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Naturally and synthetic Thiophene-Based Compounds with Potential pharmacological and Toxicological response

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ABSTRACT
Natural thiophene and its derivatives are a very important class of heterocyclic compound with potential medicinal chemistry applications.Thiophene is collected from nature and manufactured to meet specific requirement. It has become a crucial anchor for medicinal chemists in the development of combinational tools and the pursuit of lead compound. It has been claimed to have a wide spectrum of therapeutic capabilities with numerous application in medical prospects, industries and academic interest. Thiophene is highly effective chemical in terms of biological and physiological properties. Antihypertensive, analgesic, antibacterial, antifungal, anticancer, biocidal, anti-inflammatory, and antioxidant activities, all are highlighted and documented for thiophenes.

Keywords: Heterocyclic compound, natural and synthetic thiophene, toxicology

I. INTRODUCTION

In the hunt for bioactive metabolites, heterocyclic molecules play an important role. It's worth noting that heterocyclic moiety is included in the chemical skeleton of about 75% of clinically used medications [1]. Chalcogens are the 16 group elements in the periodic table, and sulphur is one of them. In medical chemistry, sulphur is a widespread heteroatom that may link to a variety of elements, including nitrogen, oxygen, carbon, halides, and phosphorus. Several sulfur-based functionalities have emerged as preferred pharmacophores in the development of novel therapeutic candidates [2]. It has the unique property of having a wide range of redox potentials and redox states in live organisms, resulting in a large number of sulphur species involved in many biological processes. By contributing electrons to other organic species, thioethers and thiols can generate sulfonium ions [3].
They can be converted to sulfoxides and sulfones, which have different biological functions. S-adenosylmethionine, for example, mediates the majority of metabolic methylation processes in cell metabolism [4].
Heterocyclic compounds are widely distributed in nature and have a wide range of synthetic applications and biological activity, which has aided medicinal chemists in developing new techniques to drug development [5]. Thiophene derivatives are essential heterocyclics in medical chemistry, with several applications in various fields. Thiophenes are a key component of a major group of heterocyclic mixes that contain a five-membered ring with one sulfur-like heteroatom and C4H4S. Thiophene and its derivatives are found in crude oil. Thiophene is derived from the Greek words theion, which means sulphur, and phaino, which means'shining.'.
Thiophene can be found in a variety of unique objects and is also present in a variety of pharmacologically dynamic mixes. Thiophene subordinates have been well-known in restorative science for their therapeutic benefits. Thiophenes are among the heterocyclic compounds that have piqued researchers' curiosity in recent decades. They are a kind of sulfur-containing molecule made up of one to five thiophene units joined at the -position, with different alkyl groups attached to the terminal ring'-carbon [6]. The dye, pharmaceutical, and agrochemical sectors all benefit from thiophene derivatives [7,8]. S-containing species have a strong electron-withdrawing character, resistance to sulphur reduction, stability against hydrolysis, and preference for two electrons over radical processes, which makes this category of compounds useful to various therapeutic research disciplines [9]. Their varied pharmacological potential makes them the first choice for hybrid approach inclusion.

II. PHYSICAL NATURE OF THIOPHENES

The significant reactivity of thiophenes shortly before sulphonation induces partition of thiophenes from benzene, which is difficult to isolate by refining, due to their comparative limitations at 4°C contrast under direct force [10, 11]. Thiophenes ar

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e a combustible and poisonous sulfur-particleenclosing compound that is insoluble in wat er but soluble in natural solvents like liquor and eth er [12]. At room temperature, thiophenes have seve ral synthetic properties comparable to benzene, suc h as acting as a dismal fluid with a pleasant scent [13-15].

Fig. 1. Carbon Skeleton of Thiophenes and its Derivate.

