Chapter 4

Design, Synthesis and Antimicrobial Activities of Some Novel Thiophene Derivatives

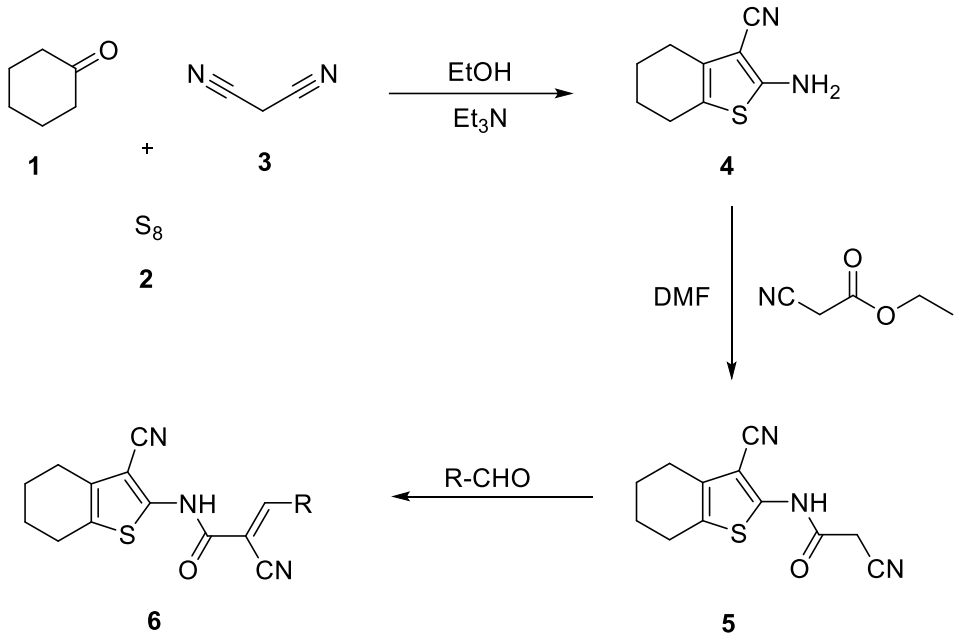
4.1 Introduction

Victor Meyer identified thiophene as an impurity in benzene in 1882. Thiophene's composition was produced by the interaction of succinaldehyde or succinic acid with phosphorus pentasulfide during its production. It was discovered that the substance was heterocyclic.[140] Thiophene exhibits widespread substitution reactions, which suggests that it is aromatic. Single sulphur heteroatom makes a 5-membered ring in the heterocyclic complex class that includes thiophene. Thiophene is a poisonous, volatile, colorless liquid that at ambient temperature smells moderately sweet and resembles benzene.[141] It is soluble in most organic solvents, such as alcohol and ether, but insoluble in water. The electron pairs on sulphur are greatly delocalized in the π system.[142] This makes it a very reactive benzene analogue. Thiophene and ethanol combine to generate an azeotrope, similar to benzene. The physicochemical characteristics of benzene and thiophene are very identical. It is readily nitrated, halogenated, acylated and sulfonated but cannot be alkylated or oxidized. Certain naturally occurring substances and a number of biologically active chemicals include the thiophene backbone.[143] Prominent heterocycles present in several physiologically active and natural molecules are highly substituted thiophene analogues.

Thiophene molecules are used as corrosion inhibitors in industrial chemistry and material science.[144] Since they are important reactants in organic synthesis and often utilized as the scaffold motif of several agrochemicals, pigments and physiologically active products.[145-147] Substituted 2-amino thiophene synthesis is attractive to researchers. Because of this, a variety of strategies for the synthesis of these minerals have been documented in the literature.[148-151] The Gewald technique,[152,153] which involves a multicomponent reaction of a ketone with an active nitrile and elemental sulphur in the presence of base like piperidine and morpholine as a catalyst, is the most practical approach for producing thiophenes with a high level of functionality.

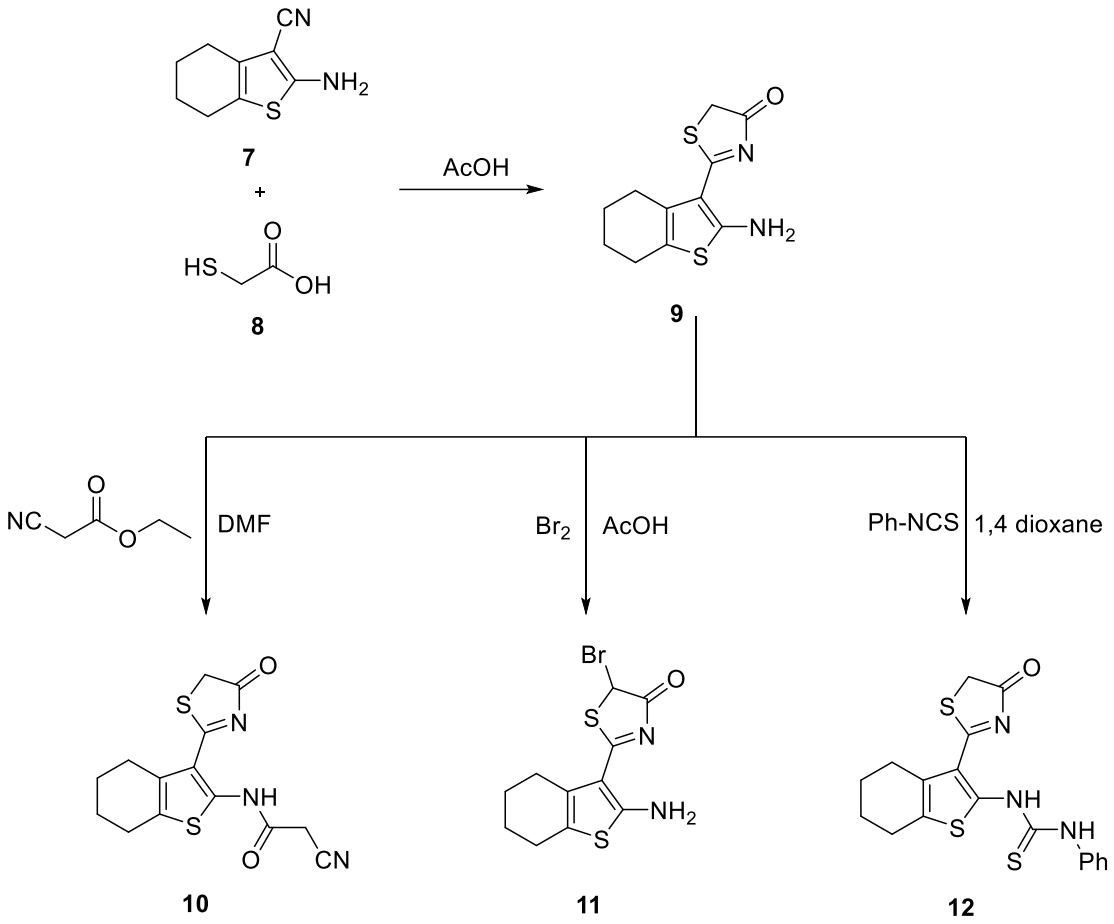
4.1.1 Synthetic approaches for substituted thiophene scaffold and its biological importance

W. Wardakhan *et al*[154] reported thiophene synthesis, starting from reaction of the cyclohexanone **1** with sulphur **2** and malononitrile **3** to form amino benzo thiophene molecule **4**, which was further reacted with ethyl cyanoacetate in DMF at reflux temperature to form molecule **5** which was reacted with various substituted aldehydes to form novel benzo thiophene molecules **6**. The synthesized molecules were screened for their anticancer activity against various cell lines such as MCF-7, NCI-H460 and SF-268. The results showed that some of the molecules exhibited excellent cytotoxicity against all three cell lines and could be examined for further trials **(Scheme 4.1)**.



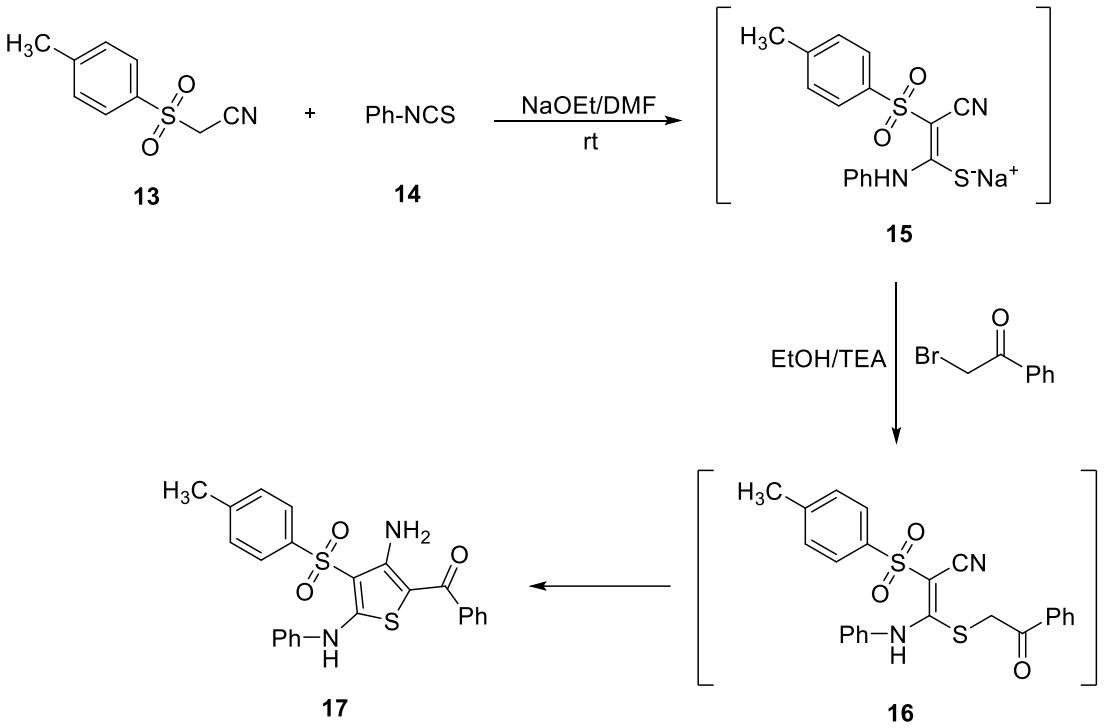
Scheme 4.1

R. Mohareb *et al*[155] reported synthesis of thiophene-thiazole molecules synthesis via reacting amino benzothiophene **7** with thioglycolic acid **8** in glacial acetic acid to form molecule **9** in good yields. Furthermore, the reaction of molecule **9** with various compounds like ethyl cyanoacetate in DMF, bromine in acetic acid and phenyl isothiocyanate in 1,4-dioxane formed series of novel benzothiophene molecules **10**, **11** and **12**. The synthesized molecules were screened for their anticancer activity against NUGC, DLD-1, HA22T, HEPG-2, MCF, HONE-1 and WI-38 cells. Some of the screened molecules showed excellent outcomes from the study. It was observed that electron withdrawing molecules showed excellent inhibitory effect **(Scheme 4.2)**.

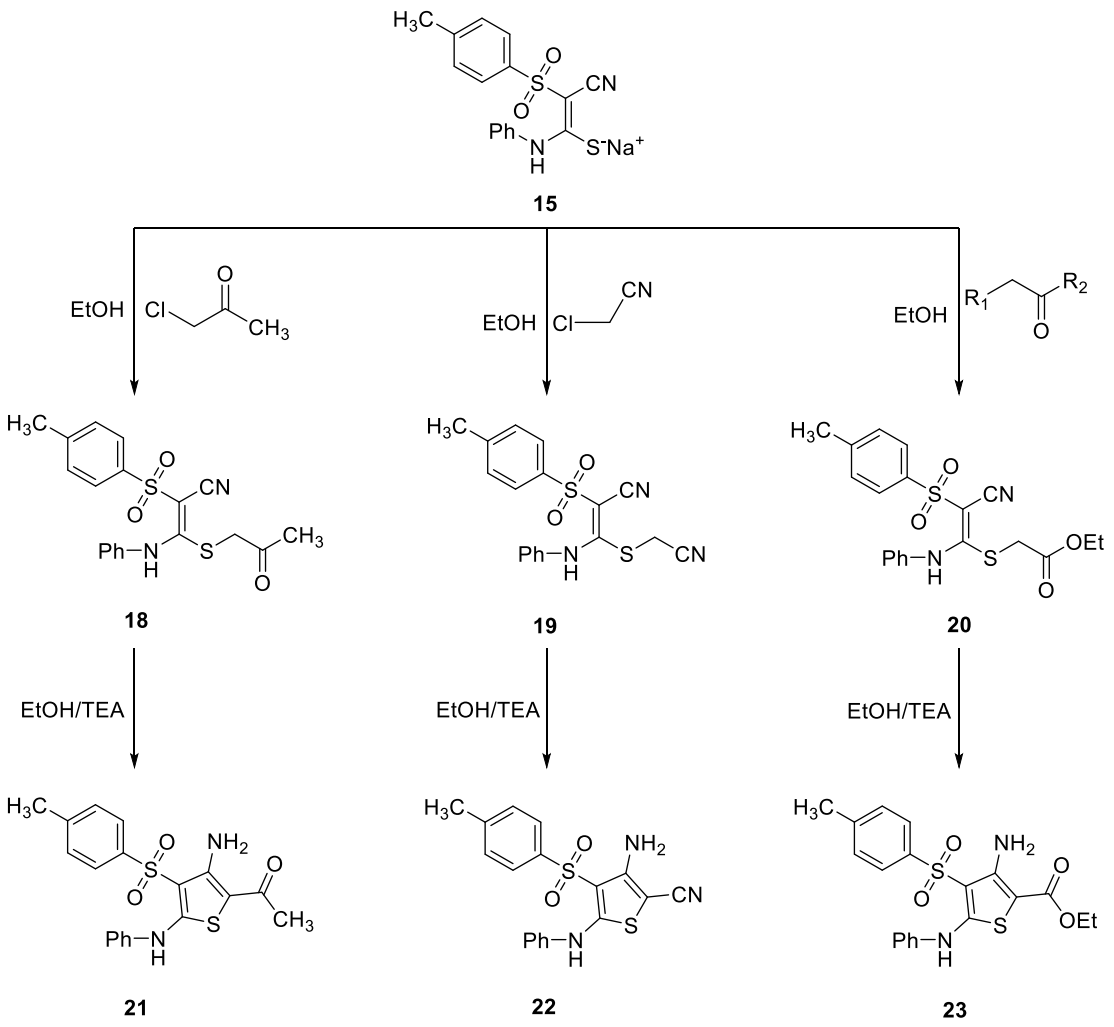


Scheme 4.2

A. Fadda *et al*[156] reported synthesis of tosyl thiophene molecule via reaction of active methylene molecule **13** with phenyl isothiocyanate **14** molecules in presence of sodium ethoxide in DMF to form intermediate salt molecule **15**. Furthermore, molecule **15** was reacted with phenacyl bromide derivatives to form another intermediate molecule **16**, which was cyclized via reflux to form thiophene molecules **17 (Scheme 4.3)**. The intermediate salt molecule **15** was reacted with various other molecules like halogen derivative, chloro acetonitrile and ketone molecule was refluxed in ethanol to form various intermediate molecules **18**, **19** and **20**. Furthermore, these molecules were cyclized in ethanol containing catalytical amount of triethylamine to form molecules **21**, **22** and **23 (Scheme 4.4)**. The synthesized molecules were screened for their antitumor activity in which molecules containing halogen substitution showed significant increase in the inhibitory activity and molecules with methoxy substitution showed moderate to excellent response as well.


H3C
O
S
O
CN
13
+
Ph-NCS
14
NaOEt/DMF
rt
H3C
O
S
O
CN
PhHN
S-Na+
15
EtOH/TEA
Br
O
Ph
H3C
O
S
O
CN
Ph–N
H
S
Ph
O
16
H3C
O
S
O
NH2
O
Ph
Ph–N
H
S
17

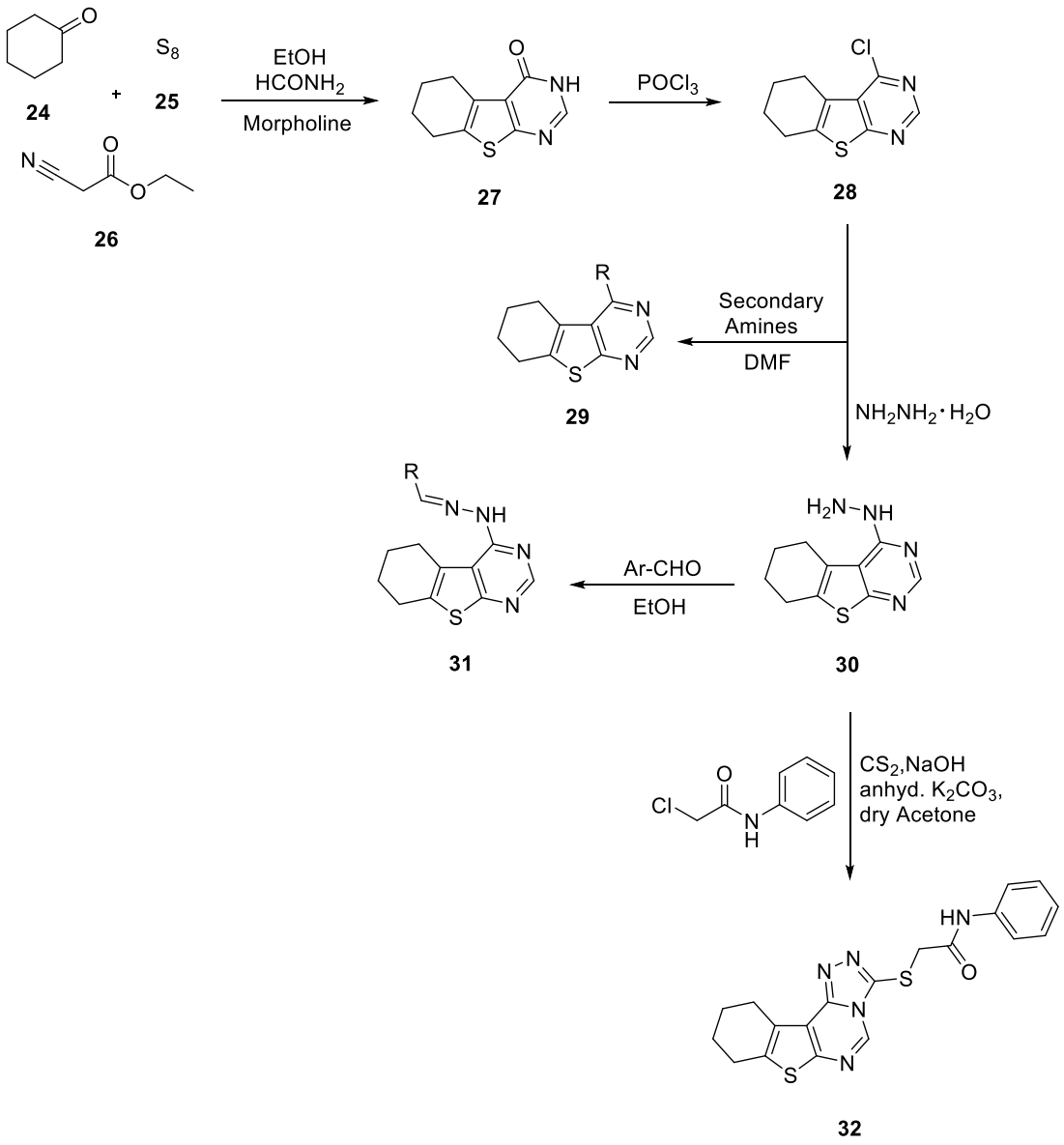
Scheme 4.3



Scheme 4.4

R. Soliman *et al*[157] reported synthesis of tetrahydro benzothiophene molecules via following gewald's methodology. The reaction of cyclohexanone **24**, elemental sulphur **25** and ethyl cyanoacetate **26** in presence of morpholine and refluxed in ethanol to form benzothiophene molecule which was further reacted with formamide to form molecule **27**. Furthermore, the chlorination of the molecule **27** via reaction with phosphorus oxychloride formed chlorinated adduct **28**, to this several secondary amines were attached via reflux in DMF to form molecule **29**. The reaction of chlorinated product **28** with hydrazine hydrate formed molecule **30**, to which different aldehydes were attached via refluxing in ethanol to form various new thiophene **31** molecules. Additionally, the reaction of molecule **30** with carbon disulphide and sodium hydroxide in dry acetone with halogenated molecule formed cyclized triazole benzothiophene **32** like molecule. The synthesized molecules were screened for their antimicrobial activity

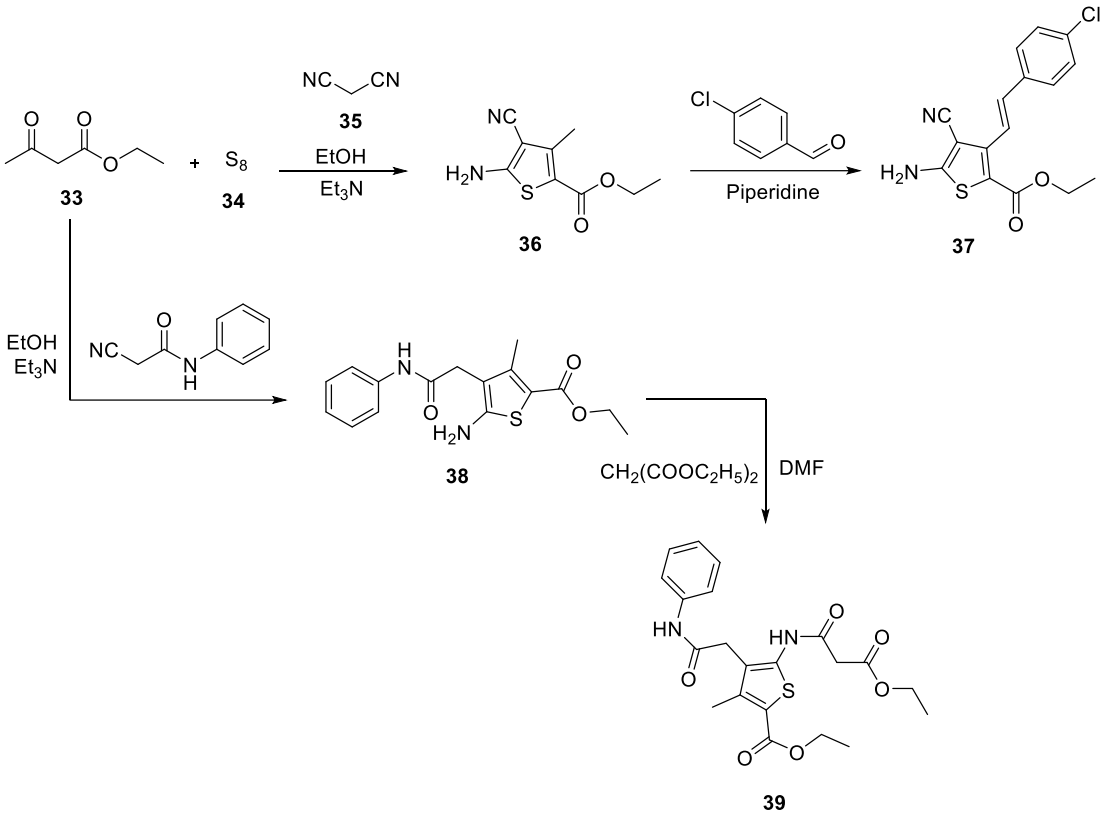
in which several molecules showed significant antibacterial and antifungal activity **(Scheme 4.5)**.



