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Diverse Thiophenes as Scaffolds in Anti-Cancer Drug Development: A Concise Review

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Abstract

As the world's population increases and health problems expand accordingly, need to discover new therapeutics will become even more tiring. Heterocyclic compounds are widely distributed in nature and are essential for life. Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulphur as heteroatom with the formula C_4H_4S. In medicinal chemistry, thiophene derivatives have been very well known for their therapeutic applications. Thiophenes have been reported to have many types of biological activities, where many of them used as therapeutic agents as antimicrobial, anticancer, anti-inflammatory and antiviral agents. Derivatives of thiophene have been a topic of constant investigation due to their versatile synthetic applicability and broad spectrum of biological applications; among which is antiproliferative activity. In spite of great progress in understanding cancer biology, current therapeutic procedures remain unsatisfactory. Chemotherapy is often followed by secondary effects with cellular toxicity negatively affecting the results. The discovery and development of new safe and efficient antitumor agents is necessary.

Keywords: *Anti-cancer; Thiophenes; Pyrrole; Calcium phosphate*

Introduction

As the world's population increases and health problems expand accordingly, need to discover new therapeutics has become a need of the hour. The design of drug molecules arguably offers some of the greatest hopes for success in present and future era. Heterocyclic compounds are widely distributed in nature and are essential for life. There are vast numbers of pharmacologically active heterocyclic compounds many of which are in regular clinical use. The investigational approaches towards Structure-Activity Relationship focusing the search of optimized candidates have become immensely important.

Thiophene belongs to a class of heterocyclic compounds containing a five membered ring made up of one sulphur as heteroatom with the formula C_4H_4S. Thiophene and its derivatives exist in petroleum or coal. Thiophene is taken from the word the ion, the Greek word for sulphur, and another Greek word phaino which means shinning. Thiophene structure can be found in certain natural products and is also incorporated in several pharmacologically active compounds.

In medicinal chemistry, thiophene derivatives have been very well known for their therapeutic applications. The simple thiophenes are stable liquids which closely resemble the corresponding benzene compounds in boiling point and even in smell. They occur in coal tar distillates. The discovery of thiophene in coal tar benzene provides one of the classic anecdotes of organic chemistry. Thiophene was discovered as a contaminant in benzene. It was observed that isatin (1Hindole-2, 3Dione) forms a blue dye if it is mixed with sulfuric acid and crude benzene. Victor Meyer was able to isolate the substance responsible for this reaction. The compound was found to be a heterocyclic compound- Thiophene. Thiophene

has a structure that is analogous to structure of pyrrole, and due to pie electron cloud, it behaves like extremely reactive benzene derivative.

Calcium-containing crystals are present in synovial fluid extracted from the knee joints of up to 70% of osteoarthritis patients, indicating that pathological calcification occurs in most of the osteoarthritis. Calcified diseases associated with osteoarthritis are correlated with the presence of calcium pyrophosphate dihydrate (CPPD) crystals (25–55% of the time) and/or of the occurrence of basic calcium phosphate (BCP) crystals (35–70% of the time) consisting of carbonate-substituted hydroxyapatite (HA) and octa calcium phosphate. The origin of CPPD crystals is associated with the increase in inorganic pyrophosphate (PPi) concentration. Upregulation of nucleotide pyrophosphatase phosphodiesterase 1 (NPP1) and of ankylosis protein (ANK, a PPi transporter) expressions in articular cartilage can contribute to an extracellular PPi excess,9 leading possibly to CPPD deposition Following the adoption of the 1958 Food Additive Amendment to the Food, Drug and Cosmetic Act (FDCA), the Flavour and Extract Manufacturers Association (FEMA) established the "generally recognized as safe" (GRAS) Program to evaluate the safety of food flavor ingredients based on scientific data. The safety of flavor ingredients is determined by the FEMA Expert Panel, a body of independent scientists in fields of biochemistry, toxicology and medicine who serve as reviewers of scientific data related to the safety of flavor ingredients. The GRAS status of flavor ingredients is re-affirmed periodically as part of ongoing FEMA GRAS re- evaluations, a key component of the FEMA GRAS Program. Re-evaluations are prioritized when there is a significant increase in exposure, or a substantial body of new scientific data that has become available since the previous evaluation.

The applications of thiophenes and benzothiophene derivatives were covered in the second edition of CHECII (1996). For this edition, which covers the literature for the period 1996–2007, all general statements made in CHEC-II(1996) are applicable also today. Owing to the extraordinarily rich chemical literature on thiophenes and their applications, the focus in this section has been directed to optoelectronic uses of thiophenes. All other areas are covered basically in the same order as in CHECII (1996) extending the applications reported there. Here, it is intended to give only selected examples and not a full coverage which enables the reader to gain quick access to the topic of interest.

