REVIEW ARTICLE

SYNTHESIS OF 1,3-THIAZOLE DERIVATIVES

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ABSTRACT

Many heterocyclic compounds containing nitrogen atom are used in drug development. Thiazole is one of the most important heterocyclic compounds in drug design, which contains sulfur and nitrogen atom. Different site reactions in thiazole compounds extend to new drug synthesis and plays an important role in medicinal chemistry. Thiazole and derivatives are found to possess widely biological activities such as anti-inflammatory, anti-diabetic, anti-microbial, anti-cancer, anti-convulsant, anti-HIV, anti-hypertensive, anti-Alzheimer, anti-oxidant and anthelmintic. The aim of this review is to corroborate procedures which are available for the synthesis 1,3-thiazole derivatives.

Keywords: Synthesis 1,3-thiazoles, substituted thiazole, Thiazole derivatives.

INTRODUCTION

Heterocyclics are cyclic compounds which contain a hetero atom such as nitrogen, oxygen and sulfur, but also contain other atoms. They have an important role in medicinal chemistry due to presence of different site reactions to design new compounds[1-3]. Terrestrial microorganisms are the main source of heterocyclic compounds. First synthesis of a thiazole was by Hantzsch in 1887[4-7]. Thiazole is a five-membered ring heterocyclic compound and contains sulfur and nitrogen in 1,3 or 1,2 positions (Fig. 1). Thiazole is a liquid, yellow in color and used for preparation of many drugs and dyes. The alkyl groups from second carbon, four and five carbon atom are increasingly nucleophilic with basic character of thiazole, but hetero atoms like nitrogen decrease nucleophilicity with basic character[8].

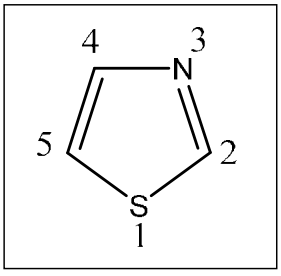

Fig. 1: 1,3 thiazole compounds[8]

Different reaction conditions, catalysts and solvents play an important role in the preparation of thiazole derivatives, green methods and microwave irradiation are common methods used for synthesis thiazole derivatives[9]. Natural compounds such as alkaloids, vitamins, steroids, pigments and flavones are containing thiazole compounds[10,11]. Benzothiazoles and mercaptothiazoles are used in vulcanization[12,13], also thiazoles are used in synthesis of liquid crystal for example sunscreens[14] and sensors[15]. Thiazolium ions are used as active catalysts for C-C formation bonds with many reaction conditions[16]. Thiazole with metal complexes are used in photo-catalysis[17]. Compounds which contain thiazole have absorption in the visible region, hence it is used in chromophores[18,19]. Recently, many publishers have focus on synthesis of thiazole compounds due to their various biological activities (Fig. 2)[20, 21].

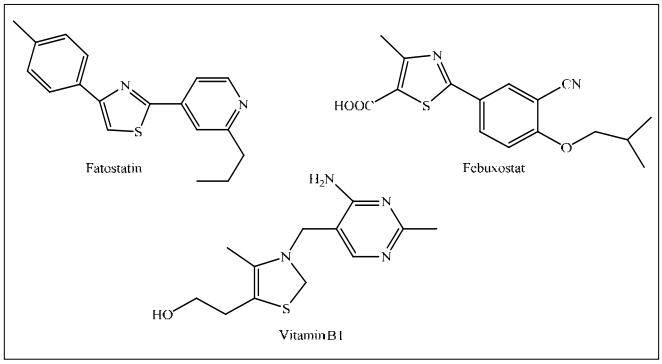

Fig. 2: Some bioactive molecule containing thiazole[21]

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Besides, many review papers in recent years discuss about thiazole as a heterocyclic compound, such as Leoni *et al* [22] patent review for novel thiazole derivatives from 2008-2012. A mini-review by Varghese *et al* describes synthesis strategies of thiazole derivatives[22,23]. A review by Chhabria *et al*. is focussed on synthesis and therapeutic importance of thiazole derivatives[24]. The aim of this review was to summarize collects the procedures for various synthesis of thiazole derivatives.

SYNTHESIS OF THIAZOLE DERIVATIVES

4-Hydroxy-6-methyl-3-(2-[-phenylmethylidene] amino-1,3-thiazol-4-yl)-2*H*-pyran-2-one

The equimolar ratio of compound **1**, thiourea **2**, benzaldehyde **3** and 15% SiW. SiO_2 (silica supported tungstosilisic acid) was mixed and refluxed for 2h in 5mL water/ethanol (1:1 ratio) at 60 ^{0}C. The reaction mixture was cooled to room temperature. The product was filtered and washed with ethanol. The solid material was dissolved in acetone to remove SiW.SiO_2. The product was filtered and dried to obtain compound 4 (Fig. 3)[25].