Scheme 4.5

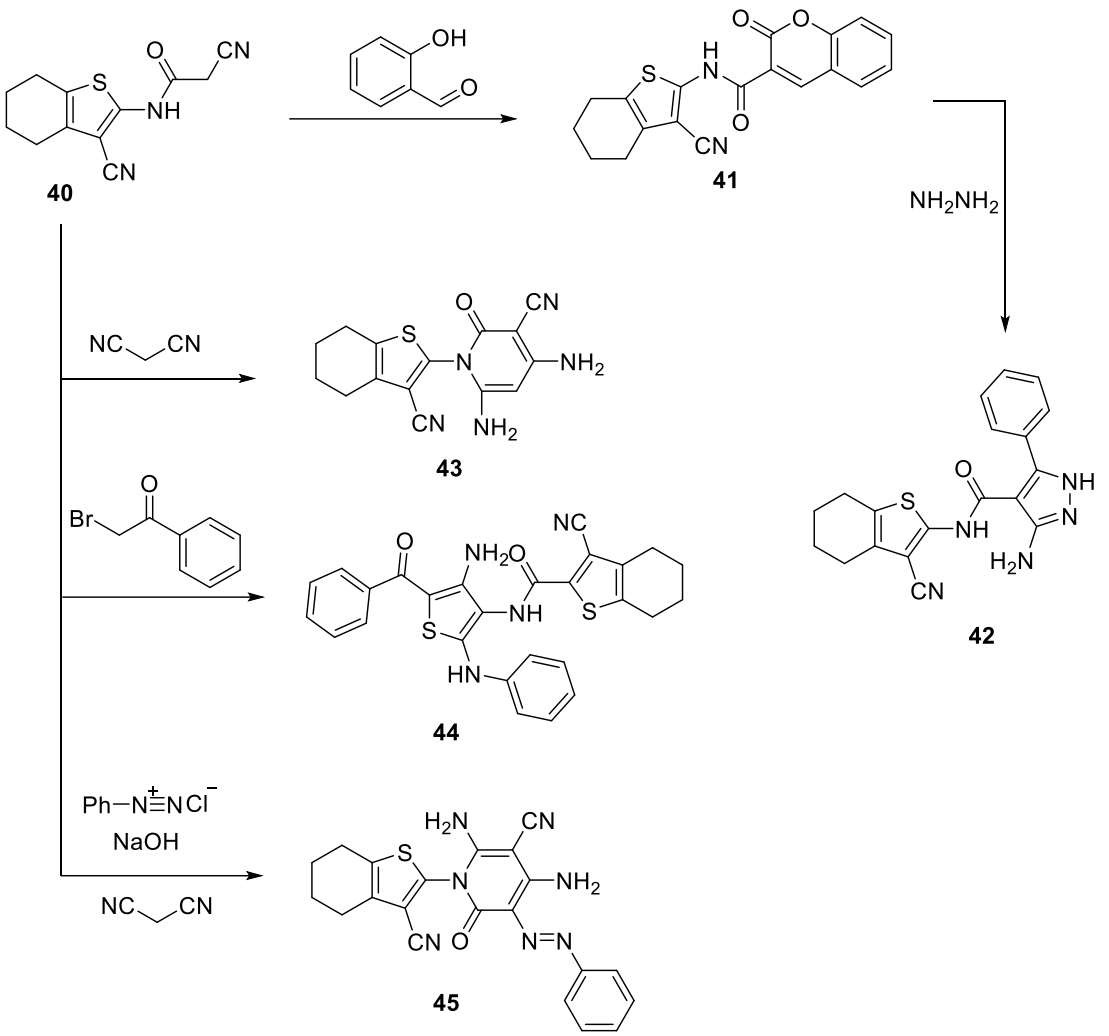
R. Mohareb *et al*[158] reported synthesis of novel thiophene molecules and screened for their cytotoxic assessment. The reaction between ethyl acetoacetate **33**, sulphur **34** and malononitrile **35** in ethanol containing catalytical amount of triethyl amine to form cyclized amino thiophene molecule **36** in good yields. Furthermore, 4-chloro benzaldehyde was attached to molecule **36** in ethanol containing catalytical amount of piperidine to form molecule **37**. Moreover, the reaction of active methylene molecule

with ethyl acetoacetate **33** and diethyl malonate in ethanol and DMF to form another highly functionalized thiophene molecules **38** and **39 (Scheme 4.6)**.



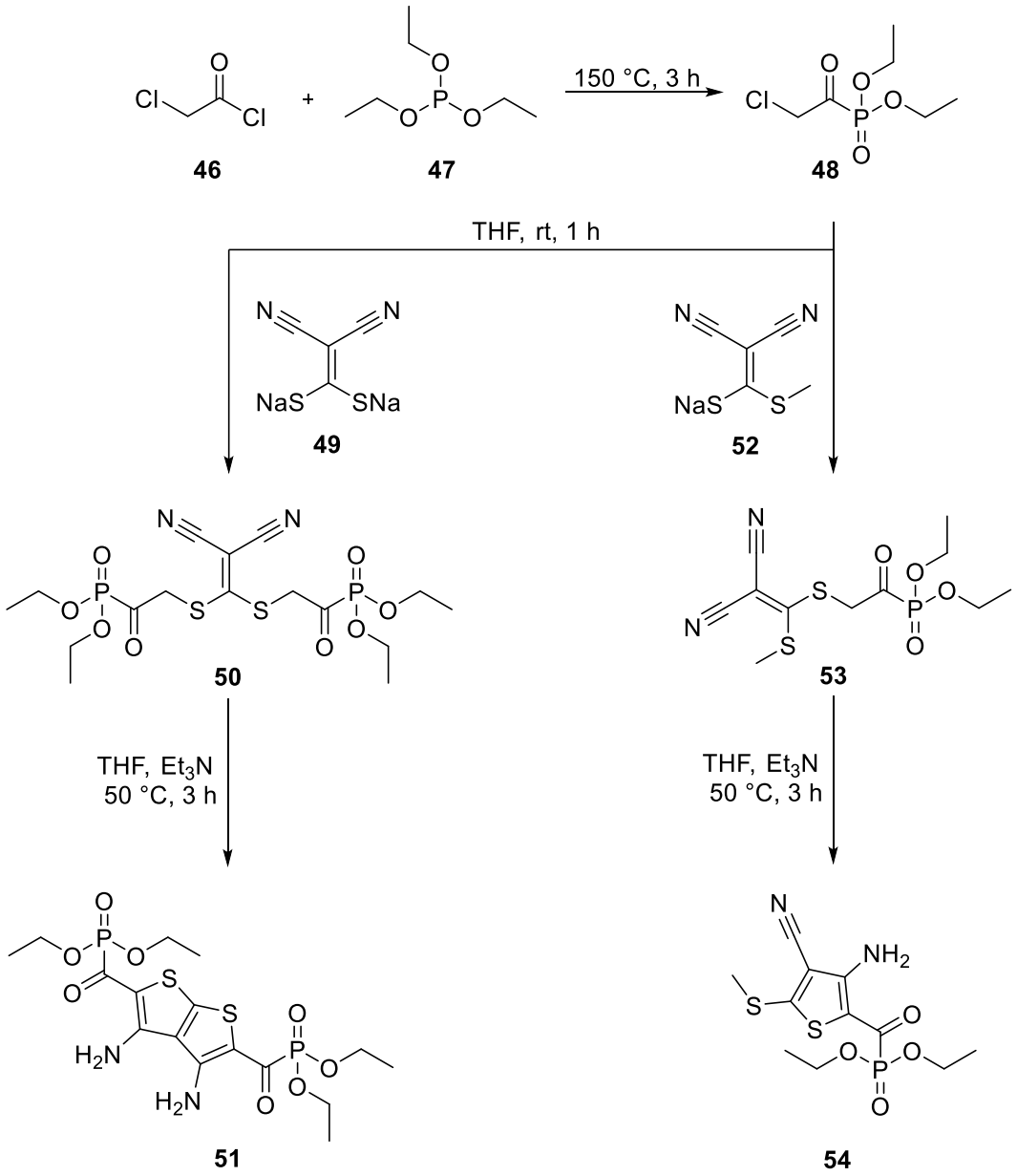
Scheme 4.6

H. Shams *et al*[159] reported synthesis of benzothiophene molecules. The reaction of molecule **40** with salicylaldehyde formed chroman benzothiophene molecule **41**, which was again reacted with hydrazine hydrate to break the chroman ring and converted into pyrazole ring **42**. The reaction of the molecule **40** with malononitrile, phenacyl bromide and diazonium salt compounds with malononitrile formed respective molecules **43**, **44** and **45**. These synthesized molecules were screened for antitumor screening in which some of the synthesized molecules showed promising antitumor activity. The synthesized molecules were also screened for their antibacterial and antifungal activity **(Scheme 4.7)**.



Scheme 4.7

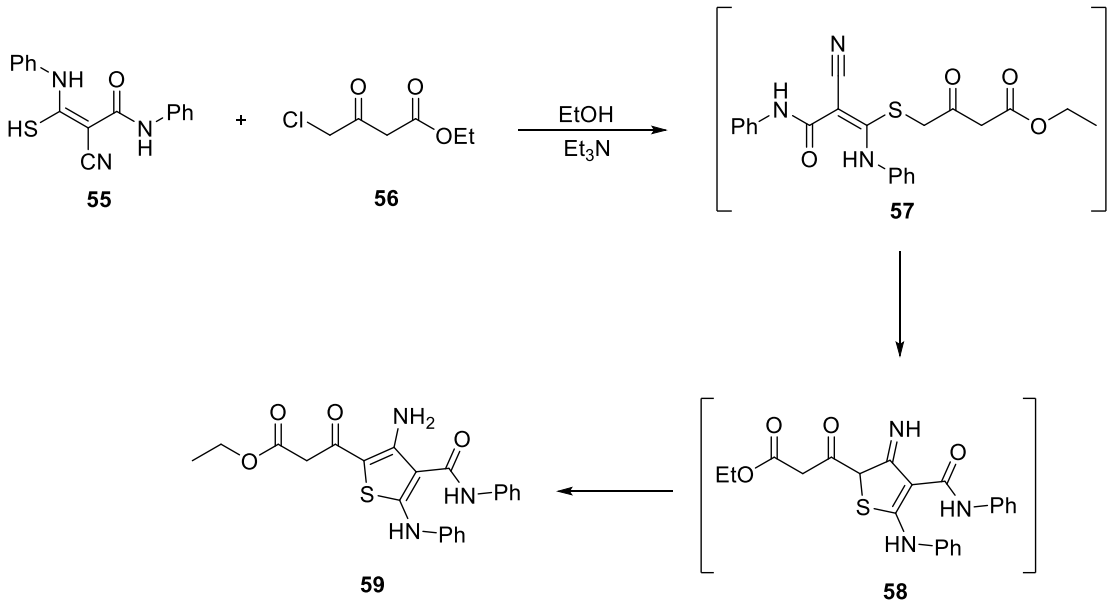
T. Ali and M. Assiri[160] reported synthesis of some novel thiophene molecules. The reaction of chloroacetyl chloride **46** and triethyl phosphite **47** formed molecule **48**. The reaction of molecule **48** with sodium 2,2-dicyanoethene-1,1-bis(thiolate) **49** to form intermediate molecule **50** which was refluxed in tetrahydrofuran containing triethylamine to form clubbed highly functionalized thiophene molecule **51**. Furthermore, reaction of the molecule **48** with sodium 2,2-dicyano-1-(methylthio)ethene-1-thiolate **52** formed intermediate molecule **53** which undergoes cyclization to form another highly functionalized thiophene molecule **54** **(Scheme 4.8)**.



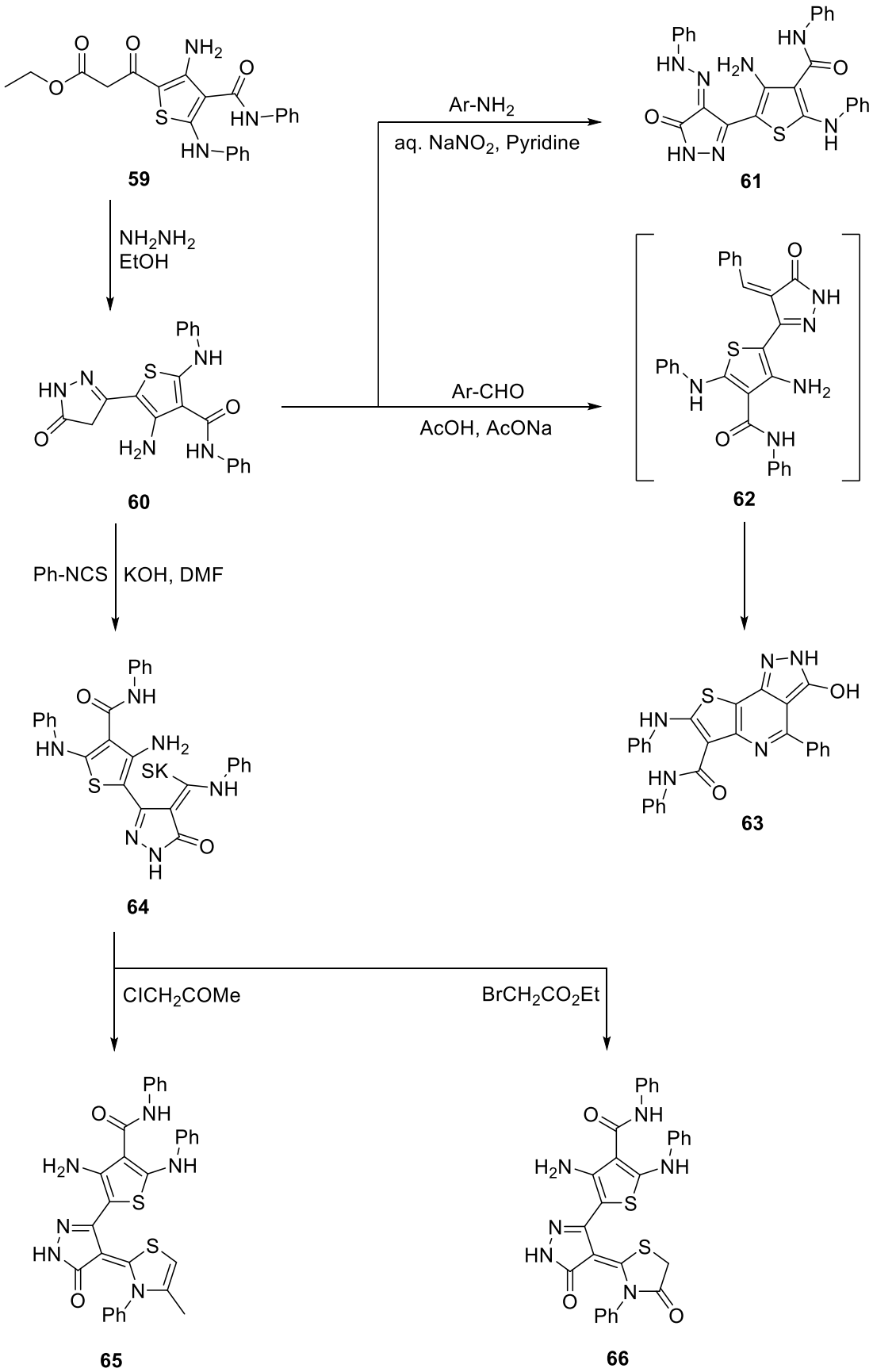
Scheme 4.8

G. Masaret *et al*[161] reported synthesis of highly functionalized thiophene molecules and screened the synthesized molecules for their anticancer activity. The reaction between thio acetanilide molecule **55** with ethyl 4-chloro acetoacetate in ethanol containing catalytical amount of triethylamine formed intermediate molecule **57** which was cyclized to form molecule **59 (Scheme 4.9)**. The reaction of the molecule **59** with hydrazine hydrate in ethanol formed pyrazole-thiophene molecule **60** in good yield. Furthermore, the reaction of molecule **60** with various substituted amines in pyridine containing sodium nitrate formed molecule **61** and reaction with various benzaldehydes in acetic acid containing sodium acetate formed cyclized highly functionalized

thiophene-pyridine pyrazole molecule in good yields. The reaction of molecule **60** with phenyl isothiocyanate in DMF containing potassium hydroxide formed molecule **64**. Moreover, the reaction of molecule **64** with chloroacetone and ethyl bromoacetate formed respective molecule **65** and **66** in good yields. The synthesized molecules were screened for their anticancer activity against HepG2, PC3 and MCF-7 cell lines. The chloro substitution showed promising anticancer activity. The synthesized molecules also subjected to molecular docking studies with hepatitis C virus **(Scheme 4.10)**.

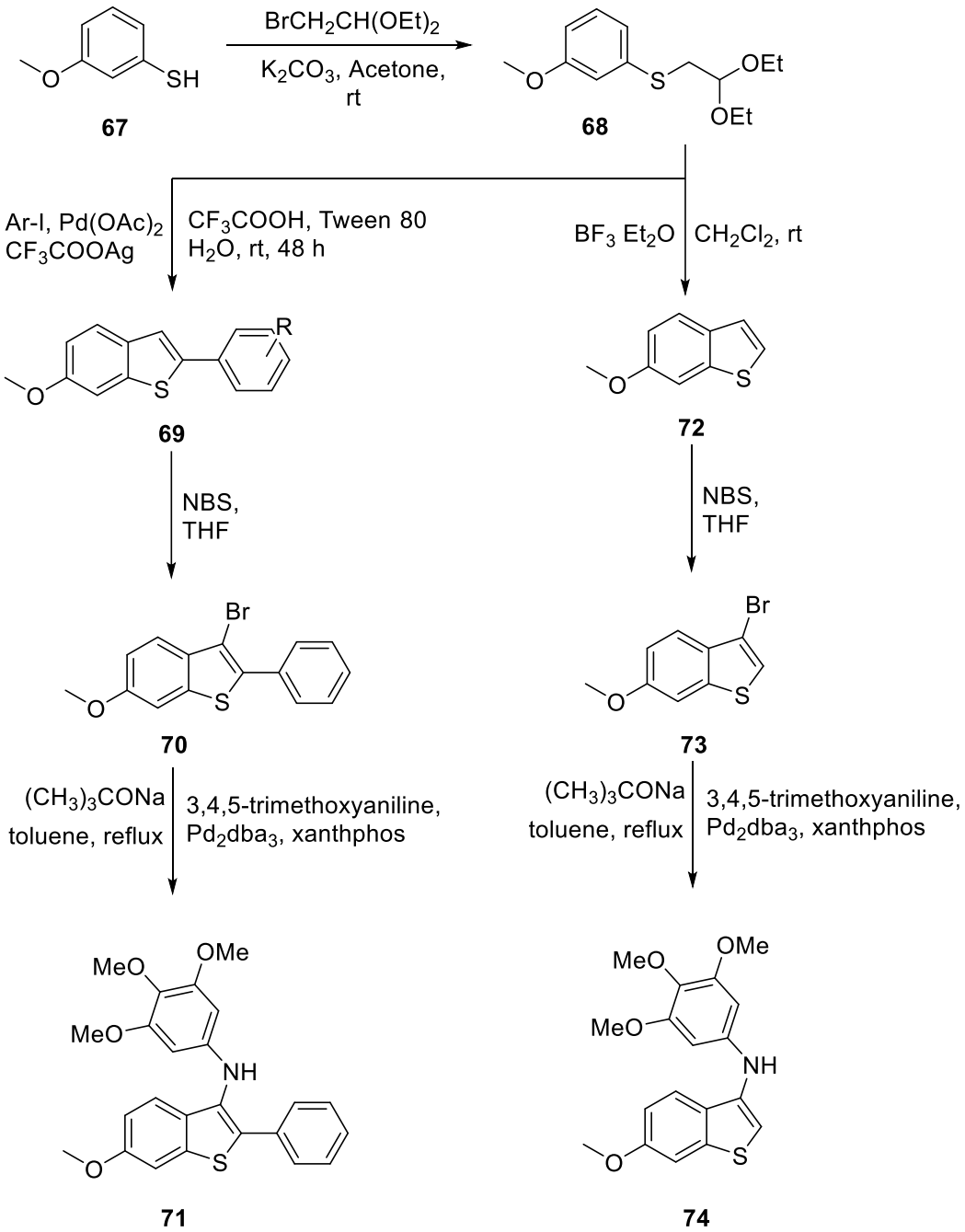


Scheme 4.9


Ar-NH2
aq. NaNO2, Pyridine
NH2NH2
EtOH
Ar-CHO
AcOH, AcONa
Ph-NCS
KOH, DMF
ClCH2COMe
BrCH2CO2Et
59
60
61
62
63
64
65
66

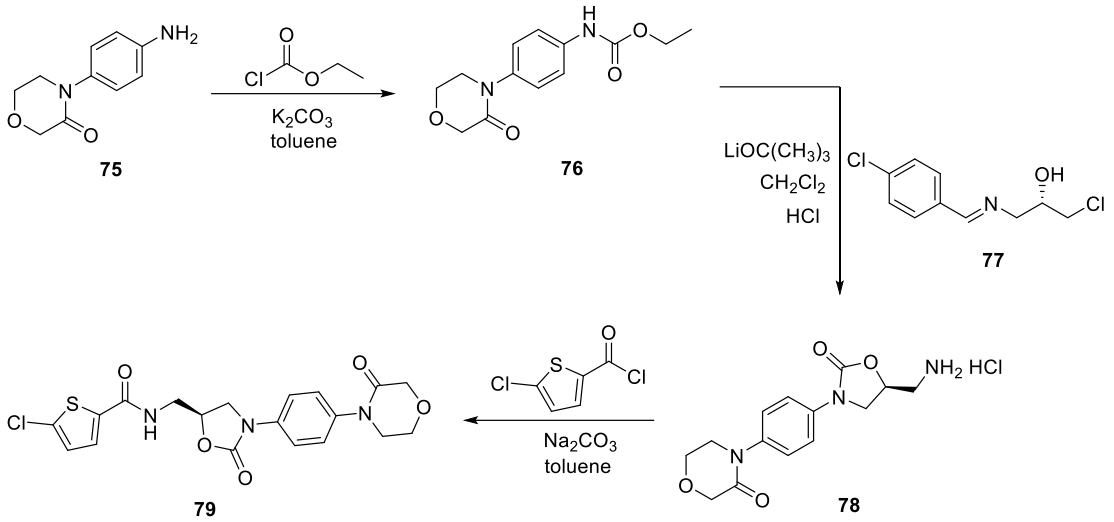
Scheme 4.10

R. Romagnoli *et al*[162] reported synthesis of thiophene molecules and derived result of screening the molecules as apoptosis inducing molecules. The reaction of methoxy thiophenol **67** derivatives with bromo acetaldehyde diethyl acetal in acetone at room temperature afforded diethyl molecule **68**. Furthermore, the reaction of molecule **68** with iodo phenyl molecule in presence of trifluoroacetic acid at room temperature afforded molecule **69** which was reacted with NBS in THF to form brominated benzothiophene molecule, to which tri methoxy amine was attached to form molecule **71**. Again, the reaction of molecule **68** with boron trifluoride etherate afforded cyclized benzothiophene molecule **72**, which was again followed same protocol as for the synthesis of molecule **71** to afford molecule **74**. The synthesized molecules were screened for their antiproliferative activity in which molecules having phenyl substitution and para fluoro substitution was found to show higher antiproliferative activity. The synthesized molecules were also subjected to screening against colon carcinoma cells **(Scheme 4.11)**.



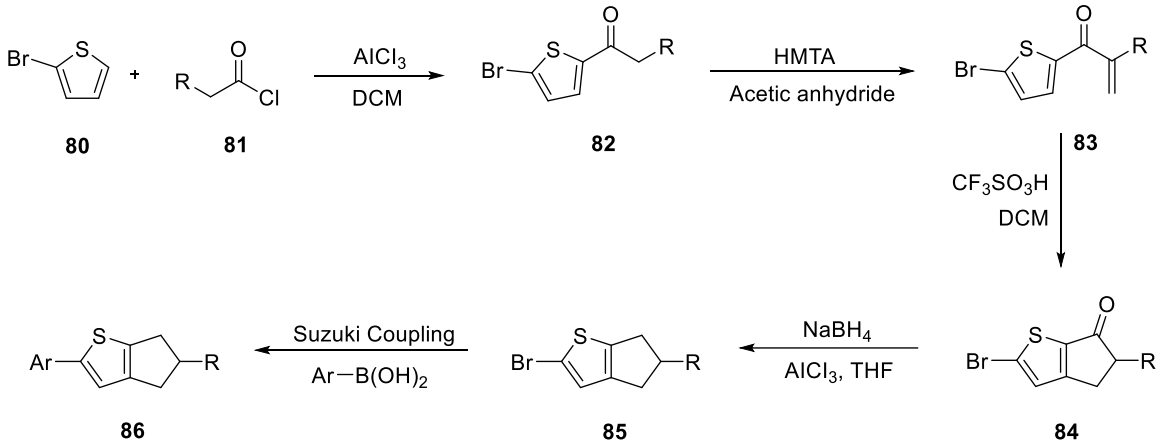
Scheme 4.11

S. Prasangi *et al*[163] reported new route of morpholine incorporated thiophene molecules synthesis which is an anticoagulant medicine. The reaction of starting precursor **75** with ethyl chloroformate afforded the molecule **76** which was reacted with lithium *tert*-butoxide and epichlorohydrin derivative in chloroform and further with hydrogen chloride to form hydrochloride salt of the molecule **78**. Furthermore, thiophene chloride was attached to it in toluene containing sodium carbonate yielded molecule **79 (Scheme 4.12)**.



