# Chapter 3

# Design, Synthesis and Antimicrobial Activities of Some Novel Thiazole-Based Hydrazide Derivatives

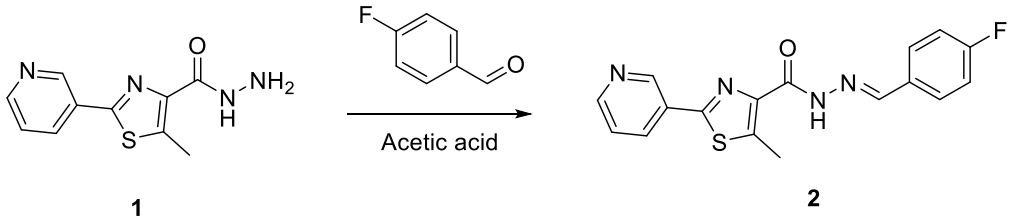
## 3.1 Introduction

Thiazole is a heterocyclic organic compound that contains a five-membered ring consisting of four carbon atoms and one sulfur atom.[103] Thiazole and its derivatives have gained significant attention in recent years due to their diverse biological activities, such as antibacterial, antifungal, antiviral, anticancer and anti-inflammatory properties.[104] In addition, thiazole derivatives have been utilized in various fields, including pharmaceuticals, agrochemicals and materials science.[105] Thiazole is a versatile building block in organic synthesis and can be easily functionalized at different positions of the heterocyclic ring to yield a wide range of thiazole derivatives with varying properties.[106] The most common way to synthesize thiazole derivatives is through the Hantzsch synthesis, which involves the condensation of α-haloketones, aldehydes, or ketones with thioamides in the presence of a base.[107] Alternatively, thiazoles can also be synthesized through the Gewald reaction, the Knorr synthesis, or the Bartoli reaction.[108]

The unique properties of thiazole derivatives are attributed to the presence of the heterocyclic ring, which imparts certain electronic and steric effects to the molecule.[109] For instance, the sulfur atom in thiazole can act as an electron-withdrawing group, making the molecule more acidic and enhancing its reactivity towards nucleophiles.[110] Furthermore, the presence of the sulfur atom can also affect the conformational preferences of the molecule, leading to the formation of twisted or planar structures.[111] In conclusion, thiazole and its derivatives have emerged as important scaffolds in drug discovery and materials science due to their diverse biological activities and versatile synthetic routes. The unique properties of thiazole derivatives make them attractive targets for further investigation and development.

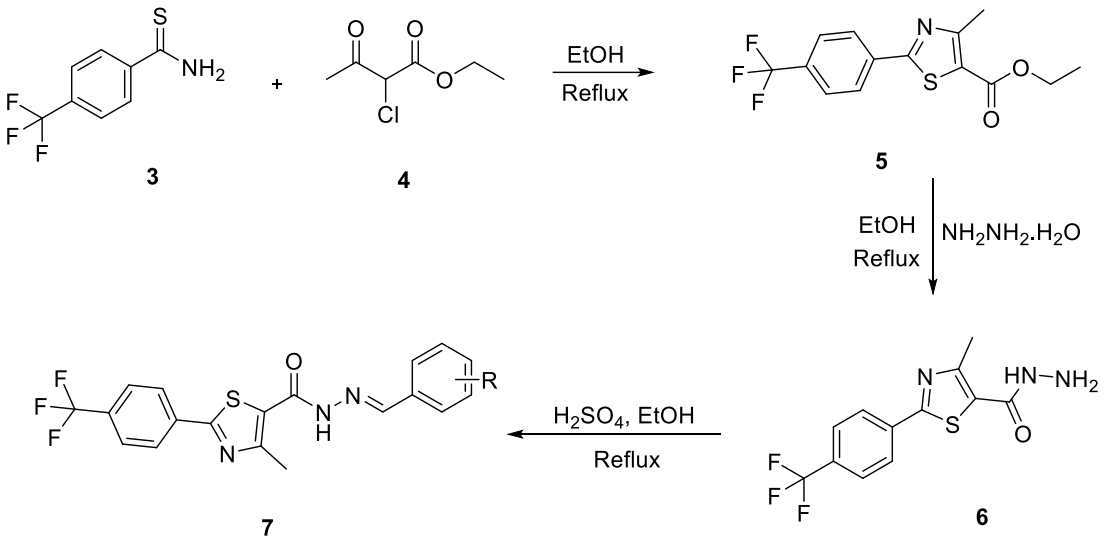
### 3.1.1 Synthetic approaches for substituted thiazole based carbohydrazide scaffold and its biological importance

V. Kamat *et al*[112] synthesized **2** thiazole derivatives incorporated with a pyridine moiety at its second position and attached various aldehydes in ethanol with a catalytical amount of glacial acetic acid and found that these thiazole derivatives possess antibacterial activity against both gram-positive and gram-negative bacteria **(Scheme 3.1)**.




**Scheme 3.1**

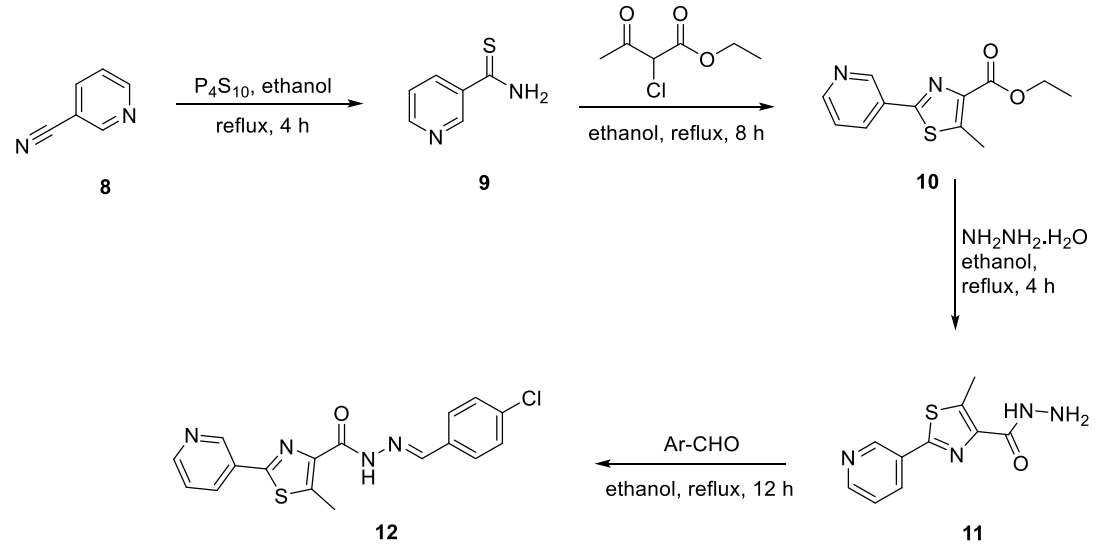
C. Nastasa *et al*[113] synthesized new acyl hydrazones **7** starting from 4-(trifluoromethyl)benzothioamide **3** reacted with ethyl 2-chloroacetoacetate **4** to get thiazole molecule **5**. Furthermore, it was reacted with hydrazine hydrate to form hydrazide molecule **6** and then various substituted aldehydes were attached with it. The thiazole derivatives were found to possess an antimicrobial effect against gram-positive strains of *S. enteritidis*. The inhibitory activity was stronger than that of the reference drug gentamicin. The molecules also possessed good antifungal activity against *C. albicans* and was higher to that of fluconazole which was used as a reference molecule. These compounds also had antiradical activity as well and were better than ascorbic acid **(Scheme 3.2)**.




3 4 5 6 7

**Scheme 3.2**

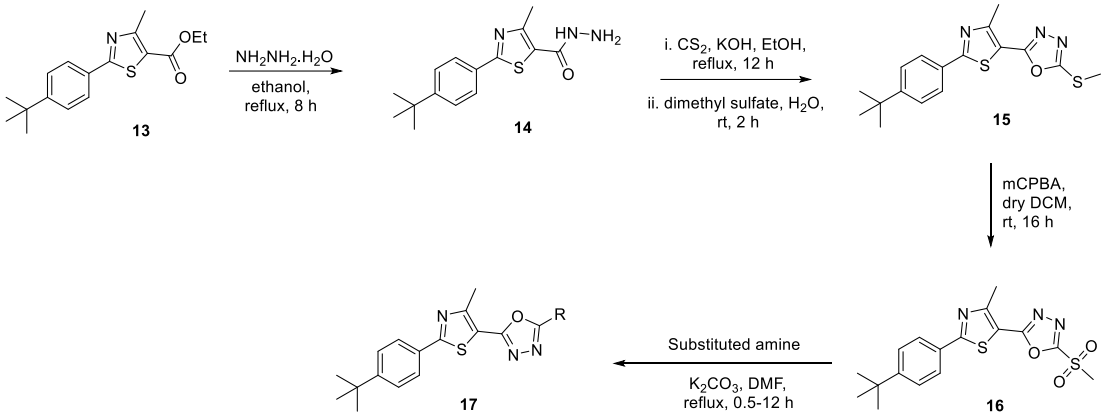
V. Kamat *et al*[114] synthesized thiazole derivatives from 3-cyanopyridine **8** and reacted it with phosphorus pentasulfide in ethanol at reflux for 4 hr and formed Pyridine-3-carbothiamide **9** which was then cyclized using ethyl 2-chloroacetoacetate to form thiazole molecule **10**. Additionally, compound **10** was reacted with various substituted aldehydes to form thiazole derivatives **12** and the anti-inflammatory properties were examined. These molecules were assessed by the bovine serum albumin technique denaturation and displayed inhibition in the range of $IC_{50}$ values 46.29 to 100.60 µg/mL. These molecules were also examined for their antimicrobial activity and the results revealed excellent results **(Scheme 3.3)**.




8 9 10 11 12

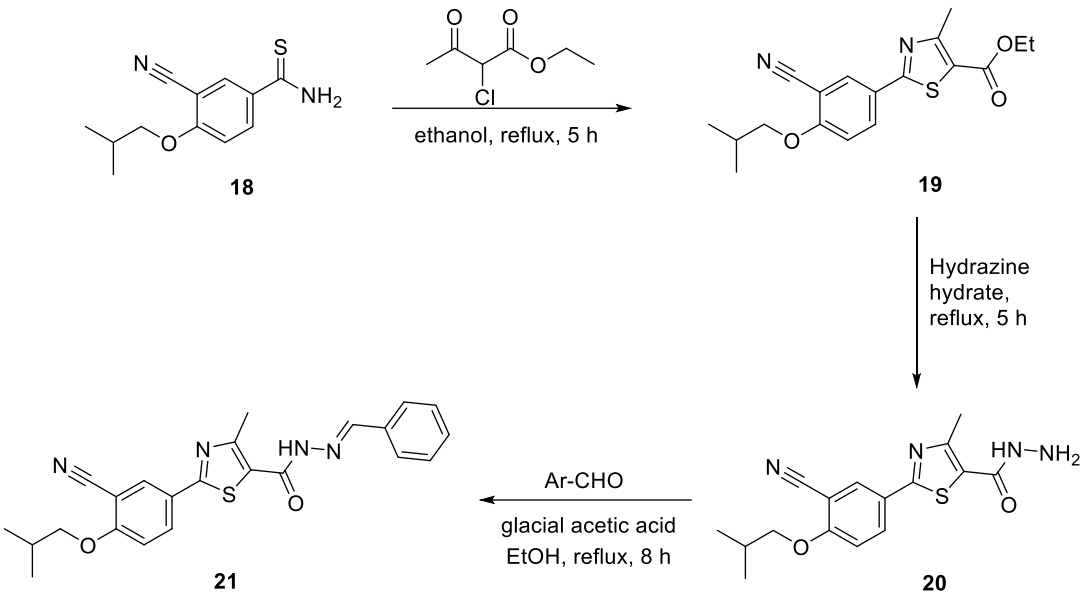
**Scheme 3.3**

A. Kotab *et al*[115] synthesized a hybrid scaffold with the *tert*-butylphenyl lipophilic part **13** and the oxadiazole linker **15**. Molecule **13** was reacted with hydrazine hydrate to form hydrazide **14** and then the hydrazide was done using carbon disulphide and potassium hydroxide in ethanol at reflux and furthermore, with addition of dimethyl sulphate, molecule **15** was formed. To increase the reactivity of SMe group, it was oxidized using *meta*-chloro per benzoic acid to form active $SO_2CH_3$ **16** which was then reacted with various amines, secondary amines and guanidine to form molecule **17.** These derivatives were assessed for their antibacterial activity and found that some of the synthesized molecules were twice better than vancomycin. The phenylthiazole derivatives in this series had a very good pharmacokinetic profile and the biological half-life was 11 times good **(Scheme 3.4)**.



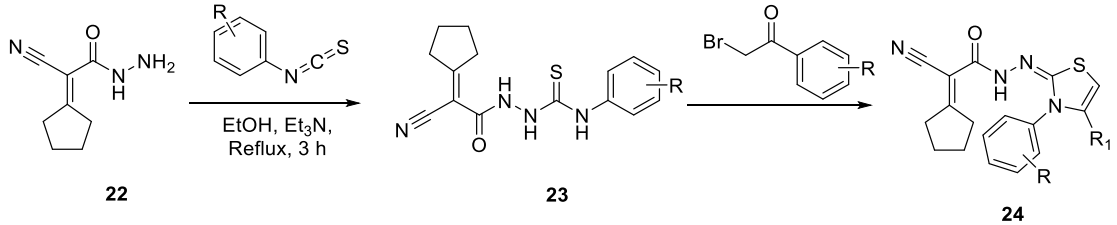

**Scheme 3.4**

P. Nefisath *et al*[116] reported the synthesis of thiazole derivatives and examined the molecules for their larvicidal effect against Anopheles arabiensis. The presence of fluorine and chlorine groups on the phenyl ring increased the larvicidal effect **(Scheme 3.5)**.




**Scheme 3.5**

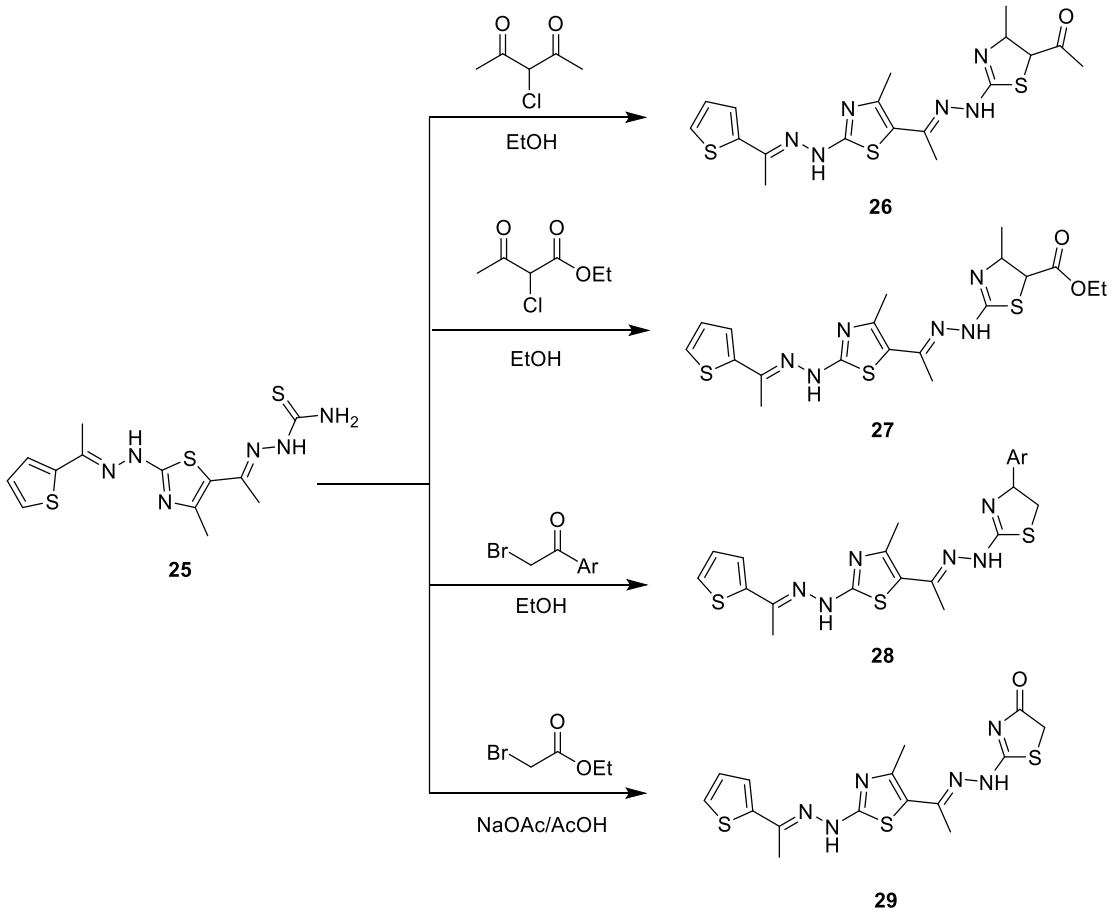
W. Wardakhan *et al*[117] reported the synthesis of some novel thiazole molecules **24** starting from 2-cyano-2-cyclopentylideneacetohydrazide **22**, which was reacted with phenyl isothiocyanate to get intermediate product **23** which was then cyclized with phenacyl bromide to form the thiazole molecule **24**. These molecules were assessed for their anti-tumor activity in which molecule 2-cyano-2-cyclophentylideneacetohydrazido-*N*-(4-cyano-3-phenyl-4-phenyl-thiazol-2-ylideno) hydrazone and 2-cyano-2-(2-phenylhydrazono)-cyclopentylidene acetohydrazide were found to possess excellent inhibitory activity against breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268) cell lines **(Scheme 3.6)**.




**Scheme 3.6**

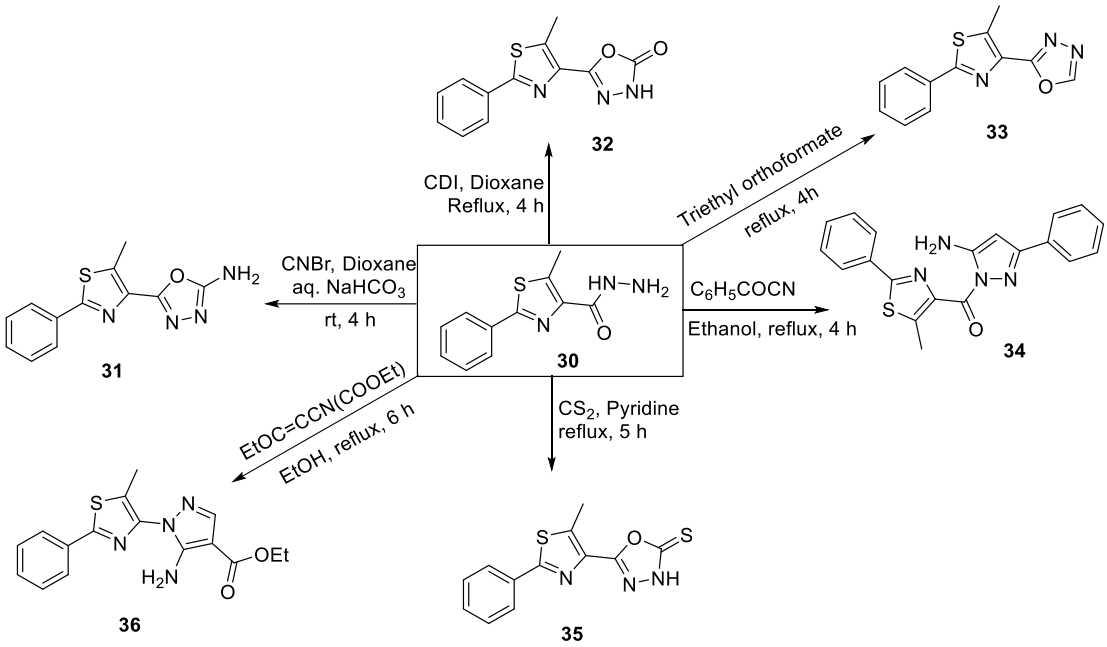
S. Gomha *et al*[118] reported several derivatives having two thiazole moieties in one scaffold. Molecule **25** was reacted with 3-chloropentane-2,4-dione, which afforded derivative **26**. Then reaction with ethyl 2-chloro acetate yielded compound **27** and reaction with phenacyl bromide and ethyl bromo acetate gave corresponding molecules

**28** and **29**. These thiophene combined thiazole moieties that were screened for anticancer activity in which few molecules showed promising cytotoxic activity against the MCF-7 cell line **(Scheme 3.7)**.



