

Recent Advances in Pharmacological Activities of thiophene Derivatives

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Abstract

Thiophene is a five-membered heterocyclic aromatic compound which containing sulfur atoms possessing remarkable pharmacological activities and structural versatility. Thiophene derivatives have gained important pharmacophore in drug discovery. Review also overview the important synthesis approaches for thiophene scaffold including Paal-knorr, Gewald, hinsberg, and Fiesselmann Synthesis. There have been numerous recent studies regarding the application of thiophene analogs for treatment and prevention of various pathological conditions. Pharmacological activities of thiophene derivatives including anti-inflammatory, anticancer, antiviral, antioxidant and neuroprotective properties are discussed. These activities are mainly based on the interaction of these compounds with biologically relevant targets and improving their pharmacokinetic profile due to rational modification. In particular, more attention is paid to those biologically effective thiophene-containing compounds that play an important role in clinical practice, including Zileuton and Tioconazole, as well as their novel derivatives with pronounced biological activity. The current review is focused on the advances in the pharmacological activities of thiophene derivatives described between 2018 and 2026. On the whole, thiophene derivatives still remain one of the significant classes of heterocycles with considerable pharmaceutical applications and future perspectives.

Key words- Thiophene derivatives, Heterocyclic compounds, Pharmacological Activities, Anti-microbial activity, Anti-inflammatory activity, anticancer activity, Paal-knorr, Gewald, hinsberg, Synthesis, Synthetic modification.

I. Introduction -:

The origin of thiophene comes from the Greek word “phaino,” which means shining. Thiophenes exist naturally within hydrocarbons like coal or petroleum. Thiophenes are stable liquids that resemble the benzene compounds, especially concerning their boiling point. (1). Thiophene is the heterocyclic compound having sulfur in it with a structure similar to furan, but instead of oxygen atom, thiophene consists of sulfur atom (2). Extensive biological and pharmaceutical importance of thiophene and its derivatives can be attributed to various biological applications (3). Thiophene was detected by Viktor Meyer to be a contaminant in benzene in the year 1882. On mixing isatin (a substance obtained from indoles) with sulfuric acid and benzene, the result was the formation of blue dye. The long held notion was that benzene reacts chemically to give the blue colored indophenin dye. However, Meyer found out that thiophene was the active substance. (4). Thiophene (Figure 1) is a heterocyclic compound having chemical formula C₄H₄S and a five-membered ring structure (5). Thiophene was isolated as an impurity from benzene. Its molecular weight is 84.14 g/mol and its density is 1.051g/mL and melting point is -38°C. It dissolves well in majority of organic solvents such as alcohol and ether. (6).

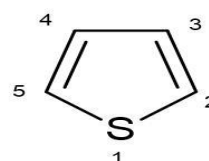


Figure 1. Thiophene

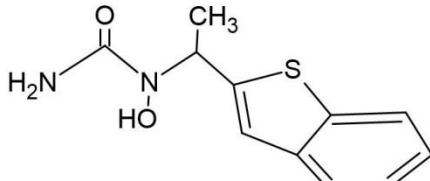
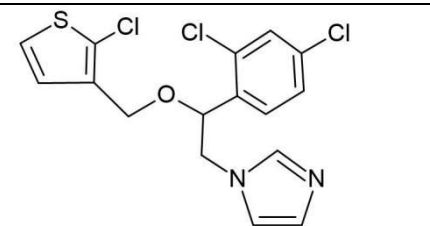
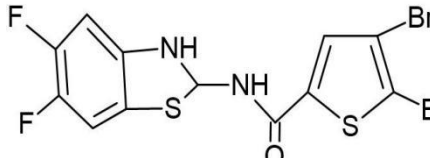
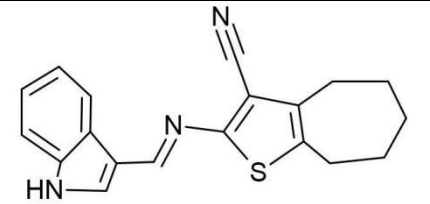
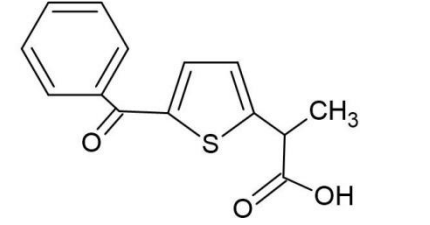
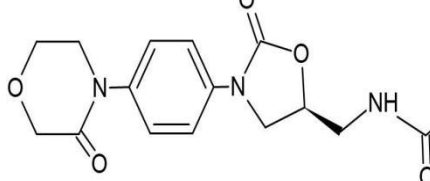
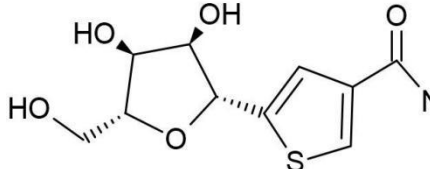
Chemical formula	C ₄ H ₄ S
Molecular weight	84.14g/mol
Appearance	Colourless liquid
Density	1.051g/ml
Melting point	-38°C
Boiling point	84°C