Thiophene has a melting point of -38°C and a maximum temperature of 84°C. Using a fixed cylinder approach, the basic temperature of Thiophenes was determined to be 579.4K [16,17]. The warmth of burning and the upsides of thermo-chemical bond energies were used to compute reverberation energy of 20 Kcal.mol-1 for thiophenes [18]. Dipole minutes were employed to investigate electron dispersion, substituent influence, and the consistency of atomic orbital predictions in thiophenes [19,20]. The EDs on sulphur are significantly delocalized in the pi-electron framework [21]. Thiophenes, in comparison to furans, have a higher level of adaptability. This is owing to the fact that sulphur has a holding range and can therefore endure prolonged exposure.

III. CHEMICAL NATURE OF THIOPHENES

Thiophenes are an artificially stable, readily available substance, and the science of thiophene and its subordinates has long been a subject of study [22]. It is the simplest delegate of a sulfur-containing sweet-smelling structure. Thiophenes do not undergo the oxidation that sulphides do. Thiophene undergoes electrophile replacement processes such as nitration, sulfonation, Friedel Crafts acylation, halogenation, and so on. Thiophenes can also undergo RTR in addition to the production of coupling diazonium salts. The warmth of ignition causes reverberation adjustment of 22-28Kcal.mol-1, which is less than the 36KCal.mol^{-1} reverberation energy of benzene. Thiophenes are considered aromatic based on these qualities.

Thiophenes have structures similar to pyrrole, in which the nitrogen transports a hydrogen atom and the oxygen or sulphur transports an unshared pair of electrons in a sp2 hybridized orbital. Thiophenes follow the (4n + 2) electron rule and are widely considered aromatic [23]. Its structure is hypothesized to be derived from benzene by replacing two annular CH clusters with sulphur. Thiophenes are an electron-rich heterocyclic because the sulphur molecule in this 5-membered ring acts as an electron-giving heteroatom by supplying two electrons to the sweet-smelling test. Examinations of alterations in the substituent in the pre-incorporated thiophenes structure have received a lot of late attention. Moreover, multiple studies have focused on the use of various thiophene subordinates in a mixture of directly and precisely polyannelated heterocyclic frameworks that were previously unknown. The isosteric replacement of benzene in pharmacologically dynamic professionals has been interesting on occasion [24].

Table 2: Some important TPs Derivates Structure with their chemical name I.

TPs Derivates Structure	Chemical Name
	2-hydroxymethylTPs

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	2-methylTPs
	3-methylTPs
	TPs
	2-chloroTPs
	2-bromoTPs
	2-TPscarboxylic acid

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	3-bromoTPs
	2-acetylTPs
	2-TPscarboxaldehyde
	2-TPscarboxlic acid methyl esters

IV. GENERAL IMPORTANCE OF NATURAL AND SYNTHETIC THIOPHENE

Thiophene derivatives are well-known in medicinal chemistry for their therapeutic uses. Many thiophene derivatives have been produced and are frequently utilised as chemotherapeutic medicines. When it comes to biological activity, fused hetero-aromatic systems are frequently more interesting than monocyclic molecules. Thiophene can be combined with a variety of heterocyclic systems to create new heterocyclic systems with increased biological activity. The thiophene nucleus is an important heterocycle with a wide range of pharmacological properties. Compounds with a thiophene moiety, for example, have a variety of functions. 1-[1, 5- dimethylthiophen- 3- yl] ethyl - The maleate salt of 1-hydroxyurea has anti-inflammatory properties (2,5-dimethylthiophen- 3- yl) - three (5- methyl- 1 H-imidazol- 4- yl) propan -1-one is a kind of serotonin antagonist used to treat Alzheimer's disease.

V. PHARMACEUTICAL IMPORTANCE OF THIOPHENES

In the chemical industry, pharmaceutically relevant substituted thiophenes are used, for example, 2-acetyl thiophenes have been used as crude material for probable fungicides as well as crude material in antidepressant licencing. It is also used as a raw material in the development of possible antiviral and relaxing drugs. [25,26].