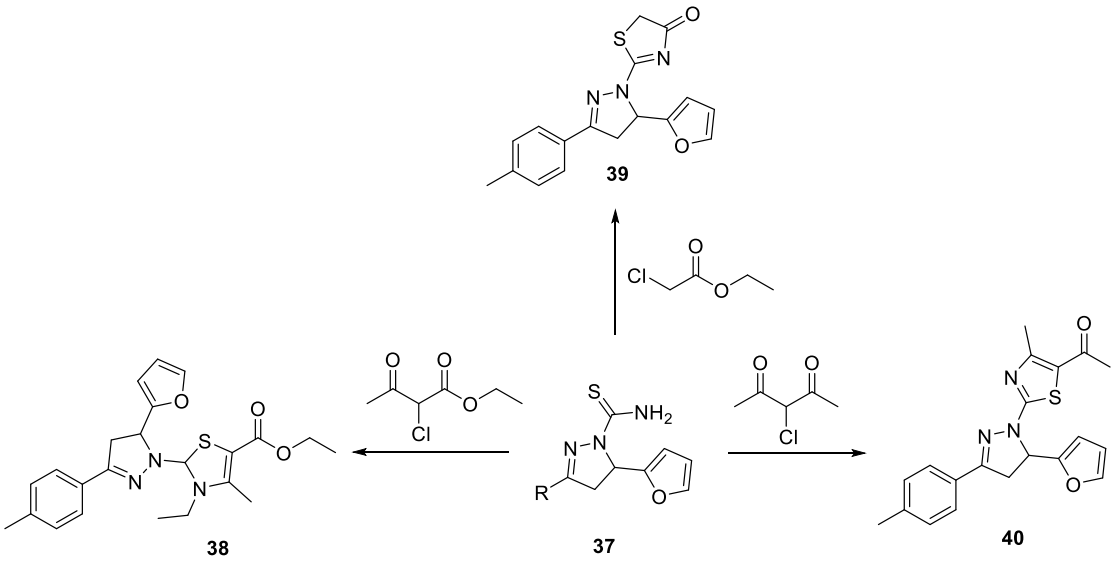

**Scheme 3.7**

S. Thore *et al*[119] reported novel thiazole derivatives with different heterocyclic moieties such as oxadizole and pyrazole at 4$^{th}$ position. Molecule **30** was reacted with cyanogen bromide in dioxane to form the oxadiazole ring **31**, while reaction with CDI in dioxane at reflux also formed an oxadiazole ring incorporated with ketone group **32**. The reaction with triethyl orthoformate gave oxadiazole ring **33** and reaction with benzoyl cyanide in ethanol at reflux formed derivative **34.** While the reaction with carbon disulphide and pyridine gave same oxadiazole ring but with sulphur atom **35**. The reaction with ethyl(ethoxymethylene) cyanoacetate gave molecule **36** with the ester group. These synthesized molecules were assessed for their analgesic and anti-inflammatory activities in which some of the molecules showed excellent inhibitory activity which is greater than the standard drug used **(Scheme 3.8)**.

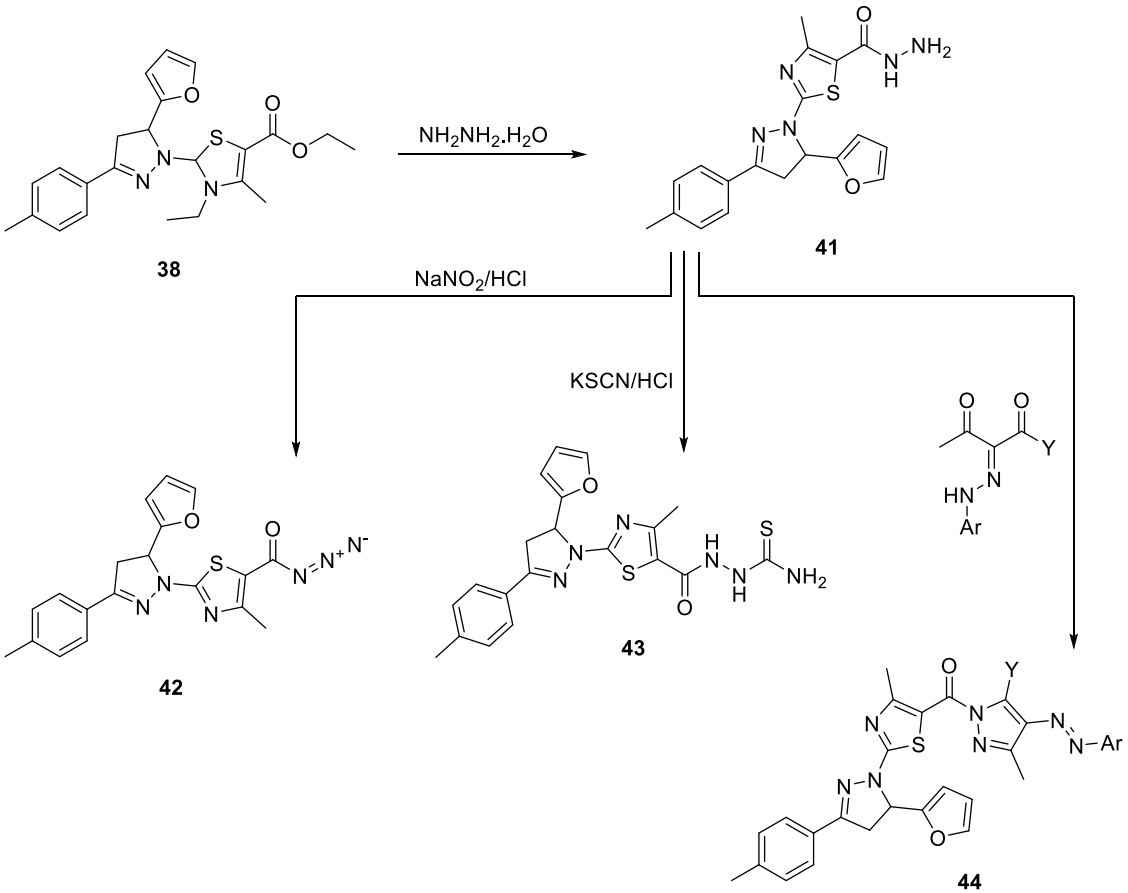



**Scheme 3.8**

A. Abdelhamid *et al*[120] reported thiazole derivatives synthesized from 5-(furan-2-yl)-3-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **37** which was then reacted with ethyl 2-chloro-3-oxobutanoate to obtain molecule **38**, ethyl 2-chloroacetate yielded molecule **39** and 3-chloropentane-2,4-dione gave molecule **40** in ethanol and catalytical amount of triethylamine. Furthermore, the ester group molecule **38** was converted to hydrazide **39** which was then reacted with sodium nitrite and hydrochloric acid to form azide molecule **40 (Scheme 3.9)** and then with potassium thiocyanate, which gave thiourea linkage **41**. Reaction with ethyl 2-(2-arylhydrazono)-3-oxobutanoate afforded molecule **42**. Furthermore, antibacterial and antifungal activities were examined and it was found that some of the synthesized molecules gave moderate inhibitory activity compared to ampicillin and gentamycin **(Scheme 3.10)**



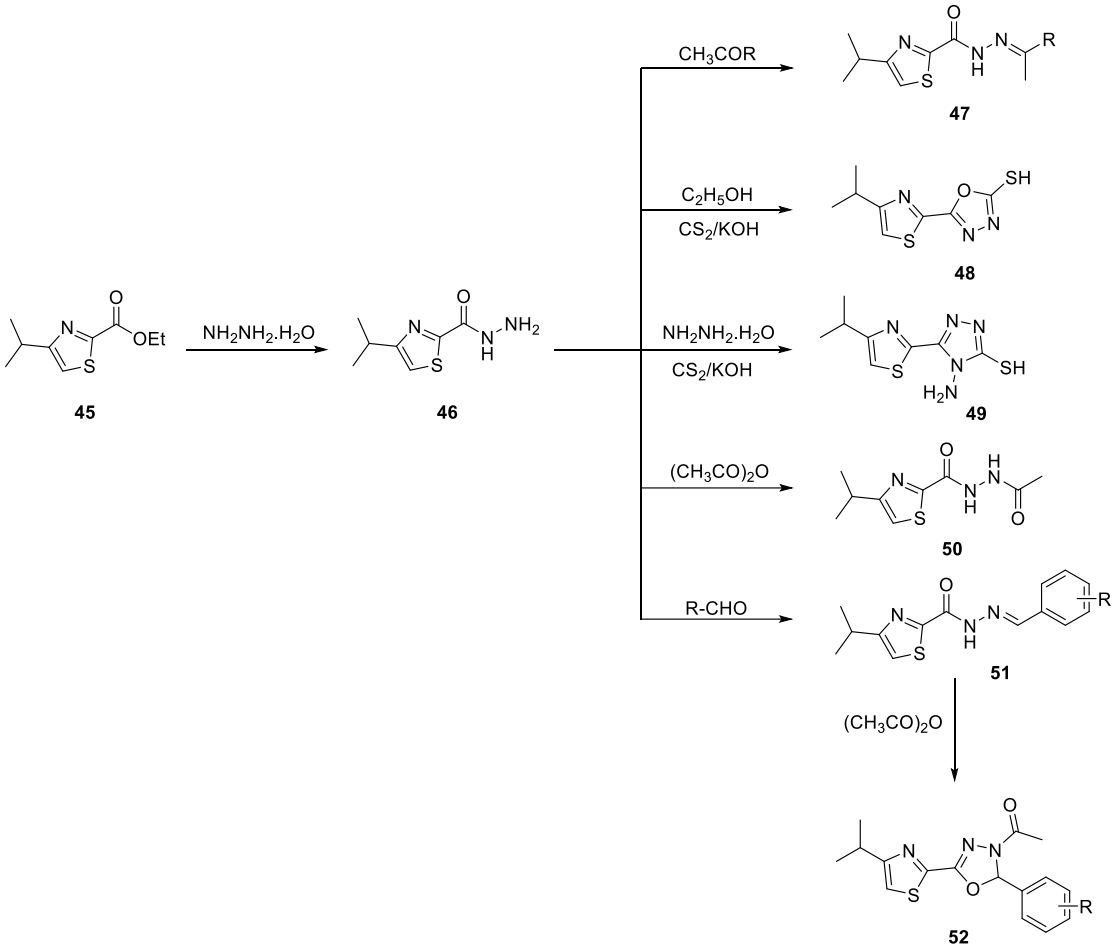
**Scheme 3.9**



**Scheme 3.10**

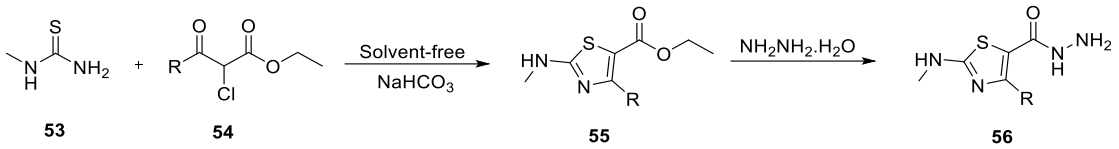
B. Mallikarjuna *et al*[121] has reported isopropyl thiazole clubbed with oxadiazole, thiazole, triazole. 4-isopropylthiazole-2-carbahydrazide **46** was synthesized and reacted with acetophenone derivatives to form molecule **47**. When reacted with carbon

disulphide and potassium hydroxide in the presence of methanol it gave derivative **48**, moreover same reaction condition with addition of hydrazine hydrate provided novel derivatives of triazole **49**. The reaction of acetic anhydride with hydrazide gave acetylated molecule **51** and the reaction of various substituted aldehydes formed molecule **51** which was cyclized using acetic anhydride and formed molecule **52**. Some of the synthesized molecules were screened for their antimicrobial and anti-tuberculosis activity **(Scheme 3.11)**.



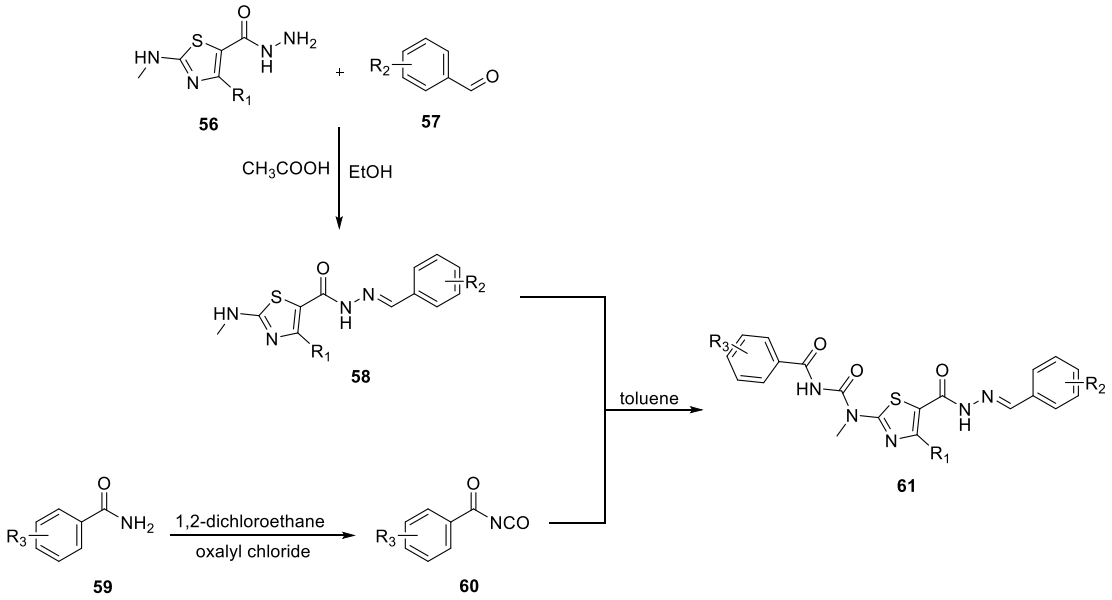

**Scheme 3.11**

H. Haifeng *et al*[122] has reported 2,4,5-trisubstituted 1,3-thiazole derivatives **62** starting from the hydrazide molecule **56 (Scheme 3.12)** which was synthesized using 1-methylthiourea. Molecule **58** was prepared by attaching various substituted benzaldehydes in ethanol using acetic acid as a catalyst. Molecule **58** was reacted with molecule **60** to form a novel 2,4,5-tri-substituted thiazole derivatives **61**.



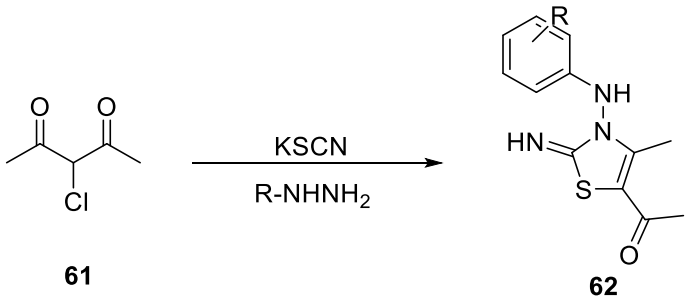

**Scheme 3.12**

Most of the synthesized molecules from **61** were evaluated for their anticancer activity in MCF-7, HepG2, BGC-823, Hela and A549 cell lines **(Scheme 3.13)**.



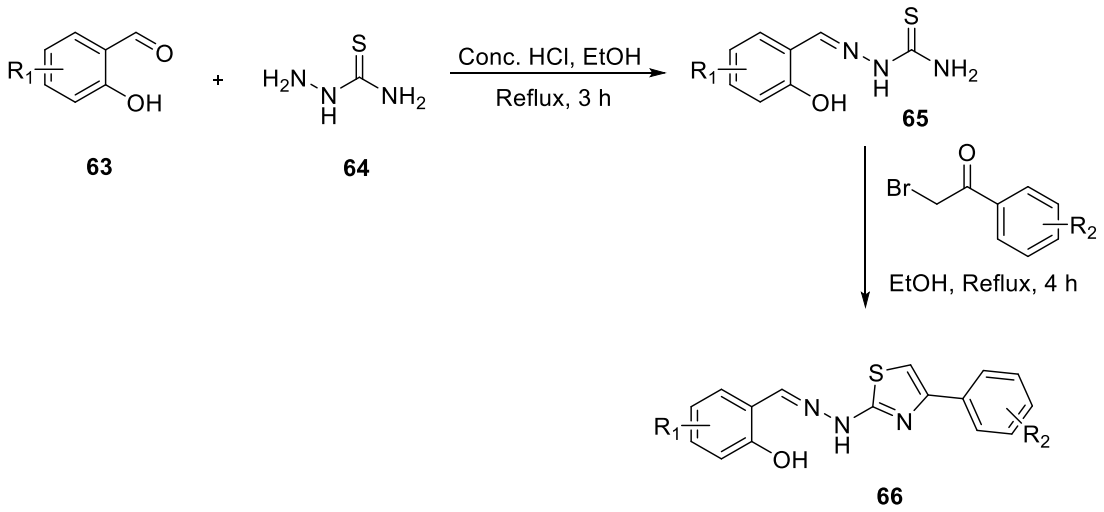

**Scheme 3.13**

B. Hamid *et al*[123] reported highly functionalized derivatives of thiazole using 3-chloro acetone **61** reaction with potassium thiocyanate and further cyclization of the ring using phenyl hydrazine derivatives to form functionalized thiazole molecules **62 (Scheme 3.14)**.



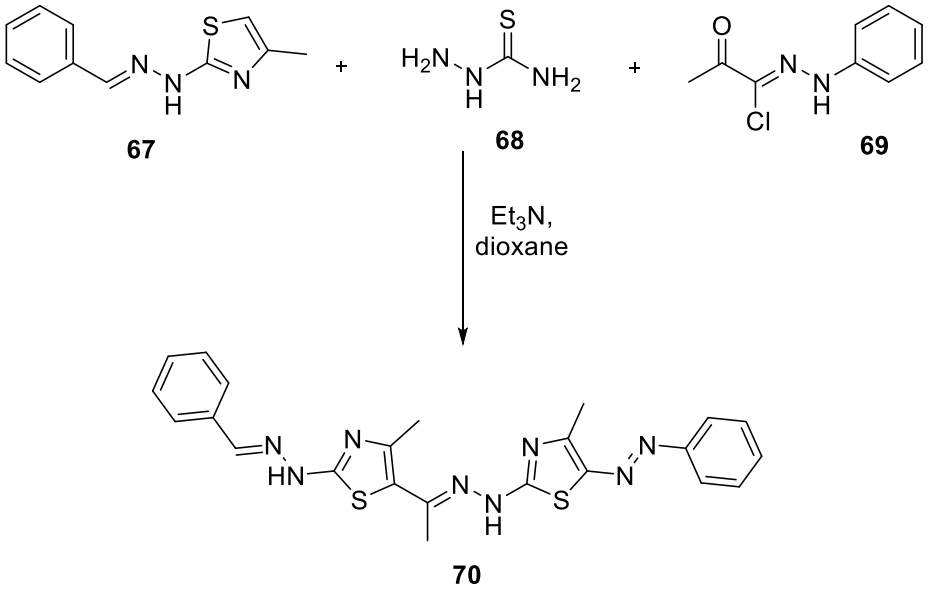

**Scheme 3.14**

V. Gore *et al*[124] reported thiazole derivatives starting from substituted salicylaldehyde **63** which was reacted with thiosemicarbazide **64** to form hydrazide molecule **65** which was cyclized via reaction with phenacyl bromide derivatives to form novel thiazole derivatives **66**. Synthesized molecules were screened for their antimicrobial and antimalerial activity in which it was found that most of the synthesized molecules were active against *E. coli* and *C. albicans*. Antimalarial activity in contrast to *Plasmodium falciparum* showed a reasonable activity **(Scheme 3.15)**