Scheme 4.12

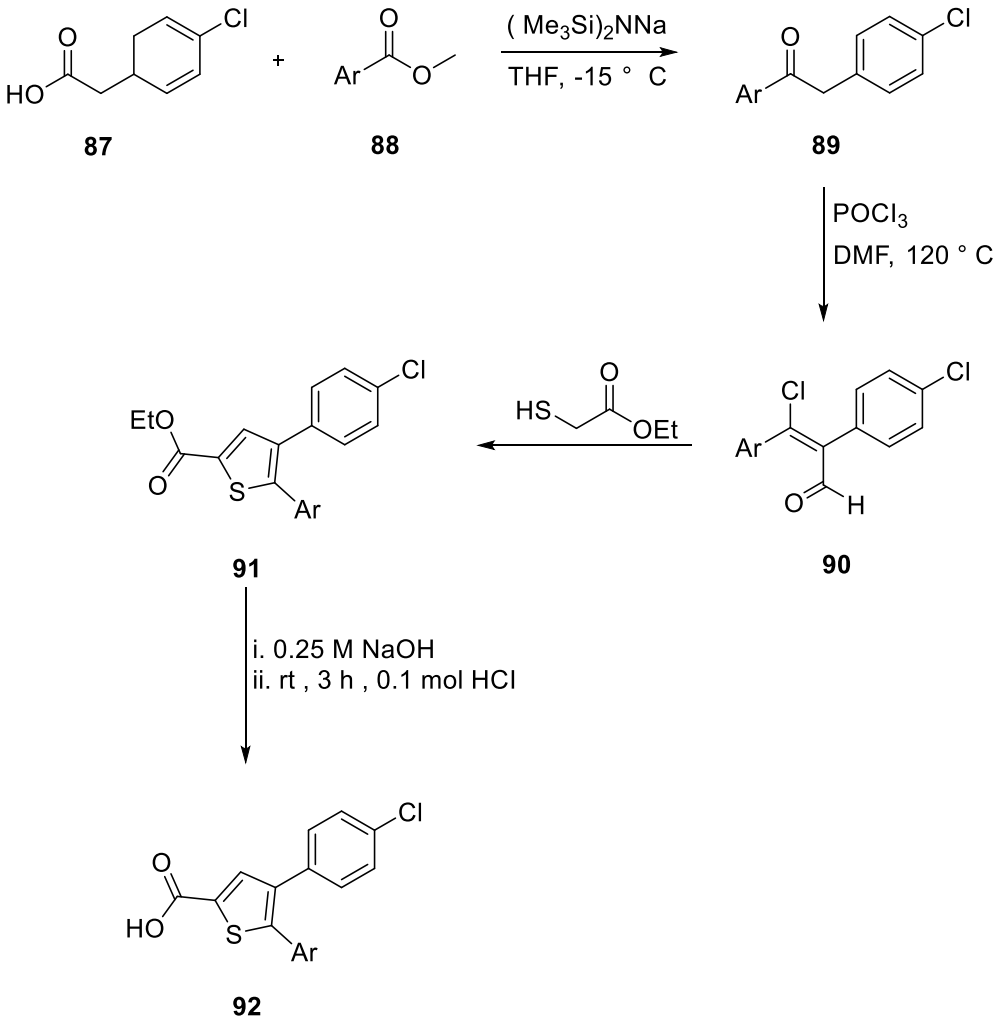
D. Wan and co-workers[164] reported synthesis of cyclopenta[b]thiophene and analyzed for its liquid crystalline properties. The reaction of bromo thiophene **80** with alkyl acyl chloride **81** derivative in DCM with aluminum chloride to form molecule **82** which was reacted with hexamethylenetetramine and acetic anhydride to form molecule **83** which was cyclized via reaction with trifluoromethanesulfonic acid to form molecule **84**. Moreover, the reaction of the molecule **84** with sodium borohydride to reduce the ketone to form molecule **85**, to which various boronic acids were attached to form series of novel thiophene molecules **86** **(Scheme 4.13)**.



Scheme 4.13

A. Arasavelli *et al*[165] reported aryl thiophene acid molecules synthesis and examined the synthesized molecules for their biological activity. The reaction between acid

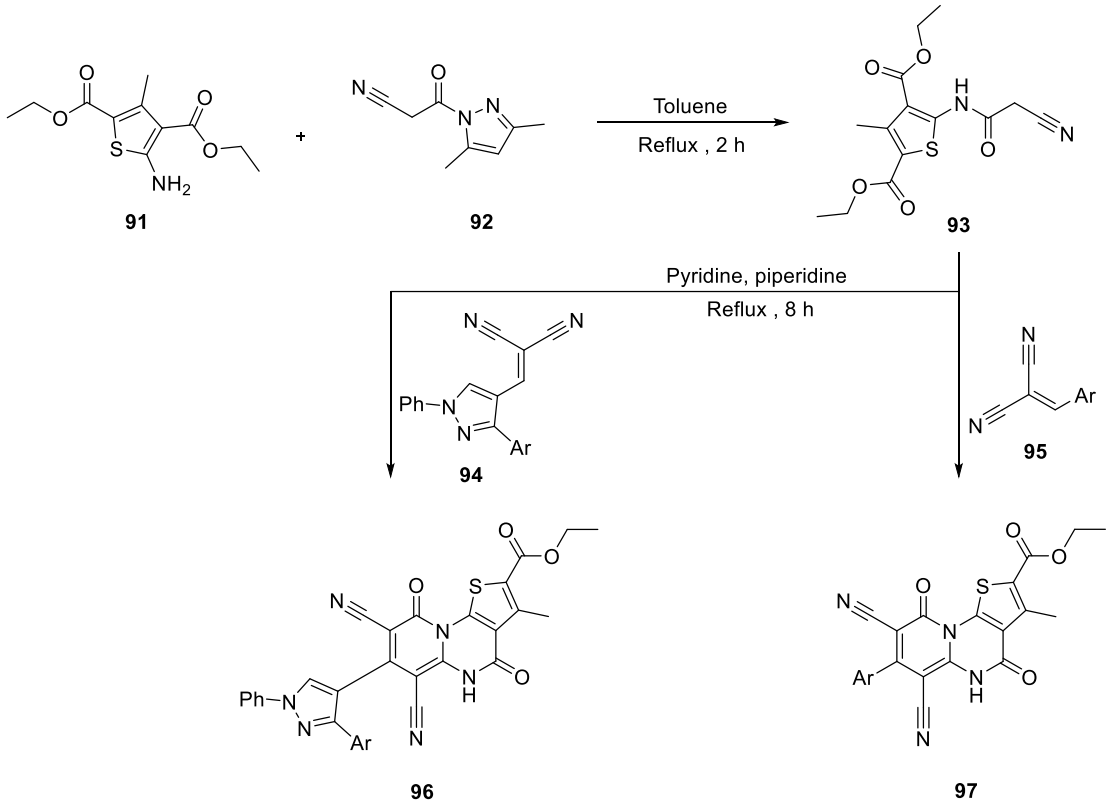
molecule **87** and ester **88** in THF containing bis(trimethylsilyl)amide at very low temperature formed molecule **89**. Furthermore, the reaction of molecule **89** with phosphorus oxychloride and DMF formed chlorinated aldehyde molecule **90** which undergoes cyclization via reaction with thioglycolic acid ethyl ester to form thiophene molecule **91**. Moreover, ester thiophene molecule **91** was converted to acid via reaction with sodium hydroxide to form acid thiophene molecules **92**. The prepared molecules were screened for their antibacterial activity against gram-positive and gram-negative bacteria, also anticancer examination was also done against human prostate cancer cell line PC-3 **(Scheme 4.14)**.



Scheme 4.14

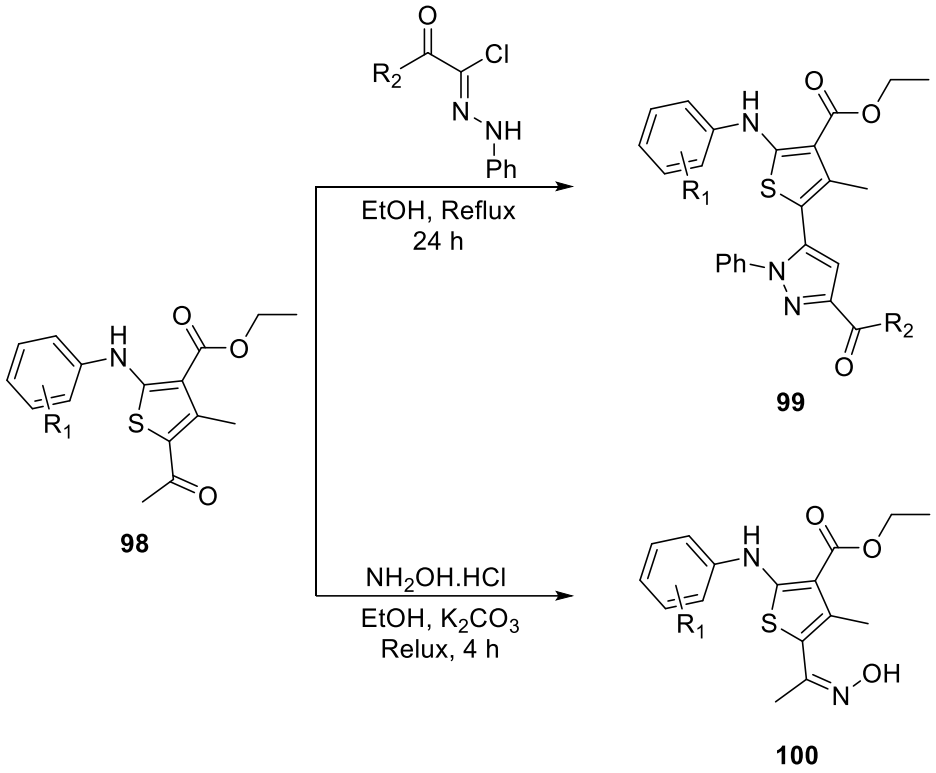
A. Abdelmoniem *et al*[166] reported synthesis of fused thiophene molecules. The reaction between diethyl amino thiophene **91** molecule with cyan acetylating agent in toluene formed molecule **93**. Furthermore, the reaction of cyano acetylated molecule with two

different arylidene malononitrile **94** and **95** afforded respective molecules **96** and **97** in good yield. The synthesized molecules were screened for their antibacterial activity against five bacteria and showed moderate to good inhibition zone **(Scheme 4.15)**.



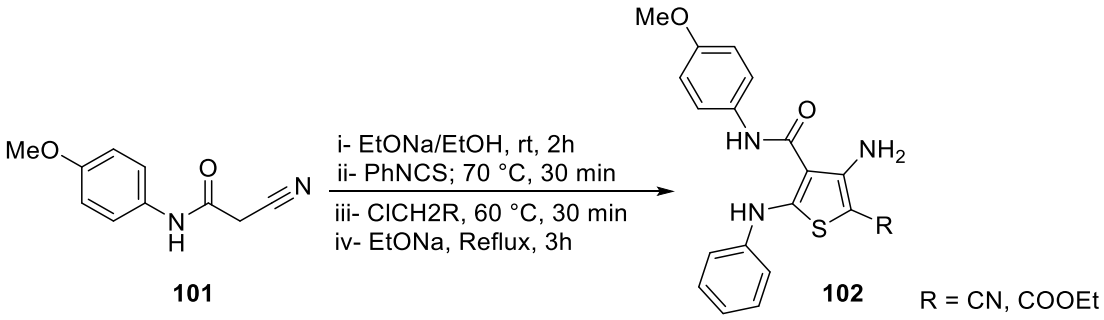
Scheme 4.15

A. Alsayari *et al*[167] reported synthesis of thiophene molecules and screened them for their antimicrobial and anticancer activity. The reaction of thiophene **98** molecule with hydrazonoyl chloride derivative in ethanol at reflux temperature for 24 hr formed pyrazolo thiophene molecule **99**. The reaction between hydroxyl amine hydrochloride and molecule **98** in ethanol containing potassium carbonate at reflux temperature formed hydroxy imino derivative **100**. The results showed moderate to excellent antibacterial and antifungal activity. The cytotoxic activity against HCT-116 IC_{50} value 11.13 μM **(Scheme 4.16)**.



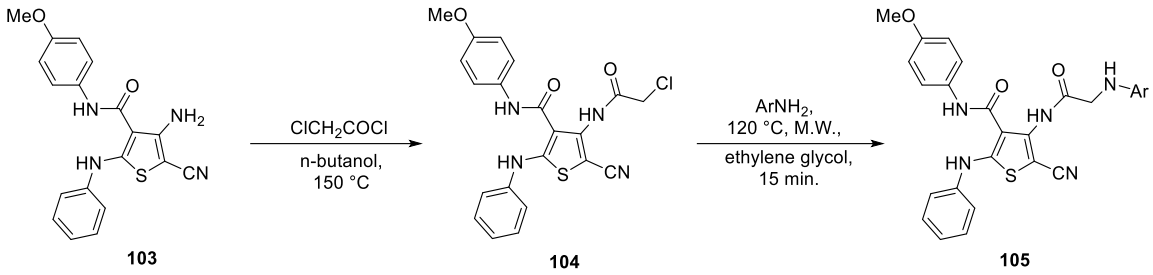
Scheme 4.16

M. Abdelhameid and co-workers[168] reported highly substituted thiophene molecules synthesis, starting from reaction of acetamide derivative **101** with sodium ethoxide in ethanol, the mixture was stirred at room temperature for 2 hr to generate charge, followed by addition of phenyl isothiocyanate derivative to the reaction afforded intermediate molecule which was cyclized via reaction with halogen derivative and sodium ethoxide afforded cyclized thiophene molecule **102 (Scheme 4.17)**.



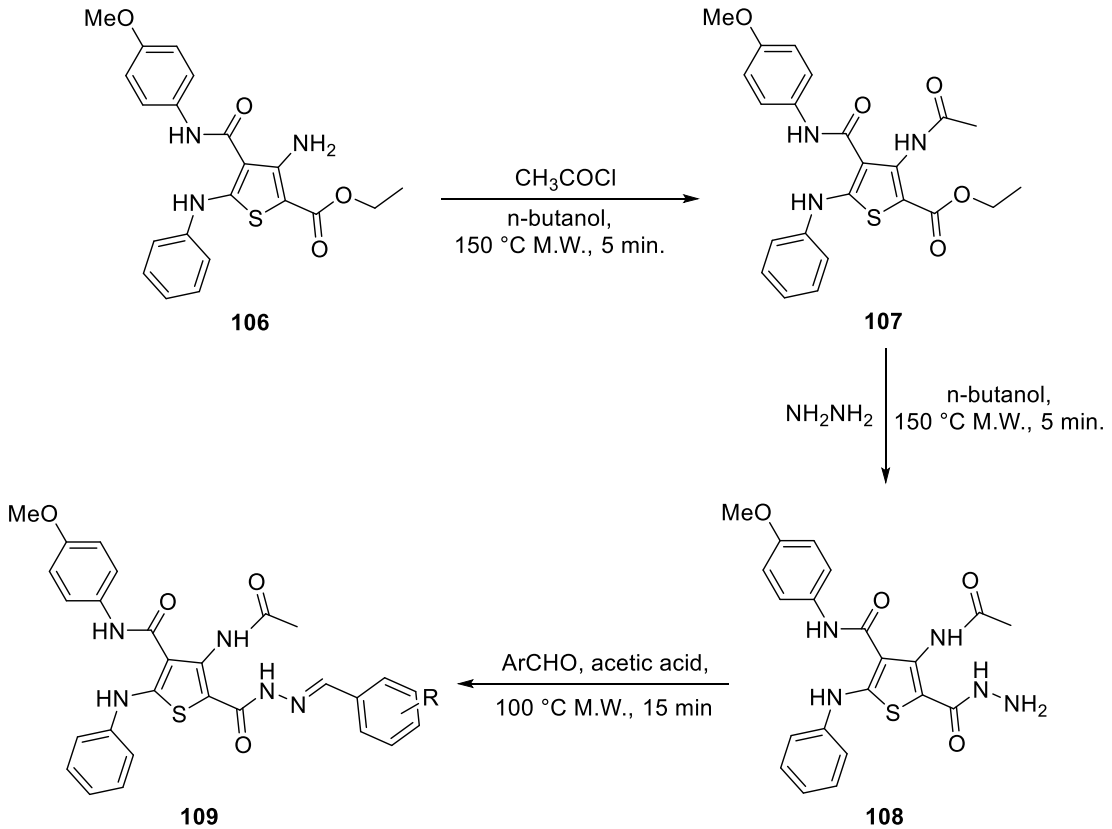
Scheme 4.17

Moreover, molecule **103** with chloroacetyl chloride in butanol formed molecule **104**, to which various aromatic amines were attached in microwave irradiation in presence of ethylene glycol for 15 min to form thiophene derivative **105 (Scheme 4.18)**.



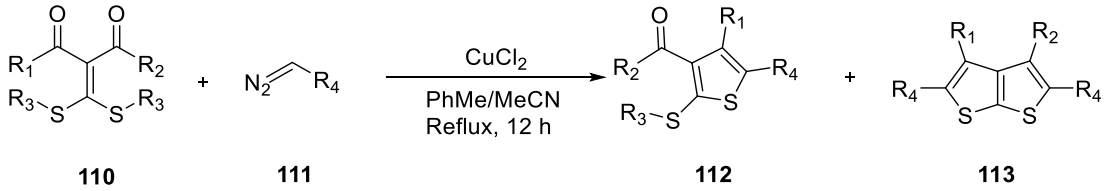
Scheme 4.18

Another reaction of molecule **106** was reacted with acetyl chloride to form molecule **107**, to this hydrazine hydrate was reacted to form hydrazide molecule **108** and various substituted aldehydes were attached to in presence of glacial acetic acid in microwave irradiation to form molecule **109**. The synthesized molecules were screened for dual vascular endothelial growth factor receptors and mitotic inhibitors. Also, the synthesized molecules were screened for anticancer evaluation against HepG-2 and HCT-116 gastro cancer cell lines. Molecular docking studies were also performed to analyze the various docking possibilities with VEGFR-2 and tubulin binding sites **(Scheme 4.19)**.



Scheme 4.19

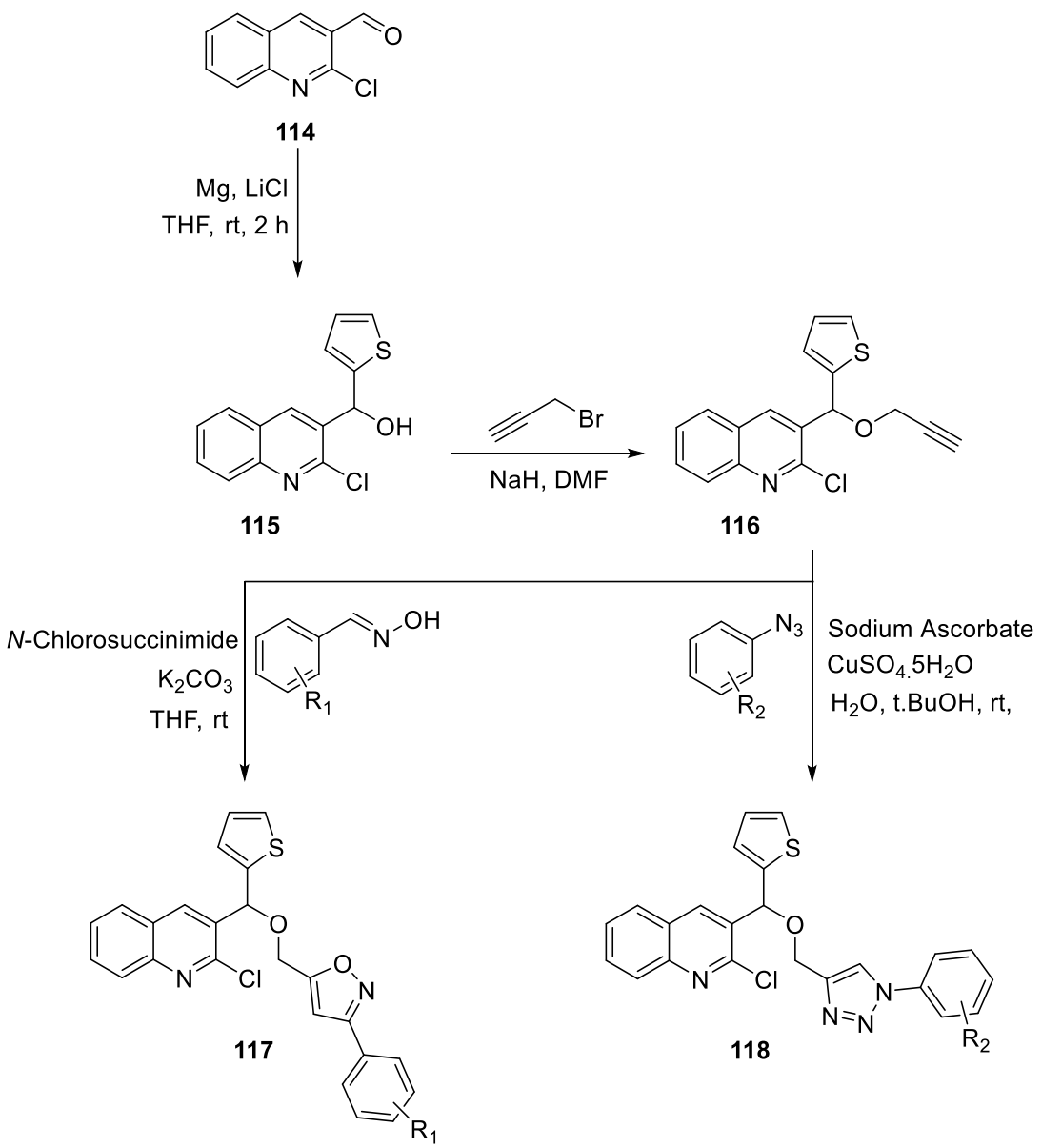
H. Yuan *et al*[169] reported synthesis of copper chloride catalyzed highly substituted thiophene and fused bis-thiophene molecules. The reaction between ketene dithioacetal and diazo **111** molecule in toluene and acetonitrile mixture congaing copper chloride catalyst formed mixture of fully substituted thiophene and bis thiophene molecule **112** and **113**. This newly developed method can be used to construct various novel molecules with great potential **(Scheme 4.20)**.