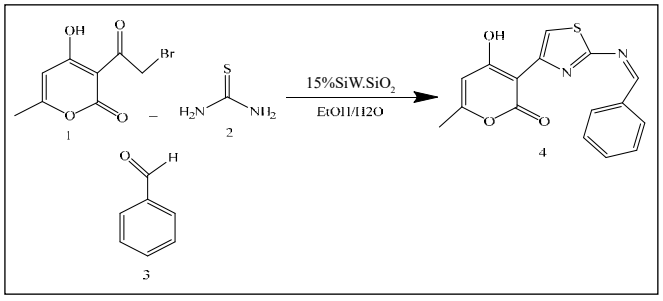

Fig. 3: Synthesis of 4-hydroxy-6-methyl-3-(2-[-phenyl-methylidene] amino-1,3-thiazol-4-yl)-2*H*-pyran-2-one[25]

2-Anilino thiazole

A mixture of compound **5** (1M) and 2-chloro-1,1-dimethoxyethane 6 (1M) with a few drops of HCl was dissolved in 100mL H_2O. The mixture was refluxed for 2 h then was added 100 mL cold water. The reaction mixture was followed by addition of aqueous NaOH to alkaline reaction. The final precipitate was filtered and washed with cold H_2O. The product was recrystallized from hexane and chloroform (1:3 V/V) to obtained compound 7 (Fig. 4)[26].

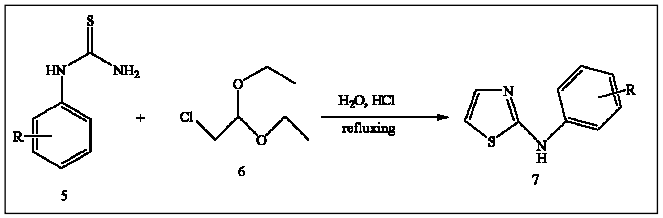

Fig. 4: Synthesis of 2-anilino thiazole[26]

3,3'-Dimethoxy-*N*4,*N*4'-bis(4-phenylthiazol-2-yl)-[1,1'-biphenyl]-4,4' diamine

A mixture of compound 8 (1.0 mMol) and (2.0 mMol) phenacyl bromide in 15mL ethanol was refluxed for 3h. After the reaction mixture was cooled, the solid product was filtered dried and recrystallized from ethanol to form compound 9 (Fig. 5)[27].

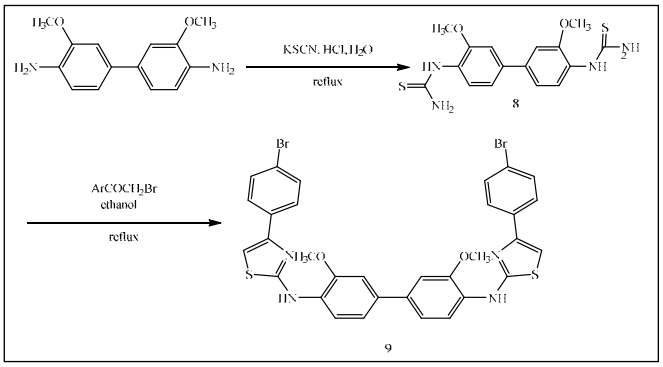

Fig. 5: Synthesis of 3,3'-dimethoxy-*N*4,*N*4'-bis(4-phenylthiazol-2-yl)-[1,1'-biphenyl]-4,4' diamine[27]

3β-Chloro-5α-cholestane-6-ylidine-(4′-phenyl)-thiazole-2′-yl-hydrazone

A mixture of steroidal ketone 10 (1.0 mMol), phenacyl bromide 11 (1.0 mMol) and thiosemicarbazide 12 (1.0mMol) in ethanol (15mL) was stirred and heated at 65^{0}C for 40 minutes in the microwave oven. After the reaction was completed, solvent was evaporated by vacuum drying. Diethyl ether was taken in, then washed with water and sodium sulfate anhydrous used to dry the product. The solid product was purified by silica gel using ethylacetate-petroleum ether 1:4 (V/V). Recrystallization of the final product from methanol was to found to give compound 13 (Fig. 6)[28].