2-acetyl-5-methyl thiophenes have been used as a raw material for antihypertensive medications, while 3-acetyl-2, 5-dimethyl thiophenes have also been used as an antecedent for some medications in the patent writing of drug

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companies, such as antibacterial, calming as serotonin foes, and treatment of Alzheimer's disease. Higher alkylated thiophenes have a variety of applications, including 2-hexyl thiophenes as dopamine agonist licences, 2-butyl thiophenes as a raw material in the mix of anticancer drugs, and 2-octyl thiophenes in the mix of anti-atherosclerotic specialists [27,28].

Fig. 3 (2-Hexylthiophene)

Fig. 4 (2-Methylthiophen)

Fig. 5 (2-Butylthiophene)

Fig. 6 (1-(2,5-Dimethyl-3-thienyl)ethanone)

Fig. 7 (2-octylthiophene)

Fig. 8 (1-(2-Thienyl)-ethanone)

In benzene, thiophenes were discovered as an impurity [29-32]. Thiophene has a subatomic weight of 84.14 gmol-1, a width of 1.051 gml-1, and a melting point of 38°C. It dissolves in most natural solvents, including liquor and ether, but not water. Sulfur's electron sets are basically delocalized in the -electron framework and continue to be remarkably responsive, much like benzene. The arrangement of thiophenes is similar to that of an azeotrope, with ethanol resembling benzene. In benzene and thiophenes, the physiochemical properties are very similar. Under 760 mmHg, the boiling point of benzene is 81.1 °C, and the boiling point of thiophenes is 84.4 °C, therefore both are significant examples of biochemistry [33,34]. It very well may be effectively halogenated, acylated, nitrated yet can't be alkylated and oxidized. In restorative science,

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thiophenes subsidiaries are vital heterocyclic compounds showing striking applications in various orders.

Anti-inflammatory characteristics are known for thiophene-based compounds, such as the commercial medications Tinoridine and Tiaprofenic acid. Heterocyclic compounds have long been a key component in the hunt for bioactive chemicals. More than 75% of medications now in clinical use have at least one heterocyclic ring in their chemical structure [35]. Thiophene and its substituted derivatives, which are all heterocyclic compounds, have piqued our interest for nearly a decade. Thiophene derivatives are important intermediaries in a variety of scientific and industrial fields, with a wide range of uses and medicinal qualities. Thiophene compounds are of tremendous interest to academics as well as the agrochemical, pharmaceutical, and dye industries [36-38]. Thiophene compounds have exceptional biological and pharmacological capabilities as antipsychotic, antianxiety, antifungal, antibacterial, antioxidant, anticancer, and anti-inflammatory medicines [39,40]. A thiophene moiety is found in many medications, including Tioconazol, Dorzolamide, Tipepidine, Ticlopidine, Clopidogrel, Pasugrel, Citizolam, Timepidium, and Tiquizium Bromide. Different therapeutic implications of benzo[b]thiophene-based compounds were assessed [38]. The antioxidant and anti-inflammatory properties of ethyl 2-(2-cyano-3-(substituted phenyl)acrylamido)-4,5-dimethylthiophene-3-carboxylates were investigated [41].

VI. ANTIMICROBIAL ACTIVITY

Antimicrobial properties Antimicrobial activity of thiophene derivatives against diverse microbial illnesses is high. Different scientists took different ways to prove thiophene as an antibacterial agent, which led to the identification of the most active thiophene derivatives in the current scenario [42]. Microbes are responsible for a variety of diseases, including pneumonia, amoebiasis, typhoid, malaria, common cough and cold infections, as well as more serious diseases such as tuberculosis, influenza, syphilis, and AIDS. From the discovery of the molecule to the current day, several methodologies have been used to investigate the role of the thiophene moiety as an antibacterial agent.