110 **111** **112** **113**

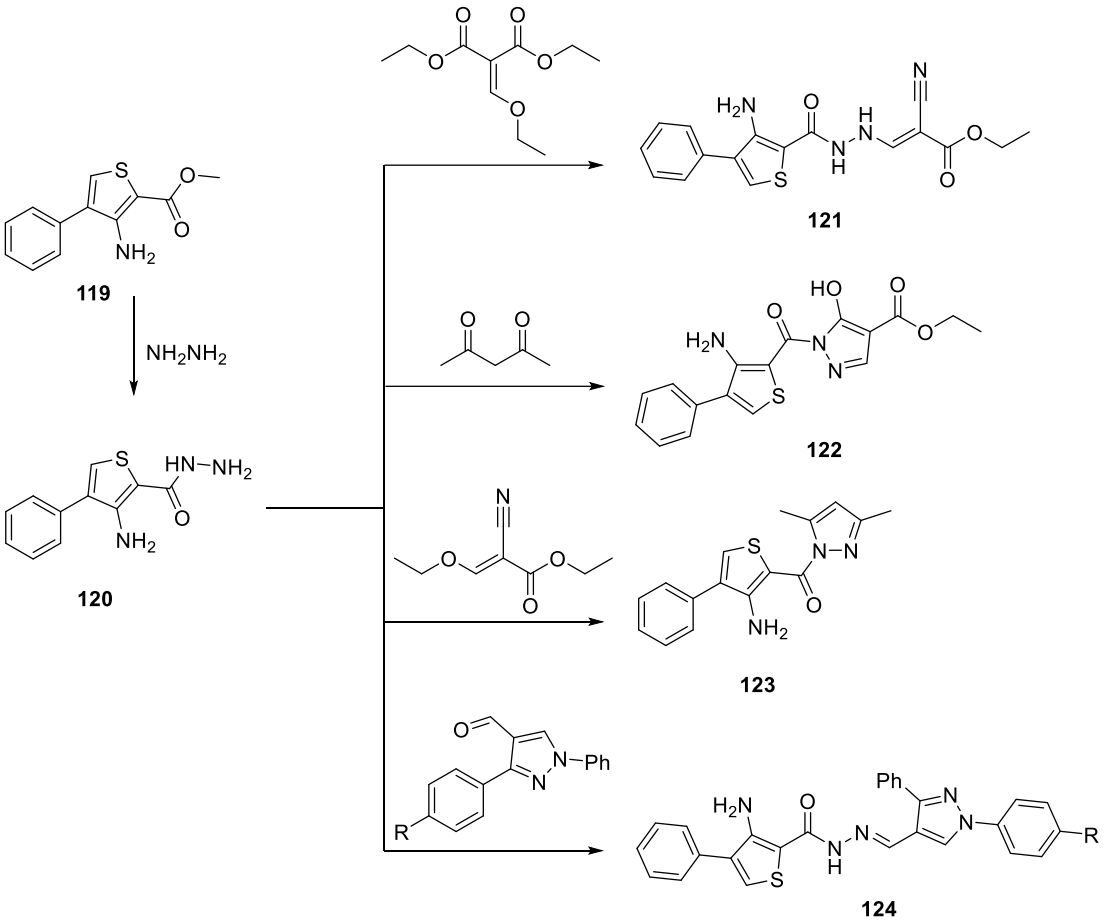
Scheme 4.20

D. Othman *et al*[170] reported synthesis of thiophene-quinoline molecules and evaluated them for anticancer activity. The synthesis of quinoline carbaldehyde **114** with magnesium metal and lithium chloride in tetrahydrofuran stirred for 2 hr and formed molecule **115**, to which propargyl bromide was attached to in DMF containing sodium hydride to form molecule **116**. The molecule **116** was reacted with oxime derivatives and azide derivatives to form respective molecules **117** and **118**. The synthesized molecules were screened for their anticancer activity against HepG-2, HCT-116, HeLa and MCF-7 cell lines in which two molecules were found to be good inhibitors against HeLa and MCF-7 cell lines **(Scheme 4.21)**.



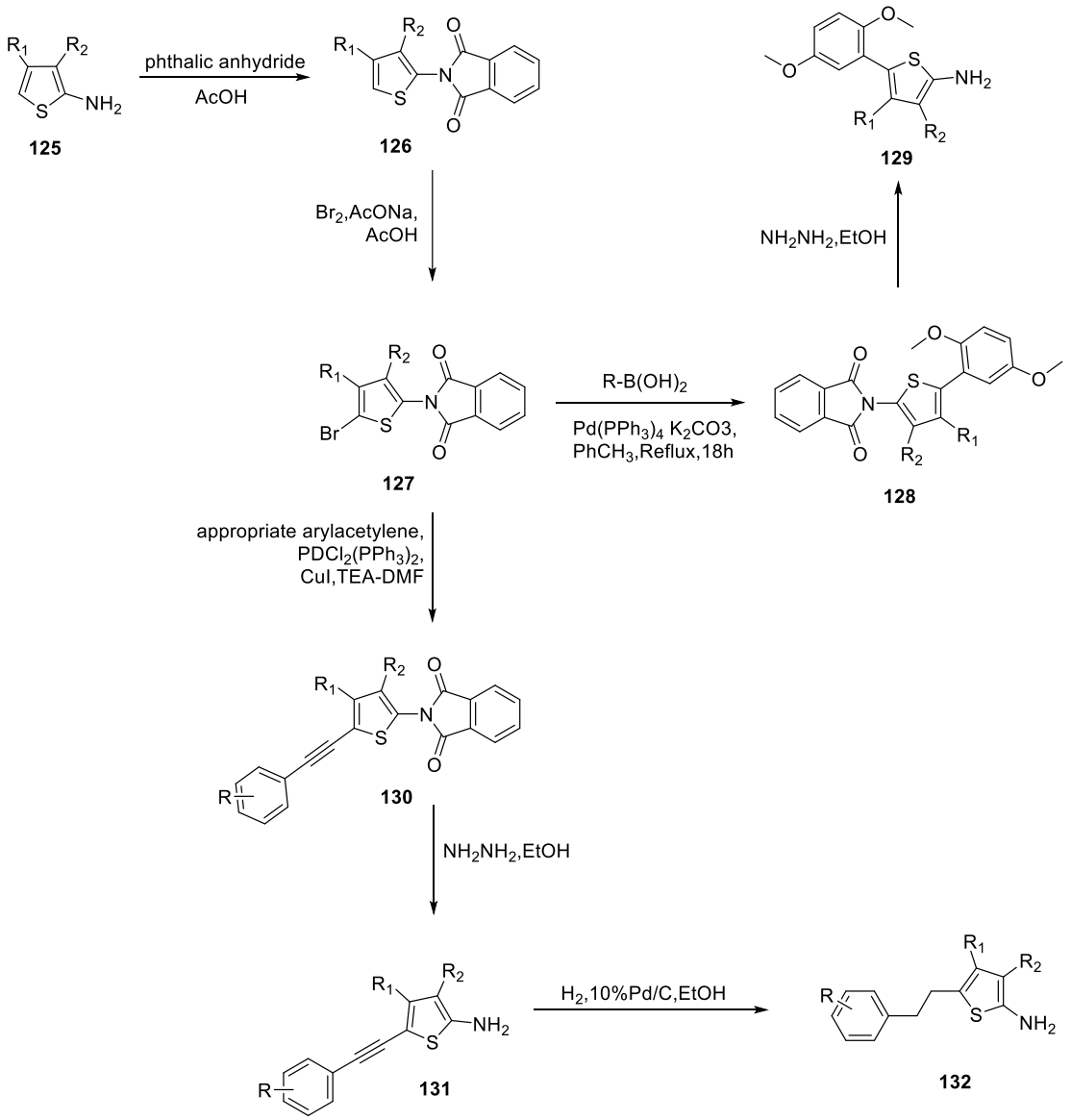
Scheme 4.21

M. Shoukrofy *et al*[171] reported thiophene-pyrazole molecules synthesis and studied anti-inflammatory properties of the synthesized molecules. The reaction of molecule **119** with hydrazine hydrate formed hydrazide molecule **120**. Moreover, the hydrazide molecule was reacted with diethyl ethoxymethylenemalonate, acetyl acetone, ethyl ethoxymethylenecyanoacetate and pyrazole carbaldehyde derivative to form respective molecules **121**, **122**, **123** and molecule **124**. The synthesized molecules were examined and stated that these molecules are nontoxic and gastrointestinal safe. Some of the screened molecules showed promising anti-inflammatory activity. The molecular docking studies were also carried out to observe binding sites **(Scheme 4.22)**.



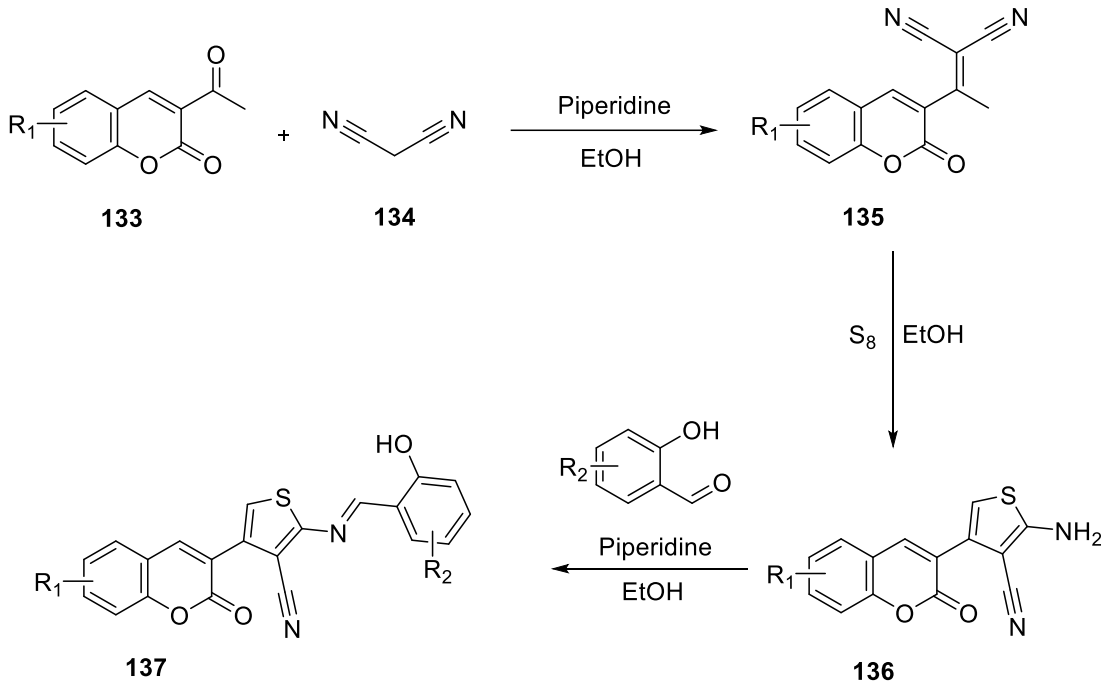
Scheme 4.22

R. Romagnoli *et al*[172] reported novel antitumor agent having 2-amino thiophene in its core structure. The molecule **125** was reacted with phthalic anhydride in acetic acid to form molecule **126**. Bromination of molecule **126** was done using bromine, sodium acetate and acetic acid afforded molecule **127**. Furthermore, molecule **127** was reacted with various boronic acid molecules to form molecule **128** and again reacted with hydrazine hydrate to synthesize 2-amino thiophene derivatives **129**. Moreover, the reaction of molecule **127** with aryl acetylene derivative afforded molecule **130**, which was again reacted with hydrazine hydrate to form 2-amino thiophene molecules **131** which was reacted with hydrogen to make molecule **132**. The synthesized molecules were screened for antitumor activity against wide range of cancer cell lines **(Scheme 4.23)**.



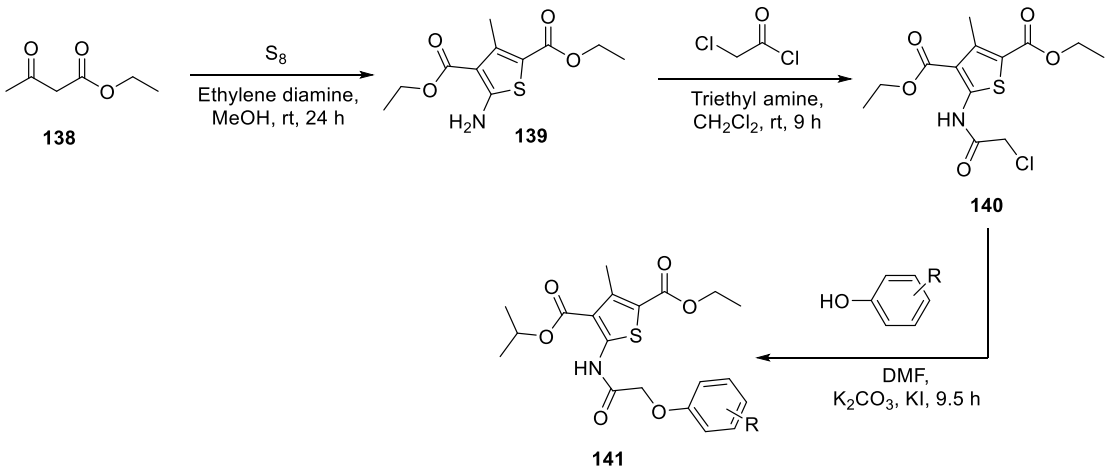
Scheme 4.23

I. Yahaya *et al*[173] reported synthesis of coumarin-thiophene molecules and examined the biological activity of the molecules. The reaction of acetyl coumarin **133** with malononitrile in ethanol containing catalytical amount of piperidine afforded molecule **135**. The gewald reaction of molecule **135** with sulphur and base in ethanol formed amino thiophene-coumarin molecule **136**, to which various salicylaldehyde derivatives were attached to form series of novel thiophene **137** derivatives. The DFT studies were also carried out. The synthesized molecules were screened for anticancer activity against fibroblasts and human lung cancer cell lines and screening of the molecules against gram-positive and gram-negative bacteria were also carried out **(Scheme 4.24)**.



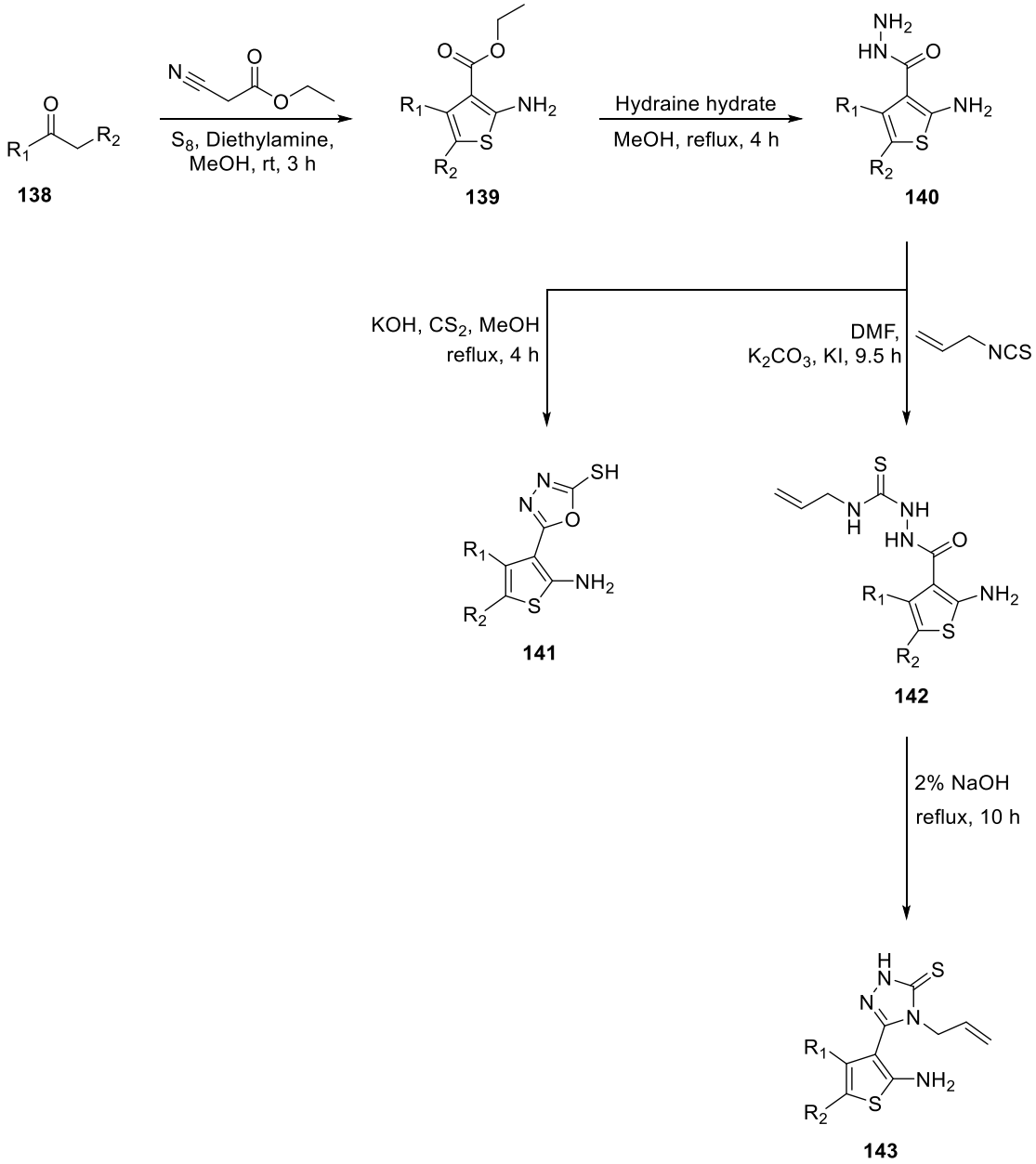
Scheme 4.24

Z. Zhong *et al*[174] reported thiophene synthesis. Starting from gewald reaction of ethyl acetoacetate **138**, sulphur and ethylene diamine in methanol at rt formed thiophene molecule **139**. The chloroacetyl chloride was attached to molecule **139** to form molecule **140**. Furthermore, various substituted aromatic phenols were attached to it in DMF containing potassium carbonate and potassium iodide to form series of molecule **141**. The synthesized molecules were screened for neuraminidase activity and results showed promising activity **(Scheme 4.25)**.



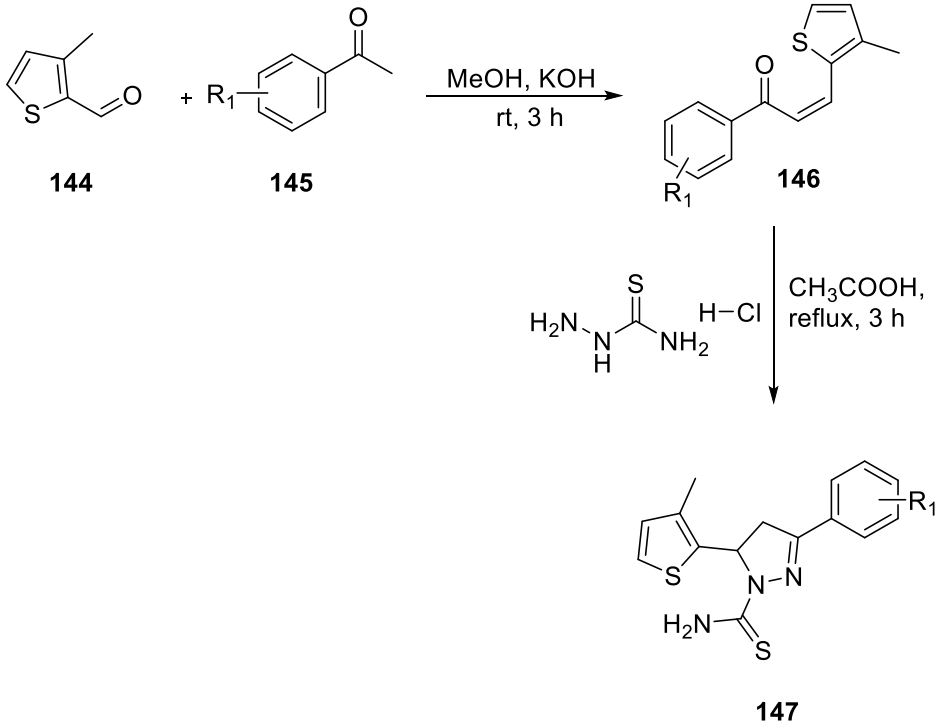
Scheme 4.25

N. Singla and co-workers[175] reported synthesis of oxadiazole and triazole incorporated thiophene molecules and studied antimicrobial properties of the molecules. The reaction between sulphur, ethyl cyanoacetate and ketone formed thiophene molecule **139**, then hydrazine hydrate was reacted with it to form thiophene hydrazide **140** molecules. Moreover, the reaction of molecule **140** with potassium hydroxide, carbon disulphide in methanol and aryl isothiocyanate correspondingly formed molecules **141** and **142**. Furthermore, the molecule **142** was cyclized via reflux in sodium hydroxide solution to afford triazole-thiophene **143** molecules. The results from antibacterial analysis showed potential inhibitory activity **(Scheme 4.26)**.



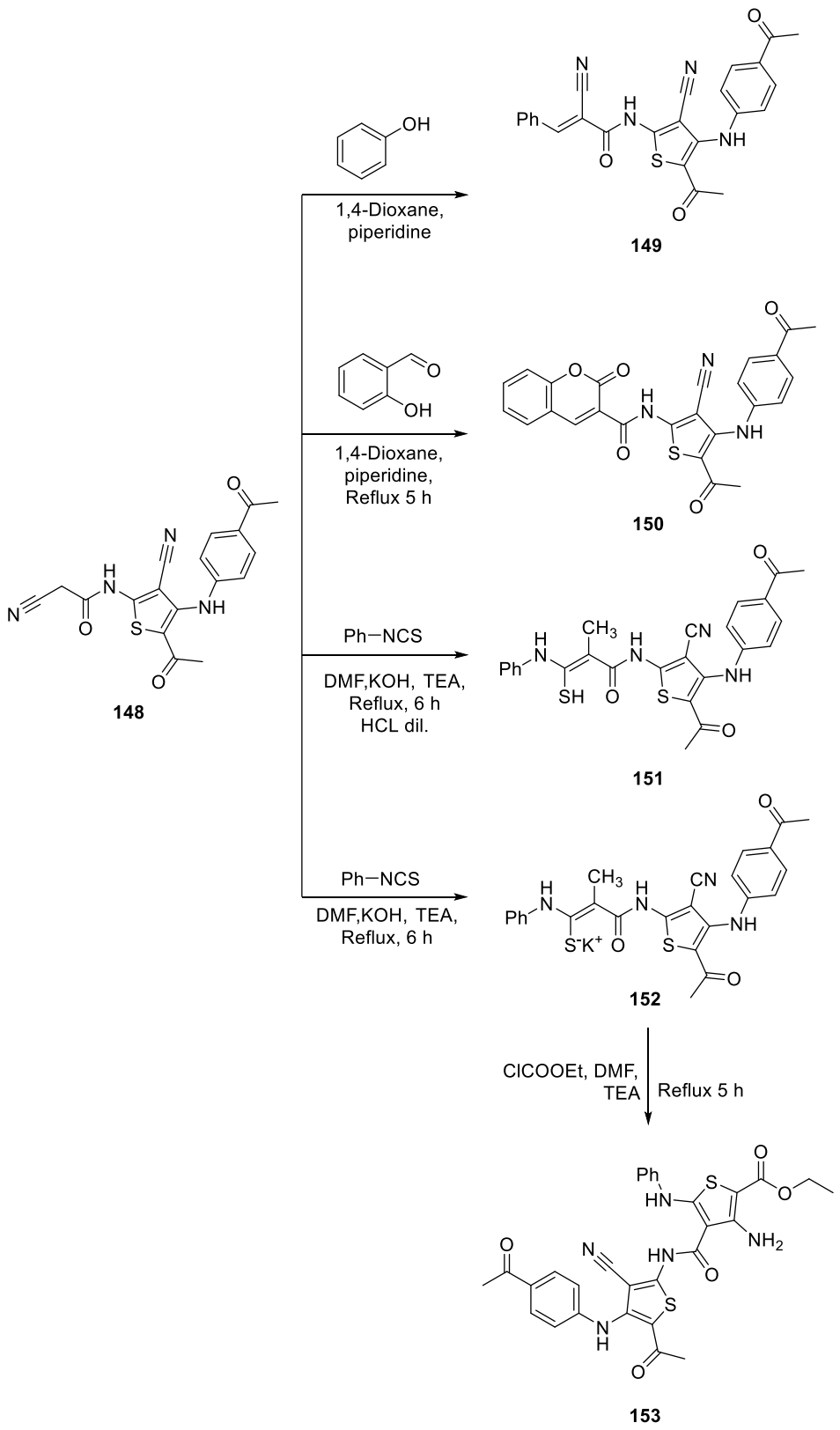
Scheme 4.26

M. Prabhudeva *et al*[176] reported synthesis of pyrazole-thiophene molecules and studied their anti-inflammatory and antimicrobial properties. The reaction methyl thiophene carbaldehyde **144** with various substituted acetophenones **145** in presence of potassium hydroxide in methanol at room temperature for 3 hr resulted in chalcone molecule **146**. Furthermore, the reaction of chalcone with thiosemicarbazide hydrochloride in acetic acid yielded thiophene-pyrazole **147** molecules in good yields. The anti-inflammatory activity results showed outstanding results. Moreover, the antibacterial activity also showed molecules were active against range of bacteria **(Scheme 4.27)**.



