A Mini Review on Thiophene-based derivatives as anticancer agents

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Abstract-
Heterocyclic compounds play a crucial role in medicinal chemistry due to their diverse biological activities, making them extensively investigated in drug design and development. Ongoing endeavors are directed towards creating medicinal agents, particularly targeting severe illnesses such as cancer. Among these compounds, thiophene, characterized by its sulfur-containing heterocyclic structure, has emerged as a well-explored scaffold for generating a library of molecules with potential anticancer properties. Studies indicate that thiophene analogs can bind to various cancer-specific protein targets, with the specific nature and location of substitutions influencing their interactions. Consequently, these analogs are found to exert their biological effects by inhibiting diverse signaling pathways implicated in cancer progression. Given that different anticancer targets necessitate distinct structural attributes, researchers have sought to synthesize new thiophene derivatives with diverse substitutions. The present review consolidates available information on thiophene-based compounds as anticancer agents, with a particular emphasis on synthetic methodologies, biological characteristics, and structure-activity relationship (SAR) studies. Additionally, it includes a discussion on several patents granted for thiophene-containing molecules with anticancer potential.

Keywords–Thiophene derivatives, SAR, Anticancer drug, biological activity

INTRODUCTION

Heterocycles are important pharmacophores and have significance to create privileged chemical structures possessing pharmacological activities.[1] Five membered heterocycl which incorporate oxygen, nitrogen and sulfur are found in broad-spectrum therapeutic agents which have an enormous significance in drug discovery and drug development processes. Because of their many biological functions, heterocyclic compounds are important in medicinal chemistry and are therefore thoroughly studied in the field of drug research and development.[2] Ongoing attempts are being made to create pharmaceuticals, particularly for deadly illnesses like cancer. One of the relatively well-studied scaffolds for the creation of a library of compounds ith possible anticancer properties is thiophene, a heterocyclic scaffold containing sulphur.[3-5]Researchers are still working hard to find new heterocyclic compounds with potential bioactivities despite the substantial work that has been done on thiophene. Researchers all over the world have been using thiophene nucleus extensively to build a variety of bioactive heterocycles that can target a broad spectrum of biological targets [7-10]. This review sheds light on the synthetic methods that have been employed to synthesize possible thiophene derivatives and then thoroughly analyse them in terms of their pharmacological implications. This review can assist researchers and medicinal chemists in creating new leads with thiophene nuclei that are highly effective and have fewer negative effects.One of the main causes of death in the globe is cancer. The majority of cancer-related deaths occur from lung and liver malignancies. One of the most significant developments in medicine over the past few decades has been the development of cancer chemotherapy. However, there is a significant frequency of undesirable side effects due to the limited therapeutic index of medications used in chemotherapy. [11-13] In medicinal chemistry and medicine, one of the most urgent research fields is the creation of novel anticancer drugs. Many new anticancer medicines have been synthesized as a result of the well-documented significance of thiophene and thiadiazol rings as scaffolding found in a variety of therapeutic medications[14-19].

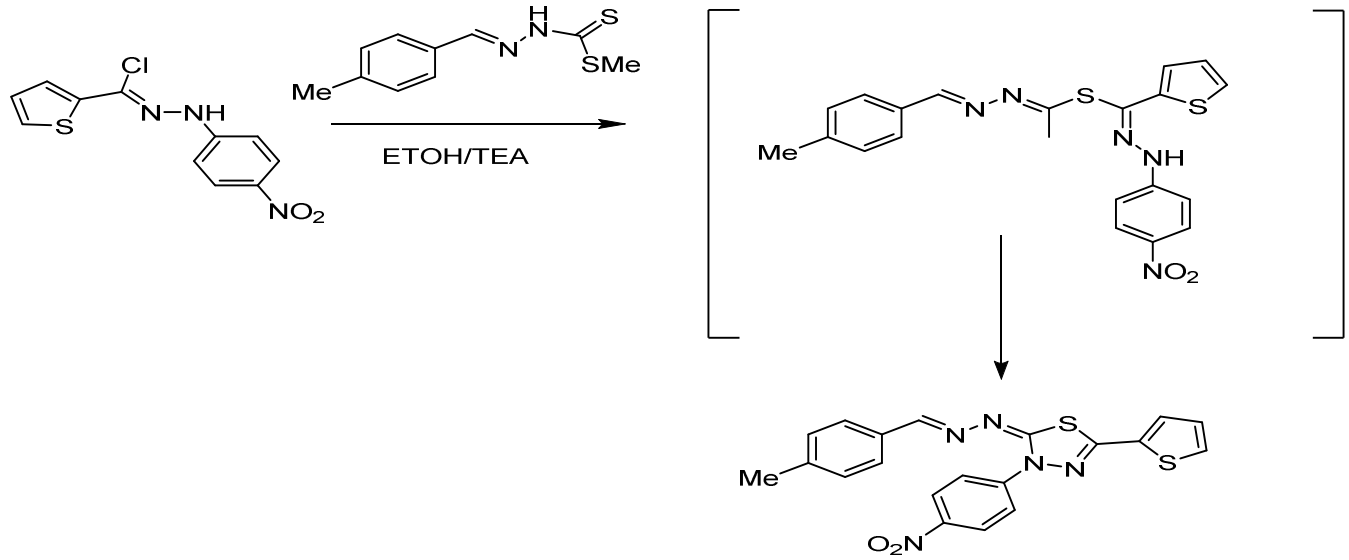
Derivatives of thiophene are widely used and considered to be among the most important chemotherapeutic drugs Thienopyridines occupy a special niche among the condensed heterocyclic compounds. Their widespread use has been attributed to their anti-tumour, antimetabolite, antiviral, anti-HIV-, antiproliferative, antimicrobial, analgesic and anti-inflammatory, as well as phosphokinase and phosphorus inhibitors of diesters IV Thieno[3,2-d] pyrimidines are among these active substances that have attracted a lot of attention because of their exceptional anticancer properties.

Therefore, as EGFR and VEGFR dual inhibitors and PI3K inhibitors (GDC-0941), substituted thieno [3,2-d] pyrimidines exhibit strong action and are employed in the treatment of malignancies [23We-26 have previously reported on a number of heterocyclic moieties with biological activity as part of our ongoing effort on the synthesis of antibacterial and anticancer drugs. In addition, sulphonamide derivatives, which exhibit antibacterial, antineoplastic, and antitubercular action, are a significant class of molecules utilized as scaffolds in medicinal chemistry. Because of their anticancer properties, molecules containing 1,2,4-triazole moieties have attracted a lot of attention recently.[29-34].

