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PHARMACOLOGICAL APPLICATION OF THIOPHENE DERIVATIVES

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ABSTRACT

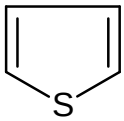
Thiophene nucleus has been established as the potential entity in the largely growing chemical world of heterocyclic compounds processing promising pharmacological characteristics.The knowledge of various synthetic pathway and the diverse physicochemical parameters of such compounds draw the especial attention of medical chemist to produce combanitorial library and carry out exhaustive efforts in the search of lead molecules. Thiophene is a five membered , sulfur containing hetero aromatic ring generally used as building block in drugs. It is structural metabolism leads to the formation of reactive metabolites. This compounds are widely spread in nature & have diversified application in design of new drug molecule. Thiophene has been established as the potential entity in largely growing chemical world of heterocyclic compounds possessing a pharmacological characteristics. A series of thiophene compound can be synthesize through various routes with pharmacological activity.

The simple five – membered heterocycle are thiophene, with sulphur atom. It also undergo electrophilic aromatic substitution very readily.Sulphur is the least electron donor as compare to nitrogen and oxygen.Thiophene is similar to benzene in reactivity. Thiophene is the least reactive of the three because the p orbital of the lone pair of electrons on sulphur that conjugates with the ring is a 3p orbital rather than the 2p orbital of N or O, so overlap with 2p orbitals on carbon is less good. Thiophene undergo more or less normal Friedel- Craft reactions, although the less reactive unhydrides(aceticunhydride, Ac2O) are used instead of acid chlorides, and weaker Lewis acid than AlCl3 are preferred. The regioselectivity is the – the 2- position is more reactive than 3- position. The present review includes the properties, synthesis, and a wide spectrum of biological activities of thiophene based scaffolds, and summary of thiophene containing active pharmaceutical ingredients (APIs) available in the market.

KEY WORDS :*Thiophene, Medicinal Importance, Biological Importance, Reaction of thiophene.*

INTRODUCTION

The heterocyclic compounds are widely distributed in nature & it essential for life[1-3]. The number of vast pharmacologically active heterocyclic compounds many of which are regular clinical use [4-7] .Thiophene belongs to the class of heterocyclic compounds containing five membered ring made up of one sulfur as a hetero atom which have formula C4H4S[8-10].Thiophene and its derivatives in petroleum or coal. Thiophene is taken from sulfur and another Greek word phaino which means shinning. Thiophene structure found in natural products & is incorporated in several pharmacological active compounds[11,12].



Thiophene was discovered as contaminant in benzene. Thiophene has a structure that is analogous of structure of pyrrole, furan, & due to pie electron cloud , it behave like as a reactive benzene derivatives[13-16]. The thiophene is used in two ways . The most interesting chemically is use of thiophene either as central ring or part of fused ring . The second use of thiophene is replacement of pendent

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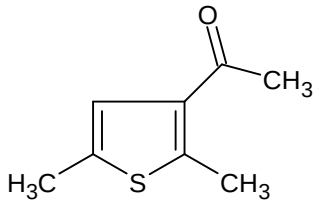
aromatic rings biologically important molecules with thiophene. In this article the most remarkable aspects of medicinal chemistry of thiophenealong with their biological activities will be reviewed[17-20].

Thiophene derivatives provides useful intermediaries in various areas of science & industry, with a wide range of applications, and therapeutic properties[21].Thiophene derivatives attract both great academic interest, and interest from the agrochemical, pharmaceutical and dyindustrie, as well. Heterocyclic compounds have historically played an important role in the search for bioactive products[22]. It observe than 75% of drugs in clinical use have at least one heterocyclic ring in their chemical structure[23]

A) ROUTES FOR THIOPHENE NUCLEUS FORMATION

A principal route to alkyl substituted thiophene is the reaction of a dicarbonyl compound with phosphorous pentasulphide[24-26].

An alternative route has that has been used in the friedel craft acylation followed by wolf- kishner reduction. Thiopheneacylate preferentially in the α position and thus 2- acyl- 5 alkylthiophene can also be accessed by this route from 2- alkyl thiophenes. When both α positions are alkyl substituted, acylation occurs in the β- position to produce 3-acyl-2, 5- dialkylthiophenes such as 2,5 – dimethyl-3- acetylthiophene[27-30].

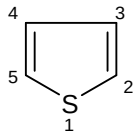


Synthetic approaches to the construction of thiophene and substituted thiophene have been efficiently developed. Thiophene ring can be constructed from non- heterocyclic precursors by two reaction pathways.