Many antibacterial therapeutic drugs containing the thiophene moiety have been created. Some novel 2,3-disubstituted-4, 5, 6, 7-tetrahydrobenzo(b) thiophenes: production and biological activities [43]. Many of these substances have antimicrobial and local anesthetic properties. Some 2'-substituted amino (2-methyl oxadiazol-5-yl)-4,5,6,7-tetrahydro benzo [b] thiophenes were synthesized and tested for antibacterial and antifungal activities [44]. They made 2-substituted (1, 3, 4) thiadiazole (2, 3-b) tetrahydrobenzothieno[3,2-e] pyrimidines and tested them for anticancer, antibacterial, and antifungal properties [45]. 10 methoxy-4,8-dinitro-6H benzothieno [2,3-c] chromen-6-ones were produced and evaluated for antibacterial activity. The thiophene moiety is a powerful fighter against practically all microorganisms [42].

Benzo[b]thiophene could be an interesting and promising pharmacophore to investigate due to its various biological activities and drug-like features. These core structures can be found in natural organic molecules and are also present in a number of medicinal molecules. The biological activities of benzo[b]thiophene compounds are diverse. Histamine H3 antagonists are benzo[b]thiophene compounds. Benzo[b]thiophene derivatives' antimicrobial activity appears to be more dependent on heterocyclic thiophene substitution [18]. Significant antimicrobial activity was found in 2-aminothiophene containing 4-hydroxy benzaldehyde. Because of the presence of 4-hydroxy benzaldehyde at the second position, the molecule outperformed all other 2-aminothiophene derivatives in terms of antimicrobial activity. Sulphur is used to make thieno[3,2-b]pyridine-2-one derivatives. The in vitro antibacterial activity of the synthesised thienopyridines derivatives against gram positive and gram negative pathogens was assessed using a paper disc diffusion assay method and compared to amoxicillin (30 g/ disc) as a reference antibiotic. The compounds had a high level of biological activity.

The fungicidal ability of thiophene isolated from n-hexane extract of Porophyllum obscurum was tested using broth micro dilution against C. albicans ATCC-10231 and 25 clinical strains of Candida spp. isolates as causal agents of oropharyngeal candidiasis. They were effective against fungus at low fungicidal concentrations [38,43].

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VII. ANTI-INFLAMMATORY ACTIVITY

Thiophene has a high pharmacological effectiveness, hence anti-inflammatory activity of the thiophene nucleus has been the subject of extensive research. Tinoridine, tiaprofenic acid, tenoxicam, and suproprofen are examples of well-defined anti-inflammatory therapeutic drugs with thiophene moiety. The researchers synthesised and tested various 2-substituted amino-3- (N-ptolylcarboxamido) 4, 5- dimethylthiophenes for analgesic and anti-inflammatory properties [44]. The anti-inflammatory and analgesic effectiveness of some newly synthesised thieno [2,3-d]pyrimidine and pyrimidopyrazolo thienopyrimidine derivatives was investigated [45]. Pyrimidines and thienopyrimidines were synthesised and screened for analgesic and anti-inflammatory action, and certain substituted thienopyrimidines-4-one were produced and screened for analgesic and anti-inflammatory activity [46].

VIII. ANTIHYPERTENSIVE AND ANALGESIC ACTIVITY

Many antihypertensive medicines containing thiophene rings, such as wise Tiamenidine and ticrynafen, have been established as well-defined therapeutic agents with antihypertensive efficacy. Similarly, the synthesis and preliminary pharmacological study of thiophene analogues of the antipyretic and analgesic agent athenzamide were evaluated based on the newly synthesised 2-substituted– amino – 3 – (N - o -tolylcarboxamido)– 4, 5- dimethyl thiophenes that exhibit analgesic and anti-inflammatory response. Benzothiazole [47] is a chemical with a wide range of biological functions. Antimicrobial assessment of tetrahydroquinazoline compounds produced and described [48,49]. The potential analgesic action of heterocycles generated from thienylchalcones has been investigated [50, 51].