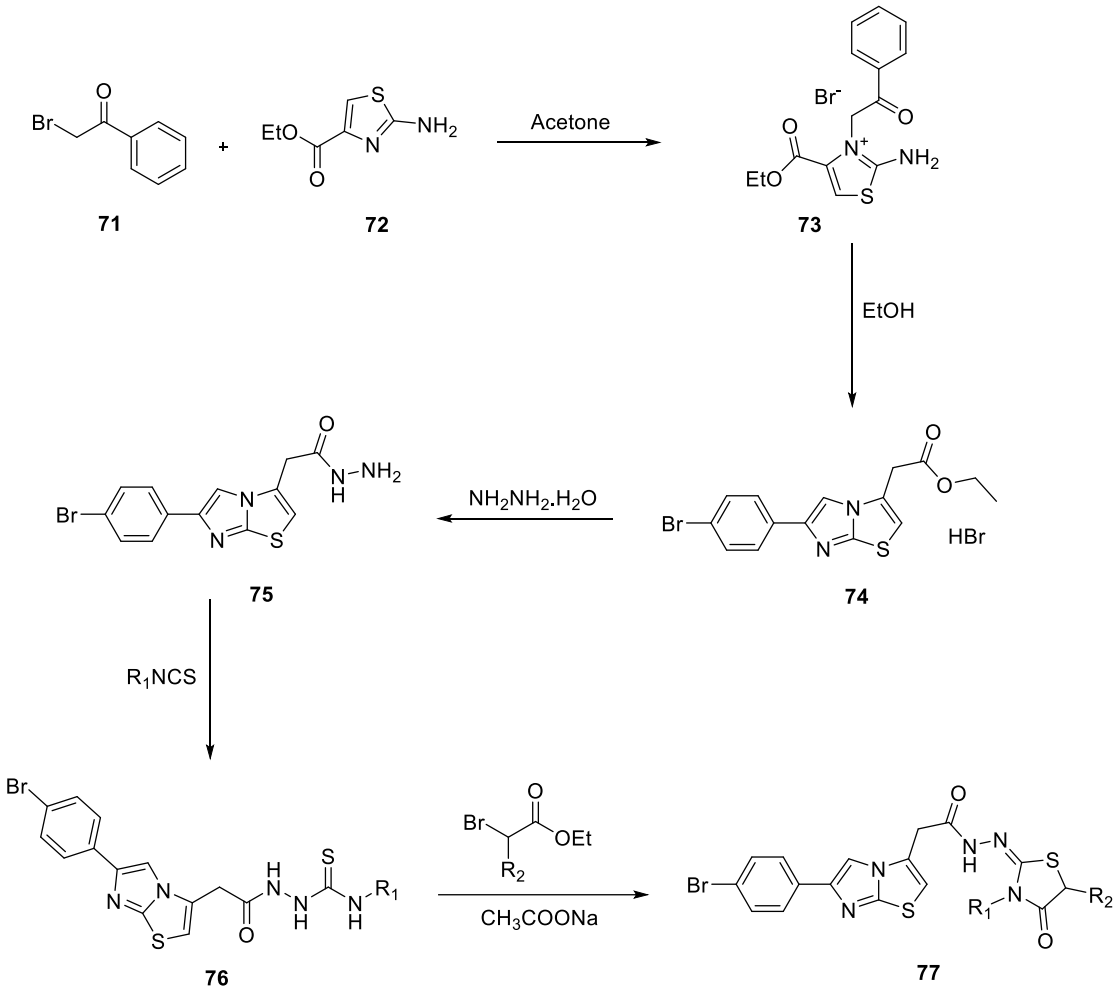

**Scheme 3.15**

A. Sayed *et al*[125] reported thiazole synthesis starting from a thiazole hydrazide **67** molecule that reacted with thiosemicarbazide **68** and molecule **69** in dioxane with the use of triethylamine as a base to form molecule **70** having two thiazole moieties with hydrazide and azo bonds present in one structure. The synthesized molecules were screened for their anticancer activities in which the molecules were found to be active against HCT-116, HT-29 and HepG2 cell lines **(Scheme 3.16)**.




**Scheme 3.16**

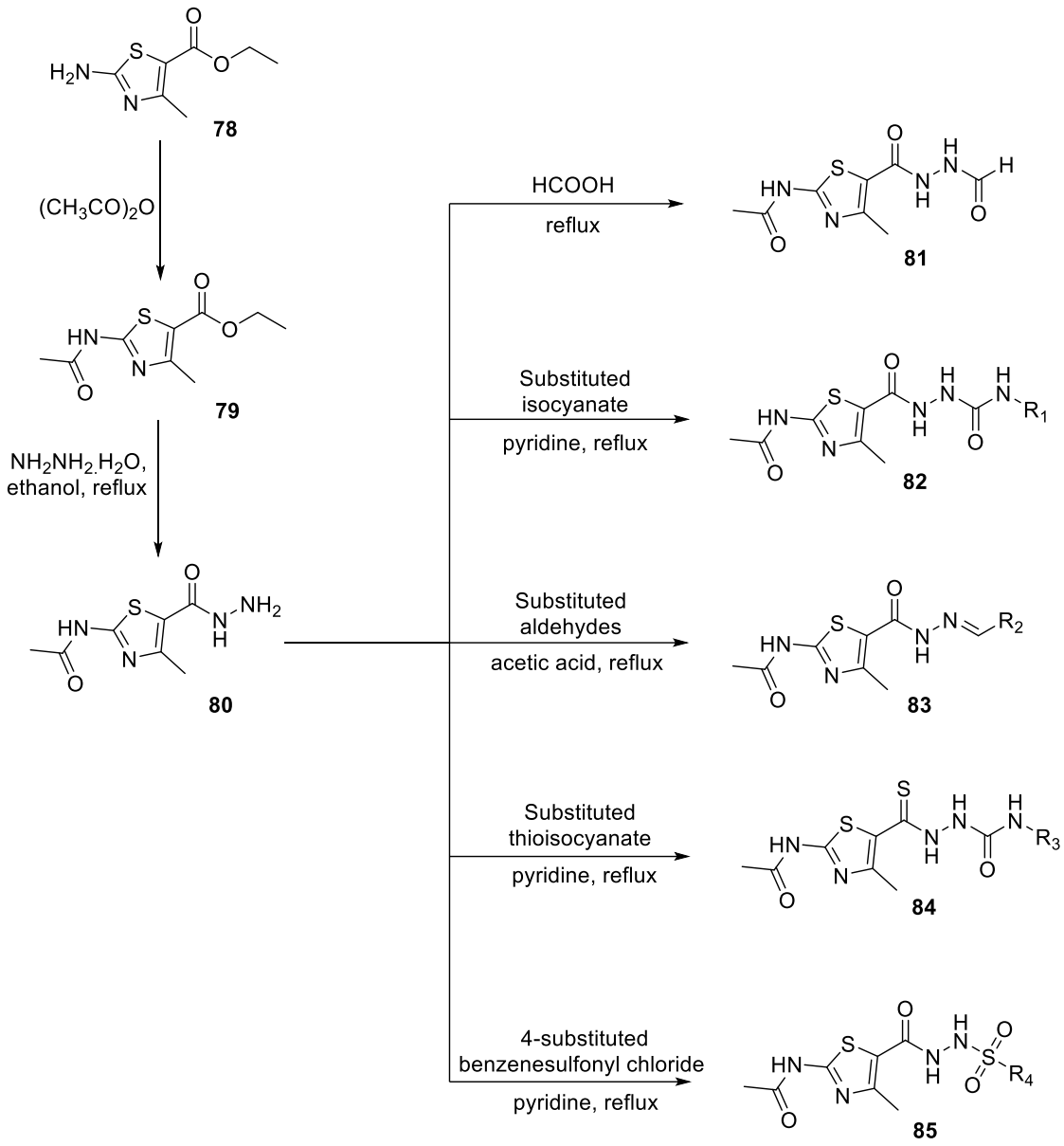
N. Ulusoy *et al*[126] reported thiazole fused derivatives starting from phenacyl bromide **71** and thiazole **72** was reacted in aceton to form intermediate product **73** which was cyclized when refluxed in absolute ethanol to form fused thiazole molecule **74**. Reaction of **74** with hydrazine hydrate formed a hydrazide molecule that was reacted with various substituted isothiocyanates to form molecule **76** and cyclization was done using various ethyl bromoacetate derivatives to form molecule **77**. The synthesized molecules were screened for aldose reductase inhibitory activity **(Scheme 3.17)**.




**Scheme 3.17**

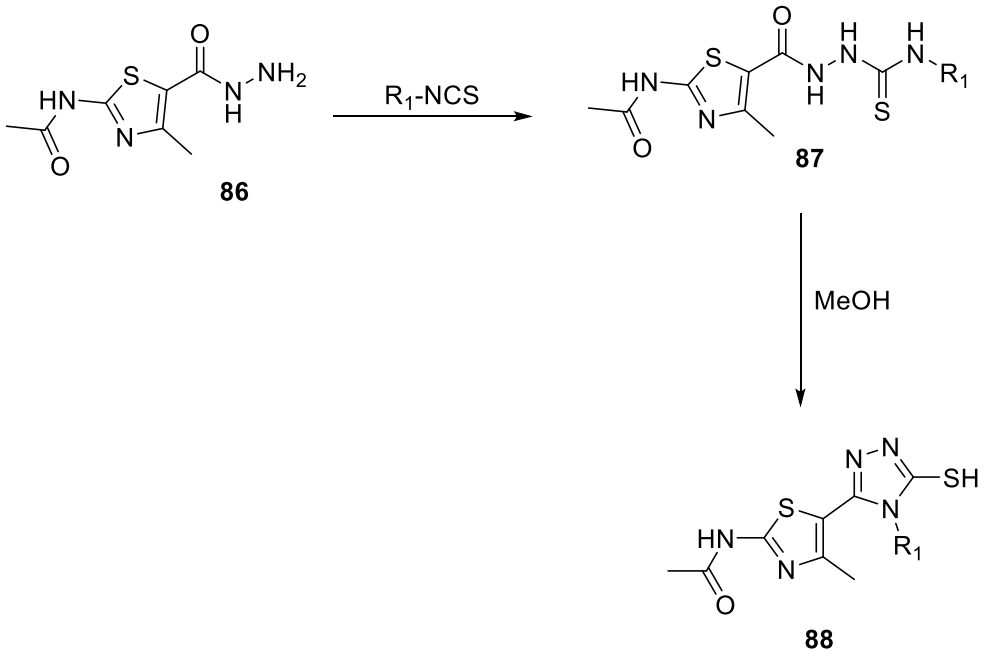
Al-Saadi *et al*[127] reported synthetic pathways to obtain various thiazole derivatives, starting with molecule **78** which was reacted with acetic anhydride to form the acetylated thiazole molecule **79**, which was then reacted with hydrazine hydrate to form the hydrazide molecule **80**. Furthermore, various derivatives have been reported starting from molecule **80**. The reaction with formic acid formed molecule **81**, reaction with substituted isocyanate in pyridine at reflux temperature formed molecule **82** and with various substituted aldehydes formed **83**, similarly, reaction with substituted thioisocyanate formed molecules **84** and with 4 substituted various benzene sulfonyl chloride in pyridine at reflux temperature gave molecules **85**. All newly prepared molecules were subjected to antimicrobial and anticancer activity. Strong antibacterial and antifungal activities were associated with molecules that have thiosemicarbazide and thioureido linkages. Fluoro derivatives showed the most potent effect against broad

spectrum of bacteria. Some molecules show inhibitory activity against various cell lines which are Hop-92, IGROV1 and SK-MEL-2 **(Scheme 3.18)**.



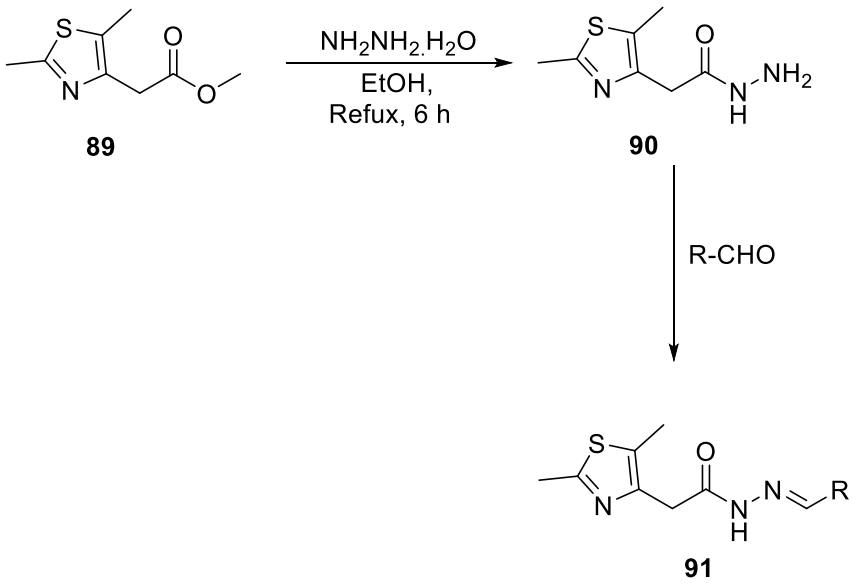

**Scheme 3.18**

H. El-Subbagh *et al*[128] reported thiazole derivatives starting from thazole hydrazide **86** molecule was reacted with substituted isothiocyanate to form molecule **87** which was refluxed in methanol to form thiazole-triazole molecule **88**. These synthesized molecules were screened for their antimicrobial and antitumor activity **(Scheme 3.19)**.



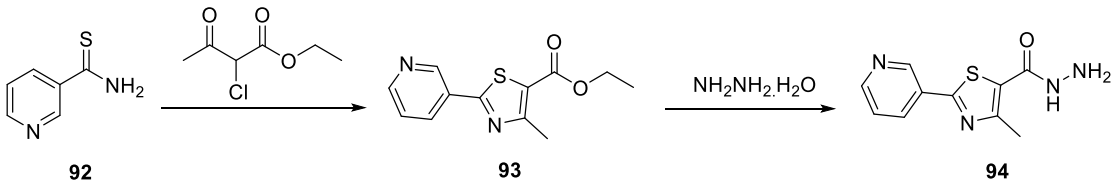

**Scheme 3.19**

M. Taha *et al*[129] reported that thiazole molecule synthesis starting from molecule **89** was reacted with hydrazine hydrate to form the hydrazide molecule **90** which was reacted with various aldehydes to form a series of molecule **91**. Furthermore, the synthesized molecules were screened for their antidiabetic activity in which it was found that most of the synthesized molecules showed inhibition in the range of 1.709 to 3.049 μM **(Scheme 3.20)**.




**Scheme 3.20**

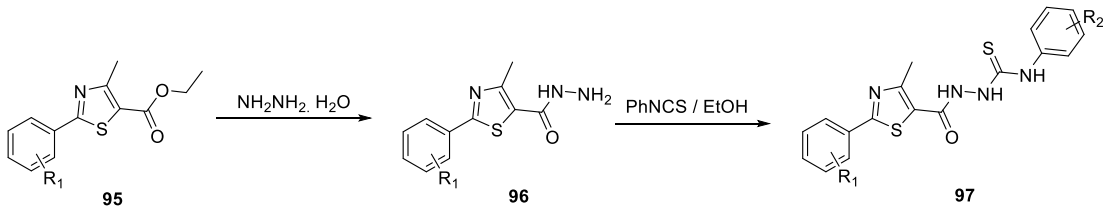
T. Salman *et al*[130] reported that pyridine-3-carbothioamide **92** was reacted with ethyl 2-chloroacetoacetate to form thiazole derivative **93** and further it was reacted with hydrazine hydrate to form the hydrazide molecule **94**. Synthesized molecule showed mild inhibitory effect of steel against hydrochloric environment **(Scheme 3.21)**.




**92** **93** **94**

**Scheme 3.21**

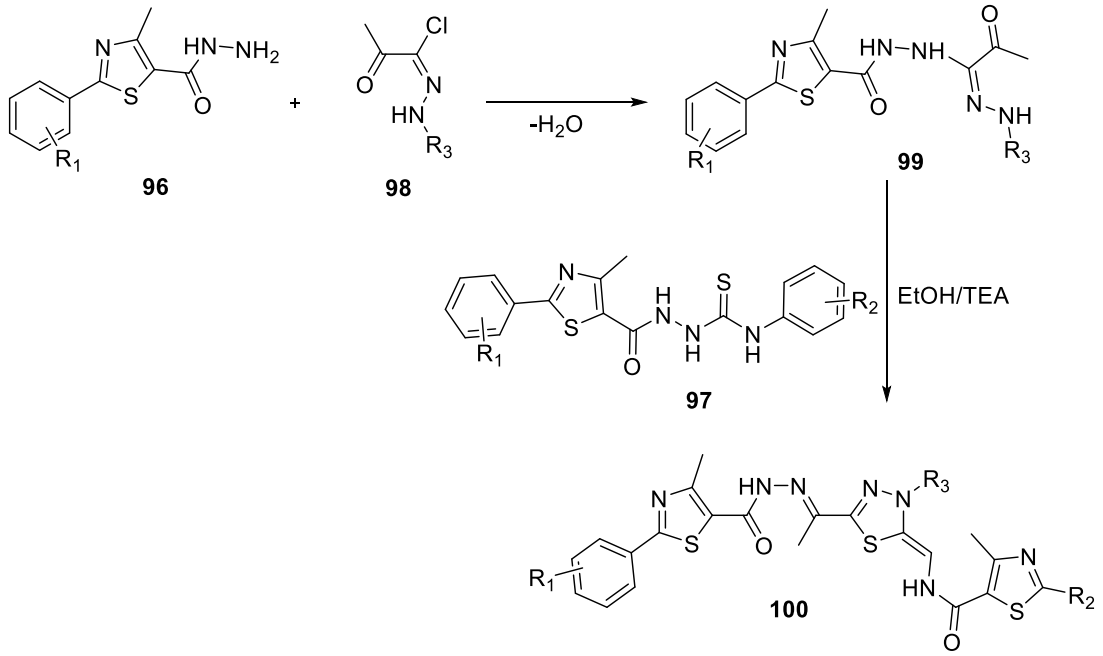
S. Gomha *et al*[131] reported synthesis of thiazole derivatives starting from molecule **95** which was reacted to form hydrazide molecule **96**. Furthermore, molecule **96** was reacted with various phenyl isothiocyanates in ethanol to form molecule **97 (Scheme 3.22)**.




**95** **96** **97**

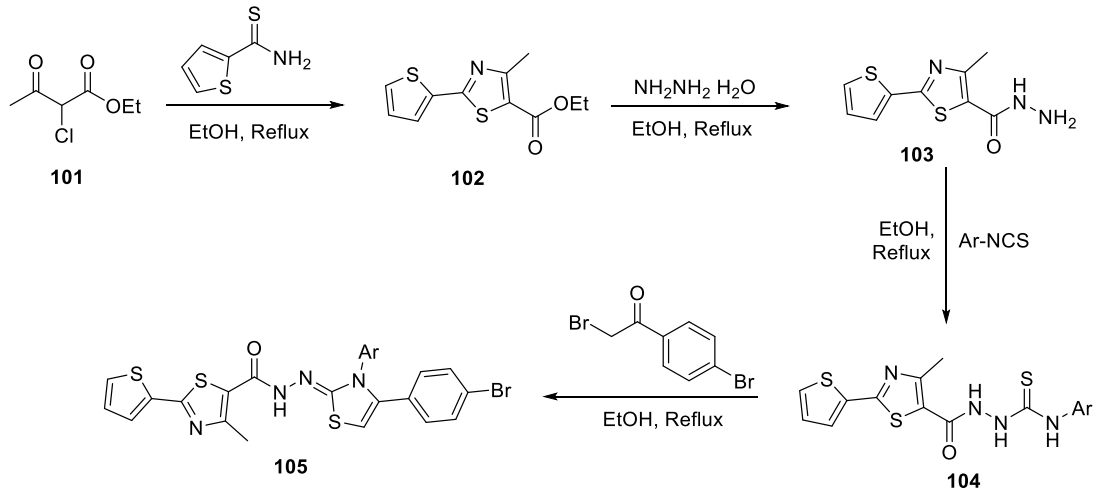
**Scheme 3.22**

Moreover, molecule **96** was reacted with suitable hydrazonoyl chloride to form molecule **98** to form molecule **99** which was again reacted with molecule **97** to form highly functionalized bis thiazole molecule **100**. The synthesized molecules were screened for their anticancer activity against the HepG-2 cell line with the help of MTT assay **(Scheme 3.23)**.



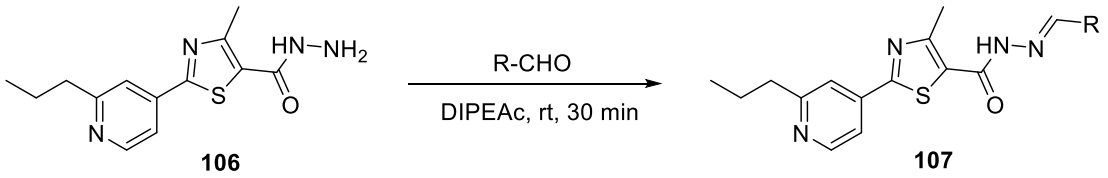

**Scheme 3.23**

S. Mhaske *et al*[132] reported synthesis of thiazole derivatives, starting from ethyl 2-chloro-3-oxobutanoate **101** reacted with thiophene-2-carbothioamide **102** in absolute ethanol at reflux temperature, cyclized thiazole molecule was obtained **102**. Furthermore, it was reacted with substituted isothiocyanate to form molecule **104**, which was cyclized via reaction with 4-bromo phenacyl bromide to afford bis-thiazole molecule **105**. Synthesized molecules were screened for their antimicrobial activity, in which it was discovered that thiosemicarbazide linkage is best active against bacterial strains and moderately active against fungal strains. While most of the other tested molecules showed normal to moderate activity against experimented organisms **(Scheme 3.24)**.