5-(thiophen-2-yl)-1,3,4-thiadiazole derivatives as possible anticancer agents

Sobhi M Gomha have synthesised a **5**-(thiophen-2-yl)-1,3,4-thiadiazole derivative catalysed by Trimethyl amine and ethanol as solvent were used

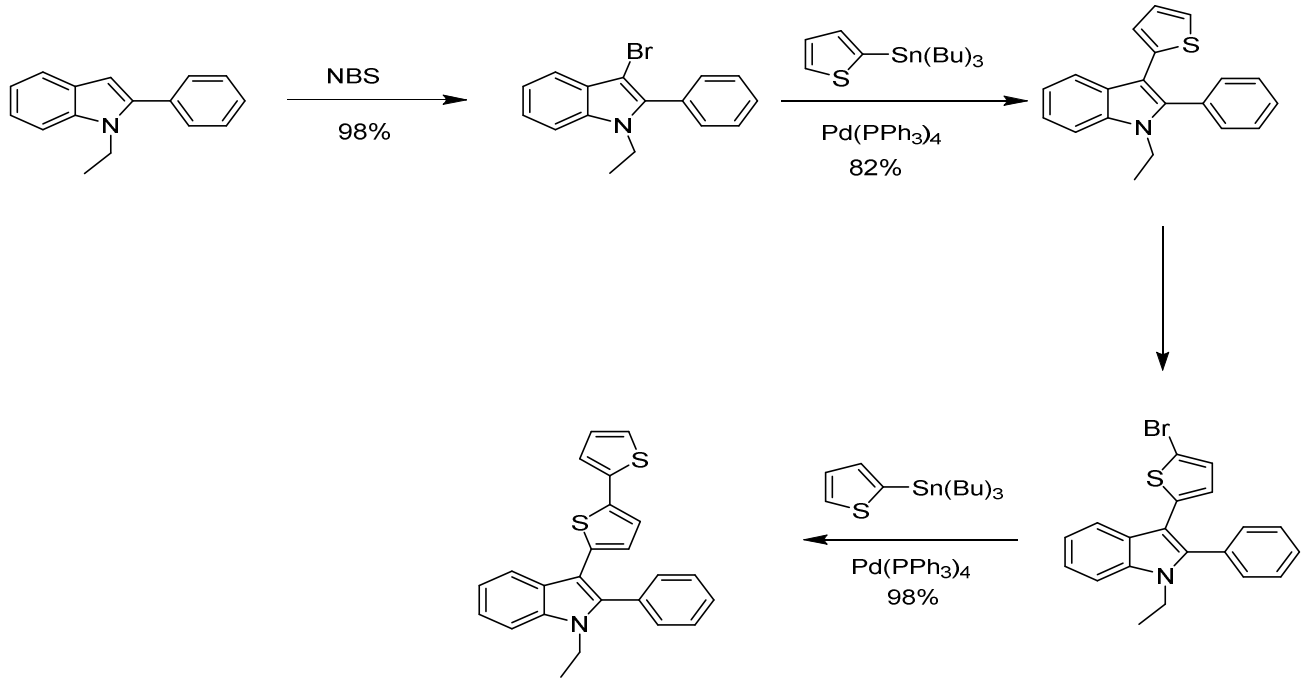
SCHEME-1



Novel Thiophene-Based Indole Derivatives: Synthesis and as an Antibacterial, and Apoptotic Anticancer Agents

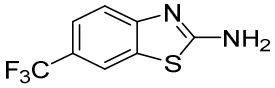
Metin Konus and et al. have synthesised3-([2,2′-Bithiophen]-5-yl)-1-ethyl-2-phenyl-1*H*-indole using electrophilic aromatic substation reaction and Pd-catalyst Stille coupling reactions. It is an active cytotoxic, antioxidant and antibacterial compound. It has also been shown to have an inhibitory effect on glutathione S-transferases (GST) isozymes and ability to induce apoptosis in liver carcinoma cells (HepG2 cells). In addition, it could be also considered as a promising medical agent in cancer treatment.

SCHEME-2



Benzothiazole derivatives as potential anti-cancer drugs

Yurttas et al. obtained 2–(4-aminophenyl) BTA derivatives substituted with different heterocyclic rings and tested their antitumor potential against 60 human tumour cell lines. The BTA derivatives 13 (2–(1H-benzo[d]imidazol-2-ylthio)-N-(4-(benzo[d]thiazol-2-yl)-3 chlorophenyl) acetamide) and 14 (N-(4-(benzo[d]thiazole2-yl) phenyl)-2-(1-phenyl-1H-benzo[d]imidazol-2-yl-thio)-acetamide) showed remarkable antitumor potential against different cancer cell lines