1. Construction of thiophene ring from appropriately substituted open chair precursors:
   This method involves the introduction of sulphur into a starting material containing the complete carbon skeleton.
2. The functionalization at the position α & β to the sulphor atom of the preconstructedthiophene nucleus.
   This method employ either the reaction of a mercaptoacetate with a 1,3dicarbonyl compound or the reaction of a thioacetate with a 1,2 – dicarbonyl compounds[31-34].

Properties of Thiophene

Thiophene is a five membered heteroaromatic compound containing sulfur atom at 1 position. It has formula C4H4S & the chemical name is thiacyclopentadiene[35-37].



Thiophene was discovered as a contaminant in benzene. It has molecular mass of 84.14g / mol& density is 1.051 g / mol& melting point is – 38°C . It is soluble in most organic solvents like alcohols & ethers but insoluble in water. The lone pair on sulfur are significantly delocalized in the pie electron system & behave like a benzene derivatives. The similarity between the physicochemical properties of benzene &thiophene is remarkable.

E.g – Boiling point of thiophene is 84.4 °C & Boiling point of benzene is 81.4 °C both are well known example of bioisoterism.It can be easily Nitrated ,Sulfonated ,Halogenated Acylated but cannot be Alkylated & Oxidized[38] .

Medicinal Importance Of Thiophene

In medicinal purpose the thiophene derivatives shows anti – inflammatory , antimicrobial , analgesic , antihypertensive & antitumor activity. They are also used in inhibitors of corrosion of metals[39] .

The substituted thiophene having significant antihypertensive activity. Many thiophene derivatives has developed as chemotherapeutic agents.Thiophene is one of the most important heterocycle exhibiting remarkable pharmacological activities.Thethiophene compound exhibits various activities like example 1- [1-(2,5 – dimethyl – thiophene – 3 yl) ethyl] -1 – hydroxyurea (1)shows antiinflamatory activity ; the maleate salt of 1 – (2 , 5 – dimethylthiophen -3 yl) – 3 – (5 – methyl – 1H – Dimethyl – 4 – yl) – 3- (5 – methyl -1 H –

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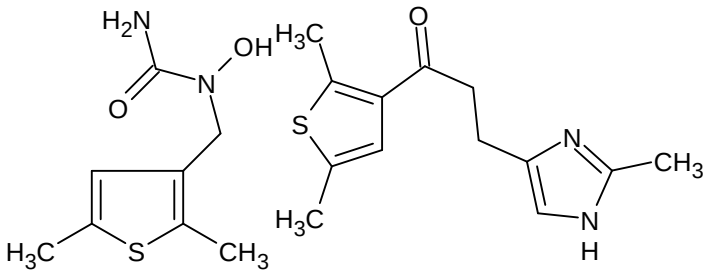
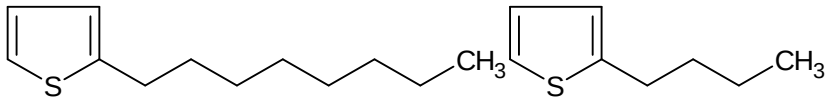
imidazole – 4 – yl)propan – 1 – one(2)act as serotonin antagonists & is used in treatement of Alzheimer's disease. The latter has also been employed in the formulation of links for computer printers by Xerox group & act as raw material for herbisides / Pesticides.



1 2

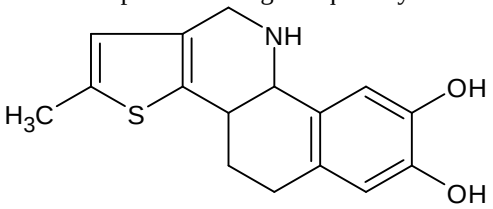
2 – octylthiophene (3) has been employed in the synthesis of anti – atherosclerotic agent. 2 – butylthiophene (4) has been employed as a row material in the synthesis of anticancer agent[40-44].