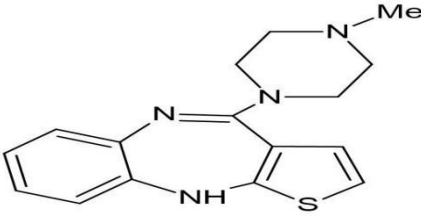
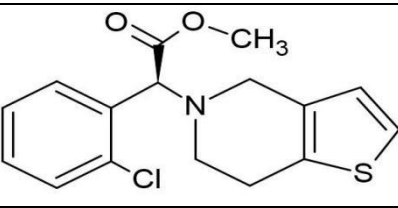
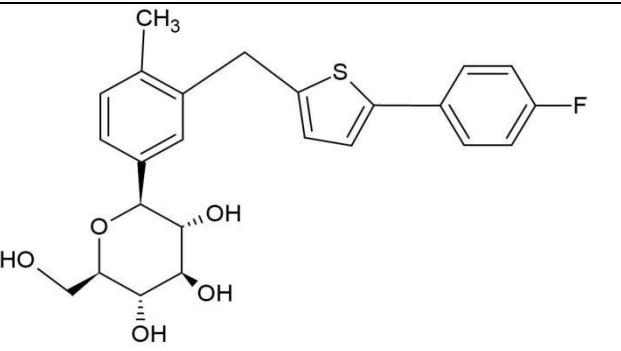
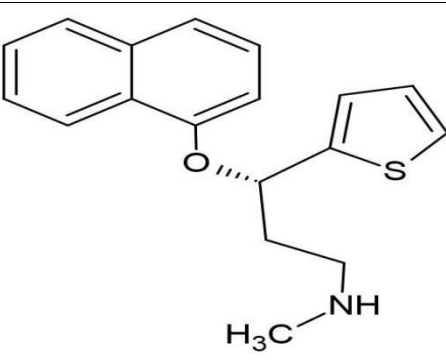
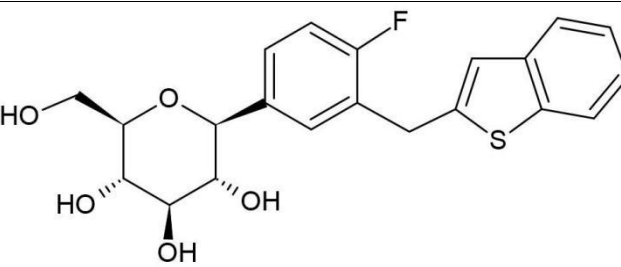
Thiophenes are some of the heterocycles whose study has been a priority for research attention for many years. Thiophenes are heterocycles that contain sulfur. They are made up of thiophene rings ranging from one to five rings connected to each other through their α position (7). The sulfur atom forms part of chalcogens that are the Group 16 elements on the periodic table. Sulfur is one of the most common heteroatoms in medicinal chemistry. (8). The thiophene moiety plays a major role in drug discovery and medicinal chemistry due to its versatile structural diversity and pharmacophoric properties. The thiophene ring provides synthetically accessible modification sites within itself and also considered an important pharmacophore capable of replacing various functionalities in a drug candidate, thus serving as an important structural element in the medicinal chemist's toolbox. Moreover, the sulphur atom within the thiophene ring enhances drug-receptor interactions by participating in additional hydrogen bonding (9) The term "wonder heterocycle" is attributed to thiophene because of its extensive applications in biology like anticancer, antimicrobial, antiinflammatory, antidepressant, analgesic, and anticonvulsant properties (10). There is a handful of research articles available on the pharmaceutical effects of thiophenes in general. However, for this particular research work, we have segregated our research into two distinct types in