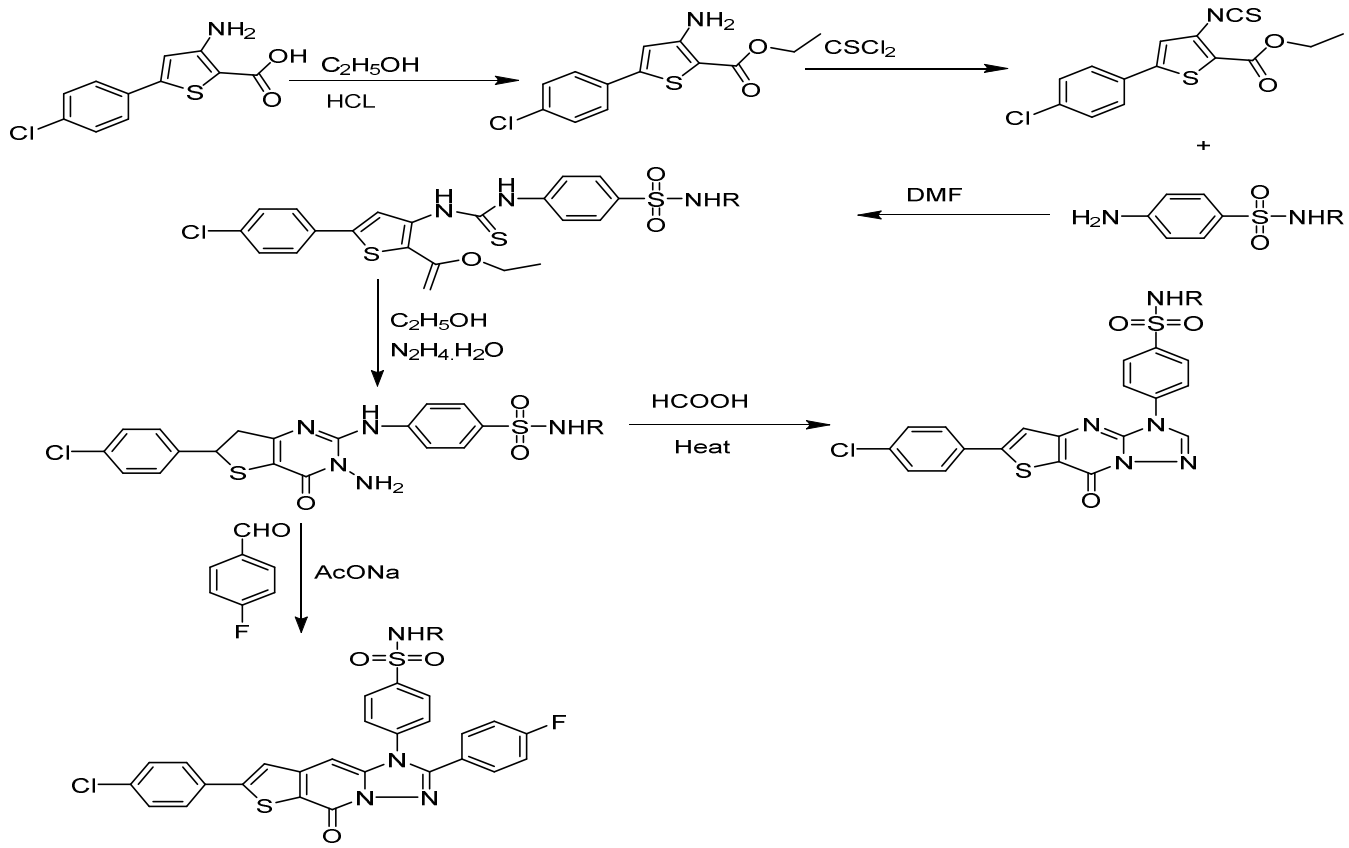


Riluzole

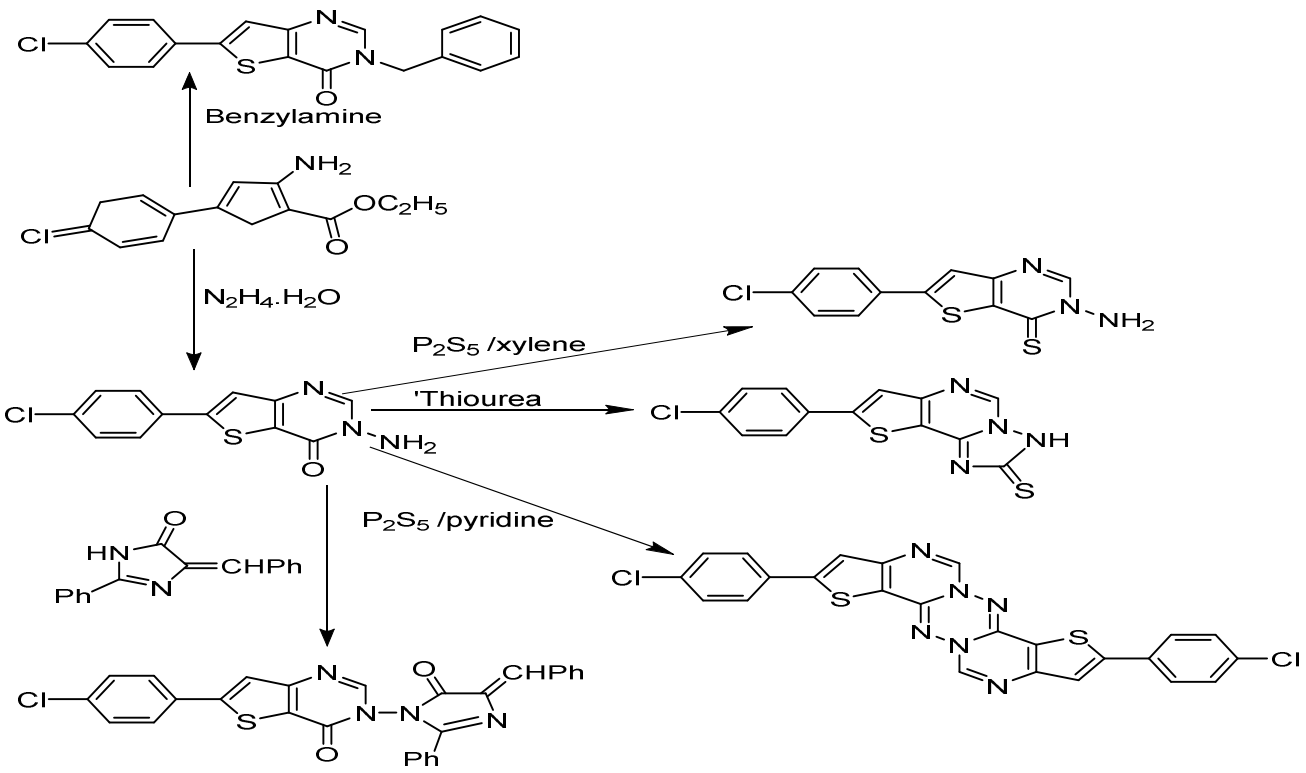
N-substituted thieno[3,2-d] pyrimidine derivatives and thiophene as powerful antibacterial and anticancer agent

HEND N. HAFEZ and et al. have synthesised a N-substituted thieon [3,2-d] pyrimidine derivatives Via a multistep reaction with help of various catalysts and solvents mainly in acidic medium