Review of literature

Review of work already done on the subject

1.Synthesis of thiophene and N-substituted thieno [3,2-d] pyrimidine derivatives as potent antitumor and antibacterial agents. Reported by Hafez Hend N et al. in the year 2017 reported in Journal Acta Pharma.

2.Novel synthesis and antitumor evaluation of polyfunctionally substituted heterocyclic compounds derived from 2-cyano-n- (3-cyano-4,5,6,7-tetrahydrobenzothiophen-2-yl)- acetamide. Reported by shams hoda Z et. al. in the year 2011 reported in journal molecules.

3.Cytochrome P450 oxidation of the thiophene-containing anticancer drug 3-[(quinolin-4ylmethyl)-amino]-thiophene2-carboxylic acid (4-trifluoromethoxy-phenyl)-amide to an electrophilic intermediate. Reported by medower C et al. in the year 2008 reported in Journal Chem Res Toxicol.

4.Pharmacological action and SAR of thiophene derivatives: A review. Reported by Kamboj A et al. in the year 2012 reported in Journal of Pharmacy Research.

5.A review on synthesis and medicinal importance of thiophene. Reported by Mishra R et al. in the year 2007 reported in International Journal of Engineering and Allied Sciences.

6. DNA-stabilized polythiophene fluorescenceprobe for label-free detection

Research gaps identified in the proposed field of investigation

Review of thiophene possessing versatile biological properties have already been published. But none of the reviews have focused on anti-cancer properties exclusively.

Objectives of the proposed study

To explore anti proliferative effects of thiophenes.

To study various substitutions on thiophene ring.

To study the effect of reported substitutions on anti-cancer potency of thiophenes.

To propose promising leads with thiophene ring for further anti-cancer research.

Sources of information

International scientific journals. Research articles.

Web articles.

Textbooks and official books.

Tools and techniques of research

Name of Instruments planned to be used in project work is pH meter.

Analytical Balance.

Condenser.
Dissolution test apparatus.
UV-visible Spectrophotometer.

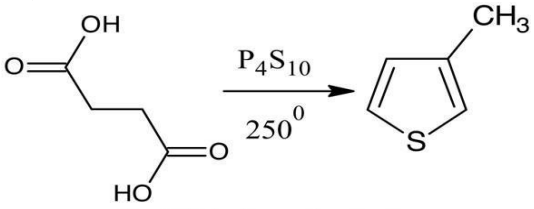
Review study

Major synthetic procedures

Well known or major synthetic procedure includes: Paal- Knorr Thiophene synthesis, Fiesselmann Thiophene synthesis Gewald Aminothiophene synthesis and Hinsberg Synthesis.

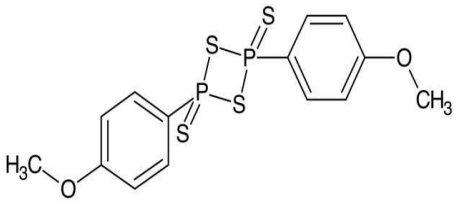
Paal-Knorr Thiophene

Synthesis This reaction is also known as Paal Thiophene Synthesis. 1, 4-Dicarbony1 compounds can be reacted with a source of sulfur to give thiophene.



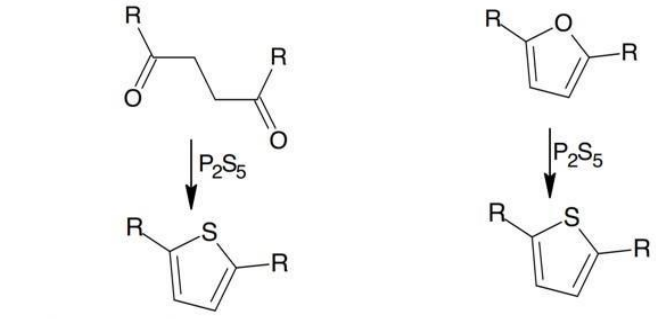
Paal Thiophene Synthesis

Source of sulfur used are traditionally phosphorus sulfides, latterly Lawesson's reagent (LR) or bis(trimethylsilyl) sulphide.