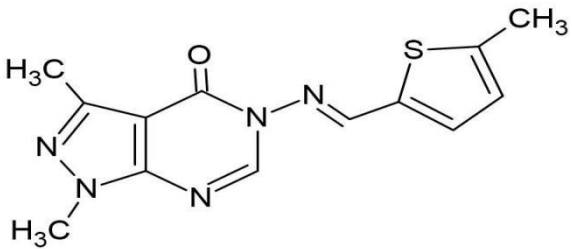
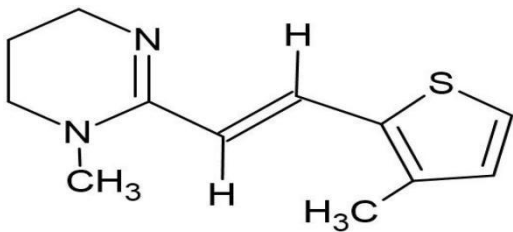
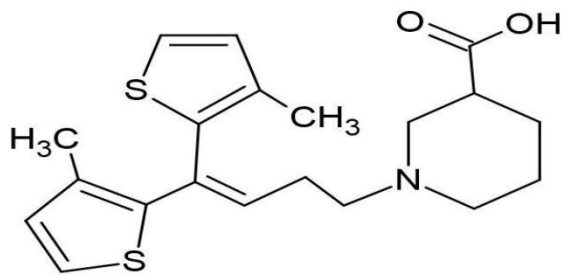
order to distinguish ourselves from other researchers. The first type entails the preparation of thiophene derivatives by adopting the conventional methods of synthesis, which is called conventional drug discovery approach. On the contrary, the second type includes computational methodologies such as structural bioinformatics, high throughput virtual screening, molecular dynamics, and machine learning (11). The geometric structure of thiophene and its electronic properties make up the basis for the chemical modifications carried out on the compound. Halogenations are among the most widely applied techniques of modifying thiophene compounds. The process generates halogenated products, which serve as intermediaries in producing various thiophene derivatives (12). The heterocyclic compounds have a significant contribution to the discovery of bioactive substances. From practical experience, it has been found that about 75% of the drugs being used clinically contain at least one heterocyclic ring. Thiophene along with its substituted analogs, which are heterocyclic compounds, have been our prime concern for nearly two decades now(13). The review also discusses the literature concerning thiophene and the derivatives with different biological activities such as antidiabetic, anticancer, anti-inflammatory, anticonvulsant, and antioxidant properties. Moreover, an article highlights the significance of structural bioinformatics with regard to the process of drug discovery. Further, the manuscript analyzes the relationship between the structures and activities of compounds and determines the chemical groups that trigger the medicinal activities of compounds. The review might offer invaluable information for researchers conducting research on thiophene nuclei to develop more effective analogs (11).

Pharmacologically Active Thiophene-Based Compounds-

Sr.No.	Compounds Name	Structure	Pharmacological Activity
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1.	Zileuton(9)		Anti-inflammatory
2.	Tioconazole(14)		Anti-fungal
3.	3,5-dibromo-N-(5,6difluorobenzo[d]thiazol-2-yl)thiophene-2-carboxamide (15)		Anti-viral
4.	2-[[1H-Indol-3ylmethylene)-amino]5,6,7,8-tetrahydro-4H[cyclohepta][b]thiophene-3carboritnle (16)		Anti-cancer
5.	Taiprofenic Acid (9)		Anti-inflammatory
6.	Rivaroxaban(17)		Anti-coagulant
7.	Tthiophenfurin(18)		Anti-tumor

8.	Olanzapine(19)		Anti-psychotic
9.	Clopidogrel(20)		Anti-platelets
10.	Canagliflozin(21)		Anti-diabetic
11.	Duloxetine(22)		Anti-depressant
12.	Ipragliflozin(23)		Anti-diabetic

13.	5-[(5-Methylthiophen-2yl)methyleneamino]-1,3-dimethyl-1,5-dihydro-4Hpyrazolo[3,4-d]pyrimidin-4one(24)		Anti-viral
14.	Morantel (25)		Anthelmintic
15.	Taigabine (26)		Anti-convulsant

