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The Significance of Thiophene in Medicine: A Systematic Review of the Literature

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Abstract: Thiophene nucleus has been established as the potential entity in the largely growing chemical world of heterocyclic compounds possessing promising pharmacological characteristics. The similar compounds synthesized through different routes bear variable magnitudes of biological activities.. An odor reminiscent of benzene characterizes this colorless liquid. It exhibits a majority of its reactions resembling those of benzene. Thiophene has a structure that is analogous to structure of pyrrole, and due to pie electron cloud, it behave like extremely reactive benzene derivative. The available analytical and informational data in literature indicate Thiophene constitute a notable class of chemicals in the medical domain, exhibiting a range of therapeutic potentials. These encompass antiviral, antimalarial, antihypertensive, antimicrobial, antioxidant anticonvulsant, anticancer, anti-inflammatory, antidepressant and antimycobacterial, properties. An examination of reveals literature that the moiety thiophene has garnered considerable attention from medicinal chemists and biochemists to formulate, design, and implement novel approaches for the discovery of new pharmaceuticals. This review article confirms that thiophene derivatives have the potential to be a valuable resource for developing new biologically active compounds. It is prudent to investigate this possibility by combining various substituted components, as this may lead to improved pharmacological effects. Therefore, it is necessary to persist in the pursuit of investigating numerous further alterations on the thiophene moiety.

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1. INTRODUCTION

C4H4S and Its substituted counterparts are an important type of compounds that are aromatic. with intriguing possibilities in medicinal chemistry. The creation of combinatorial libraries and the execution of comprehensive searches for lead compounds have become indispensable tools for medicinal chemists. This compound has generated significant interest in both industry and academia due to its documented extensive therapeutic properties and broad applications in medicinal chemistry and material science. The aforementioned drugs have shown effectiveness within the present setting of the related disorders. The exceptional effectiveness of these compounds is attributed to their biological and physiological characteristics, including anti- Properties including anti-inflammatory, antipsychotic, antiarrhythmic, anxiolytic, antifungal, antioxidant, estrogen receptor modulation, antimitotic, antimicrobial, kinase inhibition, and anticancer effects. Therefore, the task of characterising and synthesizing Therapeutic chemists focus on developing and analyzing new structural prototypes with enhanced pharmacological activity, as well as synthesizing and characterising new thiophene moieties with wider therapeutic effectiveness. In addition, thiophene nuclei are present in Numerous commercially accessible pharmaceuticals, include benocyclidine, biotiodin, tiquizium bromides, timepidium bromide, dorzolamide, tioconazole, citizolam, and sertaconazole nitrate. Consequently, it is clear that obtaining up-to-date data is crucial for comprehending the present state of the thiophene nucleus.. medicinal chemistry research[1-2].

1- Singularity and incidence

In 1882, Viktor Meyer established thiophene as a benzene impurity.[3] The combination of isatin, an indole, with sulfuric acid and crude benzene has been observed to yield a resultant blue hue. A long-standing belief was that benzene itself underwent a chemical reaction to produce the blue indophenin. The true agent responsible for this reaction was determined by Viktor Meyer to be thiophene.[4]

Petroleum includes thiophene and its derivatives, occasionally in concentrations ranging from 1 to 3 percent. The hydrodesulfurization (HDS) process eliminates the thiophenic constituent from coal and oil. In hydrodynamic synthesis (HDS), a molybdenum disulfide catalyst is deposited onto a liquid or gaseous feed under hot water pressure. The process of hydrogenolysis of thiophenes results in the production of hydrocarbons and hydr**ogen** sulfide. That is, butane and H2S are derived directly from thiophene. The compounds benzothiophene and dibenzothiophene are prevalent and problematic in the petroleum industry.