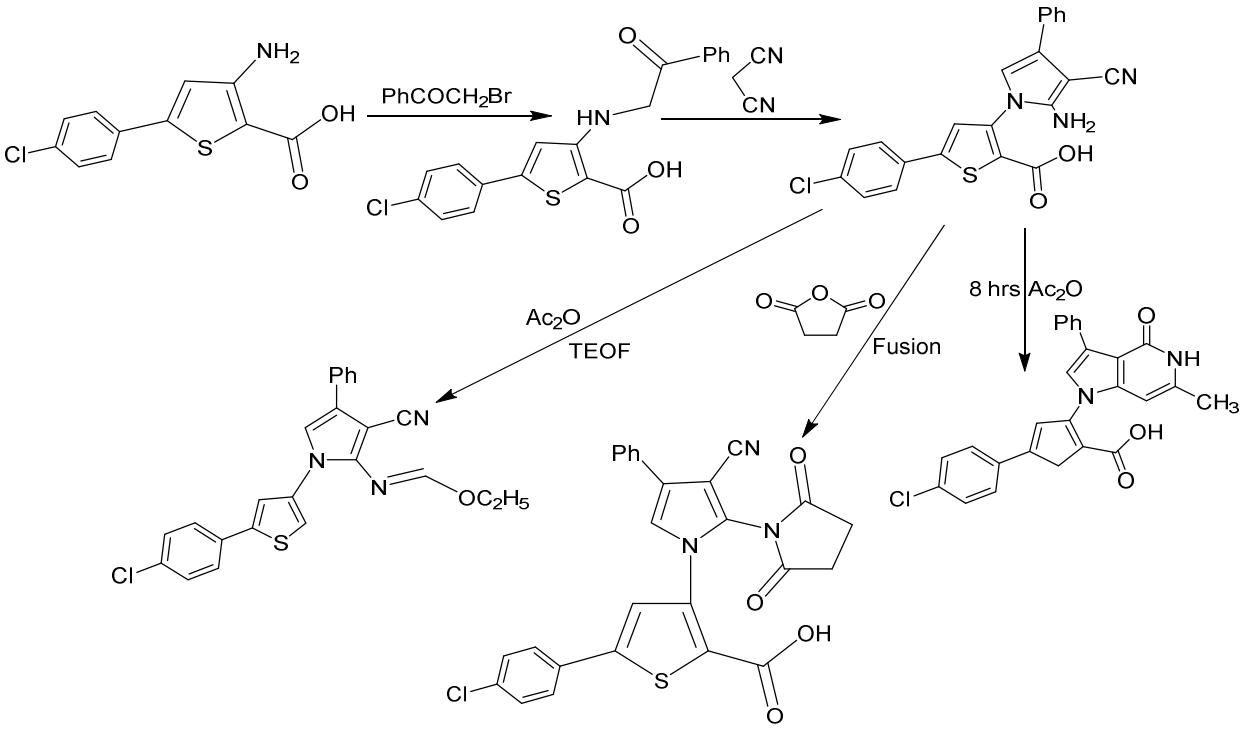
SCHEME-3


NH2
OH
C2H5OH
HCL
CSCl2
NCS
Cl
S
O
+
DMF
H2N
NHR
C2H5OH
N2H4.H2O
HCOOH
Heat
NH2
CHO
AcONa
F
N
H

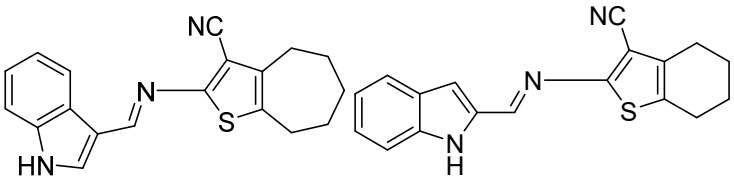
***Scheme*-4**


Cl
N
S
N
O
Benzylamine
NH2
OC2H5
Cl
O
N2H4.H2O
P2S5 /xylene
'Thiourea
P2S5 /pyridine
HN
CHPh
Ph
N
NH2
NH
S

***Scheme*-5**

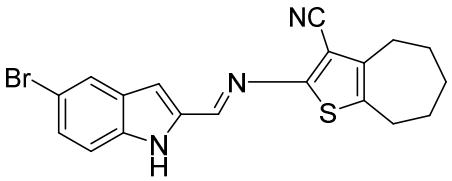


Thiophene derivatives' anticancer effects on breast cancer MCF-7 cells



2-[(1H-Indol-3-ylmethylene)-amino]-5,6,7,8-tetrahydro-4H-cycloheptane[b]thiophene-3-carbonitrile

v2-[(5-Bromo-1H-indol-2-ylmethylene)-amino]
4,5,6,7-tetrahydro-benzo[b]thiophene-3-carbonitrile



2-(((5-Bromo-1H-indol-2-yl) methylene) amino)
5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3-carbonitrile C19H17N3S C18H14BrN3S

Some Novel Chalcone derivatives containing thiophene as anticancer and apoptosis-inducing agents

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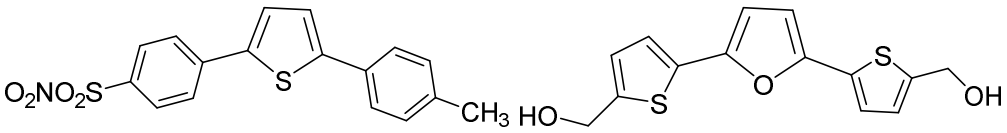
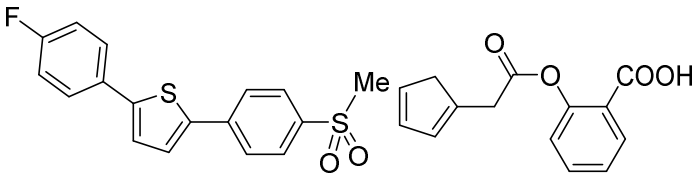
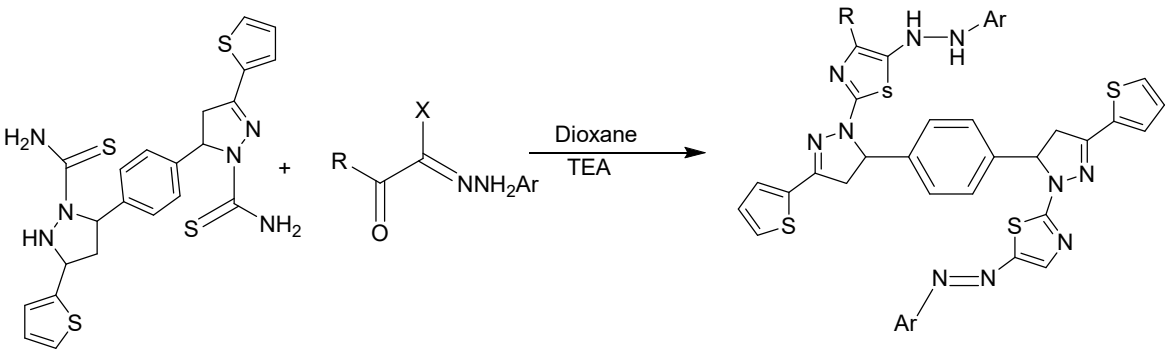