Behaviour of thiophene derivatives-

Thiophene derivatives have received much attention owing to their wide range of applications in different sectors. Thiophene derivatives have been found to exhibit various biological activities such as antimicrobial, anti-inflammatory, anticonvulsant, antifungal, and anticancer effects (27). The thiophene nucleus is found in several commercially available medicinal compounds such as benocyclidine, biotiodin, tiquizium bromides, timepidium bromide, dorzolamide, tioconazole, citizolam, and sertoconazole nitrate. It is therefore evident that up to date information is key to understanding the current situation of the thiophene nucleus(4).

A. Physical behaviour of thiophene –

Thiophene is a room-temperature liquid that is a 5-membered sulfur-containing heterocyclic compound (C₄H₄S, Fig. 1) where the aromaticity arises from two C=C bonds and one sulfur lone pair,

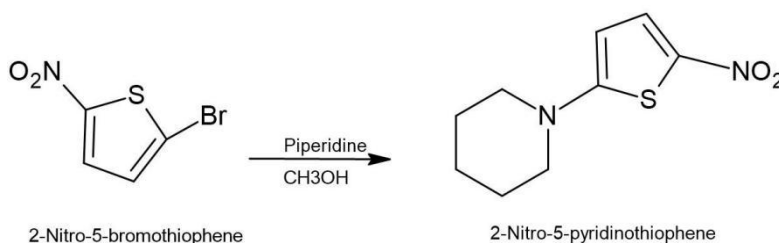
while the other lone pair is directed outwards, planar to the ring (28). A quasi fivefold rotational symmetry axis is observed orthogonal to the molecular plane. Dielectric spectroscopy was also used to confirm that the orientational disorder of the C₄H₄S crystals could indeed be achieved. The low-temperature regime of the heterocyclic aromatic molecular crystal of thiophene may exhibit distinct orientational glasses, where a disorder/order state may be manipulated by replacing protons with deuterons (29). Moreover, the presence of considerable conjugation of π -electrons in thiophene building blocks leads to decrease in the energy band gap, which makes the charge carriers move faster, making it significant for semiconducting material applications and photo switchable systems too(30).

Moreover, fusion enthalpies and melting points for 3-acetylthiophene and 2,2'-di-thiophene have been determined using differential scanning calorimetry. Solution enthalpies in benzene of the derivatives of thiophenes have been utilized to

determine their vaporization and sublimation enthalpies at 298.15K (31). The “electron pairs” in the sulfur atom have been shown to be delocalized in the π electrons system and very reactive in nature like a benzene derivative. Thiophene exists as an azeotropic mixture with ethanol similar to benzene. The similarities between the physicochemical behavior of benzene and thiophene are striking. For instance, the boiling point of benzene and thiophene at 760mmHg is 81.1°C and 84.4°C respectively. Both are a famous case of bioisosterism. Thiophene is readily sulfonated, nitrated, halogenated, and acylated but not alkylated and oxidized (6). The heat of combustion suggests resonance stabilization in a degree of (22-28 K. Cal/mol), lower than the resonance energy of benzene (36 K. Cal./mol.). Thiophene is a colorless liquid at room temperature. Azo dye derivatives may include azo pigment, which is insoluble in water and other solvents. Azo dyes are solids; the majority are salts. Arylazo compounds have strong colors, usually red, orange, or yellow due to a result of π -delocalization. Methyl orange can serve as an acid-base indicator. The colored species is mostly an anion, but there exist some azo dyes that can be cations as well. Anionic dyes are formed because of having 1-3 sulphonic acid groups, which are completely dissociated at the pH of the dyed material:

a. Reactions with Nucleophilic reagents

Nucleophilic relocations occur much faster, by a factor of at least one hundred, than benzenoid substitution reactions. The reason for this is the sulfur atom's ability to participate in charge localization (36).



b. Reactions with electrophilic reagents

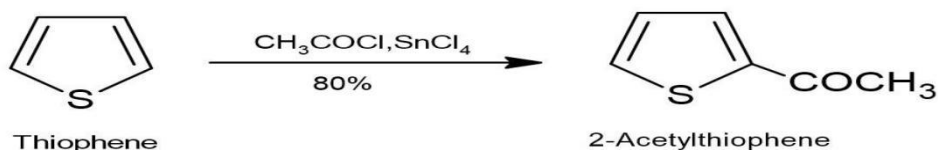
• Acylation –

Thiophenes usually provide a satisfactory yield during the reaction with Friedel-Crafts acylation under carefully controlled conditions. One of the best methods is anhydride acylation using phosphoric acid (Hartough and Kosak 1947) (37).