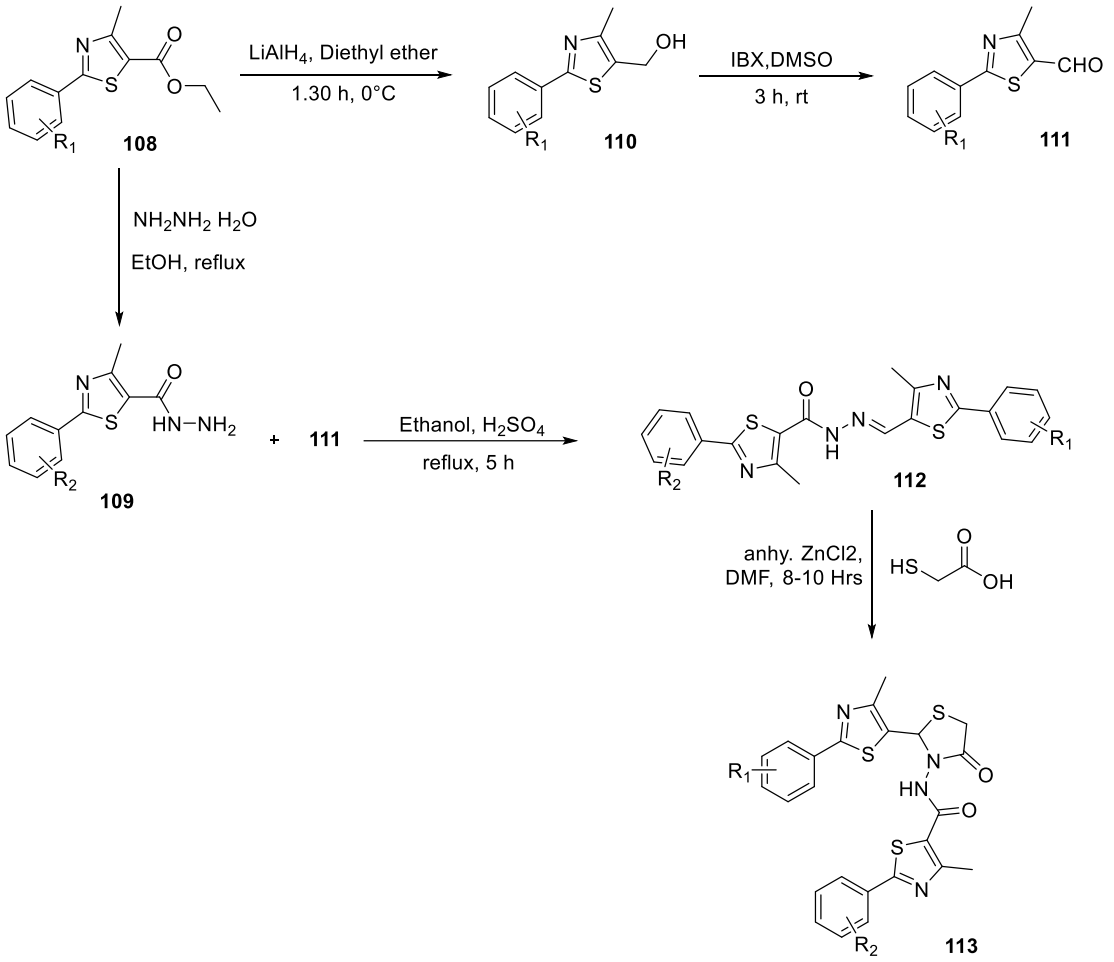

**Scheme 3.24**

M. Muluk *et al*[133] reported the synthesis of pyridine-incorporated thiazole derivatives starting from hydrazide molecule **106** that was reacted with various substituted aldehydes in di-isopropyl ethyl ammonium acetate to form substituted thiazole molecules **107**. The synthesized molecules were screened for their antimicrobial and antioxidant activities. The tested molecules showed moderate to good activity **(Scheme 3.25)**.



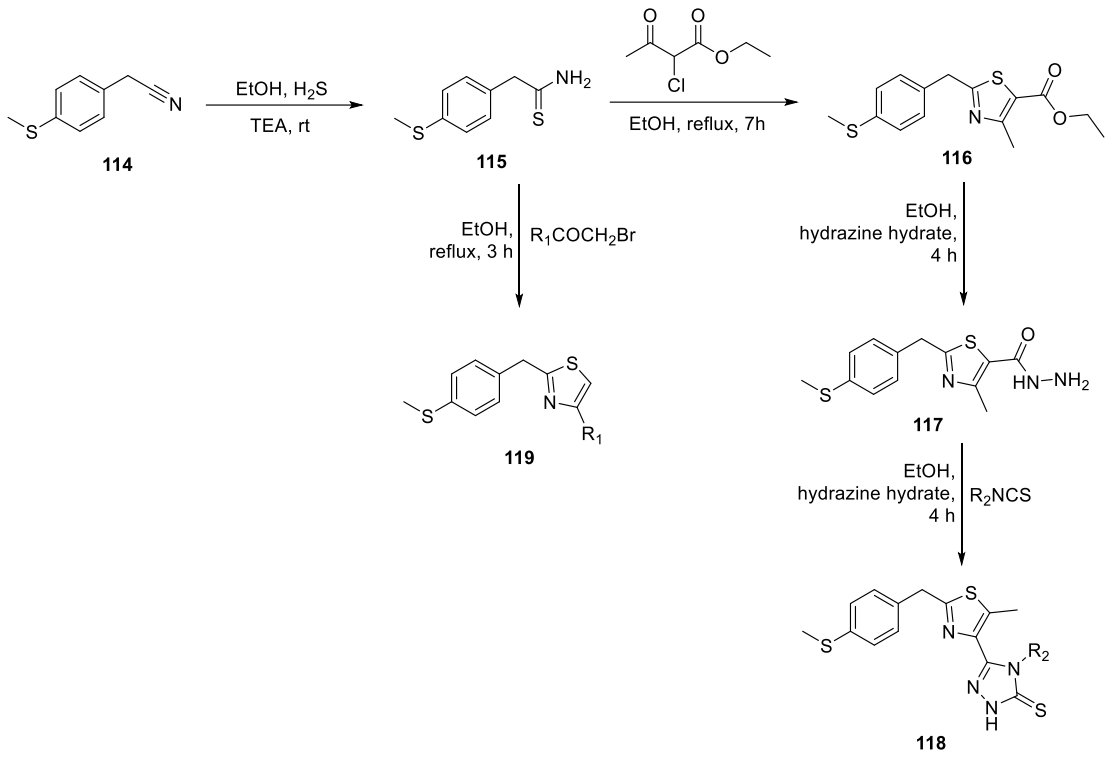

**Scheme 3.25**

R. Borde *et al*[134] reported synthesis of bis-thiazole derivatives starting from molecule **108** which was converted to hydrazide by reaction with hydrazine hydrate **109**. Molecule **108** was also reacted with lithium aluminum hydride in diethyl ether for 1.5 hr to form molecule **110**. Furthermore, molecule **110** was reacted with 2-iodoxybenzoic acid to form the aldehyde molecule **111**. This molecule was reacted with **109** in ethanol containing concentrated sulfuric acid at reflux to form the schiff base molecule **112**, moreover cyclization of this molecule was carried out using thioglycolic acid in DMF containing anhydrous zinc chloride to highly functionalized molecule **113**. The synthesized molecules were screened for their anti-inflammatory and antimicrobial properties. In which it was found that some of the derivatives of molecule **113** showed good antibacterial, antifungal and anti-inflammatory activity **(Scheme 3.26)**.



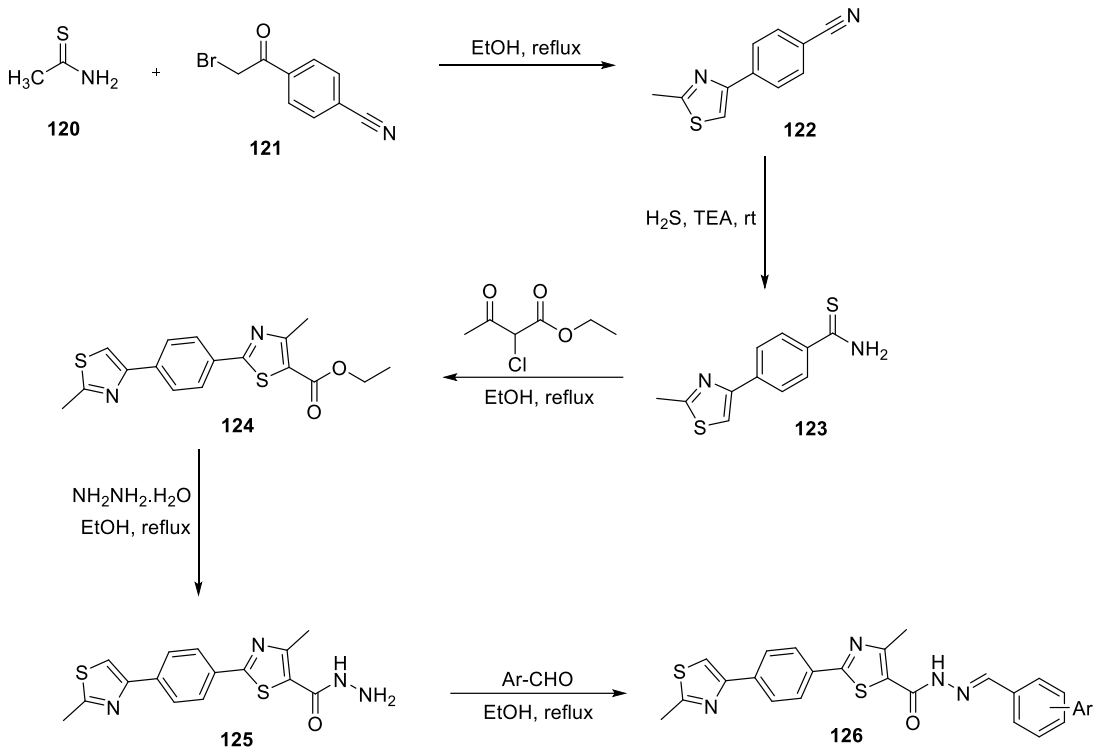

**Scheme 3.26**

R. Santosh *et al*[135] reported synthesis of thiazole derivatives starting from [4-(methylsulfanyl)phenyl]acetonitrile **114** was reacted with hydrogen sulphide gas in ethanol containing a catalytic amount of triethyl amine to form molecule **115**. The reaction of molecule **115** with ethyl-2-chloroacetoacetate gave thiazole derivative **116**, which was reacted with hydrazine hydrate to form thiazole hydrazide molecule **117** and it was reacted with various substituted phenyl isothiocyanate to form triazole-thiazole molecules **118**. The reaction of molecule **115** with different derivatives of phenacyl bromide also gave novel thiazole molecules **119**. The synthesized molecules were screened for their antibacterial activity, in which it was found that derivatives of molecule **119** and **118** showed good antibacterial activity. Furthermore, molecules containing methyl, nitro and fluoro substituted showed a broad range of activities **(Scheme 3.27)**.



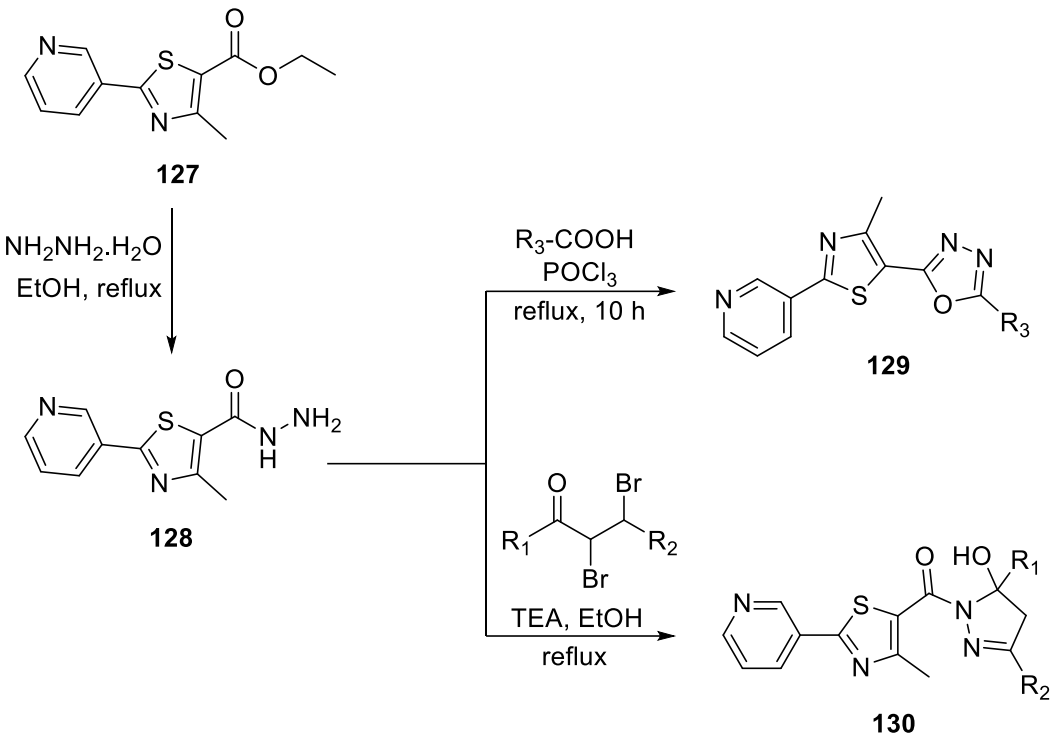

**Scheme 3.27**

A. Borcea *et al*[136] reported bis-thiazole derivative synthesis starting from thioacetamide **120** reacted with 4-(2-bromoacetyl) benzonitrile to form thiazole molecule **122**, which was reacted with hydrogen sulphide gas to form molecule **123**. Furthermore, the reaction of this molecule with ethyl 2-chloroacetoacetate to form bis-thiazole **124** and again the reaction with hydrazine hydrate formed a hydrazide thiazole molecule **125**, in which various substituted aldehydes are attached to form a series of molecule **126**. The synthesized molecules were screened for their antifungal activity against *Candida albicans*, *Candida parapsilosis* and *Candida krusei* **(Scheme 3.28)**.



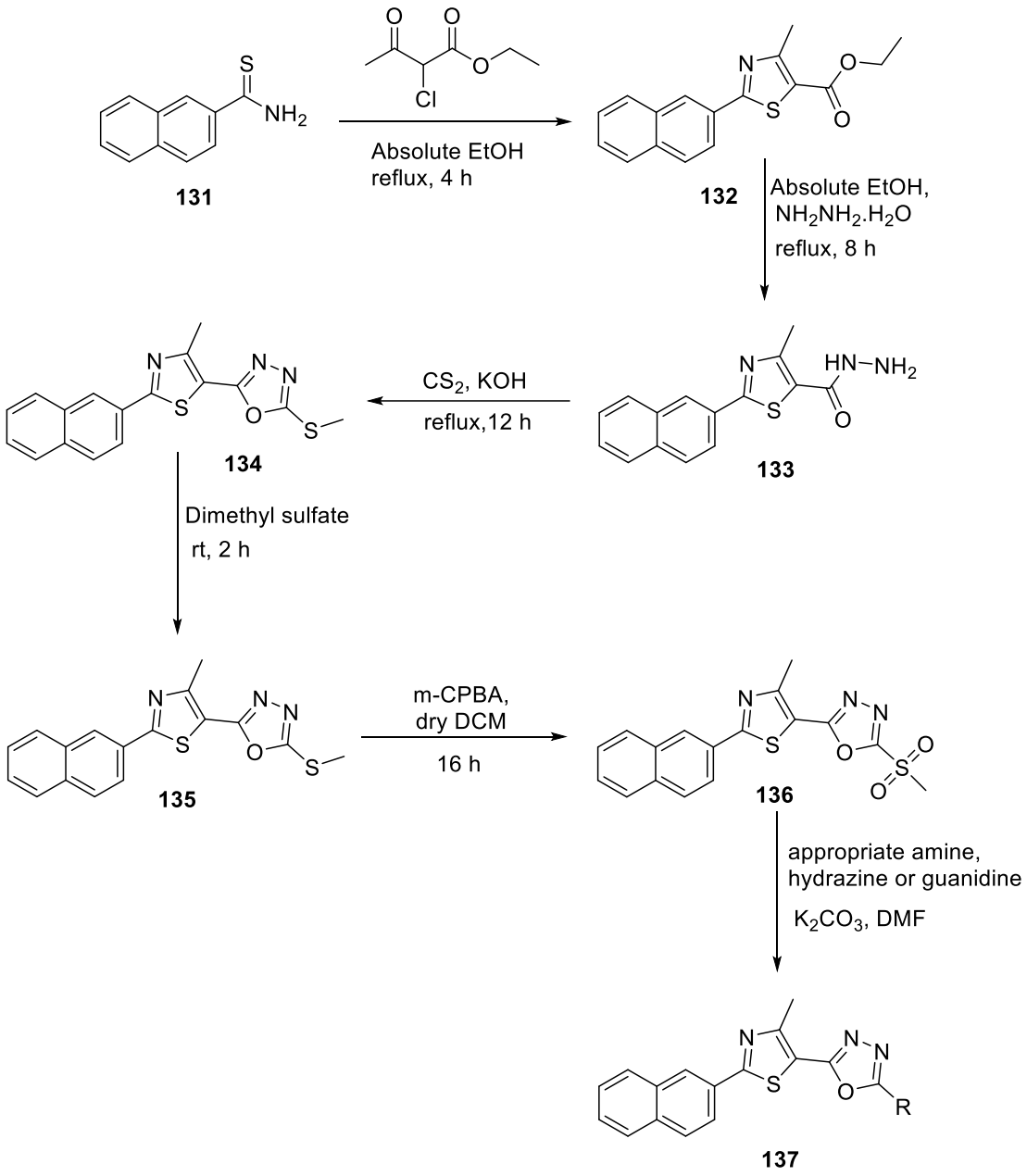

**Scheme 3.28**

R. Santosh *et al*[137] reported synthesis of thiazole molecules starting from molecule **127**, which was reacted with hydrazine hydrate to form the hydrazide molecule **128**. This molecule was reacted with substituted carboxylic acid in phosphorus oxychloride to form the oxadiazole **129**. The reaction of **128** with chalcone dibromides to form molecule **130**. The synthesized molecules were screened for their antiproliferative activity. Molecule **130** showed excellent inhibitory activity against HT-29 cells. Whereas molecules **129** and **130** both showed good growth inhibitory activity **(Scheme 3.29)**.