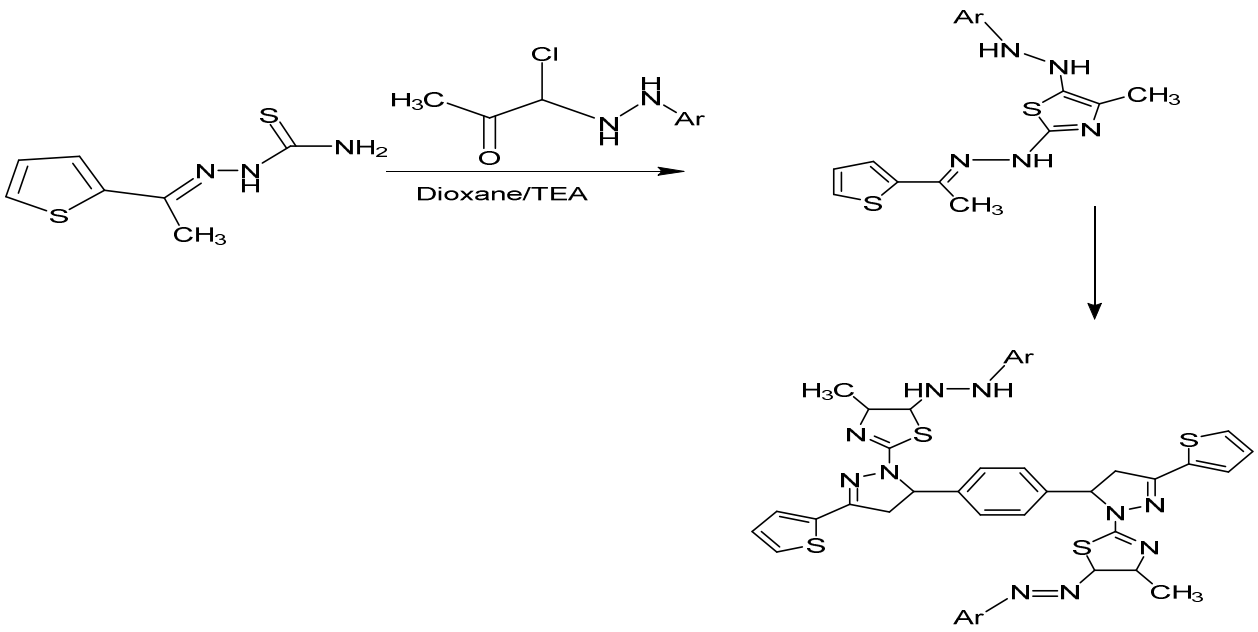
Some Novel Bis-Pyrazolyl-Thiazoles with the Thiophene Moiety Included: Synthesis and Characterization as Effective Anti-Tumor Agents

Sobhi M. Gomha and et al. have synthesized new bis-heterocyclic compounds containing 1,3-thiazole ring, Called 1,4-bis(1-(5-(aryldiazenyl) thiazol-2 yl)-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-5-yl) benzene. catalysed by Dioxane and Triethyl amine

Scheme-6



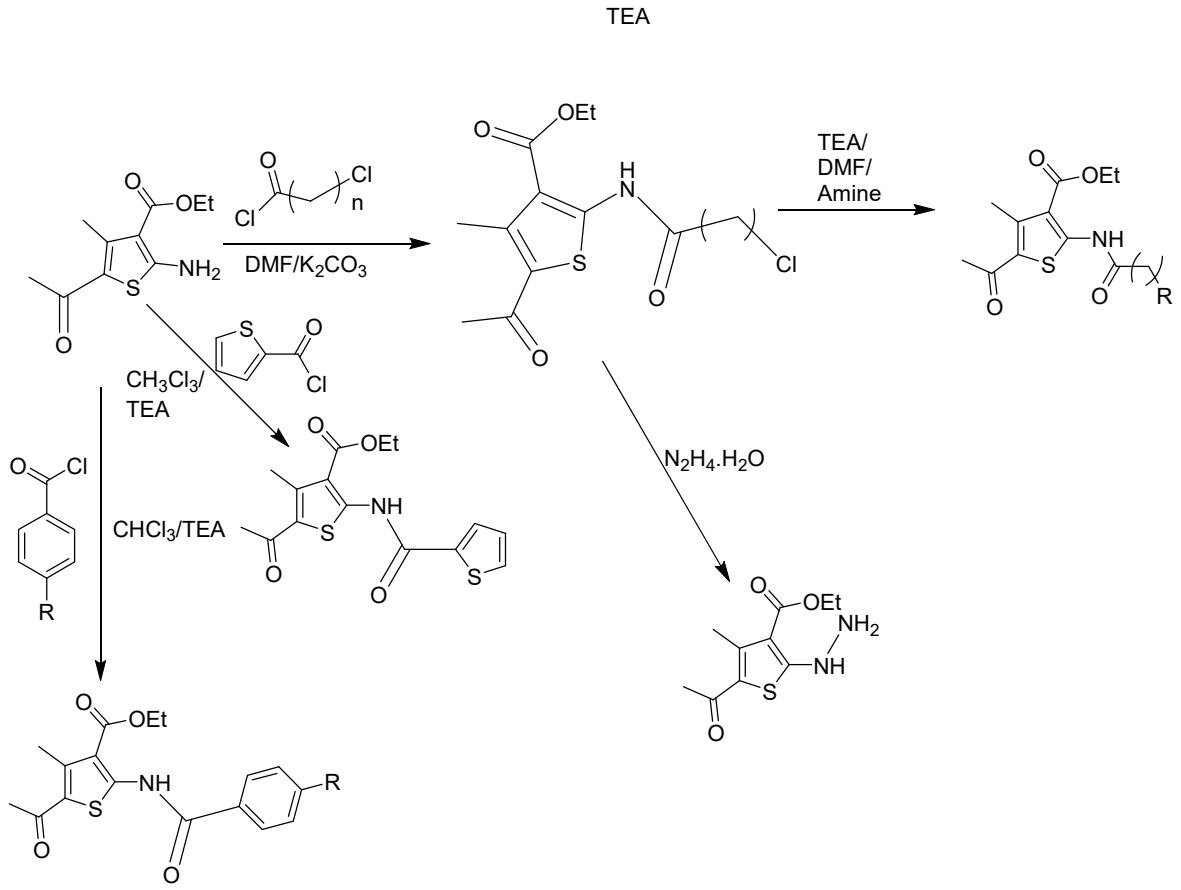
Scheme-7



Synthesis of some new thiophenes and thieno [2,3-d] pyrimidine derivatives as anticancer agent

M. Fouad and et al. synthesized ethyl 5-acetyl-2-amino-4-methylthiophene-3-carboxylate Using a multicomponent condensation process including acetyl acetone, ethyl cyanoacetate, sulfur, and diethyl amine in 100% ethanol, the proposed approach was followed to Synthesize ethyl 5-acetyl-2-amino-4-methylthiophene-3-carboxylate.

