are derived from heterocyclic structures. Heterocycles containing thiazine and thia-diazine ring system have attracted our interest due to their useful biological and pharmacological properties. The small and simple thiazine nucleus is present in compounds, involved in research aimed at evaluating new products that possess biological activities, such as anti-tumor, anti-microbial, antipsychotic, antifungal, antiviral and anti-inflammatory. Thiazines are organic compounds with molecular formula C_4H_5NS containing a six membered ring of four carbon, one nitrogen and one sulfur atoms. While thiadiazine with molecular formula $C_3H_4N_2S$ containing a six membered ring of three carbon, two nitrogen and

one sulfur atoms. Many compounds having 1,4-thiazine are known, most of them are derivatives of phenothiazine and benzothiazine. Thiazines may be 1,2-thiazine (I), 1,3-thiazine (II) or 1,4-thiazines (III). Thiadiazine may be 1,3,4- thiadiazines (IV), 1,2,4- thiadiazines (V) or 1,3,5- thiadiazines (VI)



I II III

Thiazines



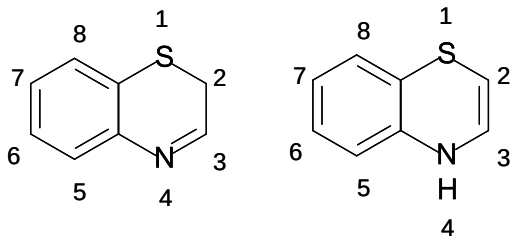
IV V VI

Thiadiazines

Six membered heterocyclic compounds have occupied a prominent place among various classes of organic compounds for their diverse biological activity and stability. Chemicals which include thiazine and thiadiazine are used for dyes, tranquilizers and insecticides.

1.4 BENZOTHIAZINES

Thiazine ring fused with the benzene ring system is commonly known as benzothiazine. The name is applied to both the 2H-(top) and 4H–(bottom) isomers of the molecule.



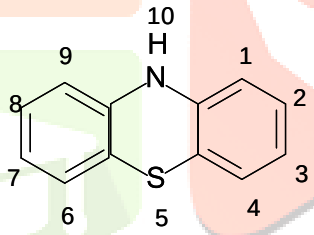
Structural specificity that 4H-1,4- benzothiazine possess a fold along nitrogen and sulfur axis, which is responsible for their pharmacological and biological activities. With respect to biological applications, these derivatives are found potent anti-inflammatory[6-8], analgesic[9], anti-pyretic[10], anti-microbial[11], anti-viral[12],

antipsycotic[13], blood platelets aggregation inhibitors[14], Ca-antagonist[15], antihypert-ensive agent[16], anticancer[17-19], antidiabetic[20] and antioxidantgent[21.] These derivatives have also been reported as synthetic intermediates for other drugs[22], stabilizers in rubber vulcanization[23], corrosion inhibitors[24] and fading preventors[25]. These are also used as dyestuffs, photographic developers[26] and UV light absorbers. Besides these activities, 1,4-benzothiazine nucleus[27-28] found in mammalian hair and feathers as luciferin and rafamycin derivatives. The vivo antitumor efficacy of 1,4-benzothiazines have attributed to a direct cytotoxic activity against neoplastic cells. 1,4-Benzothiazine dyes are used for photometric determination of uranium and uranyl compounds. 4H-1,4-Benzothiazines are also used as K_{ATP-} channel openers[29-32], phospho-diesterase 7 inhibitors[33], 5-HT_3 antagonists[34].

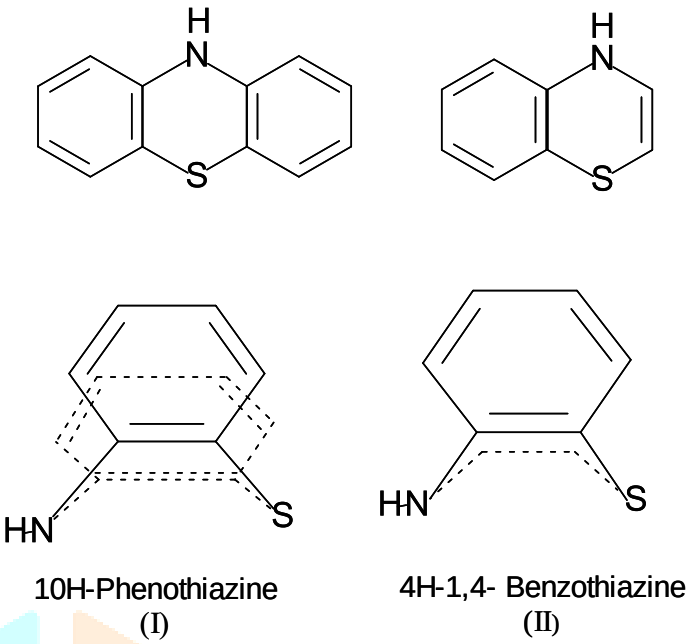
A slight change in the substitution pattern in the benzothiazine nucleus cause distinguishable difference in their biological activities. These multifarious application of 1,4-benzothiazines have directed to organic chemists to synthesize new 1,4-benzothiazines bearing heteryl pharmocophores and work for betterment of synthetic methods taking in consideration of yield and environmental hazards.