**Scheme 3.29**

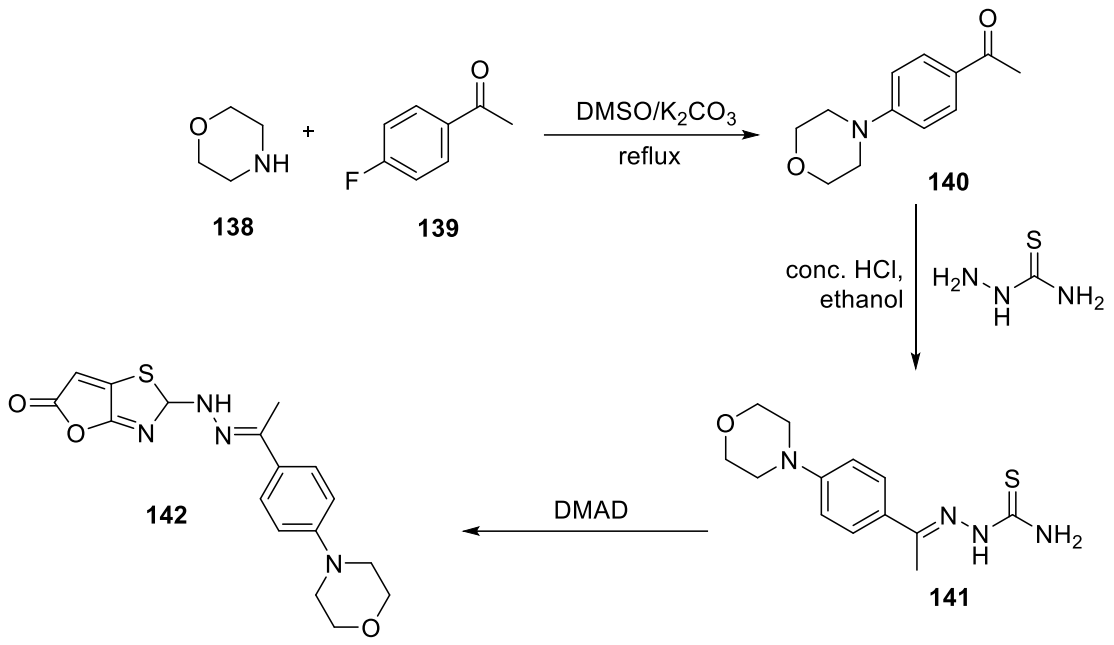
M. Hannoun *et al*[138] reported the synthesis of thiazole derivatives starting from naphthalene-2-carbothioamid **131** with ethyl 2-chloro-3-oxobutanoate to form the thiazole molecule **132**. The ethyl ester was then reacted with hydrazine hydrate to form thiazole hydrazide molecule **133**. Furthermore, this molecule was reacted with carbon disulphide and potassium hydroxide to form oxadiazole salt and moreover this was reacted with dimethyl sulphate in water for two hours to form molecule **135.** This molecule was oxidized by reaction with *meta*-perchloro benzoic acid to form a more reactive molecule **136** with which various amines, hydrazine and guanidine derivatives were attached to synthesize novel derivatives of thiazole-oxadiazole molecules. The synthesized molecules were screened for their vancomycin resistant strains of *Staphylococcus aureus*. The molecules having guanidine and *n*-methyl piperazine molecules showed potent activity **(Scheme 3.30)**.




**Scheme 3.30**

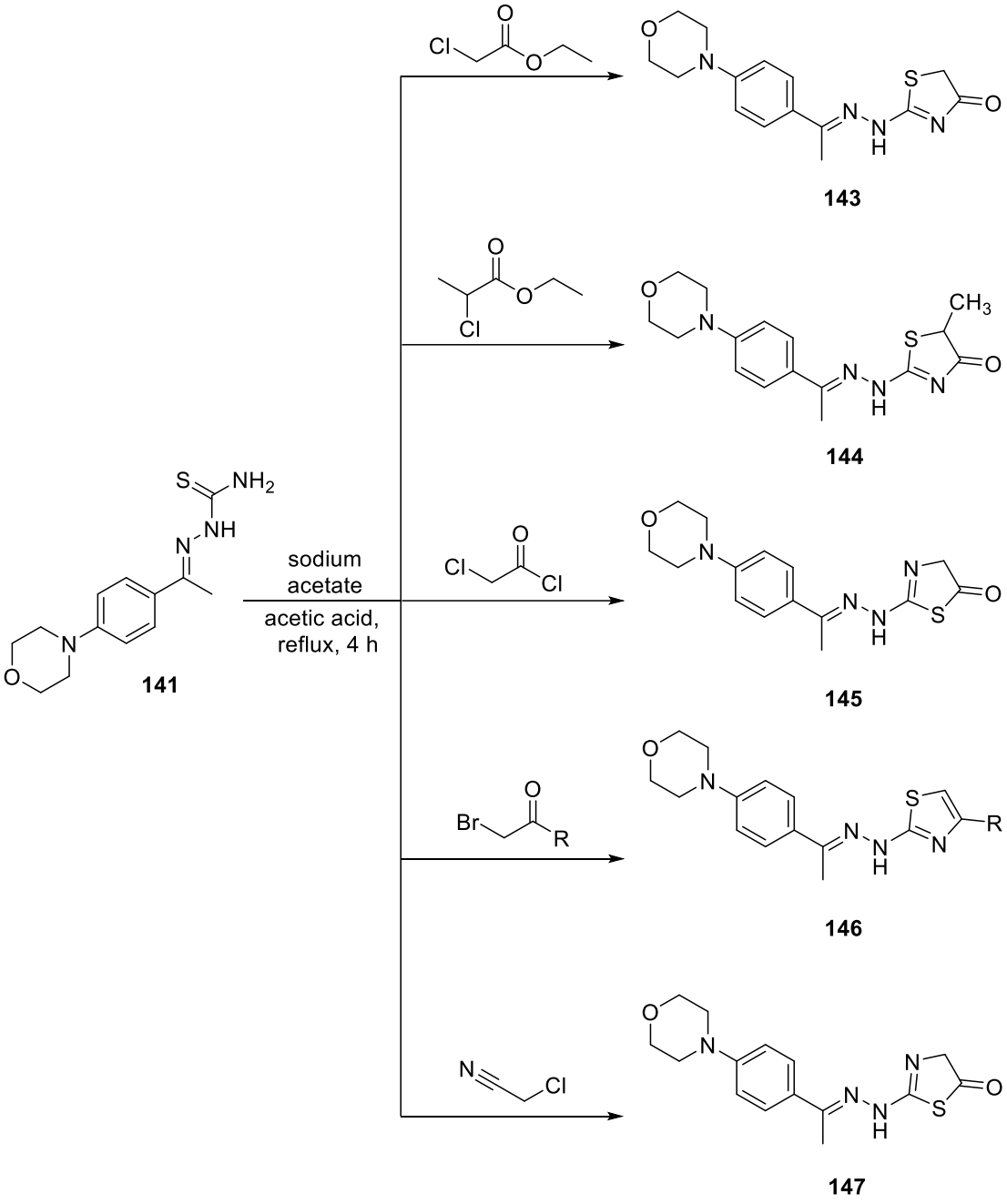
M. Helal *et al*[139] and co-workers have reported synthesis of thiazole derivative starting from morpholine reacted with 4-fluroacetophenone in DMSO containing catalytical amount of potassium bicarbonate to obtain molecule **140**. This molecule was furthermore reacted with thiosemicarbazide to obtain molecule **141**, which again reacted with dimethyl acetylene dicarboxylate to obtain fused thiazole ring **142 (Scheme 3.31)**. Molecule **141** was reacted with various compounds like ethyl chloroacetate, ethyl 2-chloro propionate, chloroacetyl chloride, chloroacetone,

phenacyl bromide, chloro acetonitrile to form various thiazole derivatives **143** to **147 (Scheme 3.32)**.



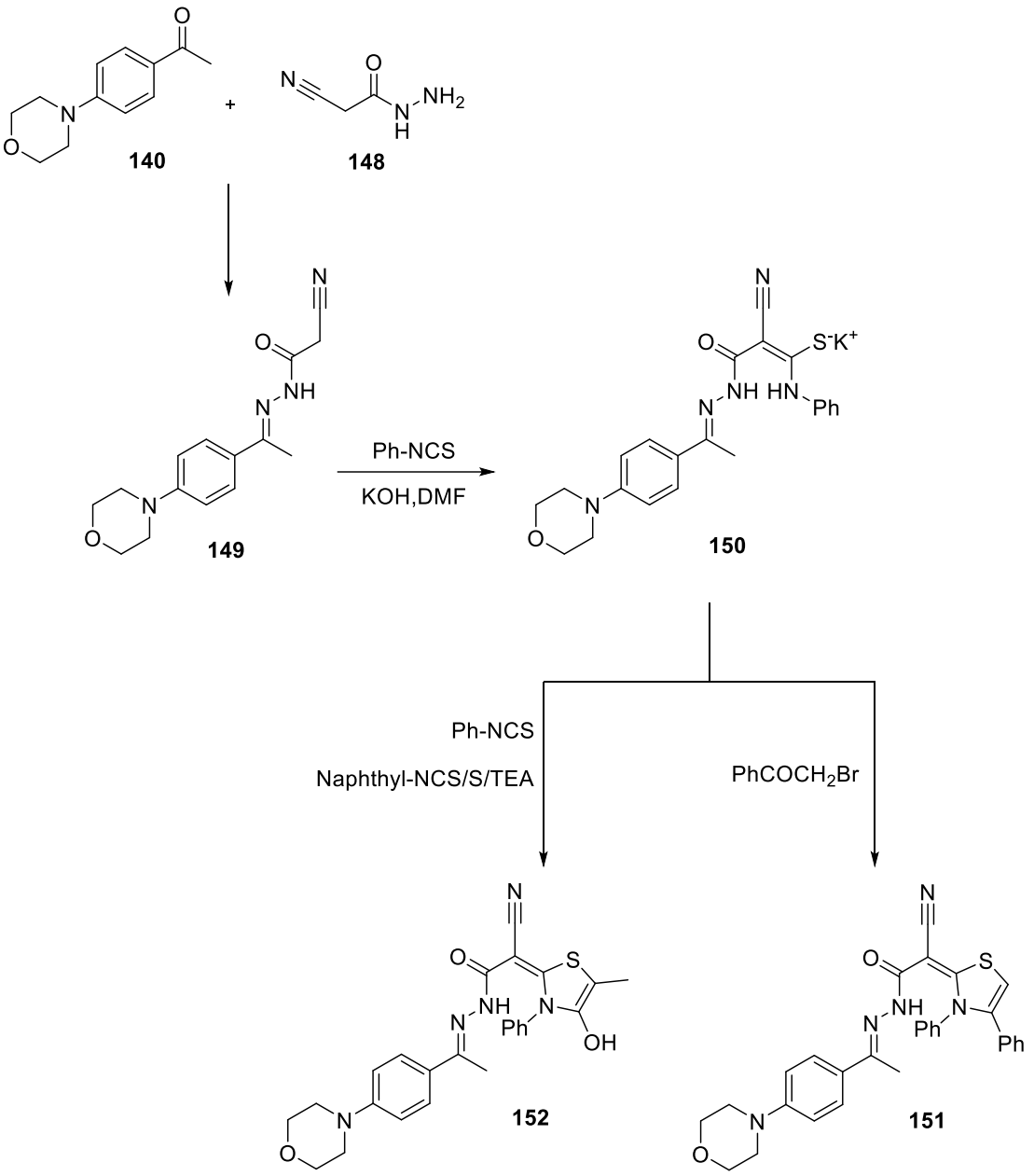

**Scheme 3.31**

The molecule **141** was reacted with cyanoacetohydrazide to synthesize molecule **149**. The reaction of molecule **149** was reacted with phenyl isothiocyanate and potassium hydroxide to form salt derivative which was further reacted with phenyl isothiocyanate and phenacyl bromide derivative to obtain molecules **152** and **154 (Scheme 3.33)**. The synthesized molecules were screened for their antibacterial and anti-inflammatory activity.




141 143 144 145 146 147

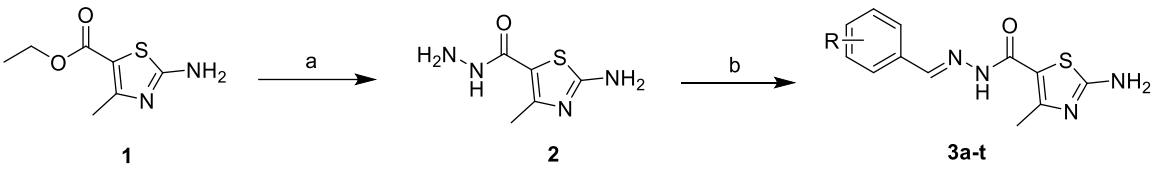
**Scheme 3.32**


140
148
149
Ph-NCS
KOH,DMF
150
Ph-NCS
Naphthyl-NCS/S/TEA
PhCOCH2Br
152
151

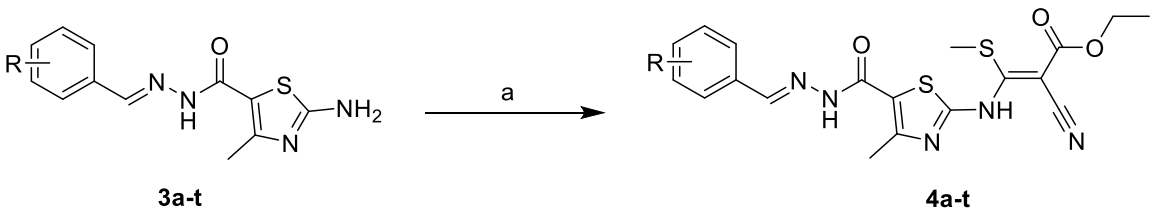
**Scheme 3.33**

## 3.2 Results and Discussion

To find novel biologically important molecules and synthesis of different heterocyclic molecules, here, we report 20 newly synthesized molecules with thiazole 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, ethyl 2-amino-4-methylthiazole-5-carboxylate **1** was reacted with hydrazine hydrate at reflux for 2 hr to form molecule 2-amino-4-methylthiazole-5-carbohydrazide **2**. Furthermore, various substituted benzaldehydes were attached to molecule **2** in methanol containing a catalytical amount of glacial acetic acid and refluxed for 30 min to form (*E*)-2-amino-*N*'-arylidene-4-methylthiazole-5-carbohydrazide **3a-t** molecules in good yield **Scheme 1**.




**Scheme 1:** Reagents and Conditions: (a) Hydrazine Hydrate, Reflux, 2 hr. (b) Substituted benzaldehydes, Glacial acetic acid, MeOH, Reflux, 30 min.




**Scheme 2:** Reagents and Conditions: (a) ethyl 2-cyano-3,3-bis(methylthio)acrylate, DMF, $K_2CO_3$, rt, 1 hr.

Moreover, the synthesized molecules **3a-t** was reacted with ethyl 2-cyano-3,3-bis(methylthio)acrylate in DMF containing potassium carbonate at room temperature was stirred for 1 hr to form novel highly substituted thiazole molecules **4a-t** in good yield as appear in **Scheme 2**.

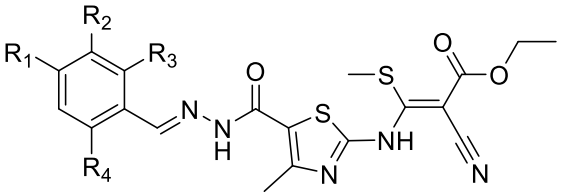
The $^1$H-NMR graph of molecules revealed that the methyl proton of ester seen at t 1.16-1.19 ppm ($CH_3$) which were triplet peaks at s 2.33 ppm ($SCH_3$) for thiomethyl protons as a singlet peak. Thiazole methyl protons were detected at s 2.54-2.55 ppm ($CH_3$) as a

singlet, ester methylene protons were seen at t 4.12 to 4.14 ppm ($CH_3$) which were triplet peaks. The hydrogen of schiff base was found in the range of 7.94-8.24 (H) as a singlet. Aromatic region was seen between 8.82-7.58 ppm. A singlet peak seen at s 11.71-11.91 ppm (NH) indicated the thiazole amine proton. A broad acetamide protons were observed at s 12.79-12.83 ppm (NH) as a singlet. To improve the experimental conditions for the preparation of molecules **4a-t**, several bases, such as anhydrous potassium carbonate and triethylamine were used in different solvents such as methanol, ethanol, tetrahydrofuran and acetonitrile. As a result, we found that the reaction of **3a-t** with ethyl 2-cyano-3,3-bis(methylthio) acrylate was faster and gave the thiazole derivative **4a-t** a good yield when potassium carbonate was used with DMF. The one-pot reaction of molecule **2**, substituted benzaldehydes followed by the addition of ethyl 2-cyano-3,3-bis(methylthio)acrylate was not clean and did not yield the desired product.

Furthermore, the reaction of novel thiazole **4a-t** derivatives with different primary and secondary amines or phenols was not promising to yield substituted thiazole 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 thiazole can be produced. We have also observed that the reaction of thiazole with hydrazine hydrate and phenyl hydrazine yielded a mixture of cyclized and non-cyclized products.

### 3.2.1 Physicochemical Properties

**Table 1. Physicochemical Characteristics of the Thiazole Molecules 3a-t**




| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Molecular weight | Molecular formula | Yield (%) | Melting point (°C) |
|---|---|---|---|---|---|---|---|---|
| THBOET-1 | Cl | H | H | H | 463.96 | $C_{19}H_{18}ClN_5O_3S_2$ | 83 | 205-207 |
| THBOET-2 | Br | H | H | H | 508.41 | $C_{19}H_{18}BrN_5O_3S_2$ | 91 | 231-233 |
| THBOET-3 | $OCH_3$ | H | H | H | 459.54 | $C_20H_{21}N_5O_4S_2$ | 72 | 213-215 |
| THBOET-4 | $NO_2$ | H | H | H | 474.51 | $C_{19}H_{18}N_6O_5S_2$ | 67 | 228-230 |
| THBOET-5 | CN | H | H | H | 454.52 | $C_20H_{18}N_6O_3S_2$ | 87 | 221-223 |
| THBOET-6 | $CH_3$ | H | H | H | 443.54 | $C_20H_{21}N_5O_3S_2$ | 89 | 230-232 |
| THBOET-7 | F | H | H | H | 447.50 | $C_{19}H_{18}FN_5O_3S_2$ | 65 | 198-200 |
| THBOET-8 | H | H | H | H | 429.51 | $C_{19}H_{19}N_5O_3S_2$ | 61 | 204-206 |
| THBOET-9 | $CH_3$ | $CH_3$ | H | H | 457.57 | $C_{21}H_{23}N_5O_3S_2$ | 86 | 237-239 |
| THBOET-10 | $N(CH_3)_2$ | H | H | H | 472.58 | $C_{21}H_{24}N_6O_3S_2$ | 90 | 223-225 |
| THBOET-11 | H | $NO_2$ | H | H | 474.51 | $C_{19}H_{18}N_6O_5S_2$ | 72 | 219-221 |
| THBOET-12 | H | H | $NO_2$ | H | 474.51 | $C_{19}H_{18}N_6O_5S_2$ | 65 | 210-212 |
| THBOET-13 | H | H | Cl | H | 463.96 | $C_{19}H_{18}ClN_5O_3S_2$ | 83 | 200-202 |
| THBOET-14 | F | F | H | H | 465.49 | $C_{19}H_{17}F_2N_5O_3S_2$ | 68 | 187-289 |
| THBOET-15 | Cl | Cl | H | H | 498.40 | $C_{19}H_{17}Cl_2N_5O_3S_2$ | 75 | 193-294 |
| THBOET-16 | $OCH_3$ | H | $OCH_3$ | H | 489.57 | $C_{21}H_{23}N_5O_5S_2$ | 83 | 231-233 |
| THBOET-17 | H | H | $CH_3$ | H | 443.54 | $C_20H_{21}N_5O_3S_2$ | 80 | 225-227 |
| THBOET-18 | $CH_3$ | H | $CH_3$ | H | 457.57 | $C_{21}H_{23}N_5O_3S_2$ | 85 | 217-219 |
| THBOET-19 | H | H | Cl | Cl | 498.40 | $C_{19}H_{17}Cl_2N_5O_3S_2$ | 80 | 209-211 |
| THBOET-20 | H | Cl | Cl | H | 498.40 | $C_{19}H_{17}Cl_2N_5O_3S_2$ | 64 | 201-203 |

### 3.2.2 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 | 8 | **21** | 10 | **13** | 10 |
| STOCN-2 | 17 | 20 | 14 | 11 | 9 |
| STOCN-3 | 14 | 10 | **19** | **13** | **17** |
| STOCN-4 | 14 | 13 | 15 | 11 | - |
| STOCN-5 | 10 | - | 13 | 12 | 8 |
| STOCN-6 | 8 | 10 | 8 | 9 | 7 |
| STOCN-7 | 12 | 13 | **19** | 12 | 14 |
| STOCN-8 | 8 | 9 | 12 | 8 | 8 |
| STOCN-9 | **19** | 12 | 14 | 10 | 6 |
| STOCN-10 | **19** | 12 | 10 | 11 | 11 |
| Ampicillin | 21 | 14 | 15 | 18 | 20 |
| Gentamicin | 20 | 12 | 21 | 20 | 14 |

## 3.3 Conclusion

In conclusion, we have described the synthesis substituted novel thiazole molecules in excellent yields. The reaction of ketene dithioacetal derivative with thiazole was afforded the new thiazole molecules with good yields in the presence of base. Potassium carbonate was found as an efficient base for the synthesis of thiazoles. 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 thiazoles containing carboxamide group with excellent yield, purity and simple isolation of products.

## 3.4 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), the 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 $\delta$ 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 Thiazole (1)**

Ethyl acetoacetate (10 mmol) and NBS in methanol was stirred at room temperature for 30 min. Then followed by slow addition of thiourea and reflux the reaction mixture. After completion of the reaction, the mass was filtered to remove elemental sulphur and the filtrate was poured onto ice, the separated solid product was filtered, washed with water and dried at room temperature to get analytically pure compound (**1**), as a white to light brown fluffy solid. Yield: 65%.