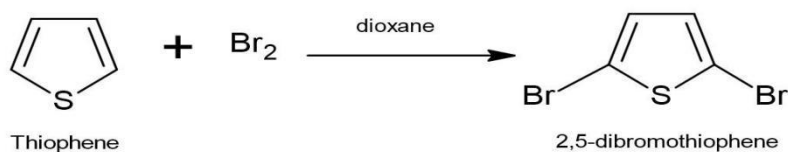
B. Chemical behaviour of thiophene –

The compound is soluble in organic solvents like ether and alcohol, but it does not dissolve in water to form azeotropic mixtures in organic solvents like ethanol. The traditional process of synthesizing thiophene used reactions such as the Paal-Knorr and Gewald reactions, which had some drawbacks including harsh laboratory conditions and inability to produce effective results using certain functional groups (32). This review provides an analysis of the structural characteristics of thiophene, which contains four carbon atoms and one sulfur atom, along with its relevance to medicinal chemistry. Thiophene analogs show great efficiency against microorganisms and form important constituents in several medicinal compounds (33). However, the common routes adopted for the synthesis of these compounds are through Lewis acid-catalyzed, halogen-catalyzed, transition metal-catalyzed, base-catalyzed, electrophilic, and acid-catalyzed ring formation reactions (34). It includes a range of techniques such as condensation reactions, acylation, suffocation, Nitrate, halogenation. Complex derivatives with enhanced pharmacokinetics and greater biological effects have been achieved due to advancements in these synthetic processes (35).

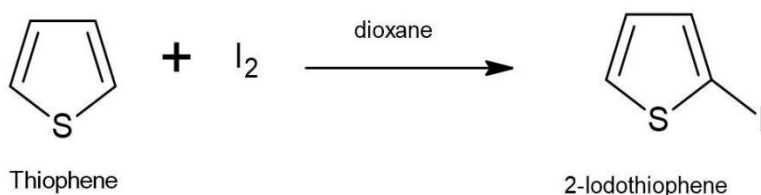


• Halogenation –

Reaction of thiophene with halogens [X₂ (X₂ = Cl₂, Br₂, and I₂)] yields 2halothiophene. In this connection, the reaction of bromine with Thiophene in the absence of any halogen carrier leads to the formation of 2,5-dibromothiophene.

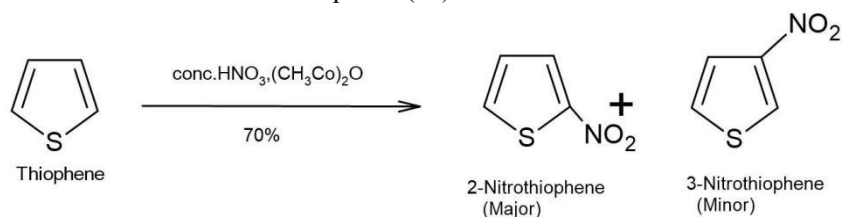


On the other hand, iodination of thiophene in the presence of yellow mercuric oxide yields 2-iodothiophene (38).



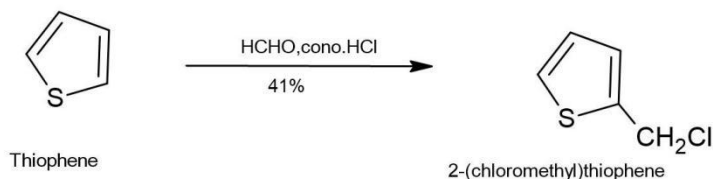
• Nitration-

Since nitrous acid can lead to an explosion, the nitration of thiophene must not involve it. Either acetyl nitrate or nitronium tetrafluoroborate is applied to avoid such an outcome. The amount of the 3-nitro isomer is approximately 10% in the dominant 2-nitro compound (36).