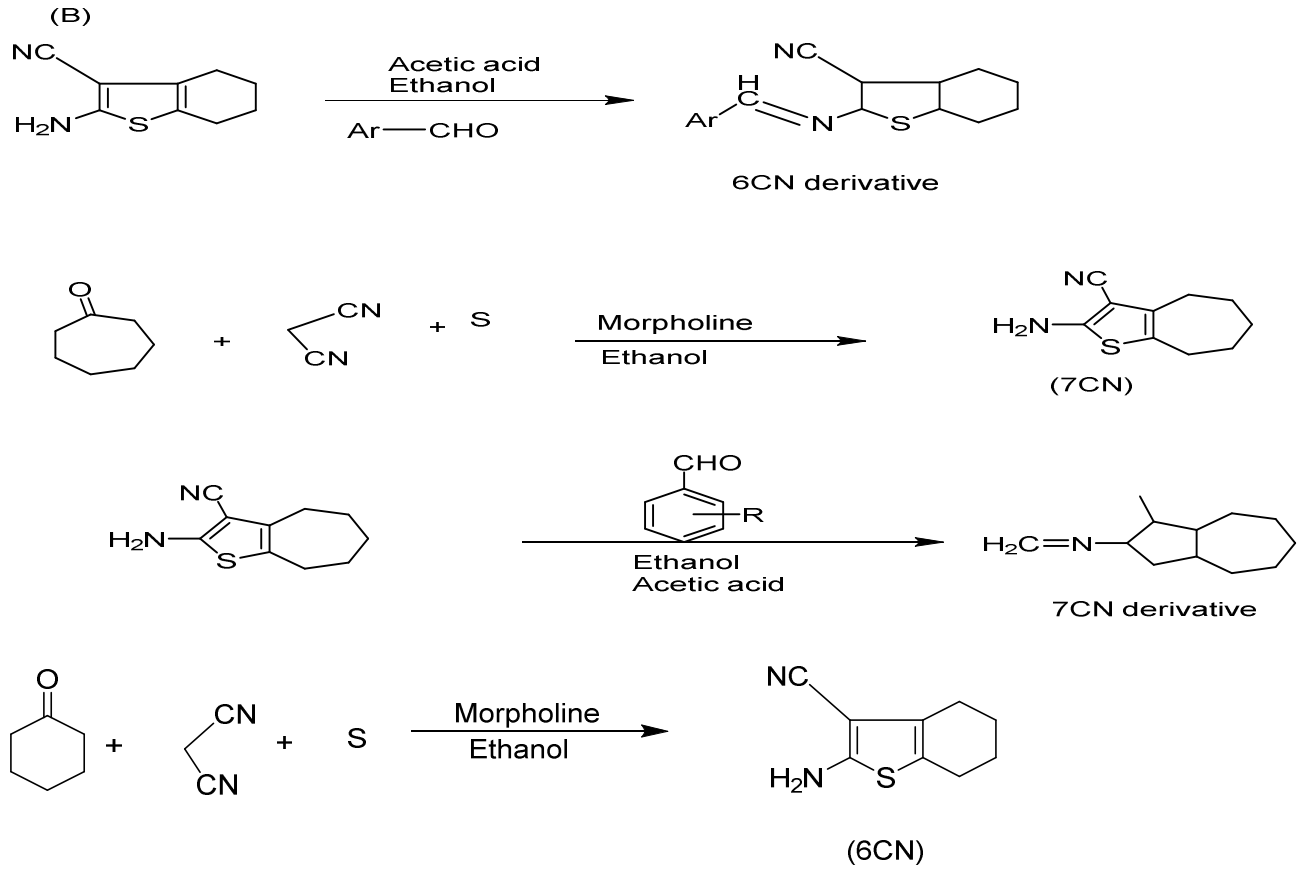
Scheme-8



Activity of 2-amino thiophene derivatives against human cancer cells lines

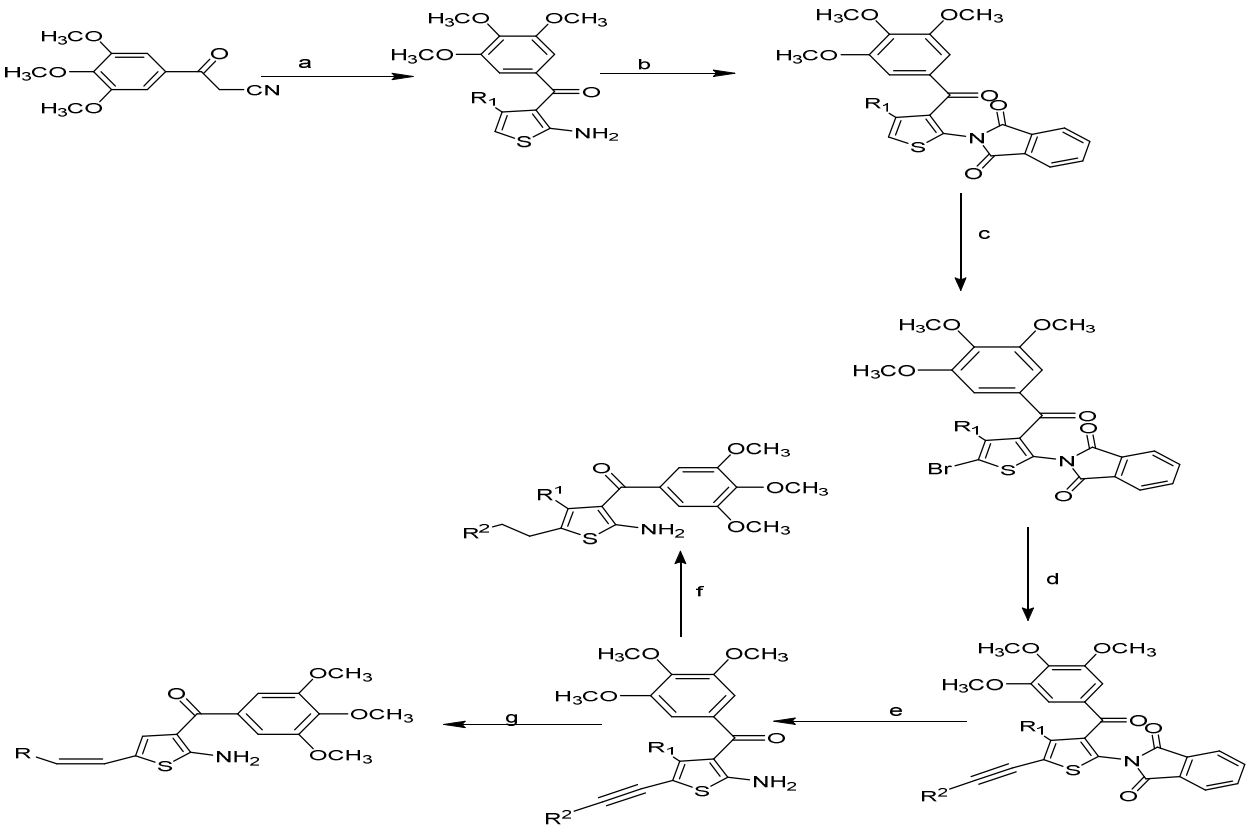
Andreza Conception Véras of Aguiar wassynthesised 6CN09 (2-[(5-bromo-2-methoxi-benzylidene)amino]-4,5,6,7-tetrahydro-4H-benzo[b]thiophene-3-carbonitrile), 6CN10 (2-[(4 Nitro benzylidene)amino]-4,5,6,7-tetrahydro-4H-benzo[b] thiophene-3-carbonitrile), 6CN12 (2-[(4-Methoxi-benzylidene) amino]-4,5,6,7-tetrahydro-4H-benzo[b]thiophene-3-carbonitrile), 6CN14 (2-[(4-Fluoro-benzylidene)amino]-4,5,6,7-tetrahydro-4H benzo[b]thiophene-3-carbonitrile), 7CN09 (2-[(5-Bromo-2 methoxi-benzylidene)amino]-5,6,7,8-tetrahydro-4H-cyclohepta [b]thiophene-3-carbonitrile) and 7CN11 (2-[(4-Chlorobenzyli dene)-amino]-5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophene-3 carbonitrile) catalysed by morpholine and Acetic acid and ethanol used as a solvent