3 4

Biological Activity of Thiophene

As far as biological activity is concerned. Fused heteroaromatic system are often of greater than monocyclic compounds.Thethiophene derivatives are known to be associated with broad spectrum of biological activity like antifungal , antibacterial , banzothieno [3,2 – e] triazolo, thieno – pyrimidines S – triazineetc.Thiophene can be fused with various heterocyclic system give rise to new heterocyclic system with enhanced biological activity[45-47].Thiophene derivative have been derivative have been very well known for their therauptic applications. Many thiophene derivatives have been developed as chemotheraupticagentsans are widely used.Thiophene nucleus is one of the most important heterocycles exhibiting remarkable pharmacological activities.It also has application in metal complexing agent and in the development of insectisides. The higher alkylated thiophenes (5) also have other uses like 2- hexylthiophene has been used extensively as a aw material in patent relating to liquid crystals.



(5) R = C_2H_5-C_6H_{13}

As far as biological activity is concerned, fused hetero-aromatic systems are often of greater interest than monocyclic compounds[48-51].

Reaction With Electrophilic Reagents

1)Nitration –

Thiophene is treated with nitrating mixture (Conc . HNO3 & conc. H2SO4) gives 2 – nitro – thiophene.

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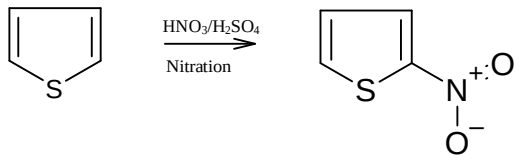
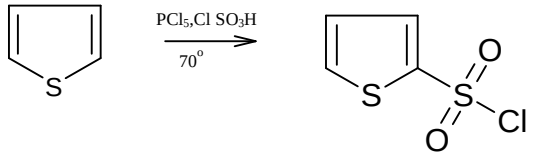


Thiophene 2- Nitro - Thiophene

2) Sulphonation

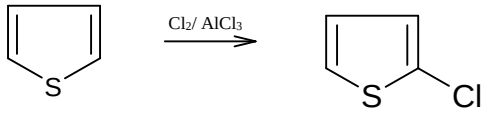
Sulphonation of thiophene by cold concH2SO4 it gives thiophene 2 – sulphonic acid& 2 – chlorosulphonation is efficient.



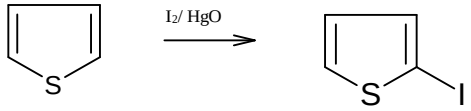
Thiophene 2 - chloro sulphonation

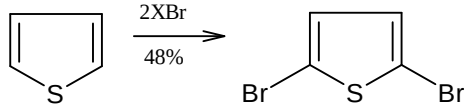
3) Halogenation

Halogenation of thiophene is carried out with Cl2 at 2 – chlorothiophene& 2,5 – dichlorothiophene while in presence of HgO ,thiophene reacted with iodine gives 2 – iodothiophene.



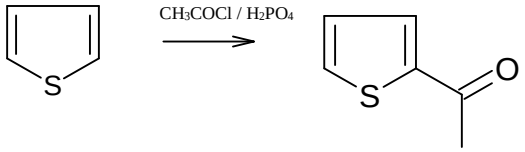
Thiophene 2 - chloro thiophene





4) Friedel Craft Acylation

Thiophene react with acid chloride in presence of H2PO4 as catalyst, it gives 2 – acetyl thiophene.



5) Vielsmeir Hack Reaction

The vielsmeir reaction of thiophene react with DMF in presence of POCl3 it gives thiophene 2 – carboxy aldehyde.

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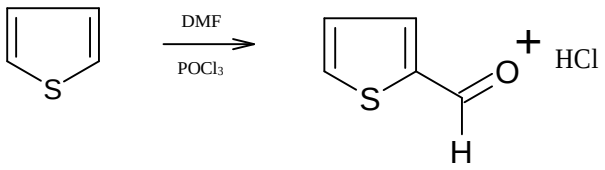
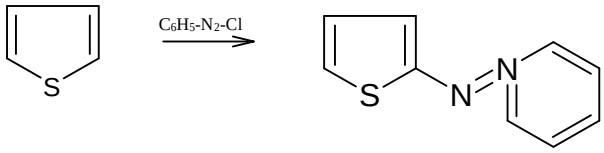


6) Diazo Coupling

Diazocoupling reaction of thiophenewith benzene diazonium chloride at 5 °C, it gives 2 – phenyl azothiophene.



CONCLUSION

For the informational data the thiophene is significantly important class of heterocyclic compound & their application is chellanging in chemotheorapy of various alignmens. A thiophenemoityhaveattracted a great deal of interest of medicinal chemist & biochemist & as a lead molecule for designing potential bioactive agents.Further we can include many other derivative of thiophene can be synthesized which will be expected to show potent pharmacological activities.

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