IX. BIOCIDE PROPERTIES

Thiophenes are photo-activated poisons that kill worms, insects, fungus, and bacteria. The thiophene generated in T. patula's hairy roots had a larvicidal impact on mosquito larvae. As a result, it was clear that organization is required for thiophene synthesis. Plant secondary metabolites and derivatives have been studied as possible alternatives to synthetic fungicides, which are persistent and less environmentally friendly [52,53]. Although many phytochemicals are known to have insect-controlling characteristics, only a few are known to have antifungal properties. Although many phytochemicals are known to have insect-controlling characteristics, only a few are known to have antifungal properties. Because of the problem of environmental pollution caused by the usage of persistent pesticides, natural insecticides are becoming more popular. The marigold (Asteraceae) family is a widely distributed plant that is well known for a variety of biological features. The herb has been linked to anti-cancer and anti-aging properties [54,55].

IX. ANTICANCER ACTIVITY

Cancer is one of the world's most difficult health concerns, and it has become a major contributor to the world's rising mortality rate. Chemotherapy and radiotherapy, which are currently accessible treatments, can only provide transient therapeutic effects and are limited by a narrow therapeutic index, significant toxicity, and acquired resistance in most types of cancer [56]. However, anticancer drug research has made significant progress over the last several decades, curing a large number of patients. Due to the complicated physiological changes in cell functioning, metastasis, and apoptotic pathways, it remains a frontier of research.

Because of the availability of numerous cell lines and screening technologies, many substances have been tested for anticancer activity in recent years. Most scientists have synthesized and examined new thiophene derivatives with physiologically active sulfonamide, isoxazole, benzothiazole, quinoline, and anthracene moieties for anticancer activity [57,58]. The antitumor activity of the synthesized compounds was tested in vitro against a human breast cancer cell line. Thiophene presented as a simple synthesis technique for the production of novel thiophenes using benzothiophene derivatives. Different tumor cell lines were used to test in vitro cytotoxicity [59].

Thiophene toxicity and anticancer activity in thiophene-acridine hybrid compounds [60]. Polyfunctionally substituted heterocyclic compounds obtained from 2-cyano-N-(3-cyano-4,5,6,7-tetrahydrobenzo[b] thiophen-2-yl)-acetamide [61] were synthesised and tested for anticancer activity. 2-Chloro-3-(5-aryl-4,5-dihydroisoxazol-3-yl)quinolines were studied for photo-induced DNA cleavage [62].

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X. ANTIOXIDANT ACTIVITIES

By cyanoacetylating substituted 2-aminothiophene with an effective cyanoacetylating agent, 1-cyanoacetyl-3,5-dimethylpyrazole, a novel class of substituted 2-(2-cyanoacetamido)thiophenes was developed. At a concentration of 100 M, all of the produced compounds were tested for in vitro antioxidant activity by scavenging 1,1-diphenyl-2-picrylhydrazyl (DPPH) and nitric oxide free radicals. The anti-oxidant activity of 2-(2-cyanoacetamido)-4,5-imethylthiophene- 3-carboxamide was shown to be the highest in both models of free radical scavenging [41].

XI. CONCLUSION

Natural metabolites containing sulphur are a diverse group of important functional compounds with diverse biological and pharmacological properties; some have even been developed into critical medications. According to the published literature, thiophene and its derivatives are a significant class of pharmaceutical chemicals with a variety of therapeutic applications. The thiophene moiety has piqued the interest of medicinal chemists and biochemists to plan, organize, and implement innovative approaches to the discovery of novel medications, according to a review of literature reports.

This review article established that thiophene derivatives could be a rich source of potential entities in the search for new generation of biologically active compounds, and that it would be worthwhile to investigate the possibility in this area by fusing different substituted moieties, which could lead to improved pharmacological activities. As a result, the search for many additional thiophene moiety changes must continue. More formulation development research is needed to improve stability and efficacy.

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