Lawesson's Reagent

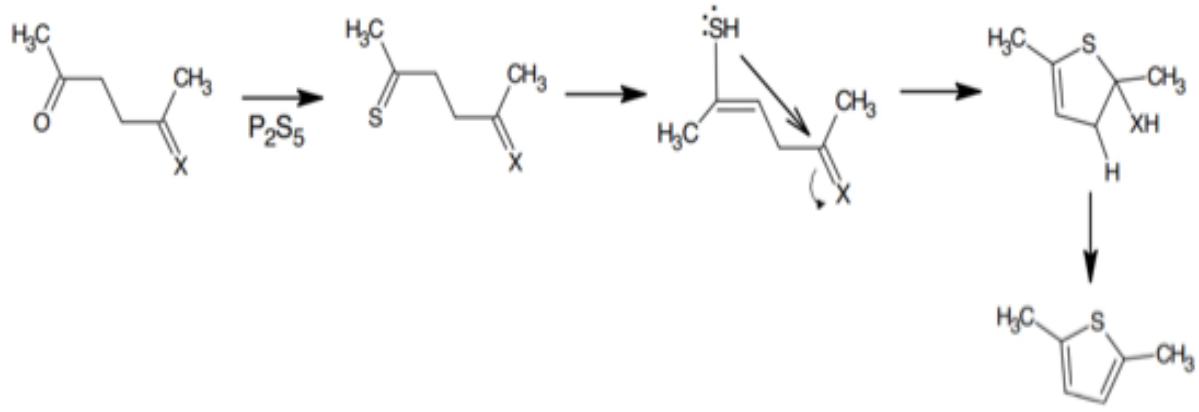
Paal and Knorr individually described the initial examples of condensation reactions between 1, 4diketones and primary amines, which became to known as the Paal- Knorr pyrrole synthesis. The basic mechanism of this synthetic procedure involves cyclization of 1,4- diketones, either in the presence of a primary amine (Paal- Knorr pyrrole synthesis), in the presence of a sulphur source (Paal Thiophene synthesis), or by dehydration of the diketone itself (Paal Furan synthesis). Reagents such as phosphorus pentasulfide or Lawesson's reagent act as sulfurizing agents as well as dehydrating agents, allowing a reaction pathway that could lead first to the formation of furans. This hypothesis was tested by campaign and co-workers in 1952. They were able to prove that Paal Thiophene Synthesis could not proceed via furan as intermediate. Instead it went through the formation of a thione. To prove this, they conducted parallel experiments. Direct comparisons were made between the reactions of 2,5-hexanedione and 1,2-dibenzoylethane with P2S5 and the reactions of 2,5 dimethylfuran and 2,5-diphenylfuran under the Paal Thiophene Synthesis conditions. Reactions utilizing the diketones provided a greater yield of the thiophene suggesting that the furan is not an essential intermediate in the reaction pathway, but rather a by-product.



R= CH_3 70% Yield
R= Ph 25% Yield

13% Yield
0 % Yield

Based on the above observations, it was proposed that the mechanism involves initial formation of thione (X = O or S), which is followed by tautomerization and cyclization. Aromaticity drives the facile elimination of either H2O or H2S resulting in the thiophene product.

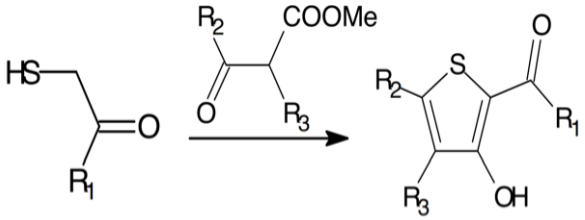


Reaction mechanism involved in Paal Thiophene Synthesis

This synthetic method for thiophene had been subjected to considerable variations and improvements over time. The standard procedure for the Paal Thiophene Synthesis is to use phosphorus pentasulphide as the sulphur atom source. The product is always a mixture containing furan due to the dehydrating effect of P2S5 as an additional property. Several other reagents had been developed to take care of the sulphur source and dehydration. Hydrogen sulphide, in the presence of an acid catalyst, was found to be more efficient than phosphorus pentasulphide at converting ketones to thione.

Fiesselmann thiophene

Synthesis Condensation reaction of thioglycolic acid with α, β- acetylenic esters, which upon treatment with base result in the formation of 3-hydroxyl-2-thiophenecarboxylic 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.



Fiesselmann Thiophene Synthesis proceeds through consecutive base-catalyzed 1, 4- conjugate addition reactions to form thioacetal. Treatment with stronger base results in the formation of an enolate while intramolecular reaction through Dieckmann condensation leads to the formation of a ketone. Eliminating methylthioglycolate and tautomerization propelled by aromaticity provides the 3hydroxyl thiophene dicarboxylate.