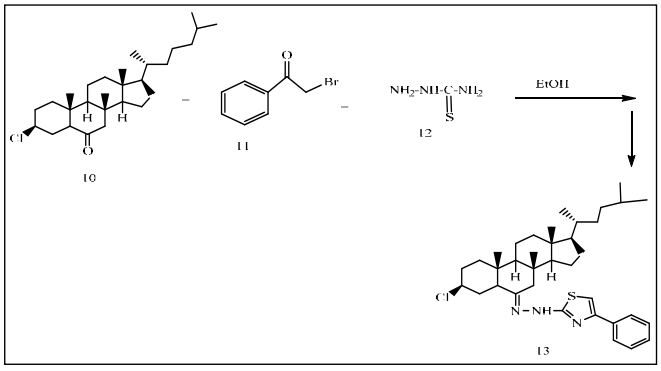

Fig. 6: Synthesis of 3β-chloro-5α-cholestane-6-ylidine-(4′-phenyl)-thiazole-2′-yl-hydrazone[28]

4-Phenylthiazol-2-amine

β-Cyclodextrin (10 mol %) was dissolved in water (20 mL) at 75 ^{0}C and phenylacetylene 14 (1.0 mMol)

was added, followed by NBS. Thiourea 15 (1.0mMol) was added to the reaction mixture after 10 min. Ethyl acetate was used to extract and the extract was filtered. The organic layer was washed with water and dried with sodium sulfate. After that, the solvent was removed and the crude product was purified using column chromatography (EtOAc & hexane) to give the compound 16 (Fig. 7)[29].

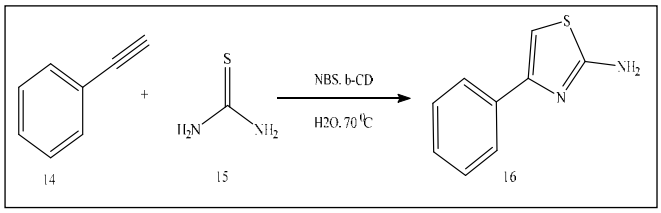

Fig. 7: Synthesis of 4-phenylthiazol-2-amine[29]

4-[(4-Ethoxycarbonylmethylene-4,5-dihydro-thiazol-2-yl)-hydrazonomethyl]-phenol

A mixture of benzaldehyde compound 17 (1.0 mMol), thiosemicarbazaide compound 18 (1.0 mMol), 4-chloroethylacetoacetate (1.0 mMol) and sodium acetate (0.02) in ethanol (20mL) was refluxed for 4h at 80 ^{0}C. TLC was used to check completion reaction, then the reaction was cooled to room temperature. The precipitate was filtered and purified, then recrystallized from ethanol to get compound 19 (Fig. 8)[30].

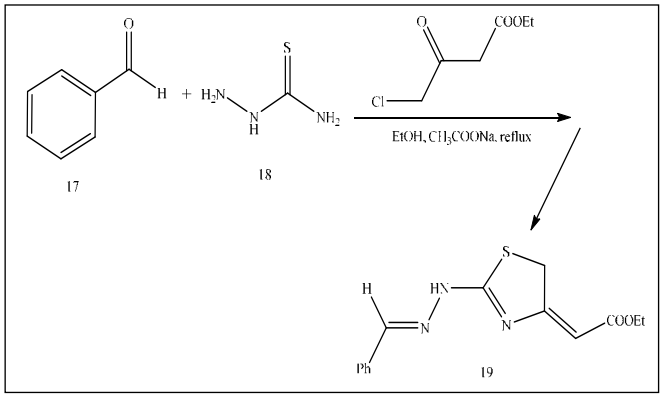

Fig. 8: Synthesis of 4-[(4-ethoxycarbonylmethylene-4,5-dihydro-thiazol-2-yl)-hydrazonomethyl]-phenol[30]

4-Chloro-*N*-[4-(2-hydroxy-4-methoxyphenyl) thiazol-2-yl]benzenesulfonamide

Compound **20** (1.0 mMol) was taken in 30mL tetrahydrofuran and potassium carbonate (1.0 mMol) and 1.1 mMol compound **21** (sulfonylchloride) were added. The reaction mixture was stirred for 3h at 25^{0}C, then diluted with $CHCl_3$ (5.0 mL). The solid inorganic layer was filtered and the solvent removed under pressure to give the residue. The residue was purified by silica gel column chromatography (methanol & dichloromethane) to form compound 22 (Fig. 9)[31].