Scheme-9


(B)
NC
H2N
S
Acetic acid
Ethanol
Ar—CHO
NC
H
C
Ar
N
S
6CN derivative
O
+
CN
CN
+ S
Morpholine
Ethanol
NC
H2N
S
(7CN)
NC
H2N
S
CHO
R
Ethanol
Acetic acid
H2C=N
7CN derivative
O
+
CN
CN
+ S
Morpholine
Ethanol
NC
H2N
S
(6CN)

Synthesis of novelantimitotic agents based on 2-amino-3-aroyl-5-(hetero)aryl ethynyl thiophene derivative
R. Romagnoli et al. synthesized 2-amino-3-aroyl-5-(hetero)aryl ethynyl thiophene derivativeas antimitotic agent

Scheme-10

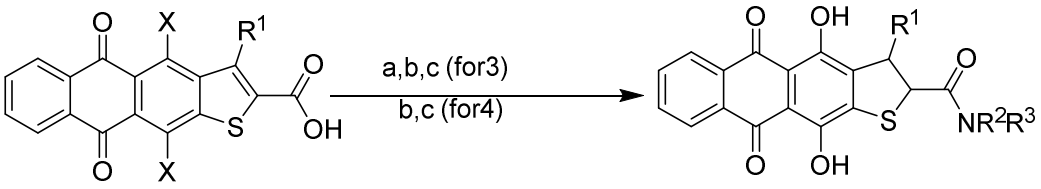


Reagents: (a) 2,5-dimethyl-(1,4)dithiane-2,5-diol or 1,4-dithiane-2,5-diol, TEA, EtOH; (b) phthalic anhydride, AcOH; (c) Br2, AcOH, AcONa, rt;
(d)(hetero)arylacetylene,PdCl2(PPh3)2,CuI,TEA–DMF(1:1,v/v),80 C;(e)NH2NH2,EtOH;(f)H2,10%Pd/C,EtOH(for5a–dand5g);(g)H2,Lindlar'scatalyst,EtOH(for5e and5g)

Thiophene-2-carboxamide derivatives of anthraquinone: A new potent antitumor chemotype

Romagnoli, and et al. Synthesisedanthra [2,3-b] thiophene-2-carboxamides 6e18. Reagents and conditions: (a) 98% sulfuric acid,100 C,1 h, yield of 5 is 80%; (b) PyBOPs, DMSO, DIPEA, N-Boc-protected diamine, rt, 15 min; (c) MsOH, CHCl3, rt

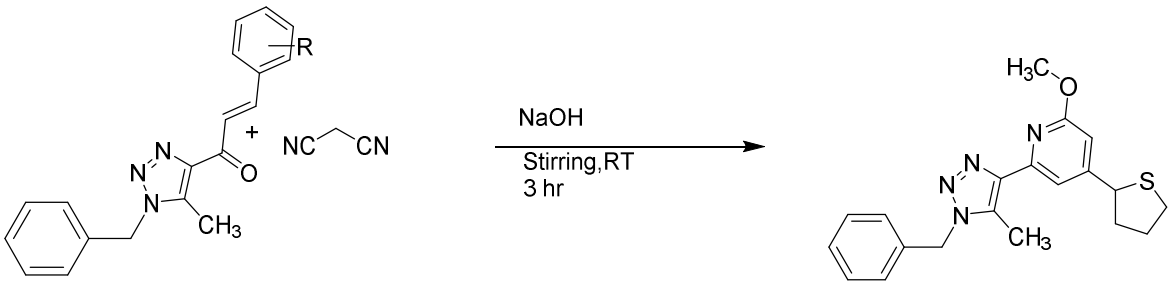
Scheme-11



Novel sulfur heterocyclic thiophene derivative containing 1,2,3-triazole and pyridine moieties as a potential human topoisomerase II inhibiting anticancer agent

Murugavel and et al. have synthesised aNovel sulfur heterocyclic thiophene derivative containing 1,2,3-triazole and pyridine moieties called BTPT [2-(1-benzyl-5-methyl-1H-1,2,3-triazol-4-yl)-6-methoxy-4-(thiophen-2 yl) pyridine] with NaOH as basic catalyst at Room temp.