- **General process for the synthesis of 2-amino-4-methylthiazole-5-carbohydrazide (2)**

A mixture of **2** (10 mmol) and hydrazine hydrate (15 mmol) was refluxed in neat condition for 2 hr. The reaction mixture 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 an analytically pure compound (**2**), as a dark brown to white solid. Yield: 20%.

- **General process for the synthesis of (*E*)-2-amino-N'-arylidene-4-methylthiazole-5-carbohydrazide (3a-t)**

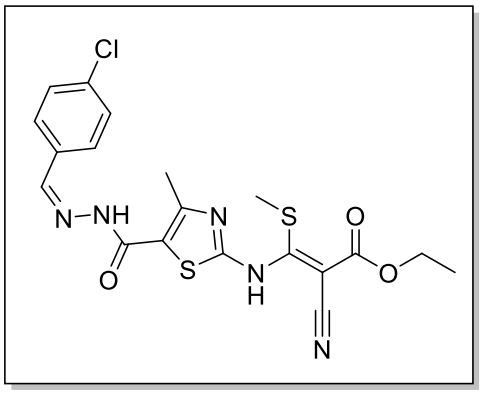
A mixture of **2** (10 mmol) and various substituted benzaldehyde (10 mmol) in 10 mL of MeOH and catalytical amount of glacial acetic acid was refluxed for 30 min. After the completion of the reaction, the reaction mixture was cooled to room temperature,

poured into ice-cold water. The separated solid was filtered, washed with water and purified by recrystallization from EtOH to afford crystals **(3a-t)**.

**General process for the synthesis of ethyl (*Z*)-3-((5-(2-((*E*)-arylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-2-cyano-3-mercaptoacrylate (4a-t)**

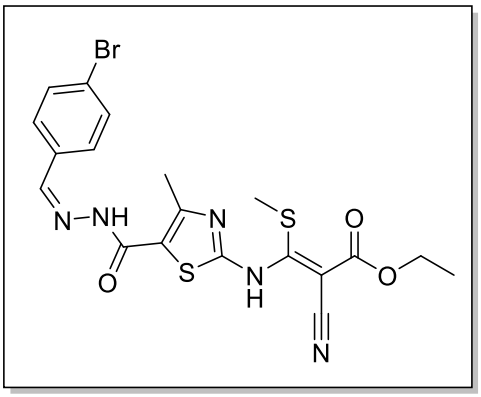
A mixture of **3a-t** (10 mmol) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (10 mmol) in 10 mL of DMF and anhydrous potassium carbonate (10 mmol) was stirred at rt for 1 hr. After the completion of the reaction, the reaction mixture was cooled to room temperature, poured into ice-cold water and neutralized 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*)-3-((5-(2-((*Z*)-4-chlorobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-2-cyano-3-(methylthio)acrylate (THBOET-1)**



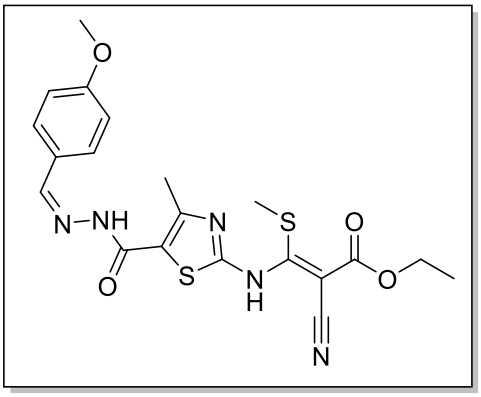

Yellow solid, Yield: 83%, mp 205-207°C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.81 (s, 1H), 11.88 (s, 1H), 8.00 (s, 1H), 7.72 (d, $J$ = 8.5 Hz, 2H), 7.46 (d, $J$ = 8.2 Hz, 2H), 4.13 (d, $J$ = 7.5 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.18 (t, $J$ = 7.2 Hz, 3H) ; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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 ($m/z$): 463 ($M^+$). Anal. Calcd. For $C_{19}H_{18}ClN_5O_3S_2$: C, 49.19; H, 3.91; N, 15.10; Found: C, 49.32; H, 3.89; N, 15.18.

**Ethyl (*Z*)-3-((5-(2-((*Z*)-4-bromobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-2-cyano-3-(methylthio)acrylate (THBOET-2)**



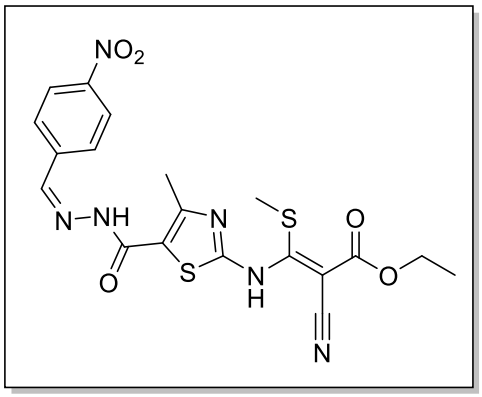

Yellow solid, Yield: 91%, mp 231-233°C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.81 (s, 1H), 11.88 (s, 1H), 8.00 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 4.13 (d, J = 7.5 Hz, 2H), 2.54 (s, 3H), 2.33 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); MS (*m*/*z*): 509 ($M^+$). Anal. Calcd. For $C_{19}H_{18}BrN_5O_3S_2$: C, 44.89; H, 3.57; N, 13.78; Found: C, 44.92; H, 3.76; N, 13.55.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-4-methoxybenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-3)**



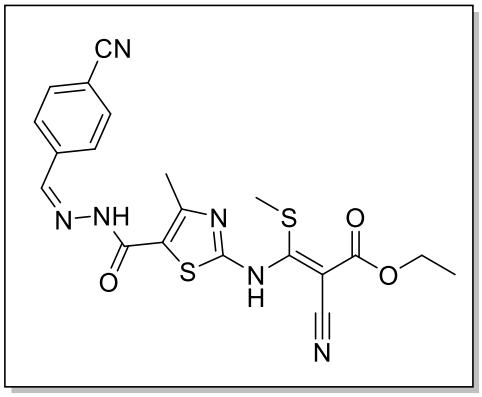

Yellow solid, Yield: 72%, mp 213-215°C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.79 (s, 1H), 11.71 (s, 1H), 7.94 (s, 1H), 7.64 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 4.12 (s, 2H), 3.81 (s, 3H), 2.55 (s, 3H), 2.33 (s, 3H), 1.16 (s, 3H); MS (*m*/*z*): 459 ($M^+$). Anal. Calcd. For $C_20H_{21}N_5O_4S_2$: C, 52.27; H, 4.61; N, 15.24; Found: C, 52.30; H, 4.59; N, 15.29.

**Ethyl (*Z*)-2-cyano-3-((4-methyl-5-(2-((*Z*)-4-nitrobenzylidene)hydrazine-1-carbonyl)thiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-4)**



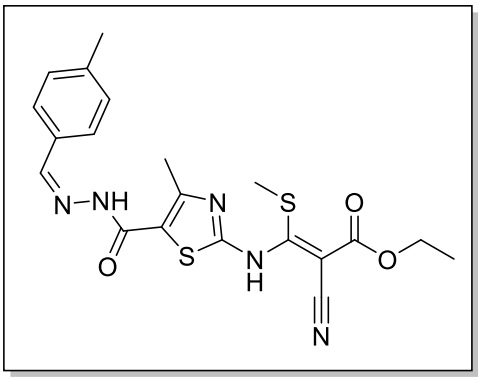
Yellow solid, Yield: 67%, mp 228-230°C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.79 (s, 1H), 11.71 (s, 1H), 8.82 (d, J = 8.4 Hz, 2H), 8.24 (s, 1H), 8.92 (d, J = 8.3 Hz, 2H), 4.12 (d, J = 8.1 Hz, 2H), 2.55 (s, 3H), 2.33 (s, 3H), 1.16 (s, 3H); MS (*m*/*z*): 474 ($M^+$). Anal. Calcd. For $C_{19}H_{18}N_6O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.01; H, 3.62; N, 17.60.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-4-cyanobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-5)**



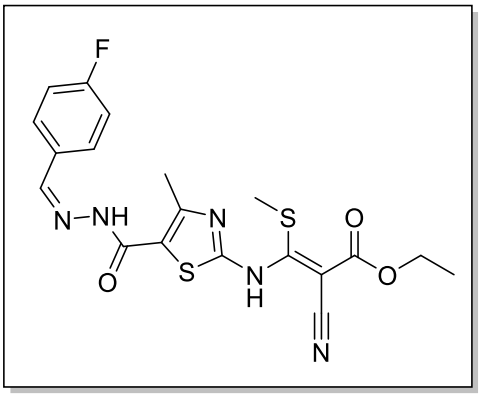
Yellow solid, Yield: 87%, mp 221-223°C; MS (*m*/*z*): 454 ($M^+$); Anal. Calcd. For $C_{20}H_{18}N_6O_3S_2$: C, 52.85; H, 3.99; N, 18.49; Found: C, 52.92; H, 4.08; N, 18.49.

**Ethyl (*Z*)-2-cyano-3-((4-methyl-5-(2-((*Z*)-4-methylbenzylidene)hydrazine-1-carbonyl)thiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-6)**



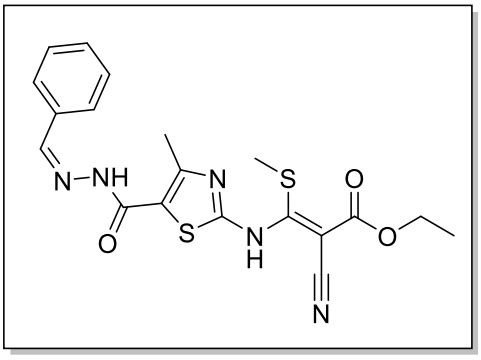
Yellow solid, Yield: 89%, mp 230-232°C; MS (*m*/*z*): 443 ($M^+$); Anal. Calcd. For $C_{20}H_{21}N_5O_3S_2$: C, 54.16; H, 4.77; N, 15.79; Found: C, 54.32; H, 4.65; N, 15.94.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-4-fluorobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-7)**



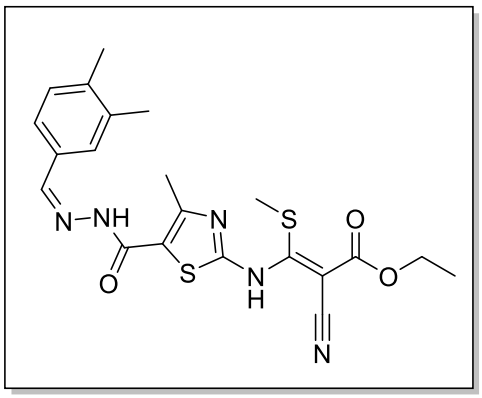
Yellow solid, Yield: 65%, mp 198-200°C; MS (*m*/*z*): 447 ($M^+$); Anal. Calcd. For $C_{19}H_{18}FN_5O_3S_2$: C, 51.00; H, 4.05; N, 15.65; Found: C, 51.10; H, 4.08; N, 15.73.

**Ethyl (*Z*)-3-((5-(2-((*Z*)-benzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-2-cyano-3-(methylthio)acrylate (THBOET-8)**



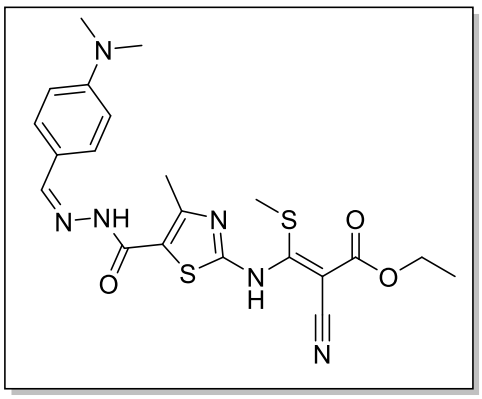
Yellow solid, Yield: 61%, mp 212-214°C; MS (*m*/*z*): 429 ($M^+$); Anal. Calcd. For $C_{19}H_{19}N_5O_3S_2$: C, 53.13; H, 4.46; N, 16.31; Found: C, 53.18; H, 4.42; N, 16.36.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-3,4-dimethylbenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-9)**



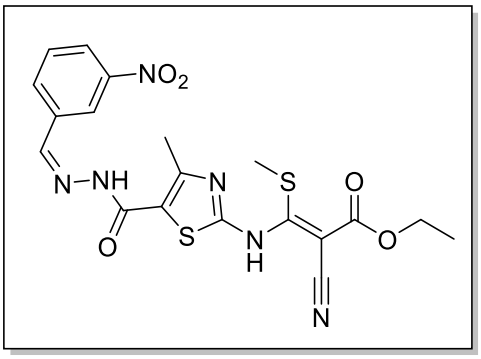
Yellow solid, Yield: 86%, mp 204-206°C; MS (*m*/*z*): 457 ($M^+$); Anal. Calcd. For $C_{21}H_{23}N_5O_3S_2$: C, 55.12; H, 5.07; N, 15.31; Found: C, 55.11; H, 5.09; N, 15.39.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-4-(dimethylamino)benzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-10)**



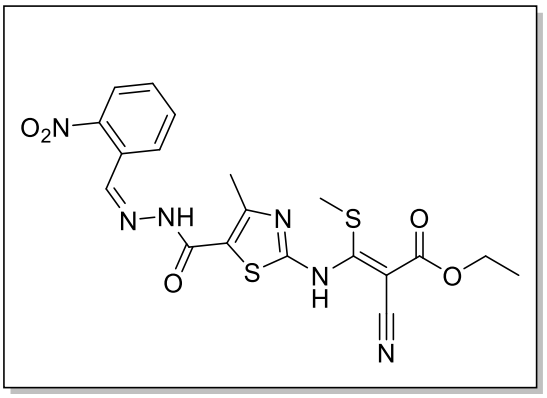
Yellow solid, Yield: 90%, mp 237-239°C; MS (*m*/*z*): 472 ($M^+$); Anal. Calcd. For $C_{21}H_{24}N_6O_3S_2$: C, 53.37; H, 5.12; N, 17.78; Found: C, 53.12; H, 5.08; N, 17.55.

**Ethyl (*Z*)-2-cyano-3-((4-methyl-5-(2-((*Z*)-3-nitrobenzylidene)hydrazine-1-carbonyl)thiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-11)**



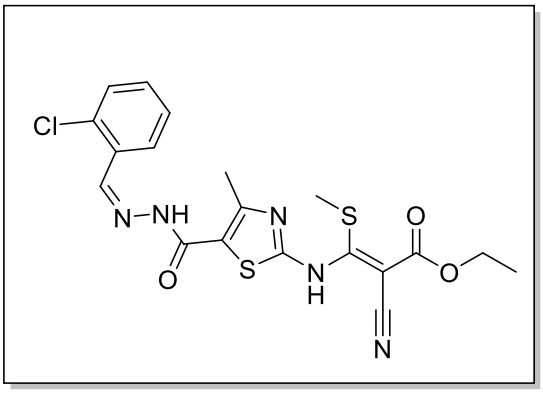
Yellow solid, Yield: 72%, mp 223-225°C; MS (*m*/*z*): 474 ($M^+$); Anal. Calcd. For $C_{19}H_{18}N_6O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.00; H, 3.65; N, 17.70.

**Ethyl (*Z*)-2-cyano-3-((4-methyl-5-(2-((*Z*)-2-nitrobenzylidene)hydrazine-1-carbonyl)thiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-12)**



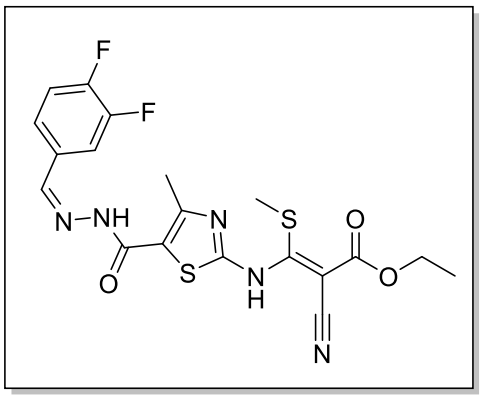
Yellow solid, Yield: 65%, mp 219-221°C; MS (*m*/*z*): 474 ($M^+$); Anal. Calcd. For $C_{19}H_{18}N_6O_5S_2$: C, 48.09; H, 3.82; N, 17.71; Found: C, 48.22; H, 3.80; N, 17.79.

**Ethyl (*Z*)-3-((5-(2-((*Z*)-2-chlorobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-2-cyano-3-(methylthio)acrylate (THBOET-13)**



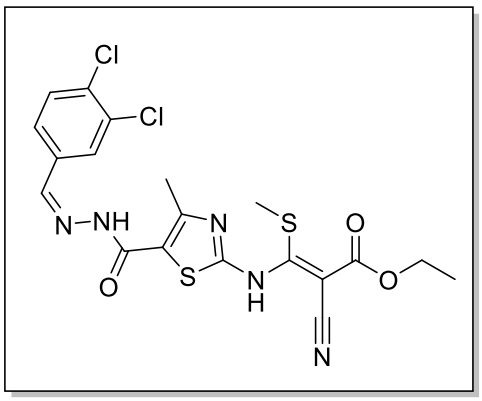
Yellow solid, Yield: 83%, mp 210-212°C; MS (*m*/*z*): 463 ($M^+$); Anal. Calcd. For $C_{19}H_{18}ClN_5O_3S_2$: C, 49.19; H, 3.91; N, 15.10; Found: C, 49.32; H, 3.99; N, 15.25.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-3,4-difluorobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-14)**



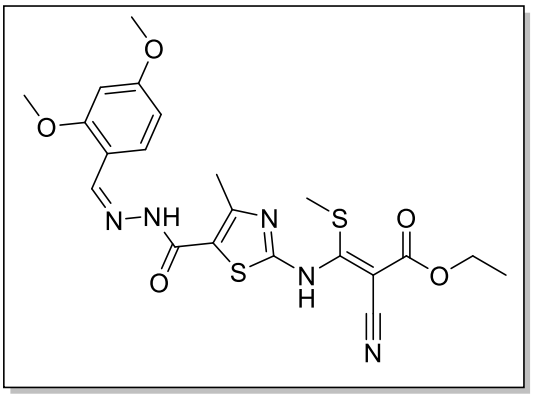
Yellow solid, Yield: 68%, mp 200-202°C; MS (*m*/*z*): 465 ($M^+$); Anal. Calcd. For $C_{19}H_{17}F_2N_5O_3S_2$: C, 49.03; H, 3.68; N, 15.05; Found: C, 49.12; H, 3.72; N, 15.07.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-3,4-dichlorobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-15)**



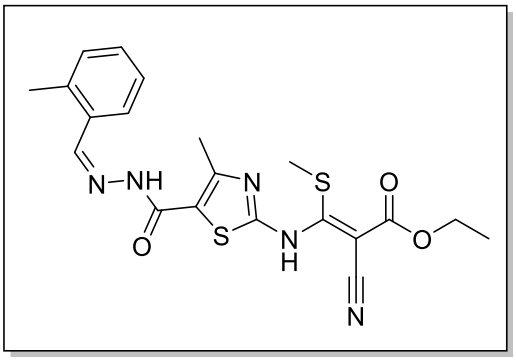
Yellow solid, Yield: 75%, mp 187-189°C; MS (*m*/*z*): 498 ($M^+$); Anal. Calcd. For $C_{19}H_{17}Cl_2N_5O_3S_2$: C, 45.79; H, 3.44; N, 14.05; Found: C, 45.81; H, 3.39; N, 14.01.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-2,4-dimethoxybenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-16)**



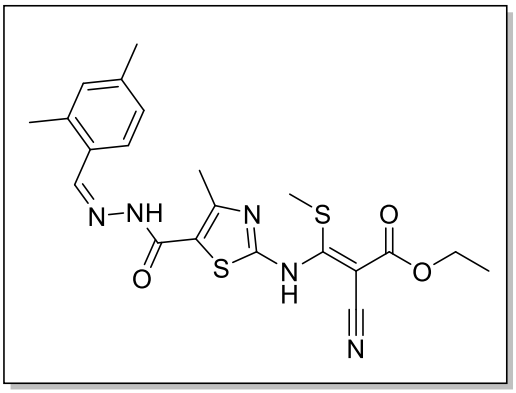
Yellow solid, Yield: 83%, mp 193-195°C; MS (*m*/*z*): 489 ($M^+$); Anal. Calcd. For $C_{21}H_{23}N_5O_5S_2$: C, 51.52; H, 4.74; N, 14.31; Found: C, 51.55; H, 4.80; N, 14.32.