2 -Presence of thiophene on Mars

From 2012 to 2017, the rover Curiosity at Gale crater on Mars detected thiophene derivatives in nanomole amounts in Martian soil layers believed to be 3.5 billion years (Formation,Murray, Hills Pahrump).[5] This event represents a crucial milestone in the extensive and challenging quest for organic matters on Mars for the Laboratory Mars Science. The Analysis Sample at Mars instrument was used to subject lacustrine mudstone samples to elevated temperatures ranging from 500° to 820 °C. spectrometry mass - chromatography Gas was employed to analyze the evolved gases, enabling of identification the several thiophene compounds, as well as aromatic and aliphatic molecules.(6)

For along time the C-S bonds found in large moleclar have contributed to their preservation . Approximately 5% of the organic compounds analyzed with the SAM instrument are estimated to contain organic sulfur. While the exact source and method of production of these molecules remain unclear [7], their identification has sparked the fascinating notion that thiophenic compounds may serve as an ancient biosignature on Mars. If forthcoming Martian rovers such as Rosalind Franklin do comprehensive investigations Conducting analysis of carbon isotopes (δ13C) at the trace level is crucial to determine if these organic compounds contain a significant amount of light carbon (12C), which is a defining feature of living microorganisms on Earth.

3- Synthesis and production

In the synthesis of thiophene, Meyer employed acetylene and elemental sulfur, a process that was documented in the same year as his subsequent discovery. In the C4H4S process by Paal-Knorr, C4H4S are conventionally produced via The response of diesters, dicarboxylates, or 1,4-diketones with sulfidizing Reagents like P4S10.

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Likewise, specific these compounds can be produced using the Gewald reaction, Gewald reaction is the Knoevenagel condensation of an activated nitrile with a ketone or aldehyde to produce an acrylonitrile.or by utilizing Reagents such as phosphorus pentasulfide as well as dehydrating agents, Furthermore, there exists cyclization of Volhard-Erdmann process.
C4H4S is manufactured in a relatively small magnitude of approximately Two thousand tons in meters annually globally. Making is the chemical process where a sulfur source, usually CS_2, reacts with a C-4 source, usually C_4H_7OH, in the vapor phase. The reagents contact an oxide catalyst at temperatures ranging from 500 to 550 °C..[9]

4- Stability
Thiophene is classified as aromatic, although theoretical studies indicate that its level compared to benzene, has less aroma. The pairs of electrons on sulfur compounds exhibit a notable degree of delocalization inside the pi electron orbital. Due to its aromatic nature, thiophene lacks the characteristics commonly observed in traditional sulfides. Specifically, the sulfur atom exhibits resistance to both alkylation and oxidation.

5- Thiophene derivatives in figure1.

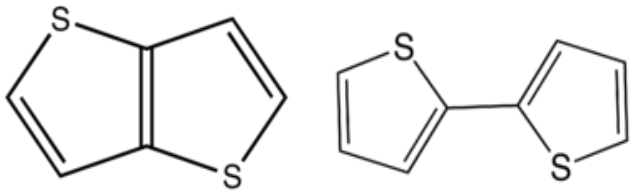

Figure 1.Represent chemical structure of the forms of Thiophene derivatives(Thieno[3,2-*b*] ‹thiophene 2,2'-Bithiophene

6- Biological activity
Given the rapid growth of the global population, health problems are emerging as a significant clinical concern. Hence, it is crucial for scientists to develop and discover innovative medicinal substances, since this may offer the most promising prospects for achievement in the present and future. Nonetheless, pharmacologically active heterocyclic compounds continue to be extensively utilized in therapeutic settings. [10].
Heterocyclic compounds, due to their extensive natural distribution, wide range of synthetic applications, and biological activity, have strongly facilitated medicinal chemists in the organization, planning, and execution of innovative approaches for the advancement of novel drugs[11].
Within the heterogeneous pentagonal rings complex thiophene, a sulphur atom is situated at the location one (Fig. 2). Characterised by the chemical formula C4H4S and the molecular name thiacyclopentadiene, it is considered a structural alert [12]. **in figure**2.