Therefore, thiophene can be synthesized from reactions of thioglycolic acid derivatives and β - keto esters, α, β -dihaloesters and α-and β-halovinyl esters, along with the corresponding nitriles, ketones and aldehydes. Furthermore, a variety of α-mercaptocarbonyl systems can be used in place of the thioglycolic acid derivatives and this extends the applicability of this reaction. iii) Gewald Aminothiophene Synthesis This method was reported by Gewald in 1966. Gewald synthesis is the usual route to 2- aminothiophenes. It consists of the basecatalyzed condensation of a ketone having an a CH2 group with a β-ketonitrile to form an olefin, followed by cyclisation with elemental sulfur. The first step in the mechanism of the Gewald reaction is the Knoevenagel condensation of an activated nitrile with a ketone or aldehyde to produce an acrylonitrile. The product of this condensation is then thiolated at the methylene position. The sulfurated compound initially decays to the mercaptidecompound which then undergoes a cyclization reaction via mercaptide attack at the cyano group. Base-catalyzedtautomerization affords the 2-aminothiophene iv) The Hinsberg Synthesis Two consecutive aldol condensations between a 1, 2-dicarbony1 compound and diethy1 thiodiacetates gives thiophene. The immediate product is an esteracid produced by a Stobbe-type mechanism,

but the reactions are often worked up via hydrolysis to afford an isolated diacid.

General synthetic procedures

From thiocarbony1 compounds 2-Keto-thiols added to alkenyl phosphonium ions followed by ring closure via Witting reaction gives 2, 5-dihydrothiophenes which can be dehydrogenated Structure.

Using carbon disulfide 2-alkylthiophenes can be synthesized by the addition of a carbanion to carbon disulfide with a subsequent S-alkylation.

From thio-nitroacetamides the S-alkylation of thio-nitroacetamides with 2-bromoketones produces 2-amino-3- nitrothiophenes.

From thiazoles When thiazoles are heated strongly with an alkyne, generates 2, 5- unsubstituted thiophenes. Though the conditions are vigorous, excellent yield can be obtained.

Anticancer properties

Cancer is a group of disease in which cells are aggressive (grow and divide without respect to normal limits), invasive (invade and destroy adjacent tissues) and sometimes metastatic (spread to other locations in the body).

Structure activity relationship revealed that:3', 4', 5'-trimethoxyphenyl of the 2-benzoyl moiety was crucial for activity.

Maximum activity was dependent on location of methoxy substituent on benzene part of benzo thiophene moiety.

The greatest activity occurred when the methoxy group was located at the C-6 or C-7 position, the least when located at the C-4 or C-5 position.

The C-5/6 dimethoxy derivative had activity on was particularly more active than either mono-substituted compound.

3-amino function can be removed and replaced with Thiophene derivatives are used as anticancer.

Romeo Romagnoli et al synthesized a series of 2-(3',4',5'-trimethoxybenzoyl)-3-aminobenzo thiophene derivatives which exhibit anticancer activity.

All the compounds inhibit tubulin polymerization, hence possess anticancer activity. Cancer may affect people at all ages, even fetus but the risk for more common varieties tends to increase with age.

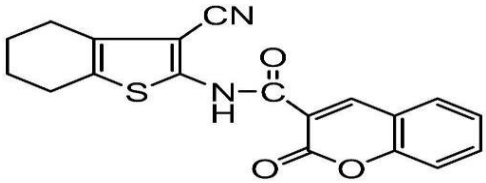
Physical properties of thiophene

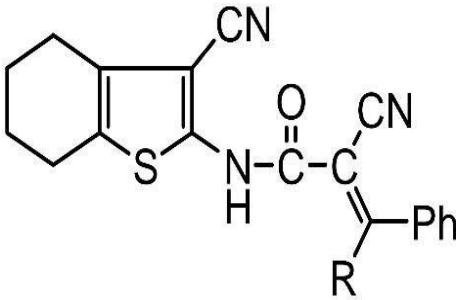
Molecular formula: C_4H_4S or SCH=CHCH=CH

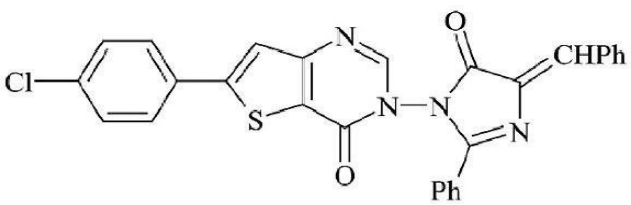
Chemical names: Thiophene, Thiole thiofuran thiophen