Scheme 4.27

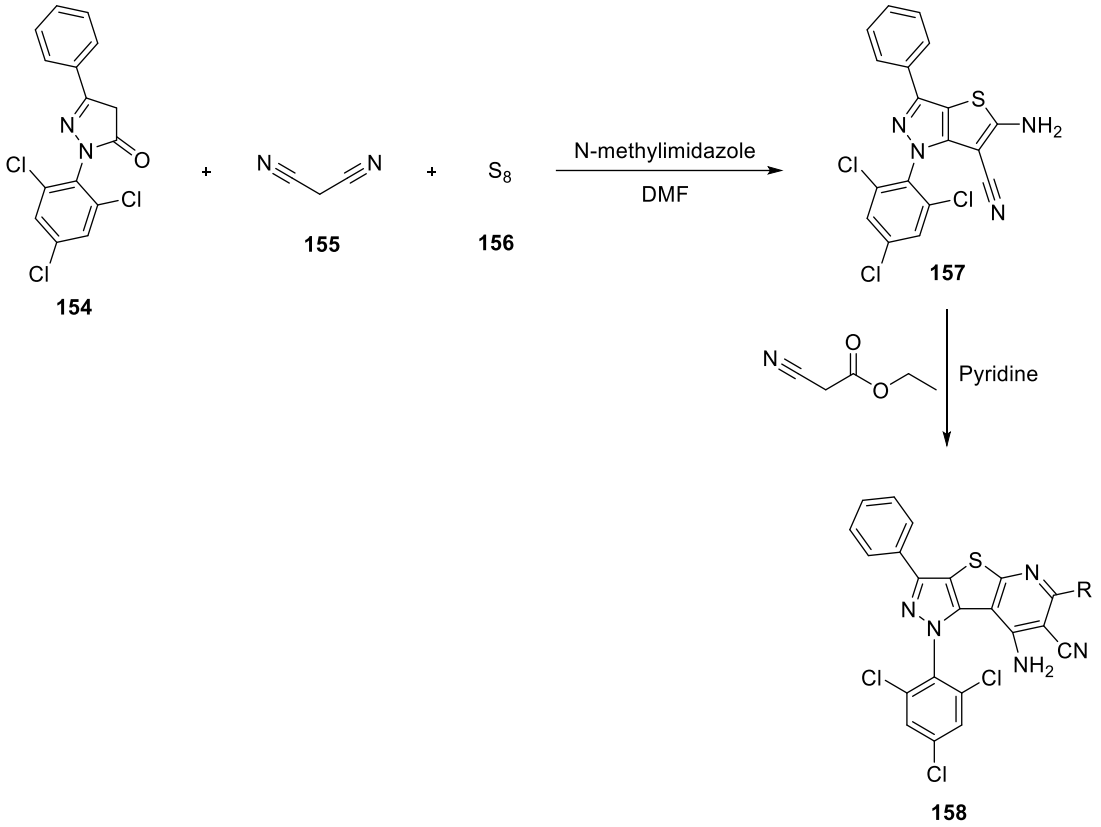
M. Khalifa *et al*[177] reported synthesis of 3,4,5 substituted thiophene molecules as human cancer inhibitors. The molecule **148** was reacted with various substituted phenols in 1,4-dioxane containing catalytic amount of piperidine formed molecule **149**. The reaction with various salicylaldehyde molecules in same reaction conditions afforded the chroman-thiophene molecule **150**. Furthermore, the reaction with various substituted phenyl isothiocyanate in DMF containing catalytic amount of triethylamine formed molecule **151** and **152** respectively. Moreover, the reaction of molecule **152** with ethyl chloroacetate yielded bis-thiophene molecule **153** in good yield. The synthesized molecules were screened against two cancer cell lines which are HEPG-2 and MCF-7 **(Scheme 4.28)**.



Scheme 4.28

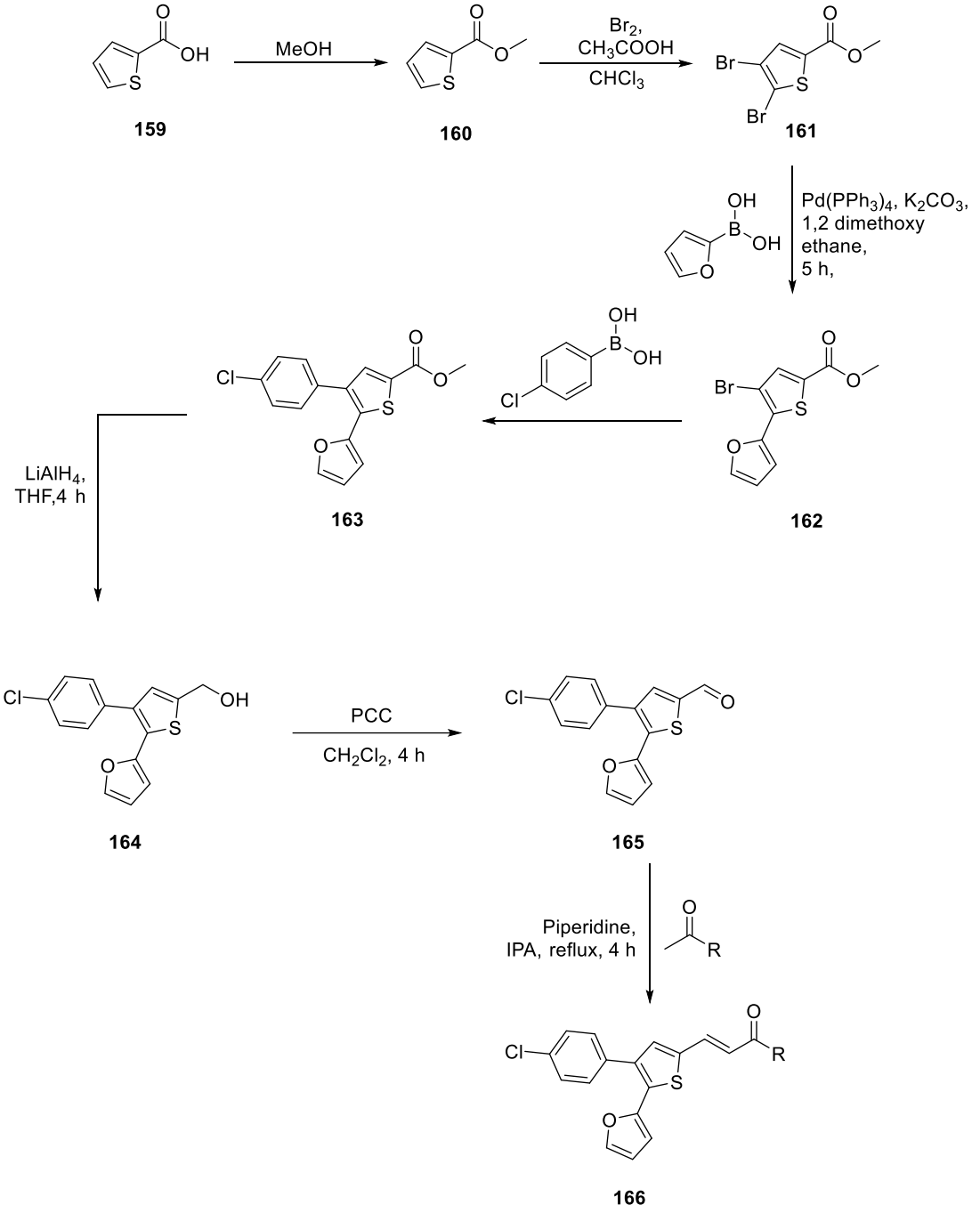
M. Elborai *et al*[178] reported pyrazole-thiophene molecules synthesis via gewald's reaction between pyrazole **154**, malononitrile **155** and sulphur **156** in DMF containing

N-methylimidazole to form pyrazole-thiophene **157** molecule. Furthermore, molecule **157** was reacted with ethyl cyanoacetate in pyridine to afford pyrazolo-thienopyridine **158** molecule in excellent yield. The synthesized molecules were screened for antibacterial and antifungal activity **(Scheme 4.29)**.



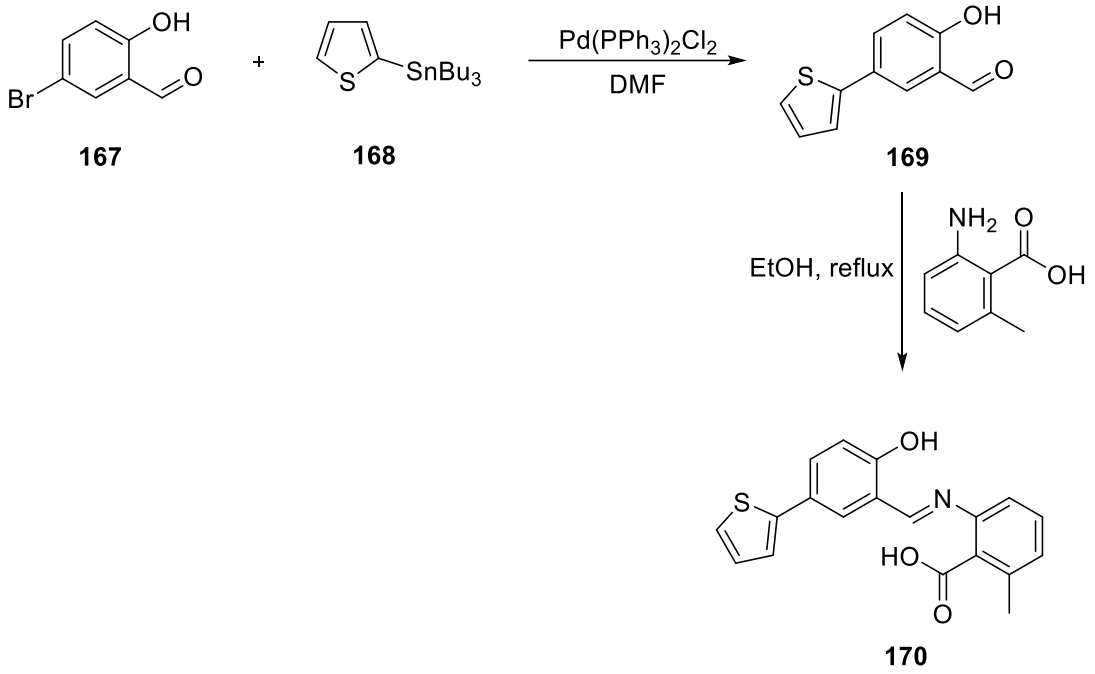
Scheme 4.29

N. Daddukuri *et al*[179] reported synthesis of new thiophene-chalcone molecules and screened them for anticancer and as an apoptosis inducing molecule. The reaction starts with thiophene carboxylic acid **159** reacted with methanol and acid to convert it into ester molecule **160**, then bromination was done to using bromine to form molecule **161**. Then boronic acid was attached to both bromine site to synthesize molecule **163**. Moreover, reduction of molecule **163** was done using lithium aluminum hydride in THF to form alcohol molecule **164** and then oxidation was done using PCC to convert it into aldehyde molecule. Finally, various acetophenone molecules were attached to thiophene aldehyde **165** to form series of thiophene-chalcone **166** molecules. The screening for anticancer activity against MCF-7, MDA-MB-453, PC-3 and A549 showed moderate to good inhibitory activity **(Scheme 4.30)**.



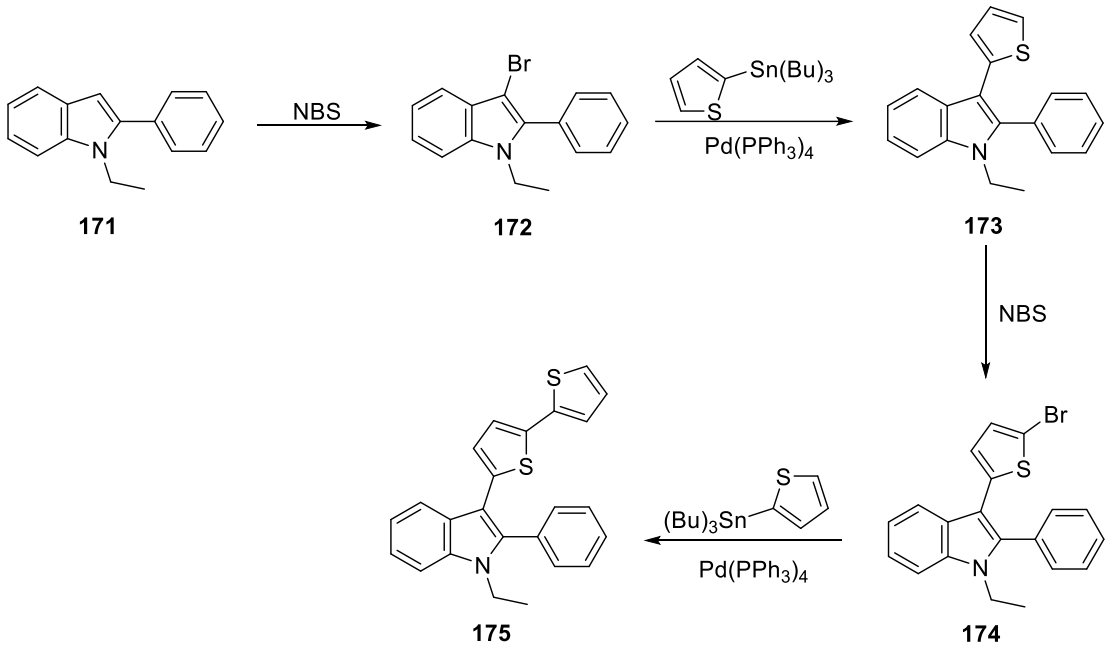
Scheme 4.30

E. Ermis *et al*[180] reported synthesis and DFT studies of thiophene molecule in the form of schiff base. The reaction between aldehyde **167** derivative and stannane **168** derivative in presence of palladium catalyst in DMF formed molecule **169**, to which amine derivative was attached in ethanol at reflux temperature to form molecule **170**. The HMO-LUMO energy values and molecular electrostatic potential were studied **(Scheme 4.31)**.



Scheme 4.31

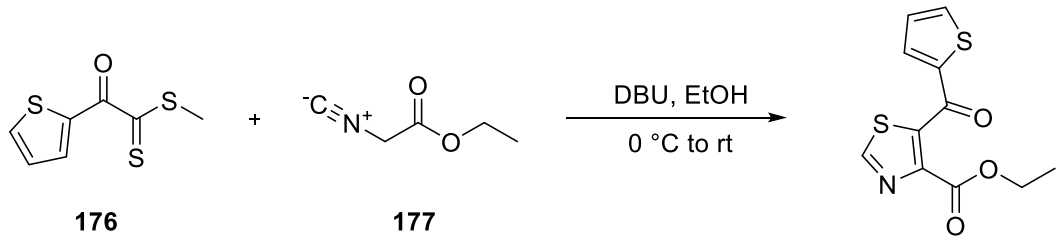
M. Konus *et al*[181] reported synthesis thiophene-indole molecules and screened them for anticancer activity. The reaction between phenyl indole **171** with NBS formed brominated product **172** to which thiophene stannane was attached to form molecule **173**. then again same sequence of bromination and stannane attachment was done to archive molecule **175**. The synthesized molecules were screened for antibacterial activity in which the screened molecule showed strong activity. The molecules also showed good inhibition of glutathione S-transferase enzyme in HepG2 cells **(Scheme 4.32)**.



171 172 173 174 175

Scheme 4.32

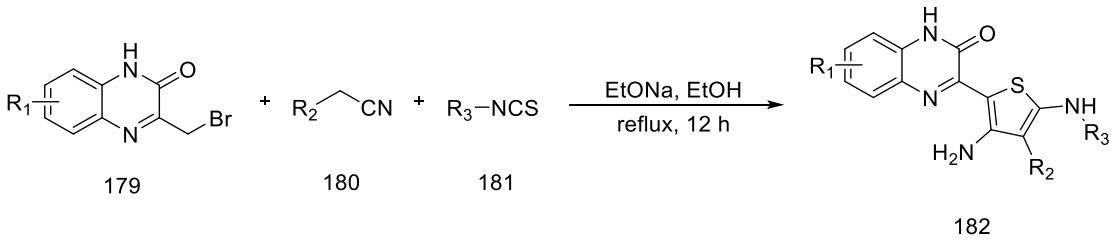
P. Akhileshwari *et al*[182] reported thiazole-thiophene synthesis and performed quantum chemical analysis. The reaction of thiophene dithioate **176** with ethyl isocyanoacetate **177** in ethanol containing DBU with cooling formed novel thiazole-thiophene **178** molecule in good yields. The intermolecular interactions were also studied and DFT calculations used to determine and observe molecular orbitals **(Scheme 4.33)**.



176 177 178

Scheme 4.33

M. Piltan *et al*[183] reported highly functionalized thiophene molecule synthesis via reaction between diamine molecule **181**, malononitrile **182** and aryl isothiocyanate **183** in ethanol containing sodium ethoxide at reflux temperature formed quinoxaline-thiophene **184** molecules **(Scheme 4.34)**.

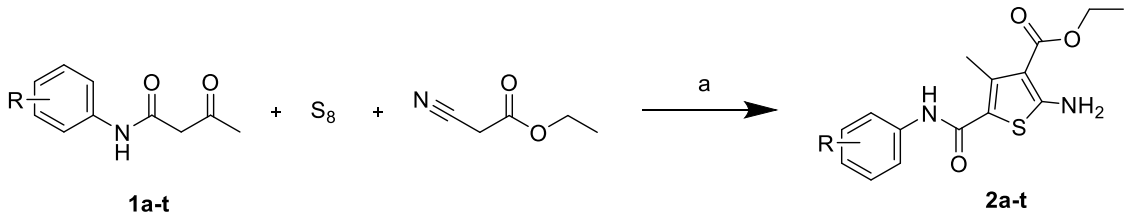


179 180 181 182

Scheme 4.34

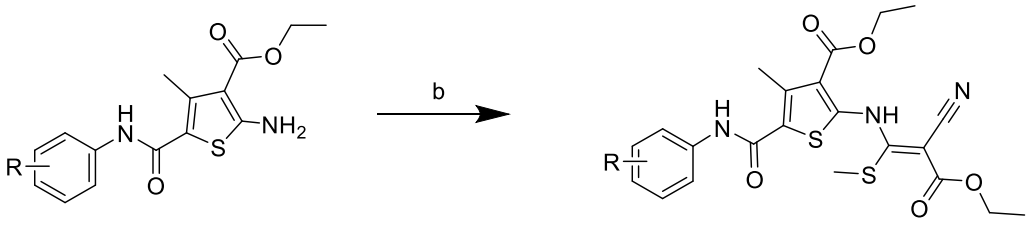
4.2 Results and Discussion

To find novel thiophene molecule, here, we report 20 newly synthesized molecules with thiophene in their main structure. The compounds **3a-t** were elucidated through inspecting their spectroscopic data like ^{1}H-NMR, FTIR and mass spectroscopy. In the first step, 3-oxo-*N*-arylbutanamide, ethyl cyanoacetate and sulphur reacted at reflux temperature in ethanol to get ethyl 2-amino-4-methyl-5-(arylcarbamoyl)thiophene-3-carboxylate **2a-t**.



1a-t **2a-t**

Scheme 1: Reagents and Conditions: (a) Ethanol, Morpholine, Reflux, 6 h.



2a-t **3a-t**

Scheme 2: Reagents and Conditions: (b) ethyl 2-cyano-3,3-bis(methylthio)acrylate, K_2CO_3, rt, 1 h.

Then, compound **2a-t** was reacted with ethyl 2-cyano-3,3-bis(methylthio)acrylate to obtain novel and highly functionalized thiophene **3a-t** derivatives as appear in **Scheme 2**.

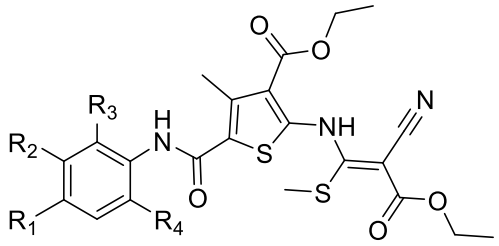
The ^{1}H-NMR graph of compounds presented that 4-methyl thiazole protons were detected at s 2.20–2.57 ppm (CH_3) as a singlet, at s 2.94–3.05 ppm (SCH_3) for pyrimidine thiomethyl protons which were singlet peaks. The aromatic region was seen between 6.94–7.83 ppm. A smaller singlet peak seen at s 9.03–10.64 ppm (NH) indicated the pyrimidine imine proton. Acetamide protons were observed at s 9.81–10.80 ppm (NH) as a singlet. To optimize the reaction conditions for the synthesis of compound **3a-t**, various bases such as anhydrous potassium carbonate and

triethylamine, were utilized in respective solvents, such as methanol, ethanol, tetrahydrofuran and acetonitrile. As a result, we found that the reaction of **2a-t** with ethyl 2-cyano-3,3-bis(methylthio)acrylate was faster and afforded the thiophene **3a-t** in good yield in the presence of potassium carbonate and DMF.

Furthermore, the reaction of novel thiophene **3a-t** derivatives with different primary and secondary amines or phenols was not promising to yield substituted thiophene derivatives because of the poor reactivity of SMe, so maybe oxidation of the sulfides to sulfones can transfer it into good leaving group thus allowing good reactivity and further derivatives of thiophene can be produced. We have also observed that the reaction of thiophene with hydrazine hydrate and phenyl hydrazine yielded a mixture of cyclized and noncyclized products. The one-pot reaction of acetoacetanilide, ethyl cyanoacetate and sulphur followed by the addition of ethyl 2-cyano-3,3-bis(methylthio)acrylate was not clean and did not yield the desired product.

4.2.1 Physicochemical Properties

Table 21 Physicochemical Characteristics of the Thiophene Molecules 3a-t



Entry	R^1	R^2	R^3	R^4	Molecular weight	Molecular formula	Yield (%)	MP (°C)
STOCN-1	OCH_3	H	H	H	503.59	$C_{22}H_{22}ClN_3O_5S_2$	83	197-199
STOCN-2	Cl	H	H	H	508.00	$C_{24}H_{27}N_3O_5S_2$	71	173-175
STOCN-3	H	Cl	H	H	508.00	$C_{22}H_{22}ClN_3O_5S_2$	78	169-171
STOCN-4	H	H	CH_3	CH_3	501.62	$C_{22}H_{23}N_3O_5S_2$	85	186-188
STOCN-5	Br	H	H	H	552.46	$C_{22}H_{22}BrN_3O_5S_2$	82	218-220
STOCN-6	F	H	H	H	491.55	$C_{22}H_{22}FN_3O_5S_2$	70	177-179
STOCN-7	H	H	OCH_3	H	503.59	$C_{23}H_{25}N_3O_6S_2$	86	185-187
STOCN-8	CH_3	H	H	H	487.59	$C_{23}H_{25}N_3O_5S_2$	82	189-191
STOCN-9	OCH_3	H	OCH_3	H	501.62	$C_{24}H_{27}N_3O_5S_2$	85	202-204
STOCN-10	H	H	H	H	473.56	$C_{22}H_{23}N_3O_5S_2$	80	180-182
STOCN-11	H	CF_3	H	H	541.56	$C_{23}H_{22}F_3N_3O_5S_2$	77	183-185
STOCN-12	H	OCH_3	H	H	503.59	$C_{23}H_{25}N_3O_6S_2$	81	179-181
STOCN-13	H	H	H	F	491.55	$C_{22}H_{22}FN_3O_5S_2$	65	169-171
STOCN-14	F	Cl	H	H	525.99	$C_{22}H_{21}ClFN_3O_5S_2$	79	174-176
STOCN-15	Cl	H	Br	H	586.90	$C_{22}H_{21}BrClN_3O_5S_2$	82	183-185
STOCN-16	H	H	Cl	Cl	542.45	$C_{22}H_{21}Cl_2N_3O_5S_2$	76	181-183
STOCN-17	Cl	Cl	H	H	542.45	$C_{22}H_{21}Cl_2N_3O_5S_2$	72	189-191
STOCN-18	H	F	H	H	491.55	$C_{22}H_{22}FN_3O_5S_2$	69	175-177
STOCN-19	H	Br	H	H	552.46	$C_{22}H_{22}BrN_3O_5S_2$	70	190-192
STOCN-20	H	CH_3	H	H	487.59	$C_{23}H_{25}N_3O_5S_2$	85	188-190

4.2.2 Antibacterial activity of synthesized molecules

The newly synthesized molecules were evaluated for their in vitro antibacterial activity against gram-positive namely *Staphylococcus epidermidis* and *Bacillus subtilis* and gram-negative *Salmonella typhi*, *Proteus vulgaris* and *Escherichia coli*.