**Ethyl (*Z*)-2-cyano-3-((4-methyl-5-(2-((*Z*)-2-methylbenzylidene)hydrazine-1-carbonyl)thiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-17)**



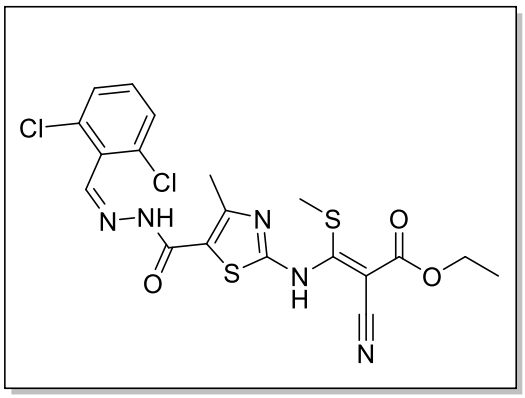
Yellow solid, Yield: 80%, mp 231-233°C; MS (*m*/*z*): 443 ($M^+$); Anal. Calcd. For $C_{20}H_{21}N_5O_3S_2$: C, 54.16; H, 4.77; N, 15.79; Found: C, 54.10; H, 4.74; N, 15.77.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-2,4-dimethylbenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-18)**



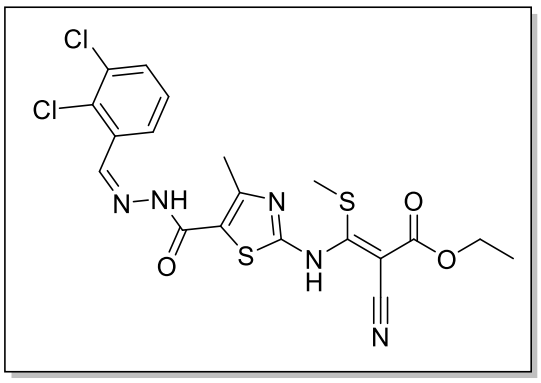
Yellow solid, Yield: 85%, mp 217-219°C; MS (*m*/*z*): 457 ($M^+$); Anal. Calcd. For $C_{21}H_{23}N_5O_3S_2$: C, 55.12; H, 5.07; N, 15.31; Found: C, 55.18; H, 5.02; N, 15.28.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-2,6-dichlorobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-19)**



Yellow solid, Yield: 80%, mp 209-211°C; MS (*m*/*z*): 498 ($M^+$); Anal. Calcd. For $C_{18}H_{17}N_5OS_2$: C, 45.79; H, 3.44; N, 14.05; Found: C, 45.89; H, 3.51; N, 14.00.

**Ethyl (*Z*)-2-cyano-3-((5-(2-((*Z*)-2,3-dichlorobenzylidene)hydrazine-1-carbonyl)-4-methylthiazol-2-yl)amino)-3-(methylthio)acrylate (THBOET-20)**



Yellow solid, Yield: 64%, mp 201-203°C; MS (*m*/*z*): 498 ($M^+$); Anal. Calcd. For $C_{18}H_{17}N_5OS_2$: C, 45.79; H, 3.44; N, 14.05; Found: C, 45.64; H, 3.31; N, 13.98.