Schme-12

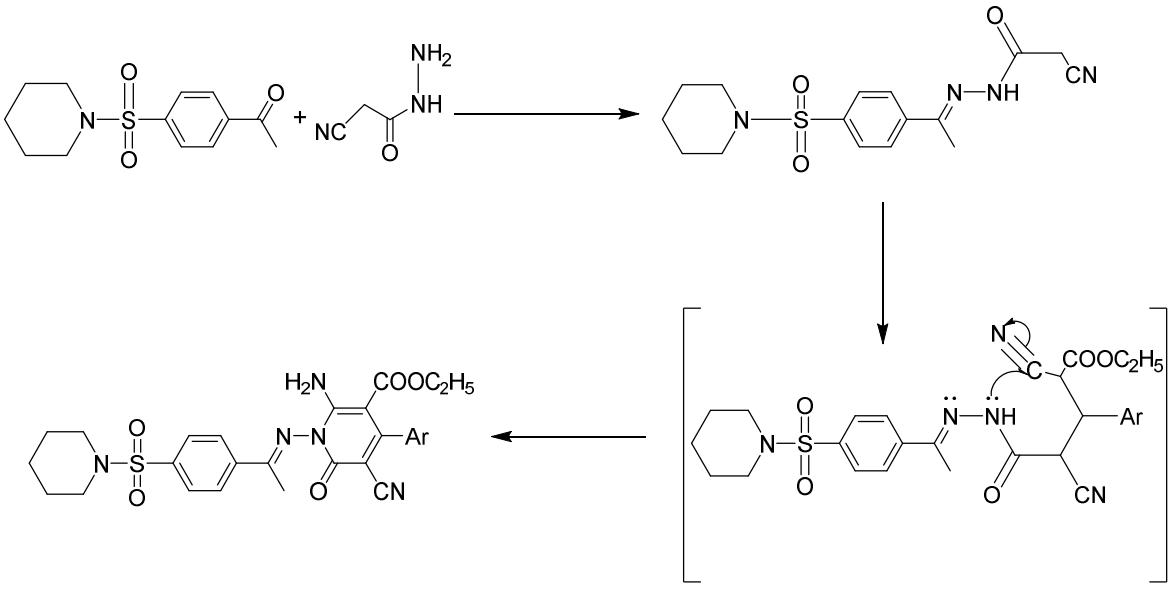


R=Thio

Thiophane, thiazole, and certain new 1,2-dihydropyridine compounds have anti-breast cancer properties.

Mansour S and et al. synthesised 1,2-dihydropyridine compounds have anti-breast cancer properties. With Reagent and conditions: i, ethyl a-cyan cinnamate derivatives/1,4-dioxane/TEA.

Schme-13

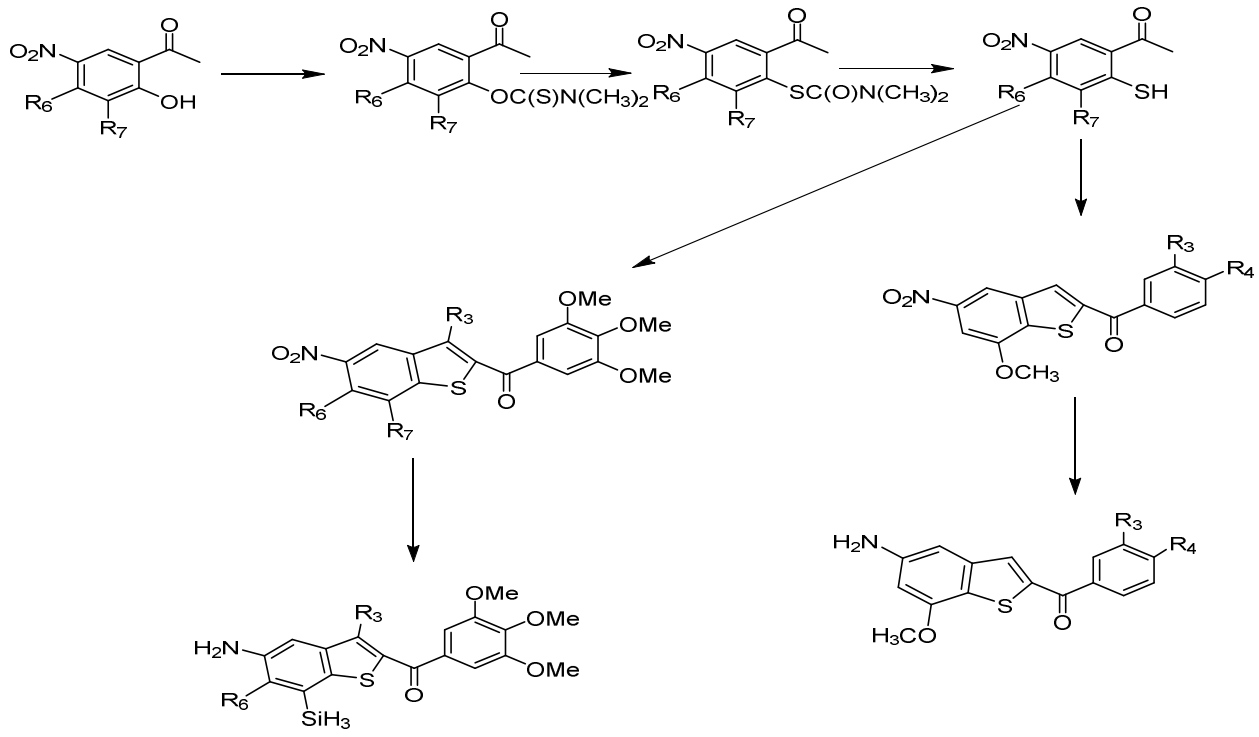


2-Aroyl-5-Amino Benzo[b]thiophene Derivatives as a Novel Class of Potent Antimitotic Agents

Romeo Romagnoland et.al synthesised2-Aroyl-5-Amino Benzo[b]thiophene Derivatives as a Novel Class of Potent Antimitotic Agents

The biological importance of microtubules makes them an interesting target for the synthesis of antitumor agents. The 2-(3',4',5'-trimethoxybenzoyl)-5-aminobenzo[b]thiophene moiety was identified as a novel scaffold for the preparation of potent inhibitors of microtubule polymerization acting through the colchicine site of tubulin. The position of the methoxy group on the benzo[b]thiophene was important for maximal antiproliferative activity. Structure-activity relationship analysis established that the best activities were obtained with amino and methoxy groups placed at the C-5 and C-7 positions, respectively. Compounds 3c-e showed more potent inhibition of tubulin polymerization than combretastatin A-4 and strong binding to the colchicine site. These compounds also demonstrated substantial antiproliferative activity, with IC50 values ranging from 2.6 to 18 nM in a variety of cancer cell lines. Importantly, compound 3c (50 mg/kg), significantly inhibited the growth of the human osteosarcoma MNNG/HOS xenograft in nude mice.

Schme-14


O2N
R6
R7
OH
OC(S)N(CH3)2
SC(O)N(CH3)2
SH
R3
R4
OMe
OMe
OMe
S
O
OCH3
H2N
H3CO
SiH3

CONCLUSION

The review extensively discusses thiophene's significant role in medicinal chemistry, particularly its potential as an anticancer agent, aiming to provide comprehensive insights for researchers to design and synthesize novel, targeted, and advanced thiophene analogs. Thiophene demonstrates a broad spectrum of biological activities and pharmaceutical properties, offering a promising scaffold for the development of potential pharmaceutical agents, supported by detailed structure-activity relationship studies. The paper outlines various synthetic approaches to thiophene and elucidates its structure-activity relationships. Consequently, this review serves as a valuable resource for researchers seeking to develop lead compounds across diverse biological domains, with a particular focus on cancer chemotherapy. While the antiproliferative properties of thiophene derivatives are well-established, there remains a need for the development of more efficient anticancer agents. Addressing the primary challenge in cancer treatment, which is toxicity to normal cells, could be achieved through the development of more selective antiproliferative agents.

ACKNOWLEDGEMENT

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