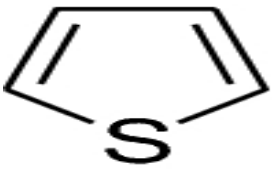

Figure 2. **Represent chemical structure of the** Thiophene

Chemical analysis revealed the presence of thiophene in benzene [13]. Its density is 1.051 grammes per cubic metre, its molecular mass is 84.14 grammes per mole, and its melting point is -38 degrees Celsius. The compound is immiscible in H_2O but readily dissolves in most solvents organic, present ether or alcohol. Because

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their significant delocalization in the π electron system, the "electron pairs" on sulfur display extremely reactive behavior similar to that of a benzene derivative. As with benzene, thiophene and ethanol form an azeotrope. The physicochemical properties of $C_4H_4S$and C_6H_6 exhibit remarkable similarity. For example, boiling point is 84°C. while the boiling point of benzene is 81.1 °C. These boiling points are widely recognized examples of bioisosterism [14]. It shows high susceptibility to nitration, halogenation, sulfonation, and acylation, but not to alkylation.[9]

Thiophene derivatives are versatile heterocycles with remarkable applications in medical chemistry. Across a multitude of disciplines. In medicine, thiophene compounds demonstrate antibacterial, analgesic, anti-inflammatory, antihypertensive, and anticancer properties. Furthermore, they find application in the material science study of light-emitting diode making [20] and serve as inhibitors against metal corrosion [19].

7- The effect of plants

Thiophene-containing compounds are becoming more and more significant in a variety of scientific and technological domains [21]. In numerous facets of material chemistry and engineering, they are being studied because of their numerous functional qualities and chemical adaptability. The based materials were Thiophene found use in optical properties have been used in bioimaging to biological monitor processes including DNA and also in electronics organic, where their semiconductor properties have been used in solar cells and thin field effect transistors

Because of its flexibility, ease of material deposition on substrates large-area, environmentally production friendly, and chemical synthesis's ability to tune electrical properties, organic electronics are predicted to supplant inorganic solid state electronics [22]. Compounds produced from thiophene have been used in many different technologies, including chemo and biosensors [26], lasers [24], light-emitting transistors [23], and electrochromic devices [25].

In medicine, ophene-based molecules continue to be preferred scaffolds [27]. Clopidogrel, for instance, is an antiplatelet agent that is a member of the thienopyridine class [28]. Tiotropium bromide is a used in treatment of obstructive chronic pulmonary disease muscarinic receptor antagonist It has two thiophene rings on it [29]. Rivaroxaban is an anticoagulant that duloxetine is a serotonin- reuptake norepinephrine inhibitor prevents blood clot formation, with a thiophene ring in its structure [30, 31].

The biological features of sulfur-containing compounds, such as their insecticidal, herbicidal and fungicidal action, have been described in relation to their widespread use as plant protection agents [32, 33, 34, 35, 36, 37]. They are frequently employed and applied to the soil. they are absorbed by the shoots and roots of seedlings emerging, or to the foliage of weeds [32, 33, 34, 35, 36, 37].

It has been revealed that heterocyclic derivatives containing sulfur is linked to cancer variety of protein targets. It has been demonstrated that a number of intriguing derivatives of heterocyclics containing sulfur, including phenothiazine, benzothiazole, thiazole, thiophene, and thiazolidinedione, block various signaling pathways linked to cancer. Because of possible binding interactions inside the ATP pocket, significant progress has also been achieved in molecular targeted therapy against particular enzymes, such as kinase receptors. The most promising active anticancer substances are heterocyclic ring metal complexes containing sulfur, such as phenothiazines, benzothiazole, thiazole, and thiophene. However, because they are metabolized to reactive metabolites, sulfur heteroaromatic rings, especially thiophene, are of high structural alarm.

Mere existence of a structural alarm does not inherently establish the toxicity of a chemical. Therefore, this study concentrates on particular discoveries that provide insight into the mechanisms that affect the toxicity. The present research examines the synthetic approaches for including the sulfur core ring into the produced derivatives, along with their structure-activity correlations. The aim is to improve our comprehension of toxicity mechanisms and provide safer treatment alternatives. This review includes sulfur-containing commercialized anticancer medications that guide the synthesis of new compounds and will contribute to the creation of powerful and safer sulfur-based anticancer drugs in the near end.

in the scheme 1.