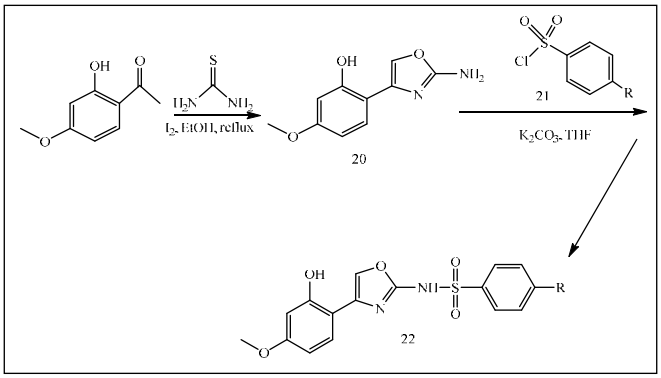

Fig. 9: Synthesis of 4-chloro-*N*-[4-(2-hydroxy-4-methoxyphenyl) thiazol-2-yl]benzenesulfonamide[31]

2,5-Diphenyl-2-methoxy-3-tosyl-4-thiazoline

O- methyl benzothioate **23** which was prepared from methyl benzoate and Lawessons reagent according to the literature[32] and treated with 4-phenyl-1-tosyl-1,2,3-triazole 24m in equimolar ratio (1.5 mMol) using (tBuCO2)4Rh2 catalyst and MS in (2.0 mL) chloroform at 70 ^{0}C for 1h. After that, the product was purified by silica gel chromatography, the compound 2,5-diphenyl-2-methoxy-3-tosyl-4-thiazline 25 produced (Fig. 10)[33] was obtained.

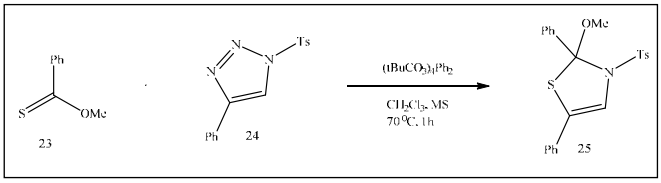

Fig. 10: Synthesis of 2,5-diphenyl-2-methoxy-3-tosyl-4-thiazoline[33]

3,6-Diphenylimidazo[2,1-b]thiazole

3,6-diphenylimidazo[2,1-b]thiazole was synthesised by microwave irradiation of 4-aryl-1,3-thiazol-2-amine 26 and 2-bromo-1-phenylethanone 27 in ethanol at 100 ^{0}C in a pressure tube. The respective compound 28 was formed

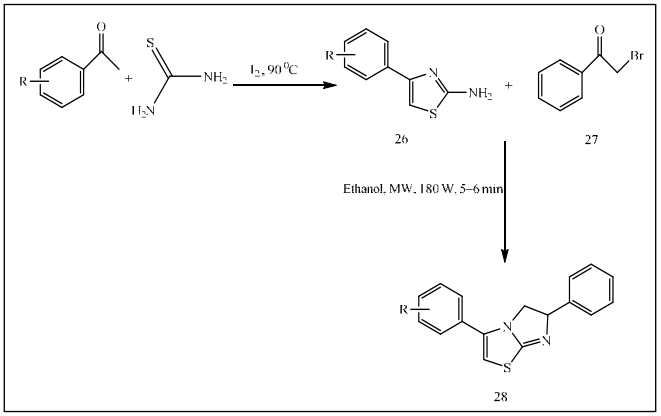

Fig. 11: Synthesis of 3,6-diphenylimidazo[2,1-b]thiazole[34]

during 6 min. Also, the compound 28 was prepared by refluxing compound 26 and 27 in ethanol under nitrogen atmosphere for 12h (Fig. 11)[34].

2,5-Dimethyl-4-(20,40,6'-trimethylbiphenyl-4-yl) thiazole

To compound 29 in ethanol (10) was added thioacetamide (1.0 mMol), this mixture was refluxed for 12 h at 80 ^{0}C. The reaction mixture was cooled to room temperature. To this, (30 mL) ethyl acetate added and washed with $NaHCO_3$. The organic layer was dried with anhydrous $MgSO_4$. The product was recrystallized from CH_3OH to give compound 4-(4-bromophenyl)-2,5-dimethylthiazole 30. The mixture of compound 30 (1.5 mMol), compound 31 (1.0 mMol), K_2CO_3 (2.0 mMol), PPh_3 (0.5 mMol) and $PdCl_2$ (0.3 mMol) were reacted in dimethylformamide (20 mL) at 90 ^{0}C for 4 -5 h. The reaction mixture was cooled and filtered. The filtrate was extracted with CH_2Cl_2, then the organic layer was removed and the product was purified using chromatography (silica gel, EtOAc/hexane (1:4)) to produce desired compound 32 (Fig. 12)[35].