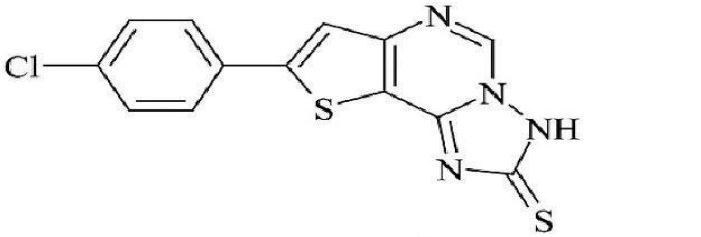
Molecular weight: 84.14 g/mol

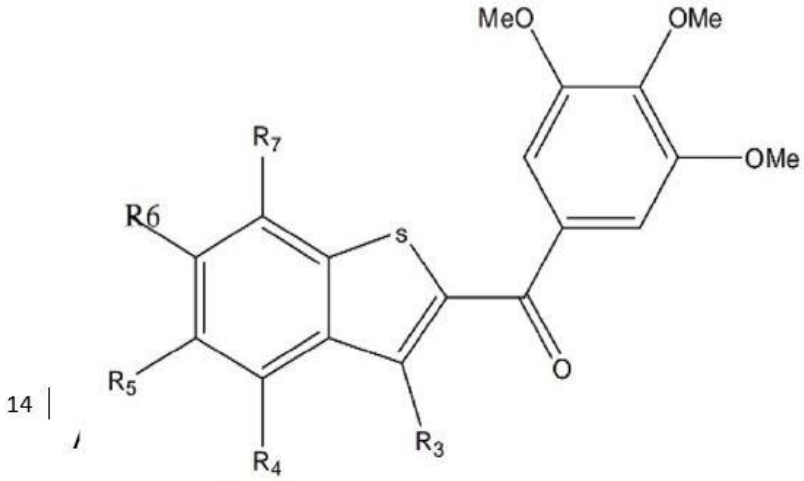
Derivatives











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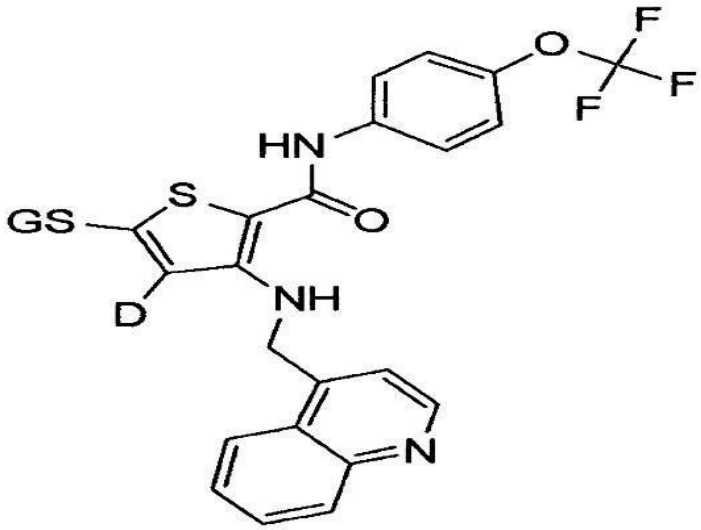
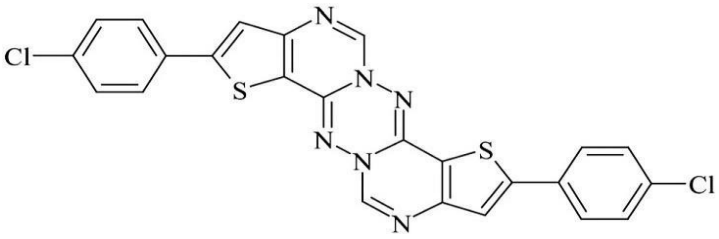
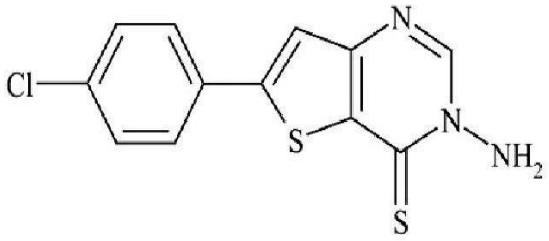
Basic structure







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Despite great progress in understanding cancer biology, current therapeutic procedures remain unsatisfactory. Chemotherapy is often followed by secondary effects with cellular toxicity negatively affecting the results. The discovery and development of new safe and efficient antitumor agents is necessary [1-5].

Conclusion

The anticancer activity of thiophene is rare discussed in the literature. The current project on the basic thiophene drug has shown potential anticancer activity. This review supports the claim to conduct extensive research on the derivatives of drug thiophene for its possible activity in the treatment of cancer.

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None.

Conflict of interest

None.

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