• Condensation with aldehyde and ketones –

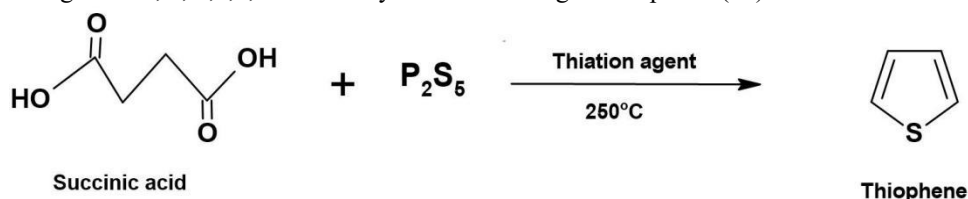
Even though chloroalkylation reactions can be carried out, hydroxyalkylthiophenes tend to be unstable in such conditions (Wiberg and McShane 2003). One has to exercise caution in choosing conditions since there exists the risk of either formation of 2,5-bis(chloromethyl)thiophene (Griffing and Salisbury 1948) or di-2thienylmethanes (Blicke and Burckhalter 1942) (37).



Synthesis of Thiophene:-

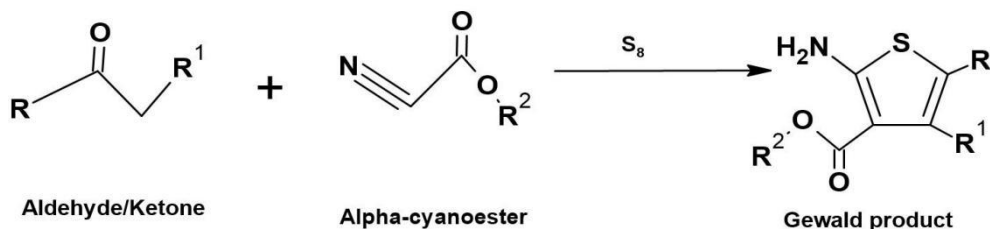
• Paal - Knorr Synthesis-

The reaction of dicarbonyl compounds with phosphorus pentasulphide (P₂S₅) was considered as a principal route to synthesize thiophenes. Succinic acid could be reacted with P₂S₅ in presence of thiation agents such as Lawesson's reagent or 1, 1, 1,3,3,3 hexamethyldisilathiane to give thiophene (39).



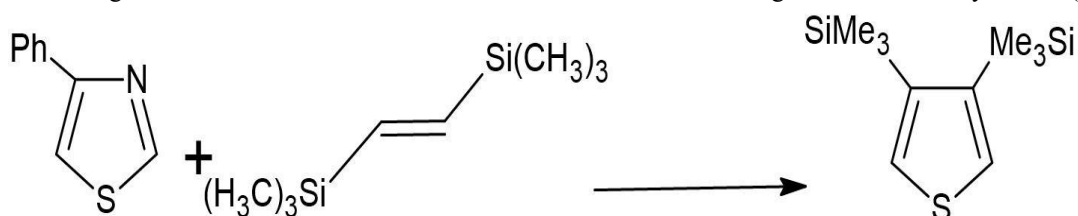
• **Gewald Synthesis-**

The Gewald reaction is a very useful and versatile method for condensation. In the Gewald reaction, aliphatic aldehydes, ketones, or β-dicarbonyl compounds condensed with active nitrile and elemental Sulphur to generate highly substituted thiophene rings. In this thiophene ring, the alkyl and/or aryl group remains in the 4- and 5 positions, an electron-withdrawing substituent in the 3-position, amino group at the 2 position (40).



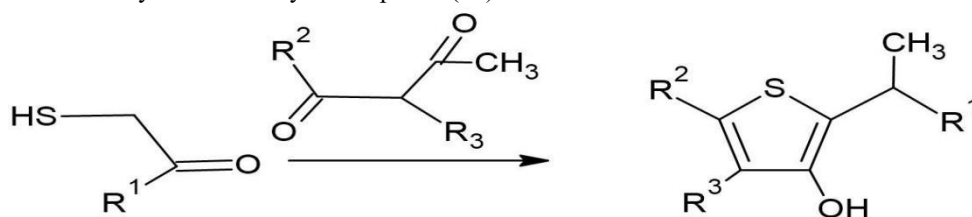
• **Hinsberg Synthesis –**

Firstly, the interaction of benzil with diethyl thiodiacetate was carried out according to Hinsberg in order to form the thiophene system. This process was mainly carried out with Claisen-type conditions, and preferably involved treating the alcoholic alkaline solution with dilute water until forming the free dicarboxylic acid (41).