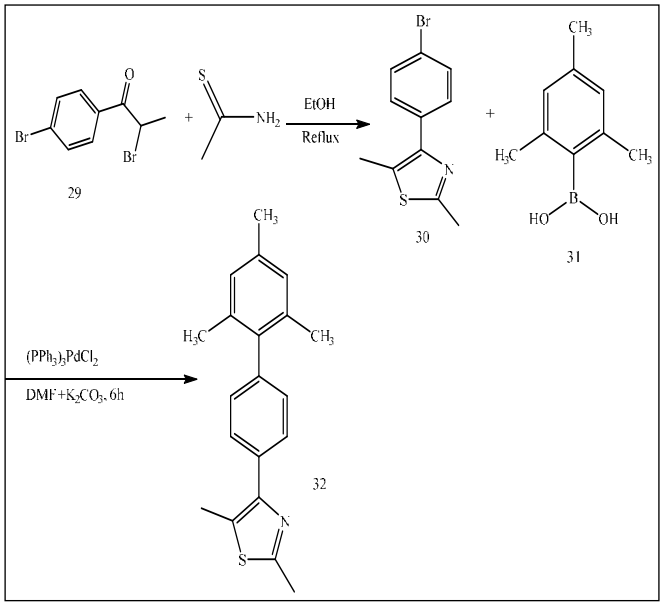

Fig. 12: Synthesis of 2,5-dimethyl-4-(20,40,6'-trimethylbiphenyl-4-yl) thiazole[35]

Thiazole-2-imines

A mixture of 2-bromo-1-phenylethan-1-one Compound 33, (1.0 mMol), phenyl isothiocyanate 34 (1.0 mMol), primary amine 35 (1.0 mMol), ethanol (5 mL) and trypsin (40 mg) take was in a round bottom flask and stirred at 500 rpm at 30 ^{0}C till the reaction was completed (TLC). The product compound 36 was purified and recrystallized by ethanol (Fig. 13)[36].

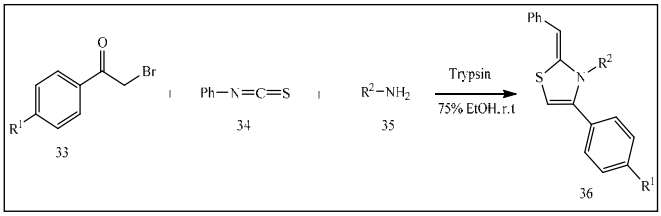

Fig. 13: Synthesis of thiazole-2-imines[36]

(E)-4-(4-Methoxy phenyl)-2-(2-(1-pyridin-2-yl) ethylidene) hydrazinyl) thiazole bromide (HL·Br)

Methanolic solution of compound 37 (10 mMol: 1.94 g) was added drop by drop to the solution of compound 38 in methanol. The mixture was continuously stirred at room temperature for 4h, by this time the temperature of the solution increased to 85 ^{0}C. The yellowish precipitate formed was, filtered then washed with methanol 3 times. The single crystalline compound 39 was obtained by removing the solvent (Fig. 14)[37].

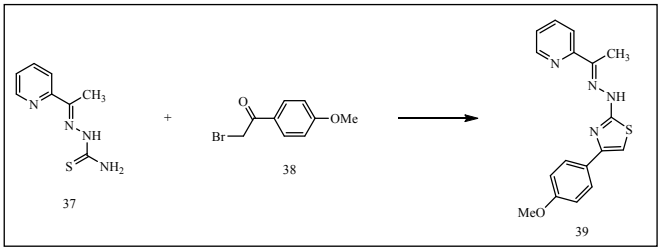

Fig. 14: Synthesis of *(E)*-4-(4-methoxy phenyl)-2-(2-(1-pyridin-2-yl) ethylidene) hydrazinyl) thiazole bromide (HL·Br)[37]

N-(2-Methoxybenzylidene)-4-methyl-2-(4 (trifluoromethyl)phenyl) thiazole-5-carbohydrazide

A mixture of thiazole carbohydrazide compound **40** (1.0 mMol) in ethanol (10 mL), substituted benzaldehyde (1.0 mMol) and a drop of H_2SO_4 was heated to reflux for 4h. the precipitate was separated by filtration and ethanol used for recrystallization to get compound 41(Fig. 15)[38].