## 3.5 Spectral Data

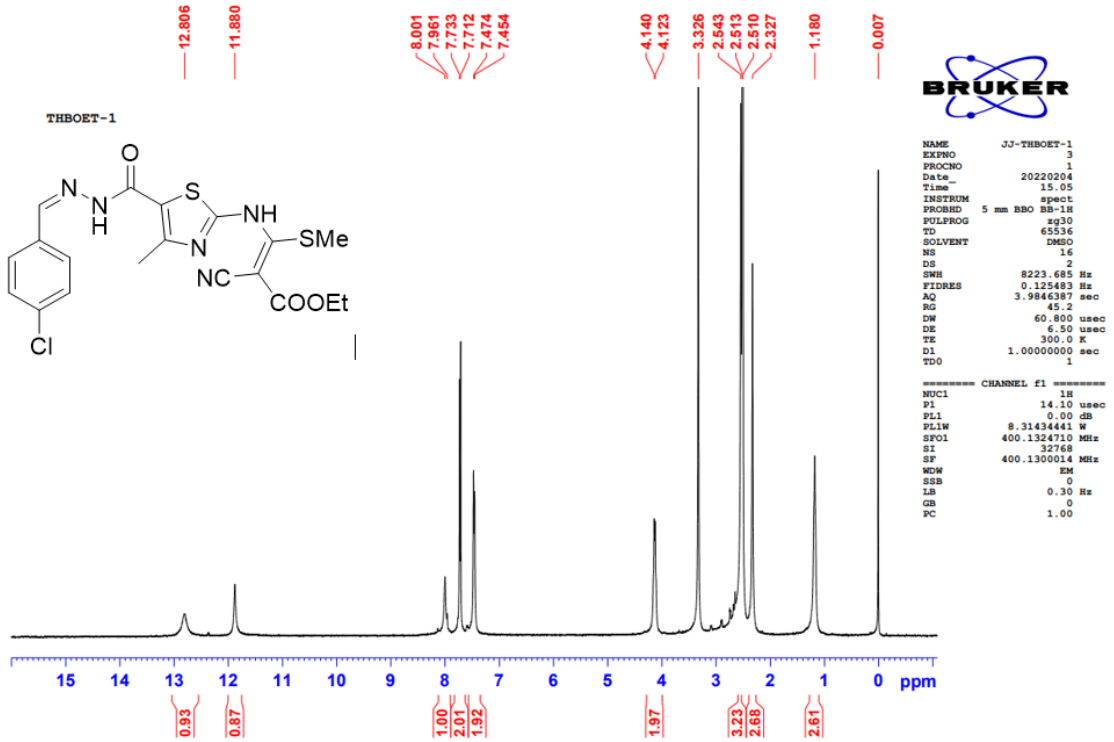



**Fig. 1.** Representative $^{1}$H NMR spectrum of compound THBOET-1

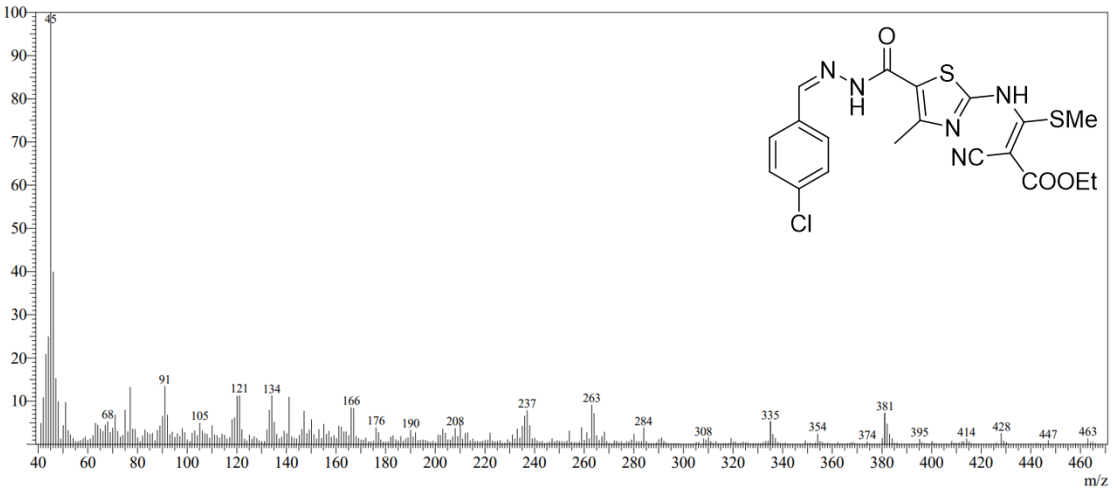



**Fig. 2:** Representative mass spectrum of compound THBOET-1

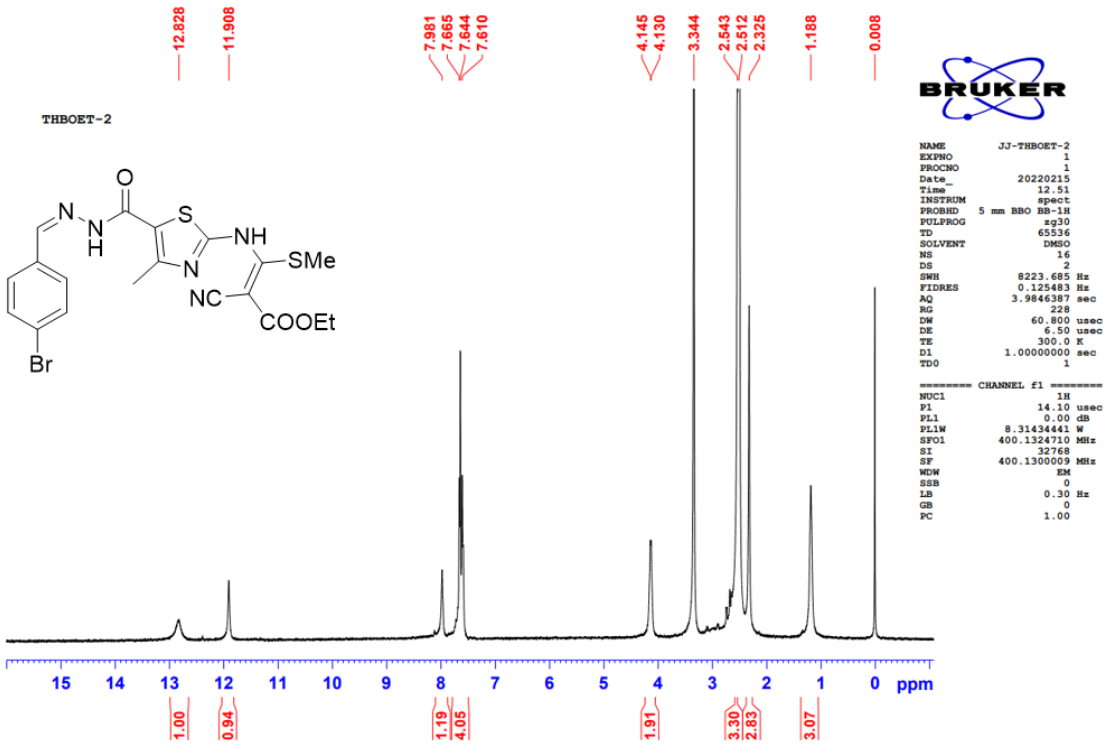



**Fig. 3:** Representative $^{1}$H NMR spectrum of compound THBOET-2

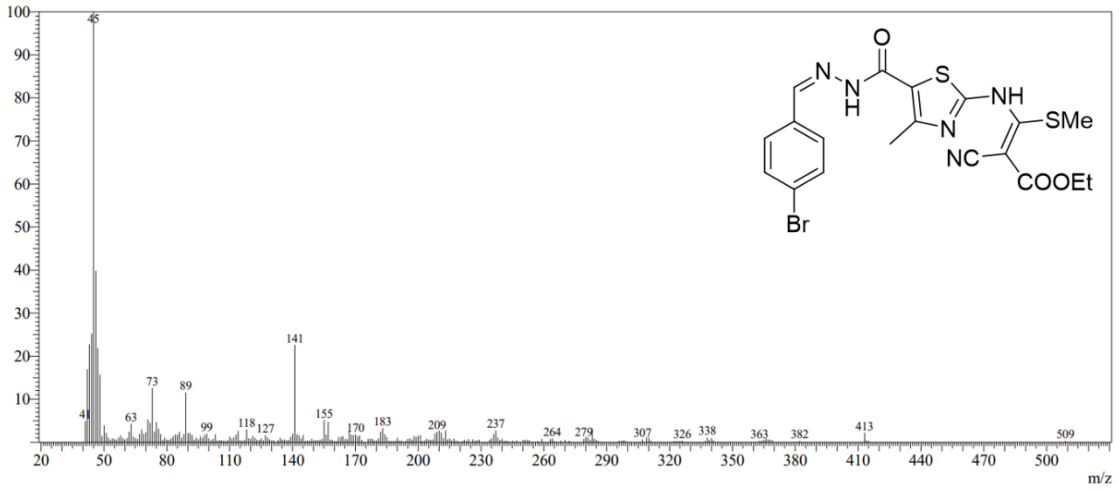



**Fig. 4:** Representative mass spectrum of compound THBOET-2

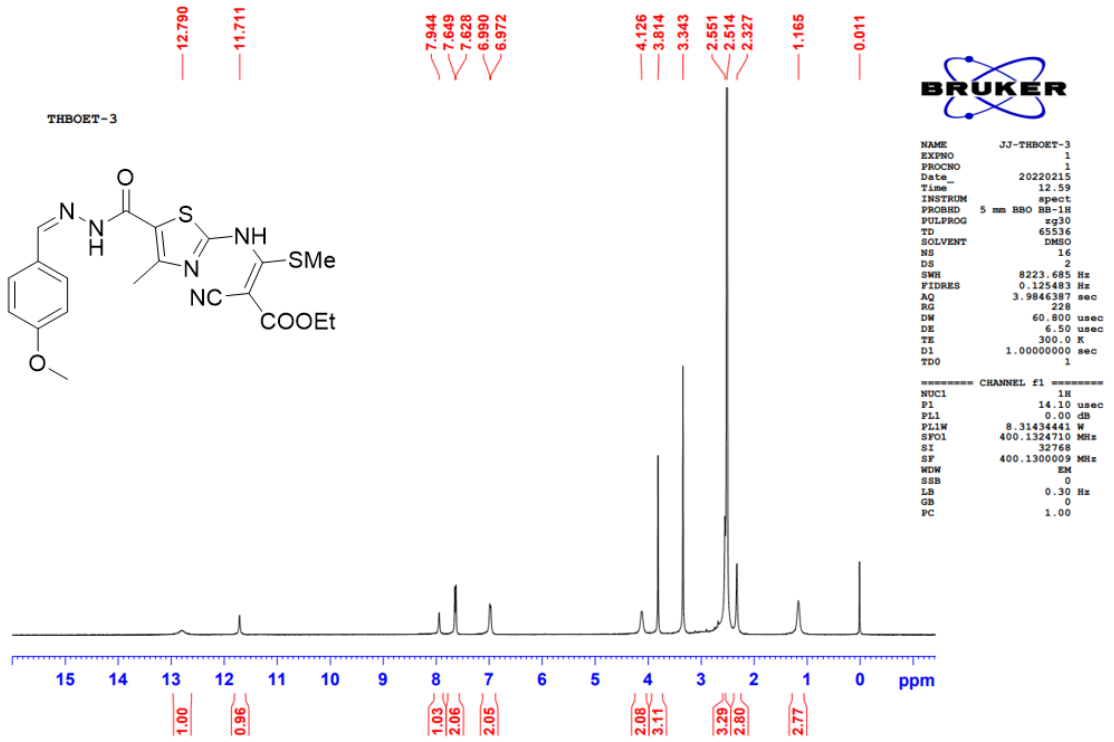



**Fig. 5:** Representative $^{1}$H NMR spectrum of compound THBOET-3

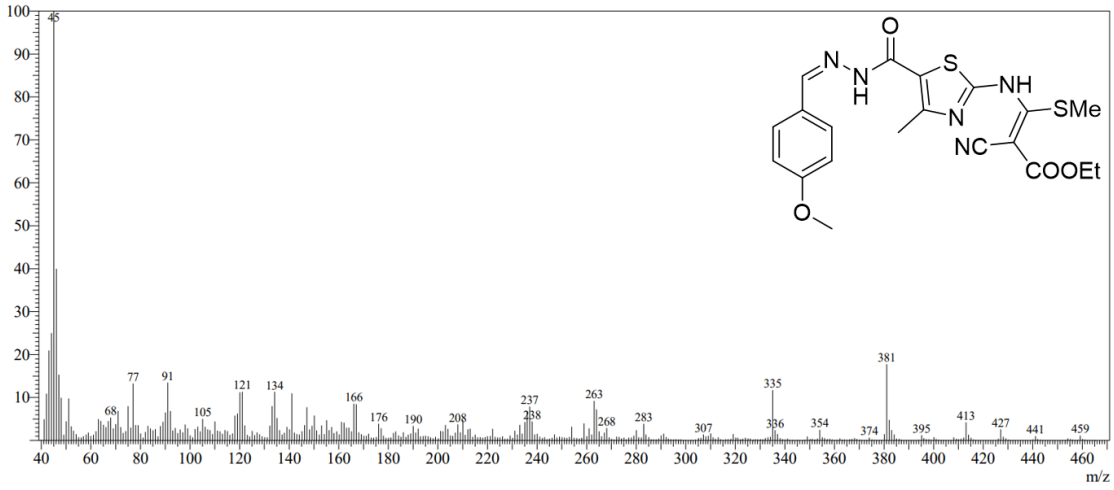



**Fig. 6:** Representative mass spectrum of compound THBOET-3

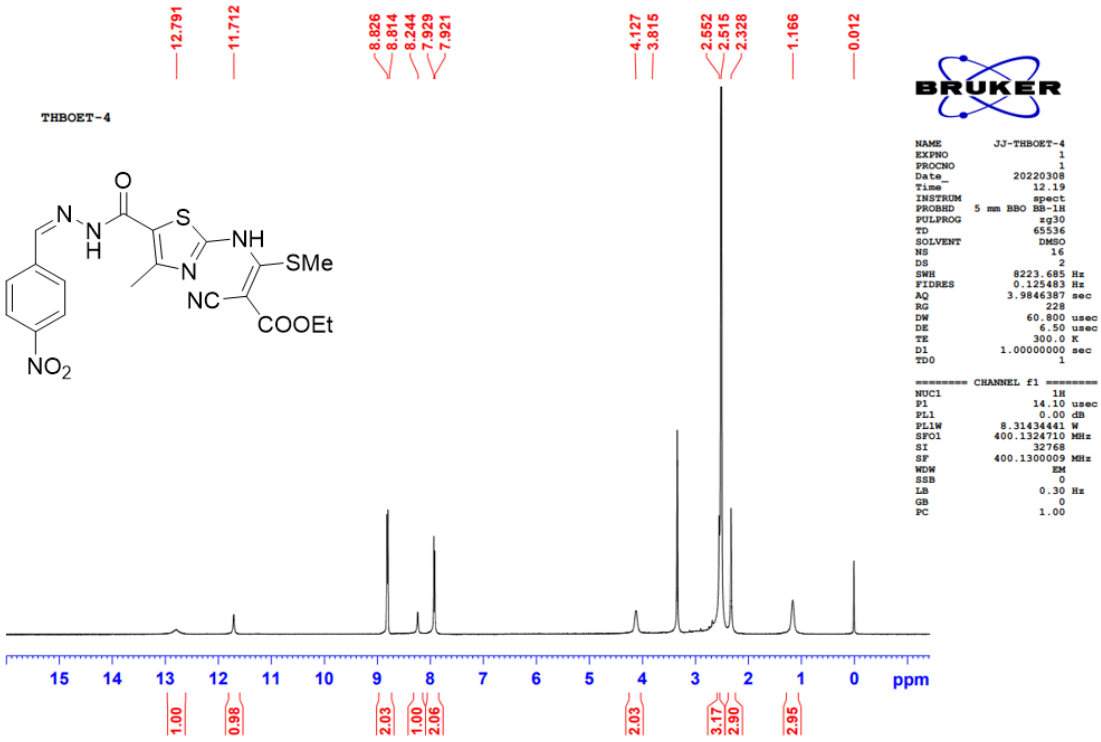



**Fig. 7:** Representative $^{1}$H NMR spectrum of compound THBOET-4

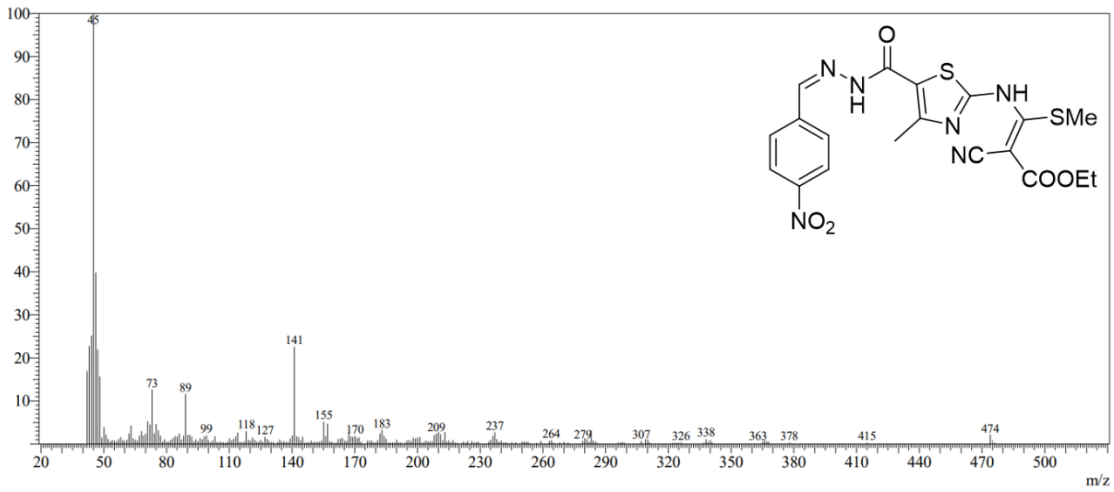



**Fig. 8:** Representative mass spectrum of compound THBOET-4

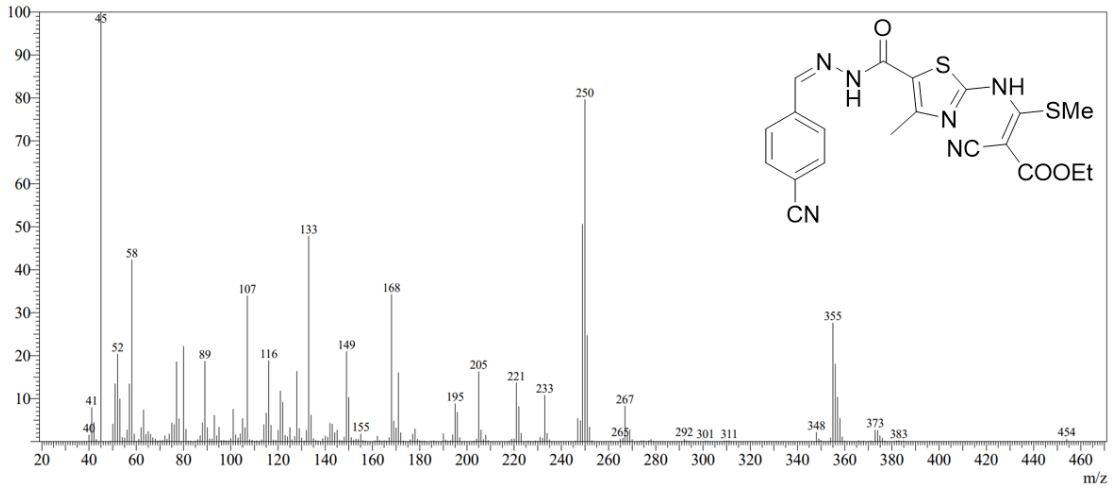



**Fig. 9:** Representative mass spectrum of compound THBOET-5

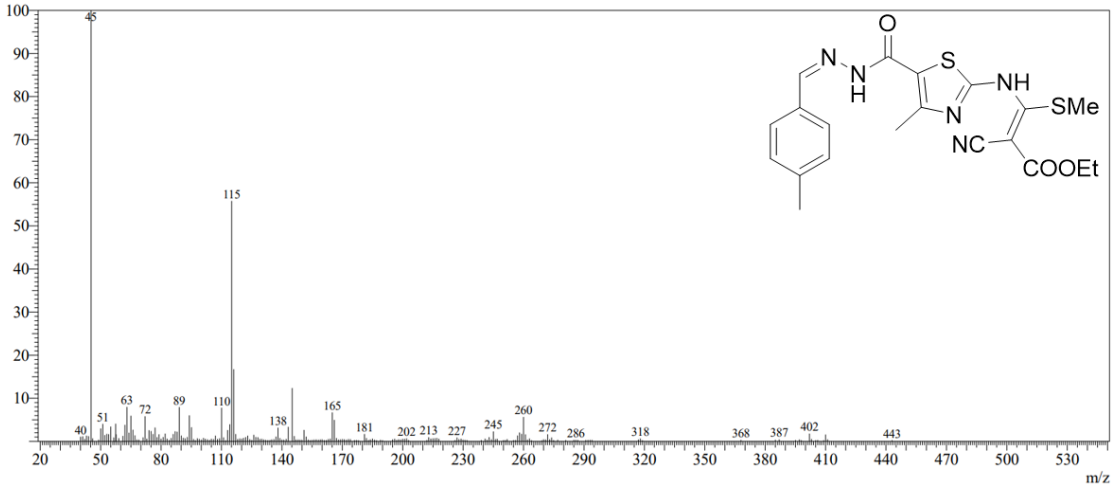



**Fig. 10:** Representative mass spectrum of compound THBOET-6

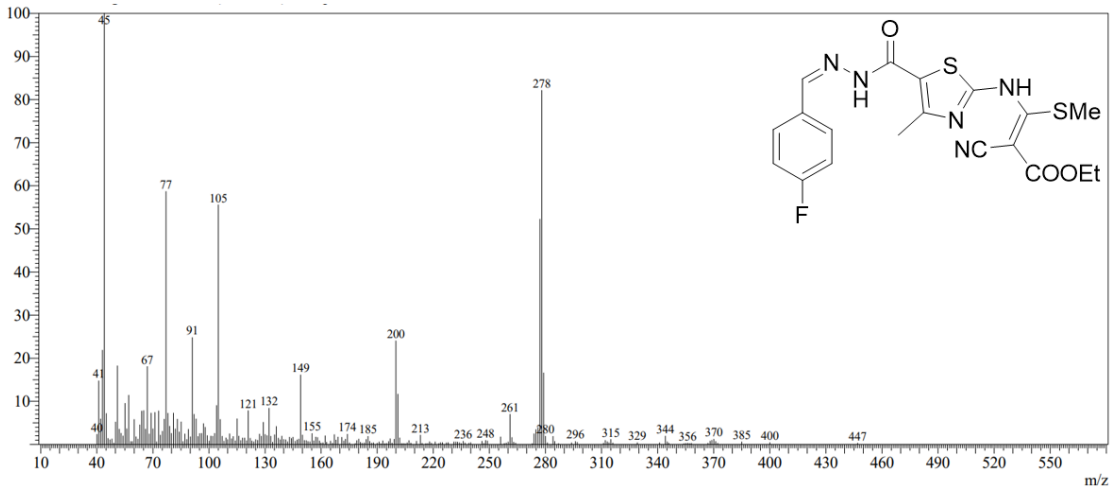



**Fig. 11:** Representative mass spectrum of compound THBOET-7

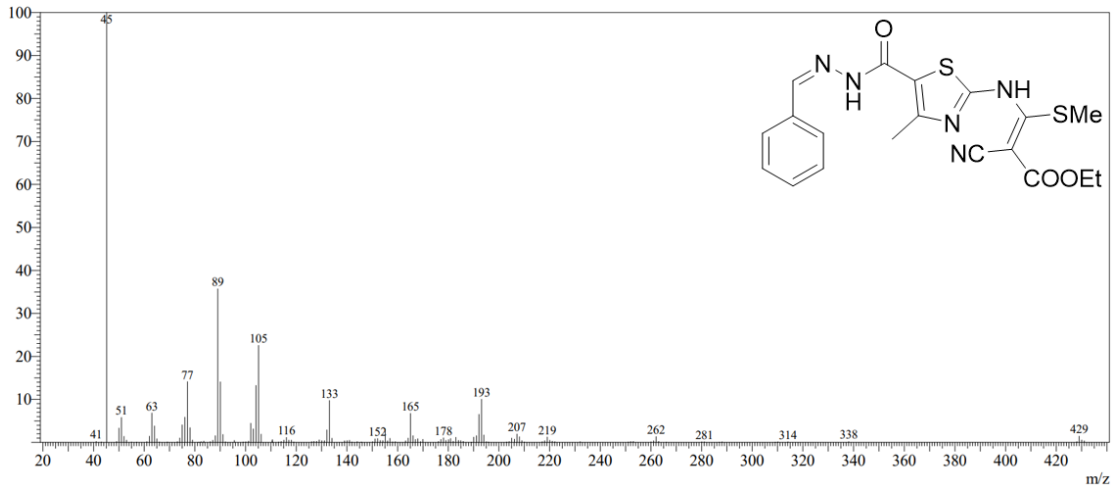



**Fig. 12:** Representative mass spectrum of compound THBOET-8

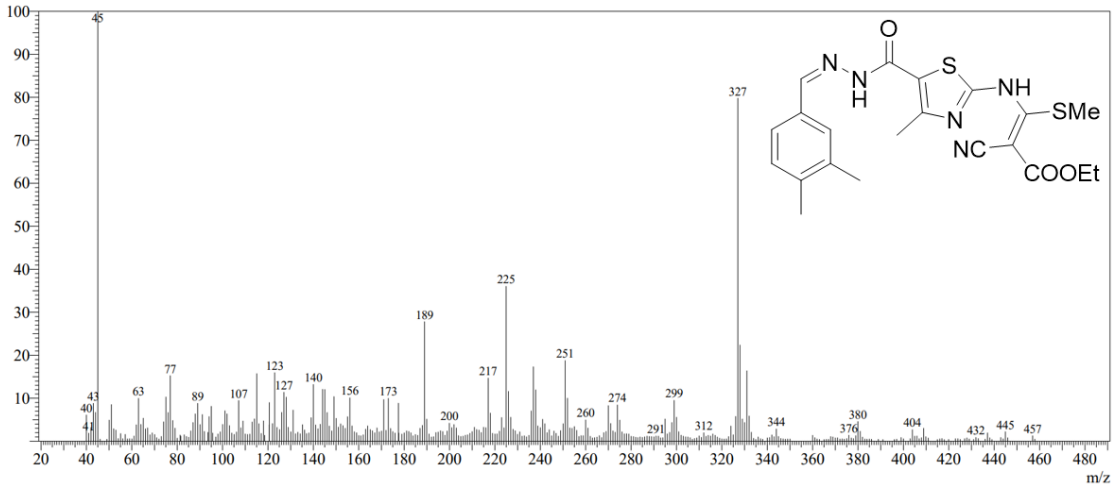



**Fig. 13:** Representative mass spectrum of compound THBOET-9

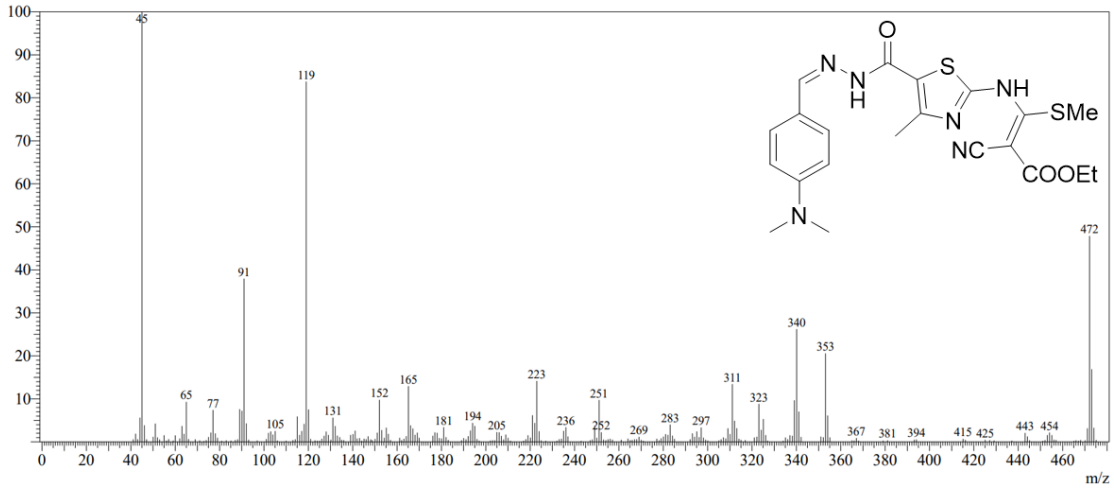



**Fig. 14:** Representative mass spectrum of compound THBOET-10

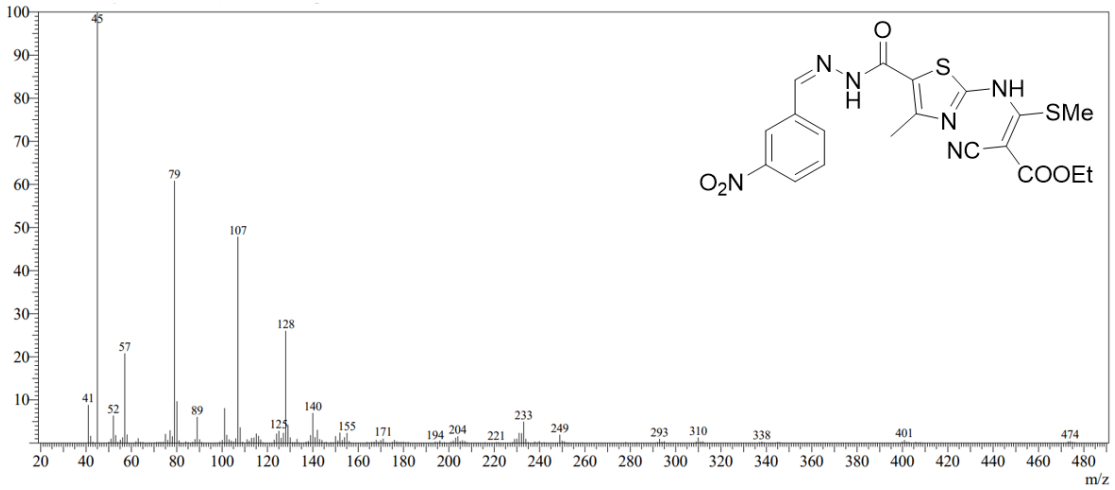



**Fig. 15:** Representative mass spectrum of compound THBOET-11

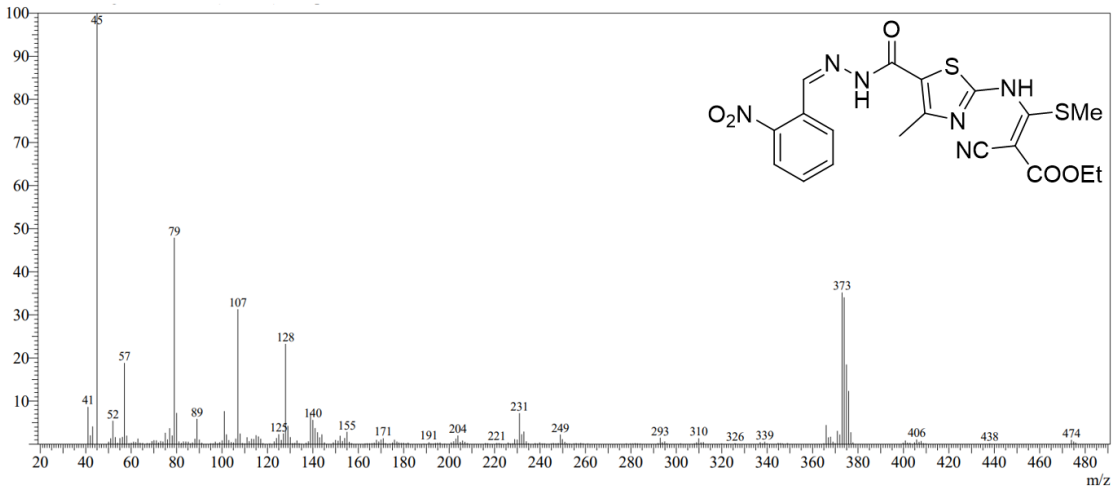



**Fig. 16:** Representative mass spectrum of compound THBOET-12

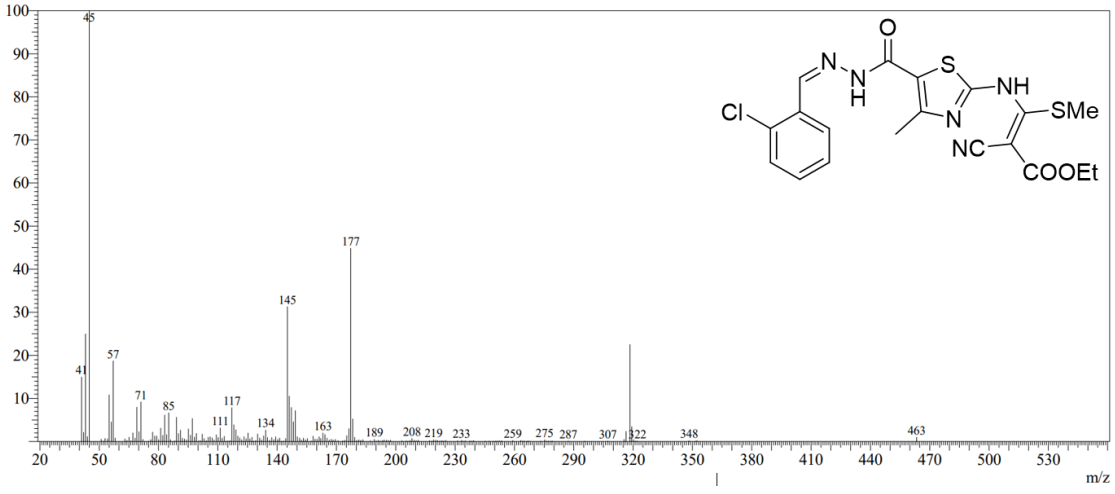



**Fig. 17:** Representative mass spectrum of compound THBOET-13

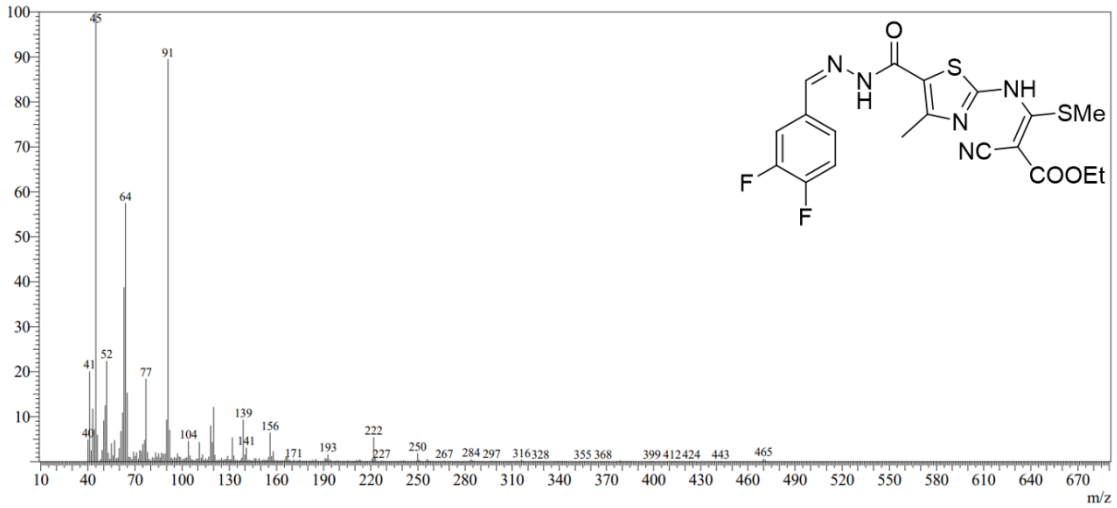



**Fig. 18:** Representative mass spectrum of compound THBOET-14

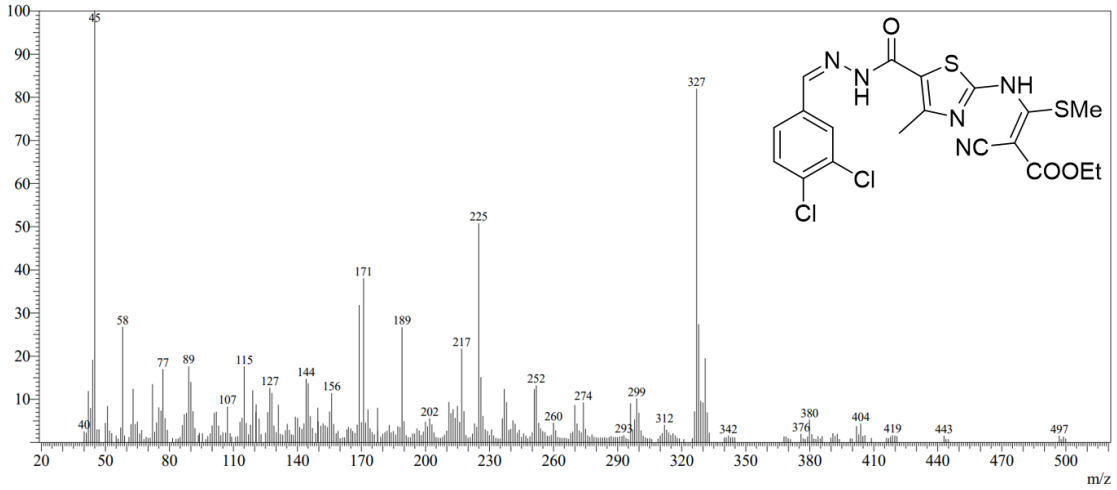



**Fig. 19:** Representative mass spectrum of compound THBOET-15