• **Fiesselmann Thiophene Synthesis-**

Synthesis Condensation reaction of thioglycolic acid with α, β- acetylenic esters, which upon treatment with base result in the formation of 3-hydroxyl-2thiophenecarboxylic acid. Fiesselmann Thiophene Synthesis is an extension of Woodward condensation of thioglycolic acid and α, β-unsaturated ester in the presence of base to produce 2carbomethoxy-3-ketotetrahydrothiophene (42).



Pharmacological activities of thiophene derivatives-

1. Anti-inflammatory -:

The production of AA and DHA results from activation of phospholipase A2 and

cyclooxygenases by cytokines/chemokines and their conversion to eicosanoids (prostaglandins, leukotrienes, and thromboxanes) that lead to neuroinflammation in the brain. Similarly, the resolvins and neuroprotectins are the metabolic products of DHA that inhibit the generation of eicosanoids. Moreover, one of the oxidation products of AA, lipoxin, is generated via 5-lipoxygenase (5-LOX) pathway and is responsible for mediating the resolution of inflammation and its anti-inflammatory effects (43). Many thiophene derivatives have also emerged as potent inhibitors of the aforementioned enzymes.

The drugs Tinoridine, Tiaprofenic acid, Tenidap, and Zileuton have gained worldwide fame among those drugs having the property of being effective in suppressing inflammatory responses with thiophene moiety as the core structure. All three Tinoridine, Tiaprofenic acid, and Tenidap belong to nonsteroidal anti-inflammatory drugs (NSAIDs) and are used to treat pain and inflammation, where the former two block the action of COX enzymes, whereas Tinoridine shows antiperoxidative and scavenging properties. Zileuton is a LOX inhibitor (44)

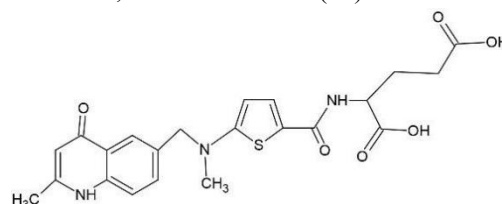
Zileuton

2. Anti-cancer

In the field of cancer therapy against different cancer cells, the structure-activity relationship for each of the derivatives showed an excellent understanding of thiophene moiety (45). Fused thiophene derivatives, such as thienopyrimidines, have demonstrated efficacy as anticancer agents. They contain the pyrimidine moiety found in the natural nucleobase adenine, which occurs in DNA, RNA, ATP, and many bioactive molecules (46). Certain thiophene derivatives showcased notable antiproliferative properties against HeLa and PANC-1 cell lines, often equating or surpassing the effectiveness of the standard drug, doxorubicin (Dox). Furthermore, approximately 70% of pharmaceuticals and agrochemical products incorporate a heterocyclic fragment, exemplified by sertaconazole, an imidazole antifungal agent, which features a thiophene ring system (47). Based on the promising anticancer activities of various tetrahydrobenzo[b]thiophene derivatives and as a continuation to our recent investigations to develop new anti-CRC agents, herein, we aim to describe the synthesis and characterization of a new series of

Tiaprofenic Acid

4,5,6,7-tetrahydrobenzo[b]thiophene-based carbamates, amides, acetamides, a cyclic imide, a formamidine, and a Schiff base (48).

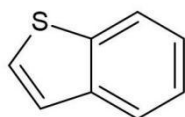


Raltitrexed

3. Anti-diabetic :-

On the other hand, various pharmacological substances have been synthesized to manage patients suffering from diabetes. Recent reports have shown that there are some pharmaceuticals which exhibit anti-inflammatory activities regardless of their effects on blood glucose level. This phenomenon led scientists and specifically chemists to develop drugs which not only exhibit anti-diabetic activities, but also act as anti-inflammatories with better toxicity profiles (49). Diabetes is a disease associated with constant hyperglycemia that affects around one hundred million patients worldwide. For the treatment of