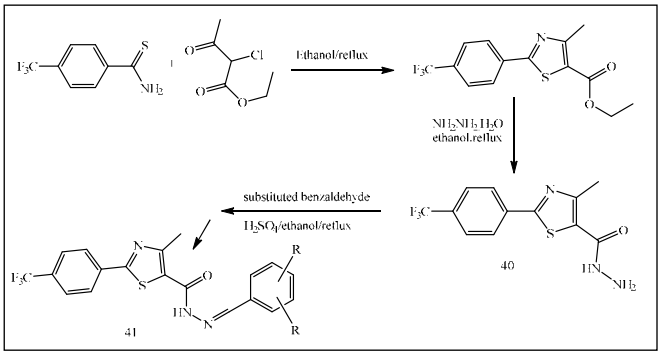

Fig. 15: Synthesis of *N*-(2-methoxybenzylidene)-4-methyl-2-(4 (trifluoromethyl)phenyl) thiazole-5-carbohydrazide[39]

3-[2-[1-(2-Methoxyethyl)-1*H*-indol-3-yl]-1,3-thiazol-4-yl]-1*H*-pyrrolo[2,3-b]pyridine

The compound 44 was synthesized from the corresponding compound 43, which was prepared from the reaction of compound 42 and chlorosulfonyl iso-cyanate in acetonitrile followed by hydrolysis of chlorosulfonyl groups. Compound 43 with Lawessones reagent was reflux in THF and the desired compound 44 was formed. The compound 44 (2.0 mMol) and bromoacetyl derivative 45 (2.0 mMol) in ethanol (8 mL) was reflux for half an hour. After the reaction mixture was cooled, the precipitate was filtered, then dried and recrystallized from ethanol to give the compound 46 (Fig. 16)[39].

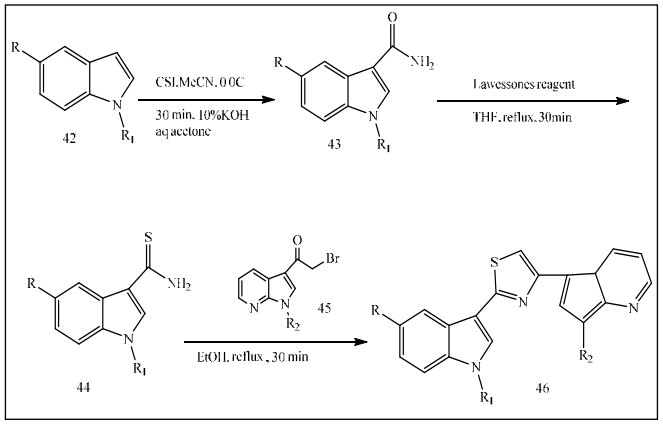

Fig. 16: Synthesis of 3-[2-[1-(2-methoxyethyl)-1*H*-indol-3-yl]-1,3-thiazol-4-yl]-1*H*-pyrrolo[2,3-b]pyridine[39]

N-(3-Chlorophenyl)-2-*p*-tolylthiazole-4-carboxamide

In a round bottom flask 2-*p*-tolylthiazole-4-carboxylic acid **47** (0.91 mMol), hydroxybenzotriazole (0.91 mMol) and *N*-ethyl-*N'*-dimethylaminopropyl carbodiimide (0.91 mMol) were mixed in CH_3CN (25 mL), the mixture was stirred for 30 min at room temperature. Aniline derivative was added, then stirring continued for 24h. TLC was used to determine the end of the reaction. After the end of the reaction, the solvent was evaporated under pressure and EtOAc/H_2O added to the residue. The organic layer was washed with $NaHCO_3$ 5% and H_2SO_4 2%. Sodium sulfate anhydrous was added to dry and was then removed by filtration. The precipitate was washed with Et_2O and n-hexane. The desired compound **48** was obtained (Fig. 17)[40].

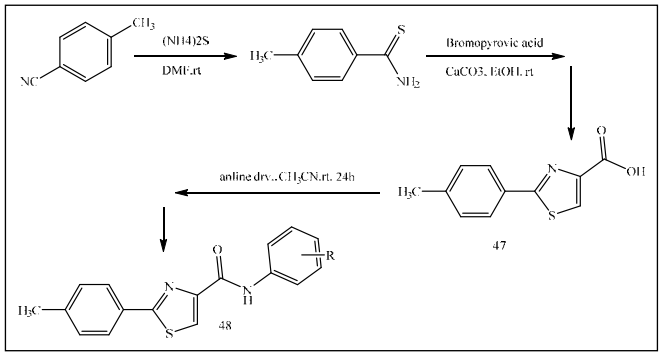

Fig. 17: Synthesis of *N*-(3-Chlorophenyl)-2-*p*-tolylthiazole-4-carboxamide[40]

N'-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)-4-methyl-2-phenyl thiazole-5-carbohydrazide

To a mixture of compound **49** (1.0 mMol) with appropriate compound **50** (1.0 mMol) in ethanol (20 mL) was added triethylamine (1.0 mMol). The mixture was refluxed for (4-6)h. The solid product formed, was washed with ethanol then dried and recrystallized from suitable solvent to give the desired compound **51** (Fig. 18)[41].