Several concentrations of the investigated molecules were evaluated for their antibacterial properties using the agar well diffusion technique. Before they were employed, the bacteria were kept at 4°C. 38 g of Mueller Hinton (MH) agar were cooked and combined with 1 L of distilled water to create the agar that would be used. In order to sterilise the prepared agar solution, it was placed in an autoclave and heated to 121°C for 15 minutes. Agar was poured onto petri plates and allowed to cool at room temperature. 20 mg of the prepared molecule were dissolved in 1 mL of DMSO to provide the stock solution for the synthetic compounds. On the prepared agar, bacteria were cultivated. Then, 5 mm diameter wells were formed on the agar surface. The wells received 100 µL of the tested substance. Ampicillin and Gentamicin were utilised as standards against gram-positive bacteria and DMSO as a standard against gram-negative bacteria, respectively. A ruler was used to measure the width of the inhibition zone surrounding each well in a petri dish after it had been incubated for 12 hours at 37°C. By measuring the diameter of the zone of inhibition in millimetres, microbial growth was calculated (mm).

Compounds	**Antibacterial activity Zone of Inhibition (mm)**				
	S. typhi	***S. epidermis***	***E. coli***	***B. subtilis***	***P. vulgaris***
STOCN-1	**16**	7	6	14	9
STOCN-2	5	11	5	15	8
STOCN-3	14	13	12	5	7
STOCN-4	13	10	8	16	9
STOCN-5	12	15	**18**	10	**19**
STOCN-6	5	13	12	9	10
STOCN-7	15	15	17	8	7
STOCN-8	15	15	14	**17**	15
STOCN-9	**16**	**16**	9	13	11
STOCN-10	13	12	11	9	10
Ampicillin	21	14	15	18	20
Gentamicin	20	12	21	20	14

4.3 Conclusion

In conclusion, we have described the synthesis substituted novel thiophene molecules in excellent yields. The reaction of ketene dithioacetal derivative with thiophene was afforded the new thiophene molecules with good yields in the presence of base. Potassium carbonate was found as an efficient base for the synthesis of thiophenes. The synthesized molecules were elucidated through inspecting their spectroscopic data like ^{1}H-NMR, FTIR and mass spectroscopy. This procedure offers a good scope for the synthesis of a wide variety of thiophenes containing carboxamide group with excellent yield, purity and simple isolation of products.

4.4 Experimental Section

Melting points were determined on an electrothermal device using open capillaries and are uncorrected. Thin-layer chromatography was performed on precoated silica-gel 60 F254 (Merck), compounds were visualized with UV light at 254 nm and 365 nm or with iodine vapor. The IR spectra were recorded on a Shimadzu FT-IR spectrometer using the ATR technique. NMR spectra were recorded on a Bruker AVANCE III (400 MHz) spectrometer in DMSO-d_6 or $CDCl_3$. Chemical shifts are expressed in δ ppm downfield from Tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded using a direct inlet probe on Shimadzu GCMS QP2010 Ultra mass spectrometer. All reactions were carried out under an ambient atmosphere. All reagents were purchased from Loba, Molychem, SRL and CDH and used without further purification.

- **General process for the synthesis of Acetoacetanilides (1a-t)**

Substituted amine (10 mmol) and ethyl acetoacetate containing catalytic amount of Potassium or sodium hydroxide lie (10%) in toluene was refluxed for approximately 24 hr. The completion of the reaction, mass was evaporated under vacuum and the residue was crystallized from methanol or ethanol to get pure acetoacetanilides.

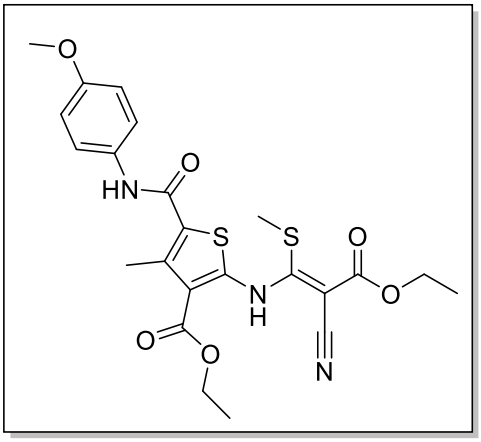
- **General process for the synthesis of thiophenes (2a-t)**

To a stirred solution of compound acetoacetanilide (10 mmol) **(1a-t)**, sulphur (10 mmol) and ethyl cyanoacetate (10 mmol) in MeOH, morpholine (10 mmol) was slowly added and refluxed for 6 hr. The reaction mixture was filtered hot and filtrate was poured with stirring into ice-water, neutralized with dilute HCl. The separated solid product was filtered, washed with water and dried at room temperature to get analytically pure compound. (**2a-t**), as a light brown to white solid. Yield: 65%.

- **General process for the synthesis of ethyl 2-amino-4-methyl-5-(arylcarbamoyl)thiophene-3-carboxylate (4a-t)**

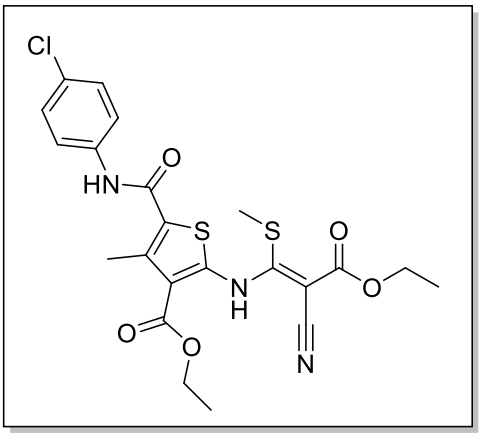
A mixture of **2a-t** (10 mmol) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (10 mmol) in 10 mL of DMF and anhydrous potassium carbonate (10 mmol) was stirred at rt for 1 hr. After the completion of the reaction, the reaction mixture was cooled to room temperature, poured into ice-cold water and neutralized with dil. HCl. The separated solid was filtered, washed with water and purified by recrystallization from DMF to afford fluffy amorphous flakes. **(4a-t)**.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((4-methoxyphenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-1)



Yellow solid, Yield: 89%, mp 197-199°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.51 (s, 1H), 10.11 (s, 1H), 7.57 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 4.25 (q, J = 7.0 Hz, 2H), 3.75 (s, 3H), 2.55 (s, 3H), 2.49 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.13 (s, 1H), 7.49 (d, J = 8.9 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 4.48 (q, J = 7.1 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 2.69 (s, 3H), 2.59 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H); MS (*m*/*z*): 503 (M^+); Anal. Calcd. For $C_{22}H_{22}ClN_3O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.01; H, 3.62; N, 17.60.

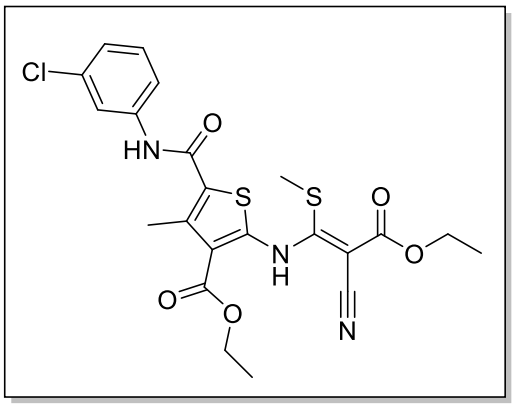
Ethyl (*Z*)-5-((4-chlorophenyl)carbamoyl)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methylthiophene-3-carboxylate (STOCN-2)



Yellow Solid, Yield: 86%, mp 173-175°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (s, 1H), 10.36 (s, 1H), 7.70 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 4.25 (q, J = 7.0 Hz, 2H), 2.56 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1

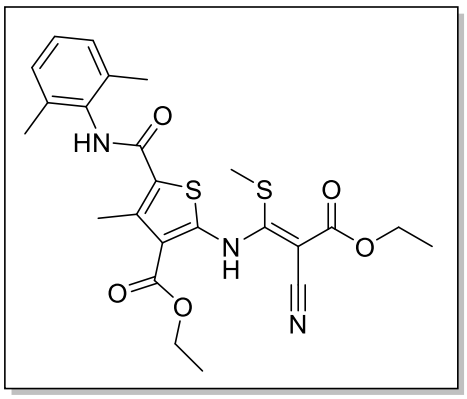
Hz, 3H); MS (*m*/*z*): 508 (M^+); Anal. Calcd. For $C_{24}H_{27}N_3O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.01; H, 3.62; N, 17.60.

Ethyl (*Z*)-5-((3-chlorophenyl)carbamoyl)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methylthiophene-3-carboxylate (STOCN-3)



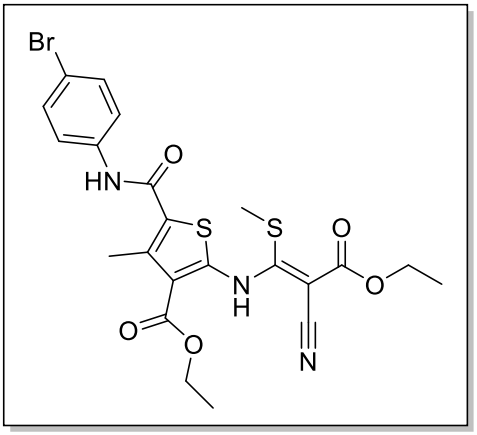
Yellow Solid, Yield: 82%, mp 169-171°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.54 (s, 1H), 10.41 (s, 1H), 7.84 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 4.35 (q, *J* = 7.2 Hz, 1H), 4.26 (q, *J* = 7.3 Hz, 2H), 2.56 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); MS (*m*/*z*): 508 (M^+); Anal. Calcd. For $C_{22}H_{22}ClN_3O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.01; H, 3.62; N, 17.60.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((2,6-dimethylphenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-4)



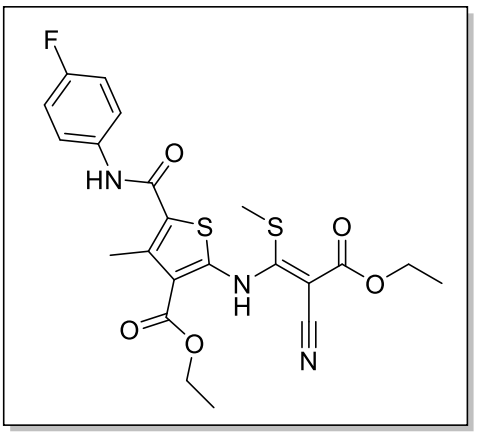
Yellow Solid, Yield: 90%, mp 186-188°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.49 (s, 1H), 9.60 (s, 1H), 7.14 (s, 3H), 4.35 (q, *J* = 7.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 1H), 2.58 (d, *J* = 8.4 Hz, 3H), 2.21 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); MS (*m*/*z*): 501 (M^+); Anal. Calcd. For $C_{22}H_{23}N_3O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.01; H, 3.62; N, 17.60.

Ethyl (*Z*)-5-((4-bromophenyl)carbamoyl)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methylthiophene-3-carboxylate (STOCN-5)



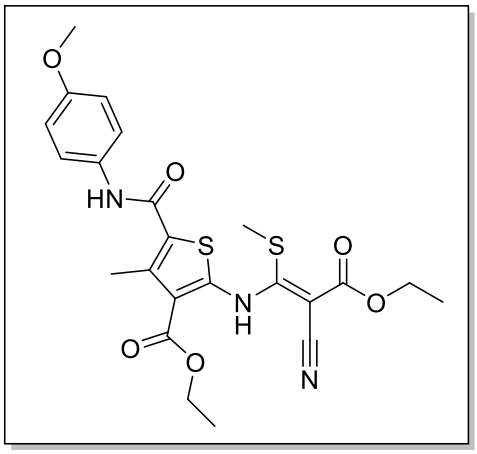
Yellow Solid, Yield: 90%, mp 218-220°C; MS (*m*/*z*): 552 (M^+); Anal. Calcd. For $C_{22}H_{22}BrN_3O_5S_2$: C, 47.83; H, 4.01; N, 7.61; Found: C, 47.80; H, 3.94; N, 7.59.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((4-fluorophenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-6)



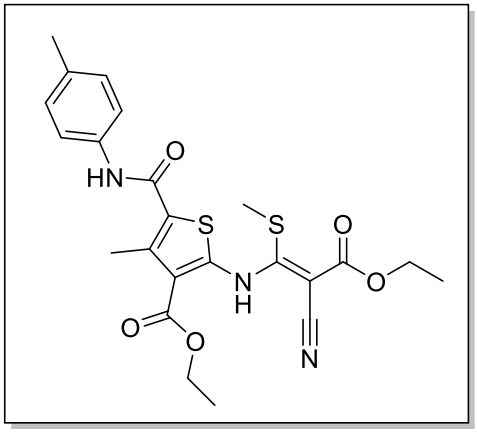
Yellow Solid, Yield: 90%, mp 177-179°C; MS (*m*/*z*): 491 (M^+); Anal. Calcd. For $C_{22}H_{22}FN_3O_5S_2$: C, 53.76; H, 4.51; N, 8.55; Found: C, 53.80; H, 4.55; N, 8.49.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((4-methoxyphenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-7)



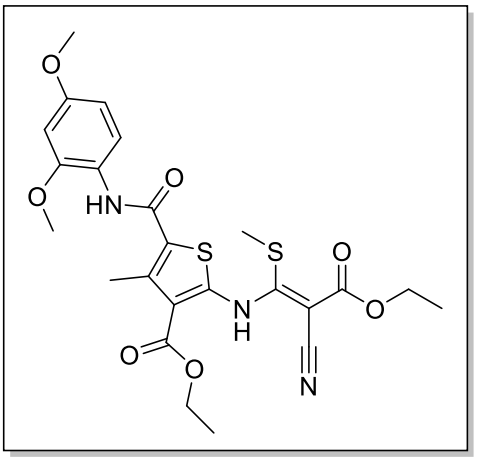
Yellow Solid, Yield: 90%, mp 185-187°C; MS (*m*/*z*): 503 (M^+); Anal. Calcd. For $C_{23}H_{25}N_3O_6S_2$: C, 54.86; H, 5.00; N, 8.34; Found: C, 54.79; H, 5.03; N, 8.31.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methyl-5-(p-tolylcarbamoyl)thiophene-3-carboxylate (STOCN-8)



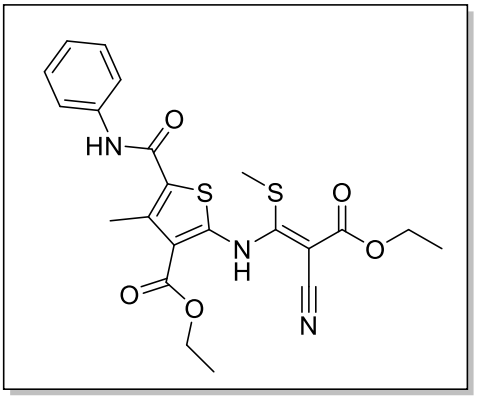
Yellow Solid, Yield: 90%, mp 189-191°C; MS (*m*/*z*): 487 (M^+); Anal. Calcd. For $C_{23}H_{25}N_3O_5S_2$: C, 56.66; H, 5.17; N, 8.62; Found: C, 56.61; H, 5.15; N, 8.55.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((2,4-dimethoxyphenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-9)



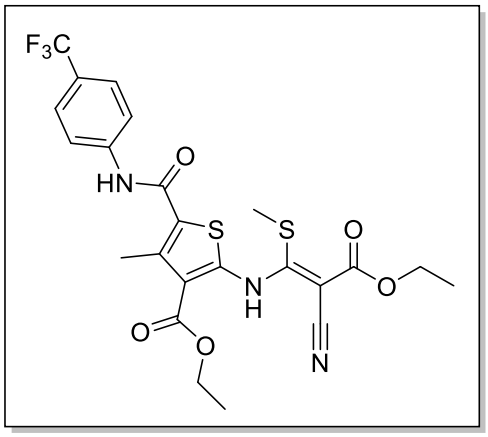
Yellow Solid, Yield: 90%, mp 202-204°C; MS (*m*/*z*): 533 (M^+); Anal. Calcd. For $C_{24}H_{27}N_3O_5S_2$: C, 54.02; H, 5.10; N, 7.87; Found: C, 54.09; H, 5.14; N, 7.86.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methyl-5-(phenylcarbamoyl)thiophene-3-carboxylate (STOCN-10)



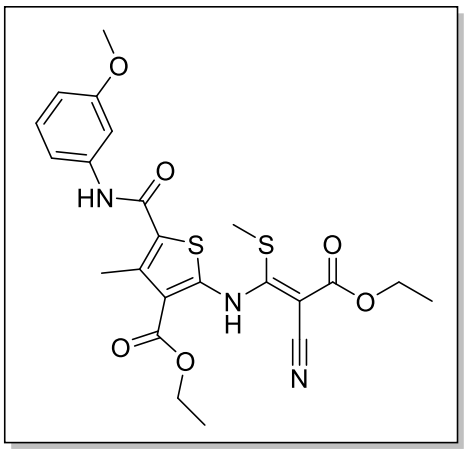
Yellow Solid, Yield: 90%, mp 180-182°C; MS (*m*/*z*): 473 (M^+); Anal. Calcd. For $C_{22}H_{23}N_3O_5S_2$: C, 55.80; H, 4.90; N, 8.87; Found: C, 55.82; H, 4.88; N, 8.92.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methyl-5-((4-(trifluoromethyl)phenyl)carbamoyl)thiophene-3-carboxylate (STOCN-11)



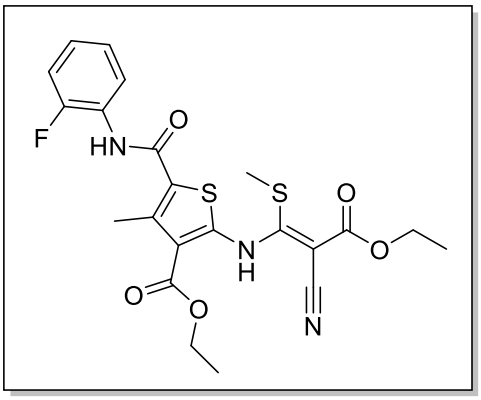
Yellow Solid, Yield: 90%, mp 183-185°C; MS (*m*/*z*): 541 (M^+); Anal. Calcd. For $C_{23}H_{22}F_3N_3O_5S_2$: C, 51.01; H, 4.09; N, 7.76; Found: C, 50.97; H, 4.01; N, 7.70.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((3-methoxyphenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-12)



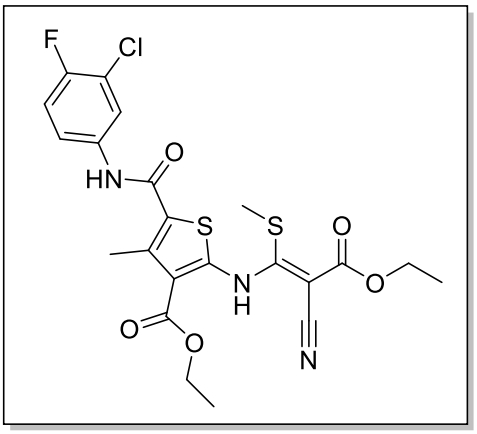
Yellow Solid, Yield: 90%, mp 179-181°C; MS (*m*/*z*): 503 (M^+); Anal. Calcd. For $C_{23}H_{25}N_3O_6S_2$: C, 54.86; H, 5.00; N, 8.34; Found: C, 54.82; H, 5.10; N, 8.31.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((2-fluorophenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-13)



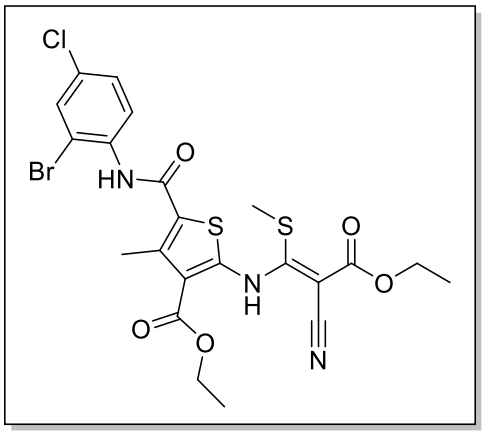
Yellow Solid, Yield: 90%, mp 169-171°C; MS (*m*/*z*): 491 (M^+); Anal. Calcd. For $C_{22}H_{22}FN_3O_5S_2$: C, 53.76; H, 4.51; N, 8.55; Found: C, 53.74; H, 4.56; N, 8.58.

Ethyl (*Z*)-5-((3-chloro-4-fluorophenyl)carbamoyl)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methylthiophene-3-carboxylate (STOCN-14)



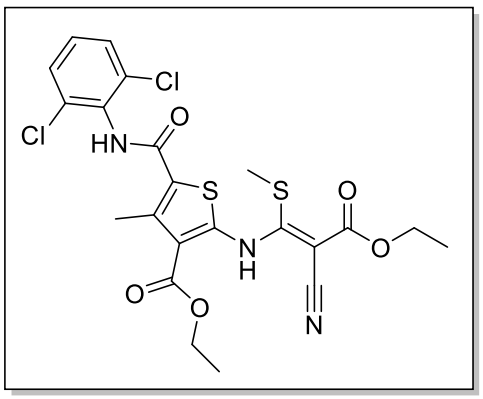
Yellow Solid, Yield: 90%, mp 174-176°C; MS (*m*/*z*): 525 (M^+); Anal. Calcd. For $C_{22}H_{21}ClFN_3O_5S_2$: C, 50.24; H, 4.02; N, 7.99; Found: C, 50.29; H, 4.05; N, 8.01.