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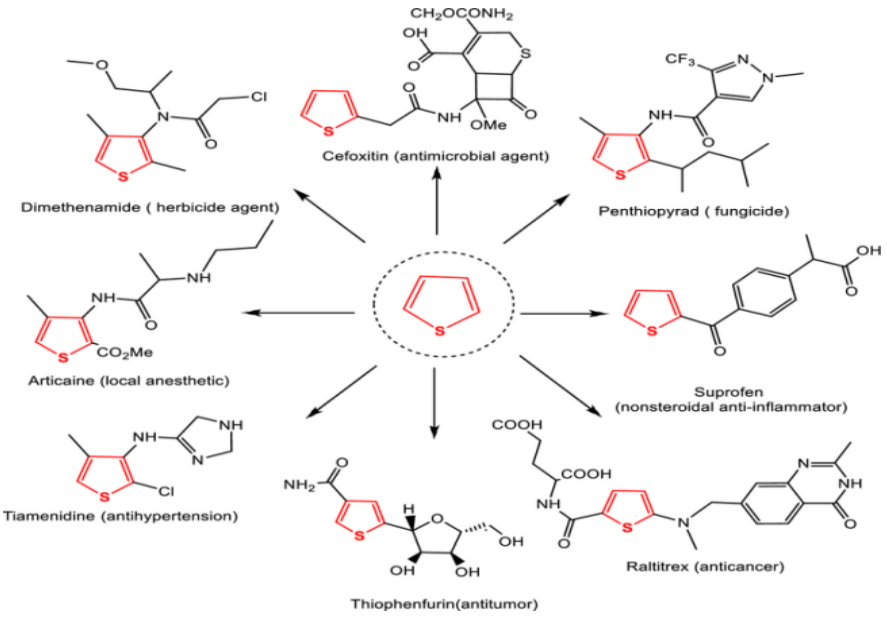

The scheme1.Represent some of the therapeutic drugs of the thiophene compound.

Epilogue

In the literature information and analytical data are available indicate that thiophene and its derivatives constitute a substantial category of chemicals in the pharmaceutical domain with varied therapeutic potentials. These encompass antimalarial, antimicrobial,anticonvulsant,antiviral,anticancer, antihypertensive,anti-inflammatory, antidepressant, antimycobacterial, antidepressant, and antioxidant properties. The assessment of literature suggests that the C4H4S component has garnered considerable interest from medicinal chemists and biochemists to strategize, structure, and execute innovative methods for the discovery of new medications.

This review article confirms that thiophene derivatives have the potential to be a valuable resource for developing new biologically active compounds. It is prudent to investigate this possibility by combining various substituted components, as this may lead to improved pharmacological effects. Hence, it is necessary to persist in the pursuit of investigating numerous other alterations on the thiophene moiety.Tenidap, Zileuton, tinoridine, and tiaprofenic acid are widely recognized commercially available anti-inflammatory drugs comprising a thiophene ring as a pharmacophoric group. Nonsteroidal anti-inflammatory drugs (NSAIDs), designated for pain and inflammation relief, are the initial trio. Tinoridine demonstrates potent antioxidative and radical scavenging properties [40], while both Tiaprofenic acid and Tinoridine inhibit COX enzymes [39, 40]. Zileuton further acts as a LOX inhibitor. [41] **in figure**3.

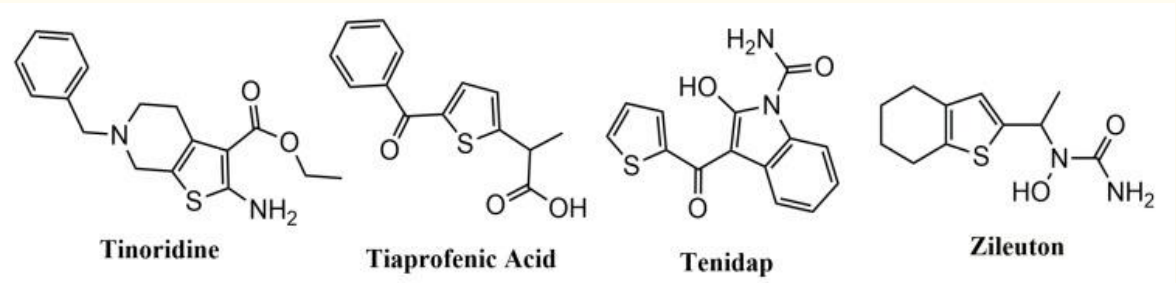

Figure 3. Represent available thiophene - containing chemical formulations for anti-inflammatory drugs (Tinoridine, Tiaprofenic acid, Tenidap, and Zileuton).

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