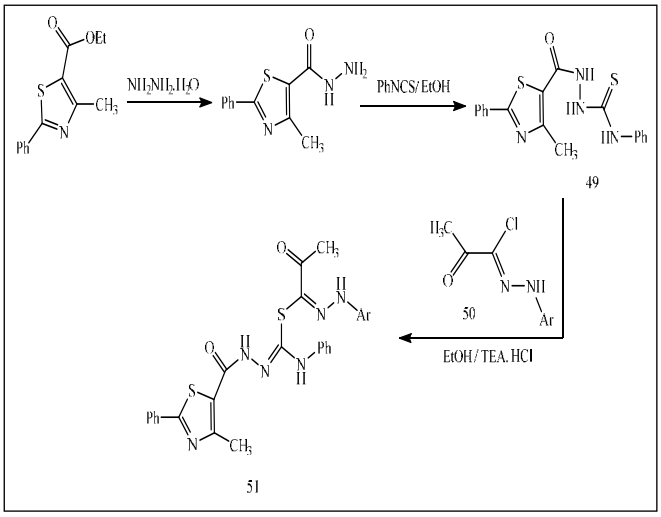

Fig. 18: Synthesis of *N'*-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2*(3H)* -ylidene)-4-methyl-2-phenyl thiazole-5-carbohydrazide[41]

5-(2,4-Diphenyl-1,3,4-thiadiazol-5-ylidene)-2-(4-(2,3-dimethyl-1-phenyl-5-oxo-pyrazol-4-yl) thiazol-2-ylimino)-3-phenyl-1,3-thiazolidin-4-one

A mixture of thiazolidine-4-one derivative **52** (1.0 mMol) and sodium hydroxide (1.0 mMol) in dimethylformamide (10 mL) was stirred for 10 min, then phenylisothiocyanate was added (1.0 mMol). The reaction was continuously stirred at room temperature for 6h. After that hydrazonoyl chloride compound **53** (1.0 mMol) was added and stirring continued for 10 to 14h. The solid product formed was filtered, washed with ethanol and water. Finally, it was dried and recrystallized from DMF. The desired compound **54** was produced (Fig. 19)[42].

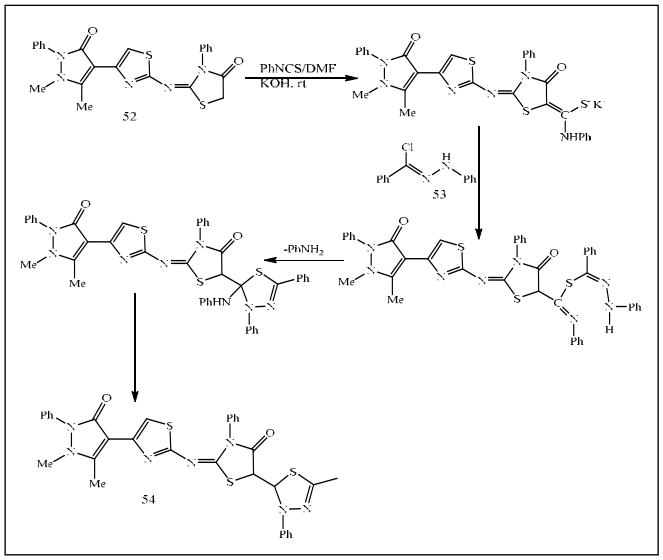

Fig. 19: Synthesis of 5-(2,4-diphenyl-1,3,4-thiadiazol-5-ylidene)-2-(4-(2,3-dimethyl-1-phenyl-5-oxo-pyrazol-4-yl) thiazol-2-ylimino)-3-phenyl-1,3-thiazolidin-4-one[42]

2-(2-((1*H*-Indol-5-yl)methylene)hydrazinyl)-4-methylthiazole

A mixture of *(E)*-2-[(1*H*-indol-3-yl)methylene] thiosemicarbazone compound **55** (0.01 M) and chlorcarbonyl compound **56** (0.01 M) in acetone/ethanol/ acetic acid (0.5/1/0.1 V/V/V) was stirred for 24h at room temperature. TLC was used to monitor the reaction. After completion, the reaction mixture was neutralized using a sodium bicarbonate solution. It was Filtered, washed and then recrystallized from ethanol to form the desired compound **57** (Fig. 20)[43].