Ethyl (*Z*)-5-((2-bromo-4-chlorophenyl)carbamoyl)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methylthiophene-3-carboxylate (STOCN-15)



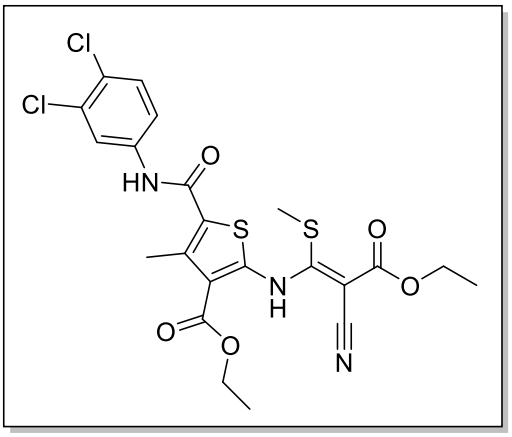
Yellow Solid, Yield: 90%, mp 183-185°C; MS (*m*/*z*): 586 (M^+); Anal. Calcd. For $C_{22}H_{21}BrClN_3O_5S_2$: C, 45.02; H, 3.61; N, 7.16; Found: C, 45.11; H, 3.66; N, 7.15.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((2,6-dichlorophenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-16)



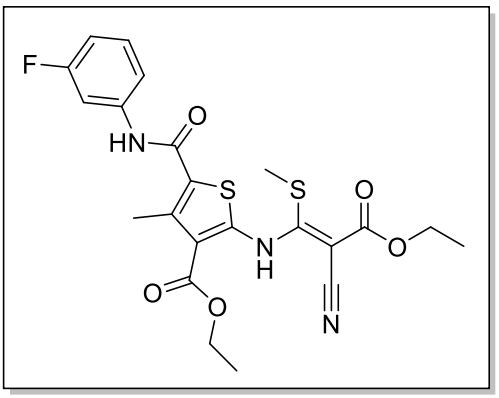
Yellow Solid, Yield: 90%, mp 181-183°C; MS (*m*/*z*): 542 (M^+); Anal. Calcd. For $C_{22}H_{21}Cl_2N_3O_5S_2$: C, 48.71; H, 3.90; N, 7.75; Found: C, 48.77; H, 3.89; N, 7.70.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((3,4-dichlorophenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-17)



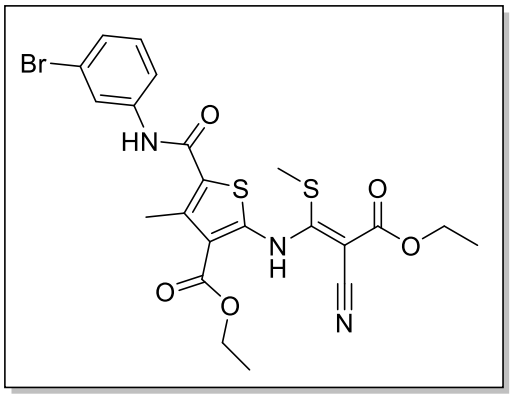
Yellow Solid, Yield: 90%, mp 189-191°C; MS (*m*/*z*): 542 (M^+); Anal. Calcd. For $C_{22}H_{21}Cl_2N_3O_5S_2$: C, 48.71; H, 3.90; N, 7.75; Found: C, 48.74; H, 3.95; N, 7.82.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-5-((3-fluorophenyl)carbamoyl)-4-methylthiophene-3-carboxylate (STOCN-18)



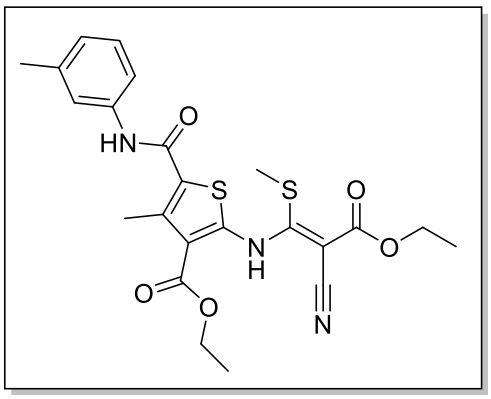
Yellow Solid, Yield: 90%, mp 175-177°C; MS (*m*/*z*): 491 (M^+); Anal. Calcd. For $C_{22}H_{22}FN_3O_5S_2$: C, 53.76; H, 4.51; N, 8.55; Found: C, 53.76; H, 4.51; N, 8.55.

Ethyl (*Z*)-5-((3-bromophenyl)carbamoyl)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methylthiophene-3-carboxylate (STOCN-19)



Yellow Solid, Yield: 90%, mp 190-192°C; MS (*m*/*z*): 552 (M^+); Anal. Calcd. For $C_{22}H_{22}BrN_3O_5S_2$: C, 47.83; H, 4.01; N, 7.61; Found: C, 47.90; H, 4.11; N, 7.60.

Ethyl (*Z*)-2-((2-cyano-3-ethoxy-1-(methylthio)-3-oxoprop-1-en-1-yl)amino)-4-methyl-5-(m-tolylcarbamoyl)thiophene-3-carboxylate (STOCN-20)



Yellow Solid, Yield: 90%, mp 188-190°C; MS (*m*/*z*): 487 (M^+); Anal. Calcd. For $C_{23}H_{25}N_3O_5S_2$: C, 56.66; H, 5.17; N, 8.62; Found: C, 56.68; H, 5.15; N, 8.60.