1.5 Phenothiazines

Phenothiazine is a another important heterocycle related to the thiazine class of heterocyclic compounds. It is very important as it occurs in various antipsychotic and antihistamine drugs. Phenothiazine was first synthesized by Bernthsen in 1883[35]. Phenothiazines (or 10H-Phenothiazines) are numbered as :



Phenothiazine also called dibenzothiazine or thiodiphenyl amine is a yellow or green crystalline compound, which is soluble in organic solvents like hot acetic acid, benzene etc. According to Gordon's model, 4H-1,4-benzothiazine**(II)** structurally resembles to 10H -phenothiazine**(I)** in having a fold along nitrogen-sulfur axis. They only differ from 10H-phenothiazine**(I)** in having an ethylene linkage instead of o-phenylene skeleton.



10H-Phenothiazine (I)

4H-1,4- Benzothiazine (II)

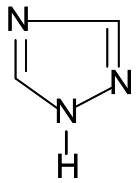
Phenothiazines which are usually stable, crystalline solid belong to the largest group of antipsychotic drugs and are being used for disorders like schizophrenias, mania, psychosis, some form of senility, hyperactivity in children and even severe anxiety. Most widely used phenothiazines, chlorpromazine (thorazine) is prescribed for treatment of overactive schizophrenics, trifluoperazine (stelazine) is used for inhibited and withdrawn schizophrenics, prochlorperazine is used for nausea and vomiting. Interestingly phenothiazines are able to cleave DNA on photochemical induction[36], possess potent biological activities as neuroleptics[37], tranquilizers[38], analgesic[39], antimalarian[40], anti-cancer[41], CNS- activity[42], antiviral[43], antibacrerials[44], antituberculotic[45], antiplatelet[46] and antidepressive[47]. These compounds also exhibit chelating properties towards various metals[48].

All Phenothiazines are readily oxidizable, particularly in the presence of sunlight and moisture. Therefore, phenothiazine is an excellent antioxidant. Phenothiazine dyes are also used for dying cellulosic materials or blends to cellulosic fibers and synthetic fibers in industries.

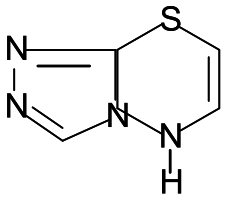
1.6 1,2,4-TRIAZOLES AND 1,2,4-TRIAZOLOTHIADIAZINES

Among heterocyclic compounds, 1,2,4-triazoles and their thiadiazine derivatives show wide spectrum of bioactivities. Besides various pharmacological activities, these have shown plant protection activities like fungicide[49-51], herbicide[52-53], insecticide[54], etc. Some of these compounds have been commercialized as excellent fungicides[55]. Compounds containing 1,2,4-triazole moieties (VII) attached to a heterocyclic system are of wide interest because of their diverse biological activities[56]. Substituted 1,2,4-triazole -1,3,4- thiadiazines (VIII) are reported to possess antifungal, antibacterial and anticancer activities[57-60]. Additional bioactivity shown by such molecules includes antitubercular, anti-inflammatory and antimolluscicidal[61-62]. The 1,3,4-thiadiaznie derivatives in which 1,4-thiazines fused with 1,2,4-triazole nucleus, are important scaffold in several natural and synthetic compounds of significant pharmacological properties and also have structural similarity with biologically most active phenothiazines in having fold along N-S axis. These heterocycles have diverse applications as powerful, anti-mycobacterial[63-64], antimitotic[65-66], antidepressant[67-68], analgesic[69], anti-

inflammatory, anticonvulsant[70], antihyper-tensive[71], antitumorial[72-73], antiviral[74], antiplatelet[75] and anti-thrombotic[76].



VII



VIII

1.7 MICROWAVE ASSISTED SYNTHESIS

Designing compounds with the desired biological activities is a time consuming and expensive process. The conventional thermal methods require long reaction time, complex handling and gives low yield of products. Microwave assisted organic synthesis[77-81] has attracted attention in recent years due to enhanced reaction rates, high yields, improved purity, ease of work up after the reaction and eco-friendly reaction conditions compared to the conventional methods. Microwave is all about dielectric heating[82] and gives selectively higher heating rates for specific type of substances. Polar substrates are found to be better recipients of microwave irradiation[83]. Microwave assisted heating under controlled conditions has been shown to be an invaluable technology for synthesis of organic compounds since it often dramatically reduces reaction time typically from days and hours to minutes or even seconds. Microwave assisted organic synthesis (MAOS) is well known to promote the synthesis of a variety of organic compounds and have attracted our substantial attention in this field enabling rapid reproducible and scaleable chemistry development. The use of microwave irradiation have become an established tool[84] in organic synthesis for achieving better selectivity, rate enhancement, high yield and reduction of thermal degradation byproducts[85]. Moreover MAOS is an acknowledged quick alternative green technology and environmentally benign synthetic organic chemistry that also provides easier work-up compared to the conventional methods.

1.8 SULFONES

Sulfones of 4H-1,4-benzohiazines and 10H-phenothiazines also constitute an interesting class of heterocyclic compounds which find a number of applications in medicine[86-89] and industry[90]. The oxidation of 4H-1,4-benzothiazine and phenothiazine by 30% hydrogen peroxide in the presence of glacial acetic acid easily provides respective sulfone derivatives. Infrared spectral investigation of the pure sample of sulfones of benzothiazines and phenothiazines reveal the remarkable shifting of characteristic vibrational bands towards higher frequencies.

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