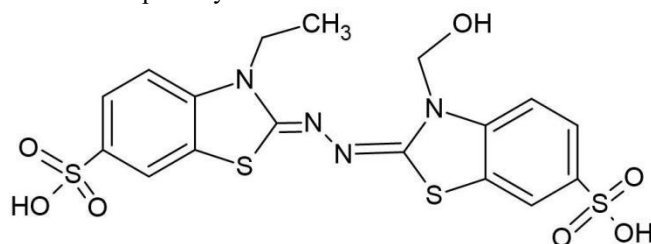
diabetes, new synthetic benzothiophenebased thiadiazole derivatives (1-17) were synthesized to evaluate their efficacy as potential inhibitors of diabetic enzymes (α -amylase and α -glucosidase) (50). Benzo[b]thiophene is reported to be an important moiety for the development of pharmacological substances against multiple biological targets. Benzo[b]thiophenebased SGLT2 and ALR2 inhibitors have been successfully developed recently for antidiabetic drug discovery but their potential as inhibitors of α -amylase remained unknown until now. Hence, a series of novel small molecules of benzo[b]thiophene-2-carboxylic acid derivatives (3a-p) were synthesized and evaluated (51).



Benzo[b]thiophene

4. Anti viral :-

Indeed, many of the human diseases that are most damaging are due to viruses, including smallpox, yellow fever, poliomyelitis, influenza, measles, and AIDS (acquired immunodeficiency syndrome). These infections result in diseases which affect all body organs like the lungs, liver, central nervous system, and intestine. Viruses account for about 20% of the cancers that affect people, and infections that cause disease of the respiratory and

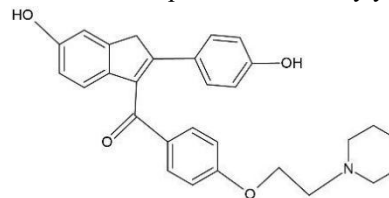


2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)

Recent Advances of thiophene derivatives (2018-2026)

S.n o.	Year	Compound derivatives	Activity	References
1.	2018	Thiophene Schiff bases	Anti-microbial	(6)
2.	2019	Bioactive-thiophene derivatives	Anti -oxidant	(3)
2.	2020	Benzothiophene derivatives	Anti-cancer	(10)
3.	2021	Thiophene Anti-inflammatory Compound	Antiinflammatory	(44)

gastrointestinal systems cause deaths among millions of children in poor nations every year (52).



Raloxifene

5. Anti oxidants :-

The antioxidant characteristics of the compounds were investigated using DPPH, TEAC, Phosphomolybdenum, and FRAP assays (53). The area of Free Radical Chemistry has become highly popular within the present-day scenario. The creation of free radicals can be attributed to various physiochemical aspects, radiation, illnesses, pollution in the environment, and as a result of metabolites of drugs. The quantity of free radicals is tightly regulated under physiological conditions due to the presence of physiological antioxidants. The excess of free radicals can lead to oxidative stress in proteins, lipids, carbohydrates, and DNA (54). The antioxidant abilities of novel thiophene derivatives were measured through the ABTS test.³⁷ The ABTS assay (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)) is frequently used to determine the total antioxidant potential of tissue, bodily fluids, cells, natural, and artificial structures (55).

4.	2021	Thienopyrimidine derivatives	Anti-fungal	(56)
5.	2023	Therapeutic thiophene derivatives	Anti-viral	(57)
6.	2025	Thiophene-based druggable leads	Anti-diabetic	(11)
7.	2025	Thienopyrimidine-Therapeutic exploration	Anti-cancer & Anti-viral	(58)
8.	2026	Noval thiophene analogs	Multifunctional Pharmacological activity	(59)

II. Conclusion

Recent studies prove that derivatization of structures is give most efficient methods of developing effect medicines. Current literature clearly shows that the importance of thiophenes is not yet exhausted and that they still remain a very interesting area of investigation because of the wide variety of pharmacological properties possessed by these compounds. The electron-rich thiophene moiety is responsible for the ability of such compounds to interact with various biological targets, which makes it possible to create highly active and selective compounds. In particular, there have been many notable achievements in the field of antimicrobial, anti-inflammatory, anticancer, antioxidant, and metabolic disorder-related activities after 2018, facilitated by the development of new synthetic approaches and structure–activity relationship-based optimization.

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