4.5 Spectral Data

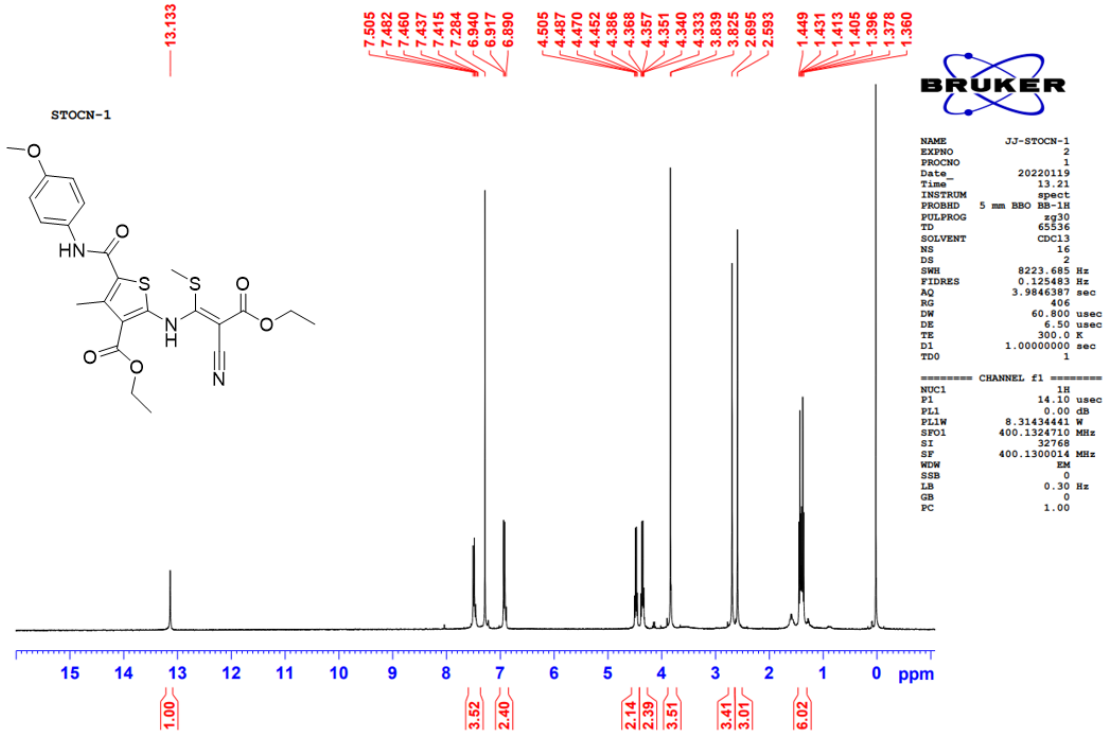


Fig. 1: Representative ^{1}H NMR ($CDCl_3$) spectrum of compound STOCN-1

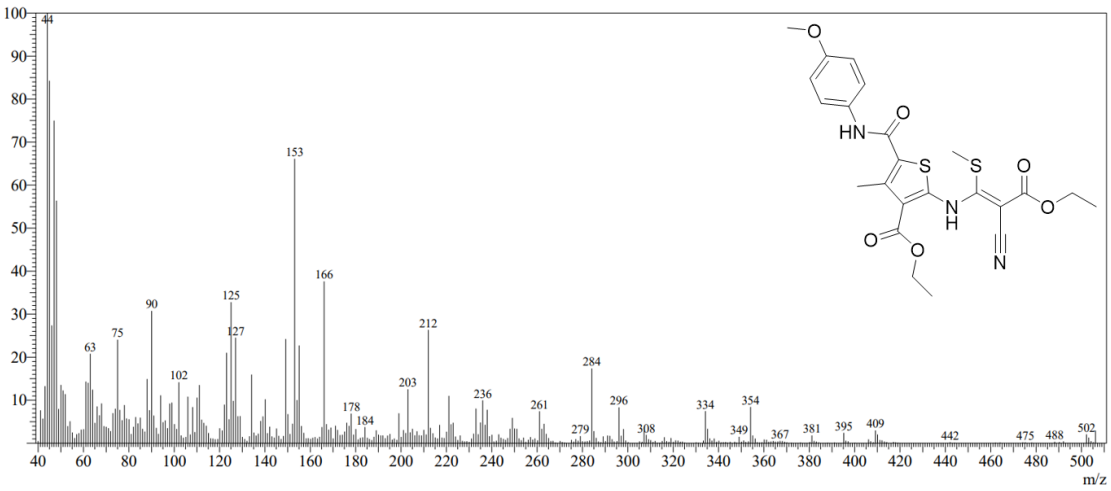


Fig. 2: Representative mass spectrum of compound STOCN-1

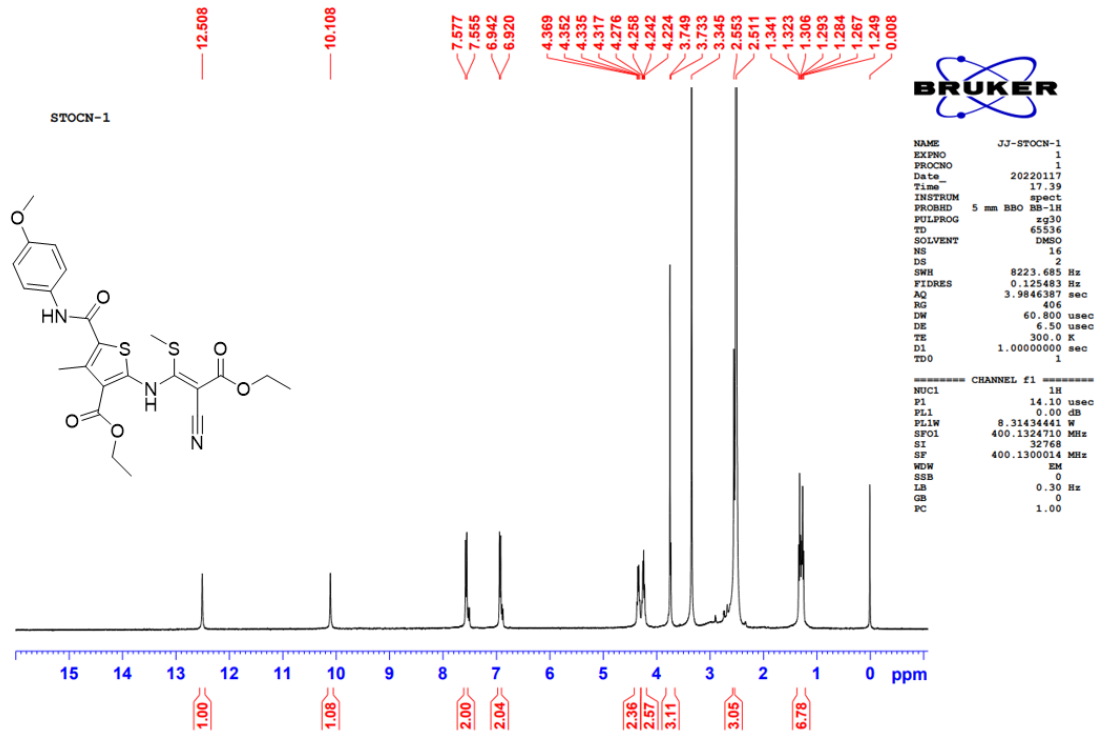


Fig. 3: Representative ^{1}H NMR spectrum of compound STOCN-1

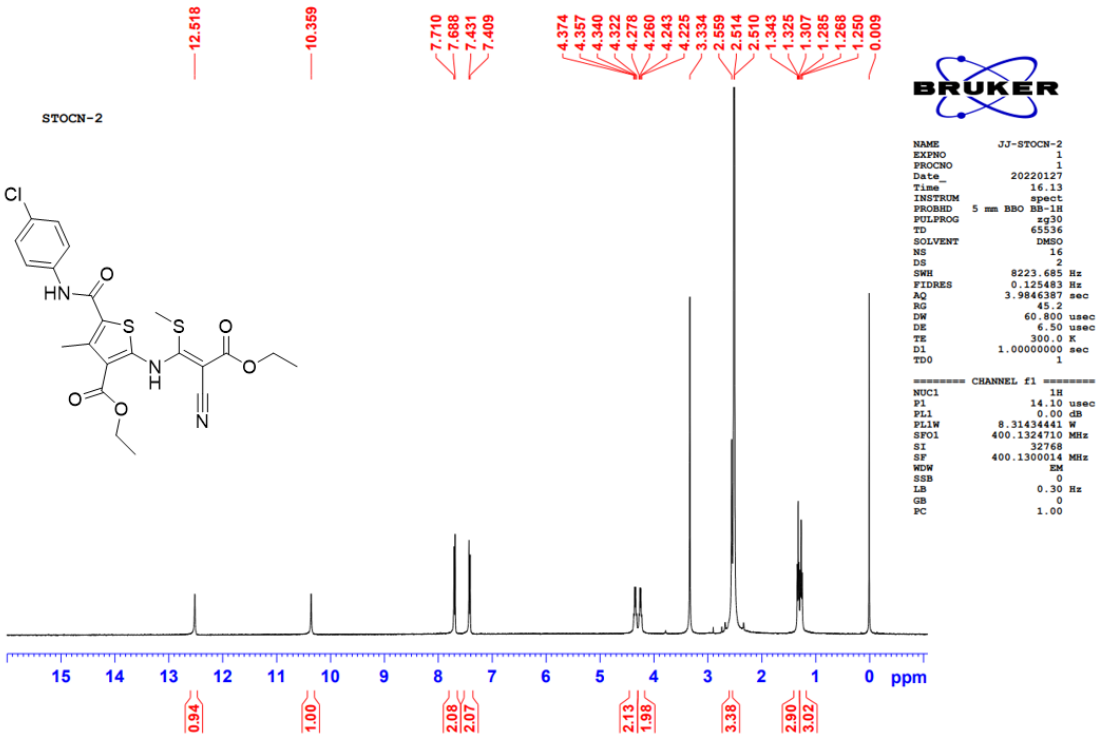


Fig. 4: Representative ^{1}H NMR spectrum of compound STOCN-2

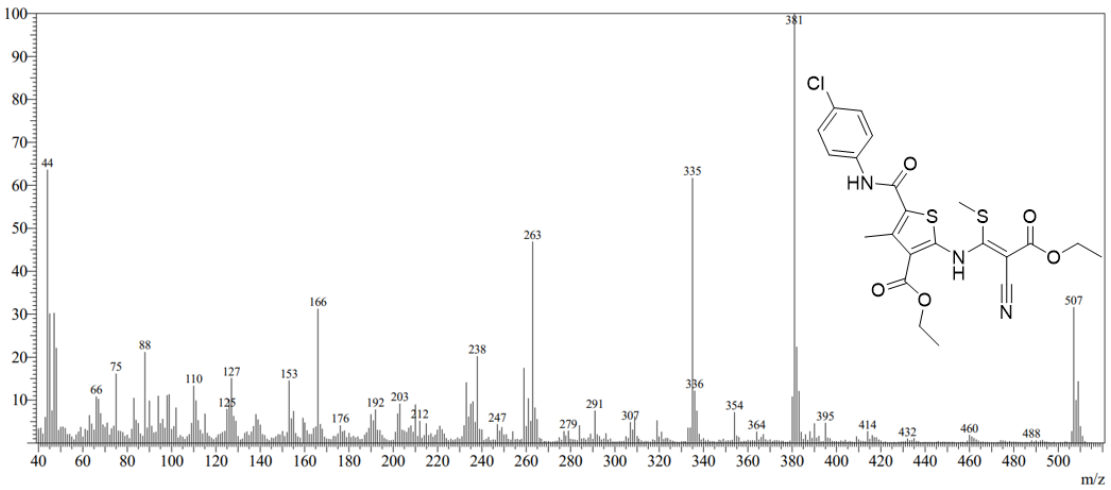


Fig. 5: Representative mass spectrum of compound STOCN-2

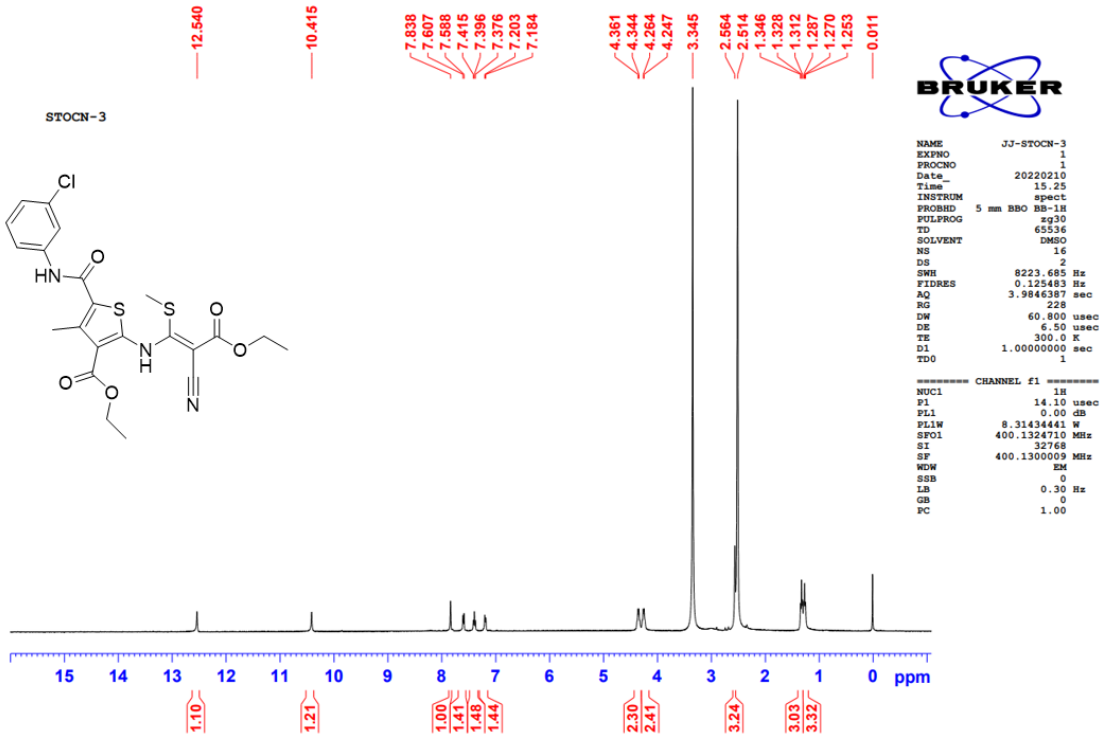


Fig. 6: Representative ^{1}H NMR spectrum of compound STOCN-3

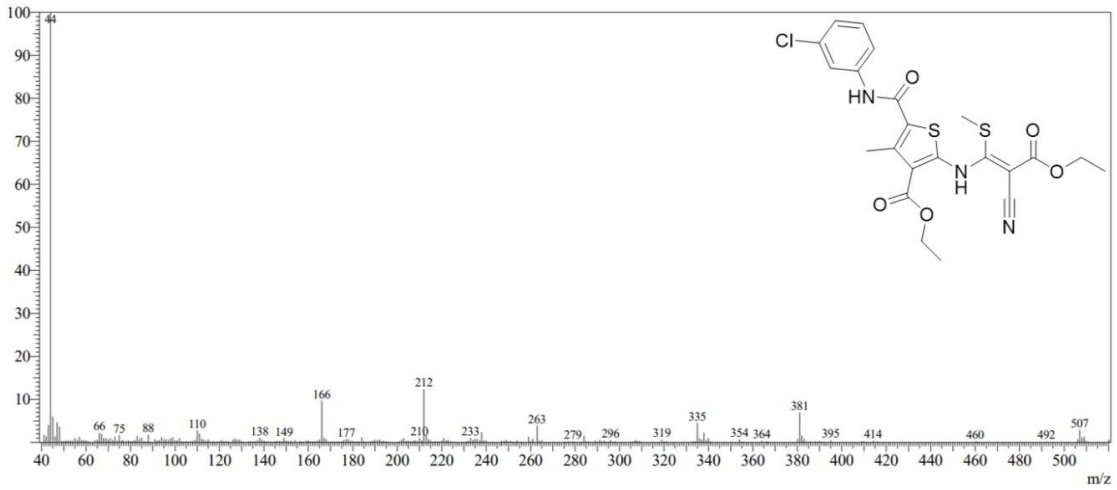


Fig. 7: Representative mass spectrum of compound STOCN-3

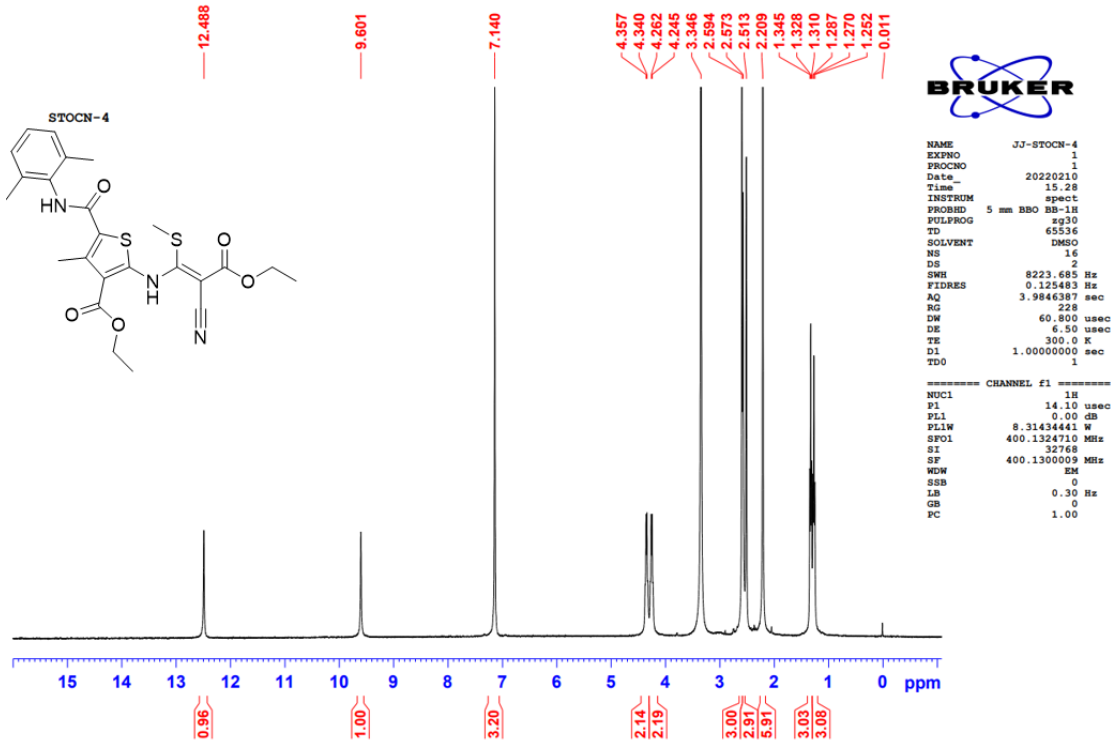


Fig. 8: Representative ^{1}H NMR spectrum of compound STOCN-4

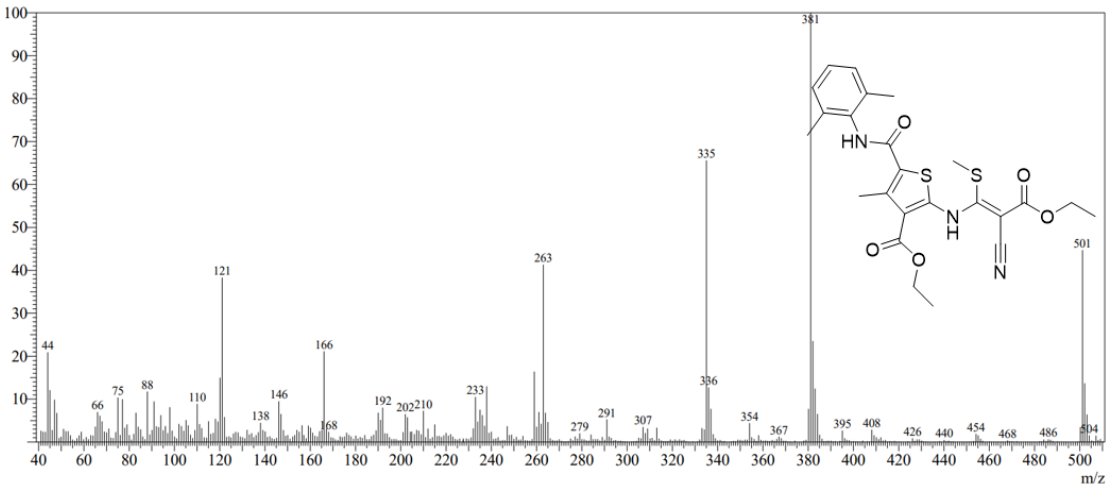


Fig. 9: Representative mass spectrum of compound STOCN-4

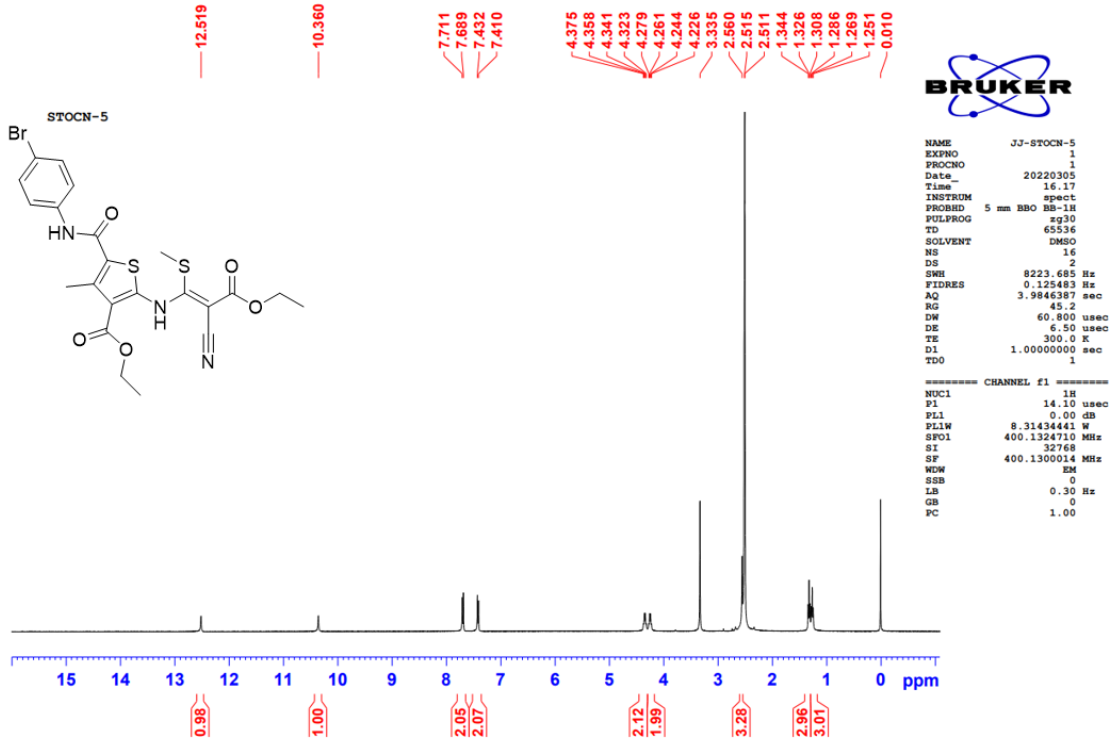


Fig. 10: Representative ^{1}H NMR spectrum of compound STOCN-5

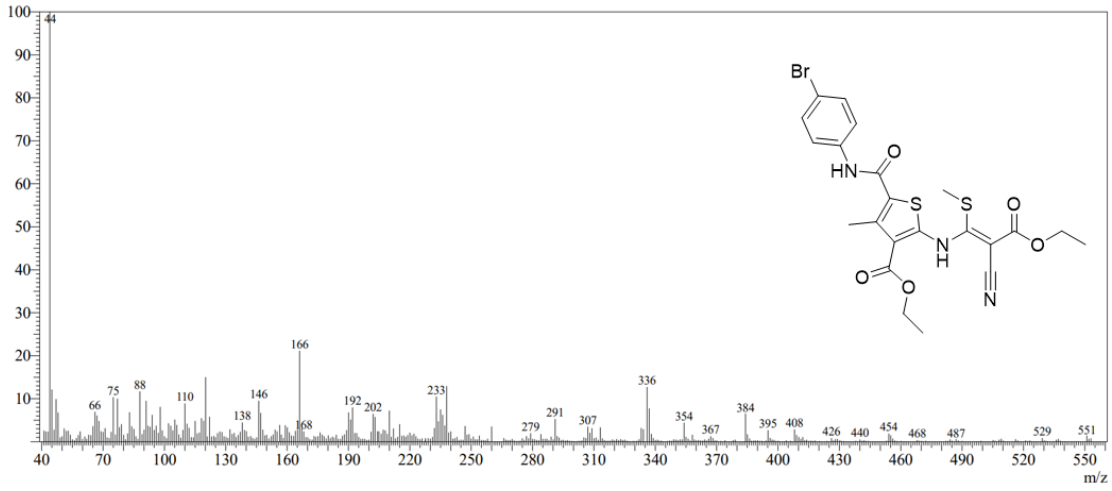


Fig. 11: Representative mass spectrum of compound STOCN-5

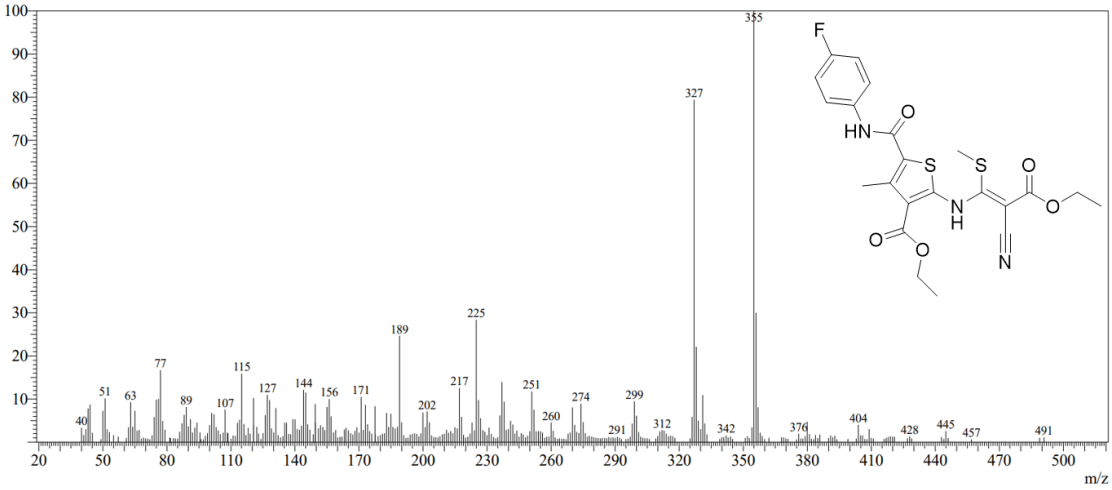


Fig. 12: Representative mass spectrum of compound STOCN-6

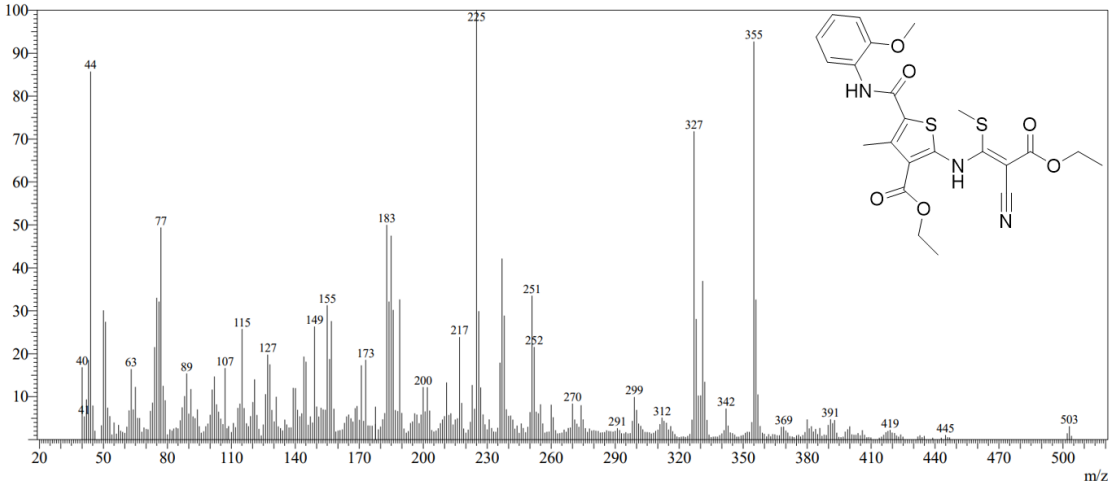


Fig. 13: Representative mass spectrum of compound STOCN-7

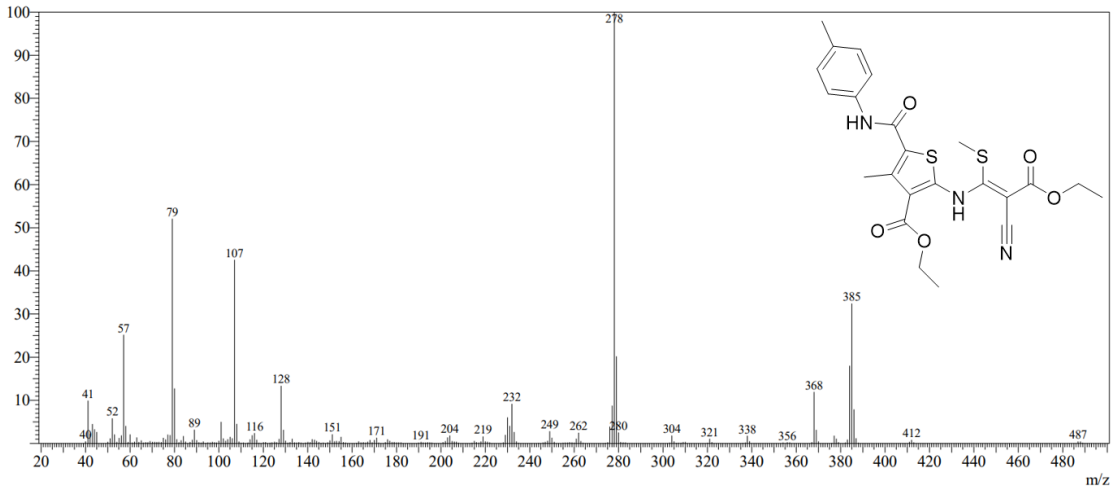


Fig. 14: Representative mass spectrum of compound STOCN-8

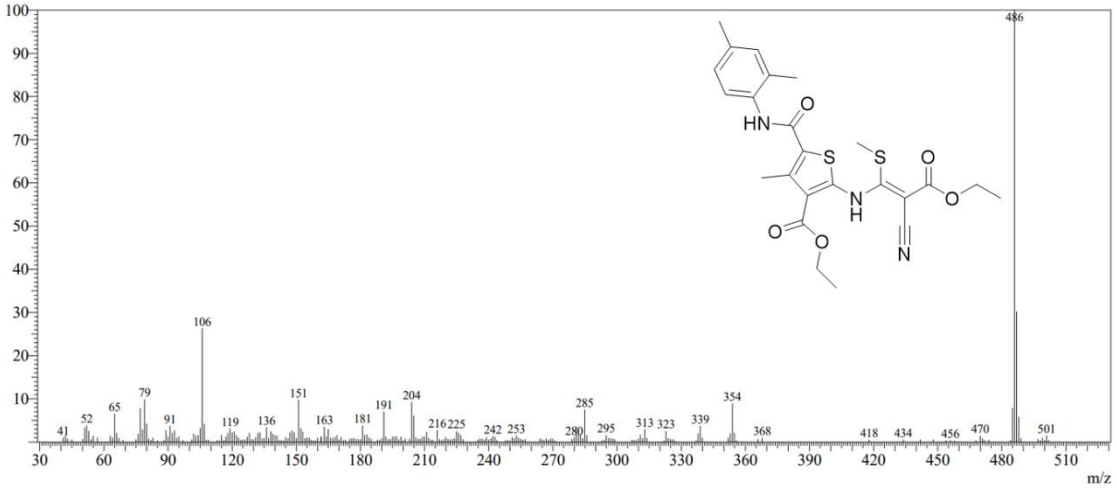


Fig. 15: Representative mass spectrum of compound STOCN-9

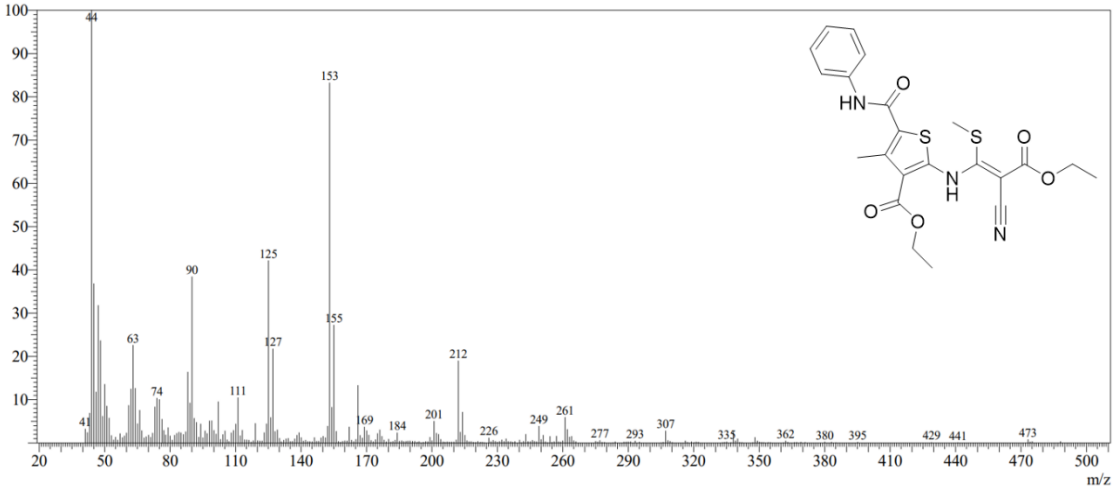


Fig. 16: Representative mass spectrum of compound STOCN-10

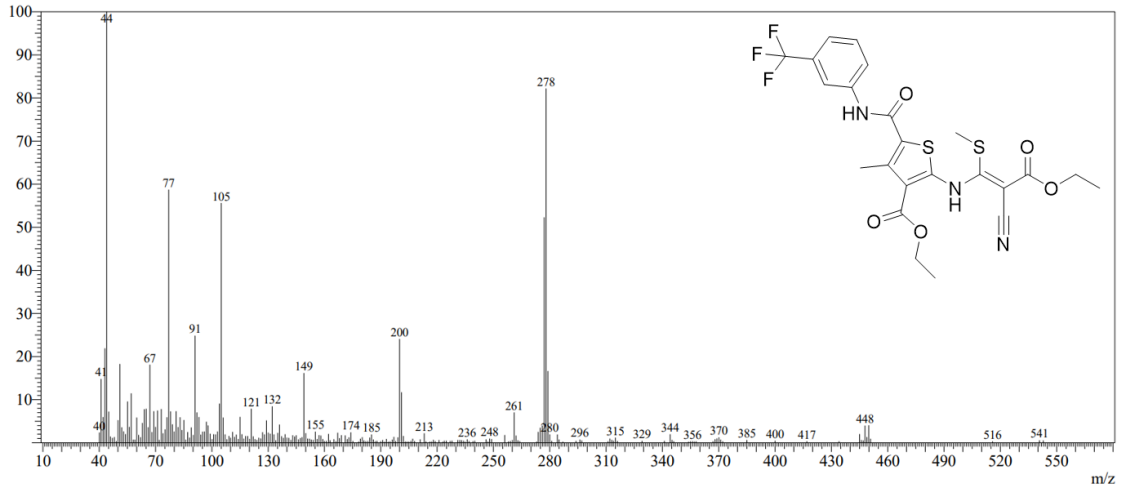


Fig. 17: Representative mass spectrum of compound STOCN-11

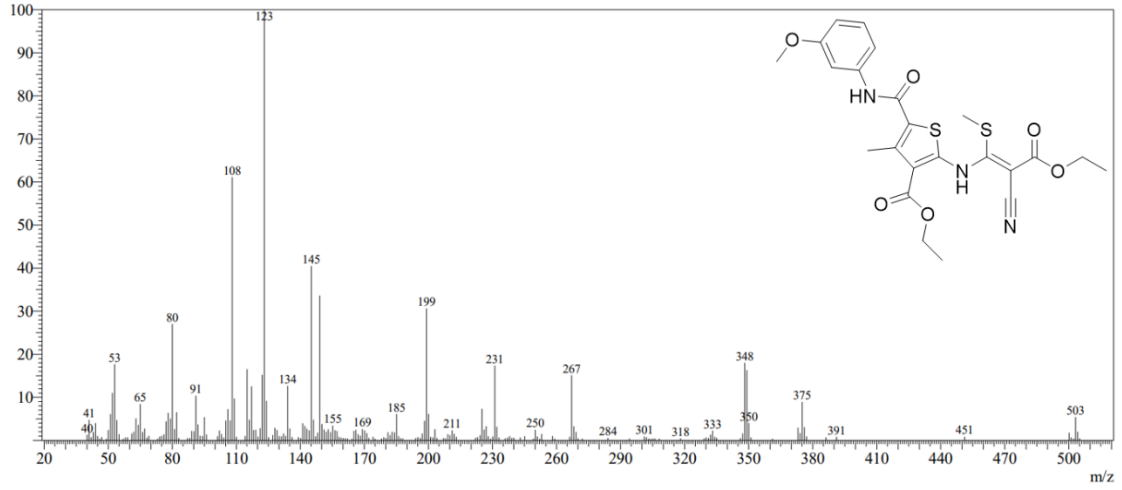


Fig. 18: Representative mass spectrum of compound STOCN-12

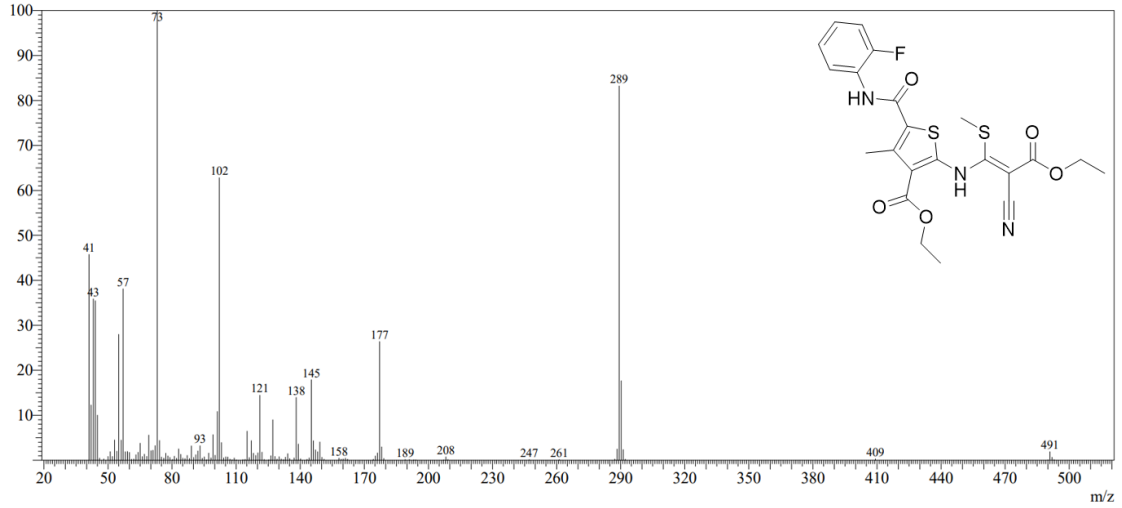


Fig. 19: Representative mass spectrum of compound STOCN-13

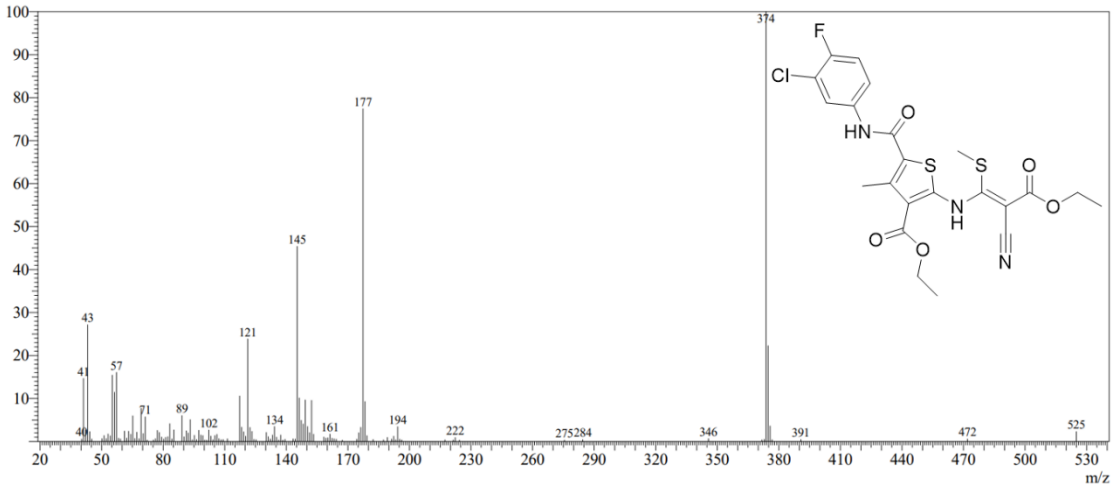


Fig. 20: Representative mass spectrum of compound STOCN-14

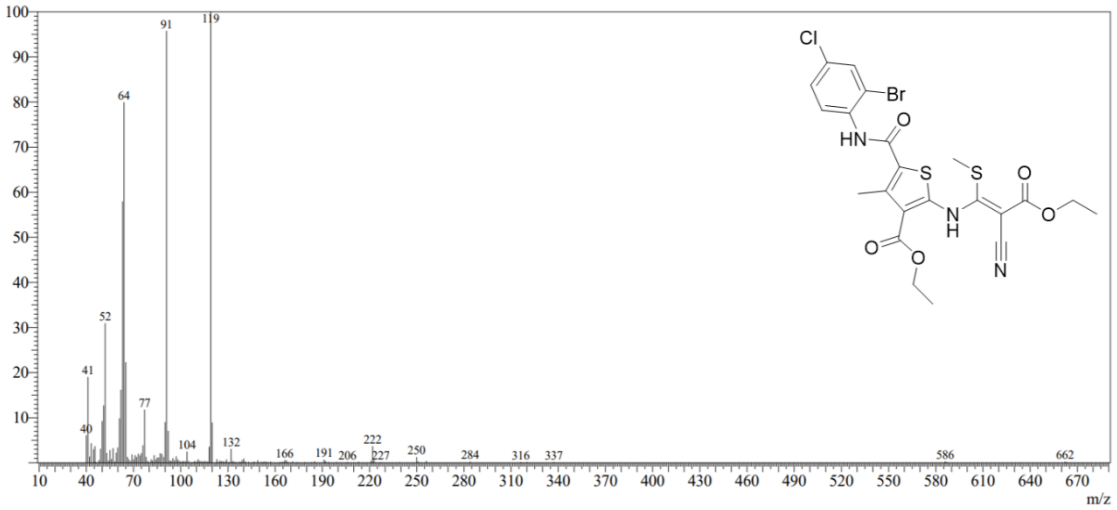


Fig. 21: Representative mass spectrum of compound STOCN-15