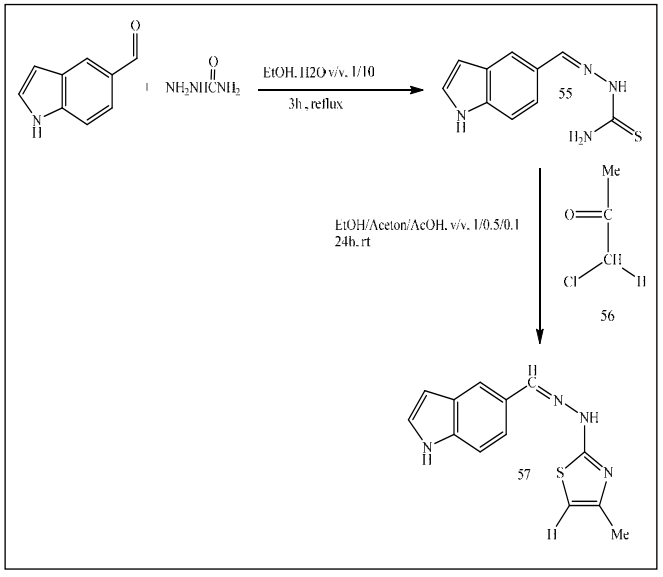

Fig. 20: Synthesis of 2-(2-((1*H*-indol-5-yl)methylene)

1-(5-(2-Chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-*p*-tolylurea

A mixture of (2-amino-4-(3-chlorophenyl)thiazol-5-yl) (2-chlorophenyl)methanone (compound **58**) (1.5 mMol) and 4-methylphenylisocynate (compound **59**) (1.5 mMol) with NaOH (2.5 mMol) in dry acetone (20 mL) was stirred for 3h at room temperature. The reaction was monitored by TLC. The solid product was filtered and washed with dry acetone three times, then recrystallized to give the compound **60** (Fig. 21)[44].

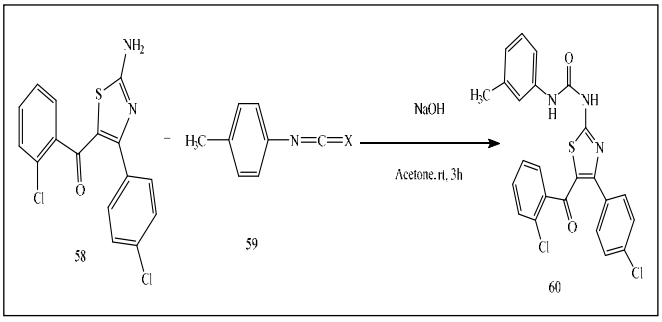

Fig. 21: Synthesis of 1-(5-(2-chlorobenzoyl)-4-(3-chlorophenyl)thiazol-2-yl)-3-p-tolylurea[44]

2-(Alkyl sulfanyl) thiazoles

2-(Alkyl sulfanyl) thiazole was prepared by one-pot, synthesis is two steps. To the compound acetophenone **61** (0.1 mMol) was added CuO/I_2 (equimolar) in ethanol and refluxed for 8h; phenacyl iodide was produced. To this was added S-alkyldithiocarbamtes and heated with reflux for 2h. The solid product formed was filtered and recrystallized from EtOH. The desired compound **62** was formed (Fig. 22)[45].

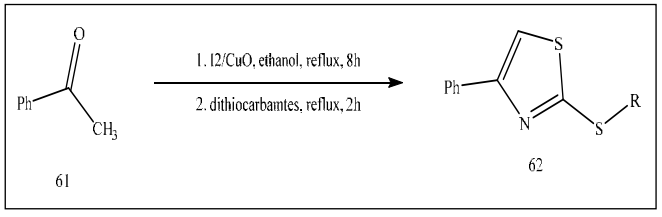

Fig. 22: Synthesis of 2-(alkyl sulfanyl) thiazoles[45]

4-(4-Chlorophenyl)-2-phenylthiazole

A mixture of (*E*)-1-chloro-4-(prop-1-en-1-yl)benzene compound **63** (0.1 mMol), N-bromo succinimide compound **64** (0.1 mMol) and thiobenzamide compound **65** (0.1 mMol) was refluxed for 5h. The mixture was then poured on ice water. The solid product was filtered and dried. Methanol was used for recrystallization of desired compound **66** (Fig. 23)[46].

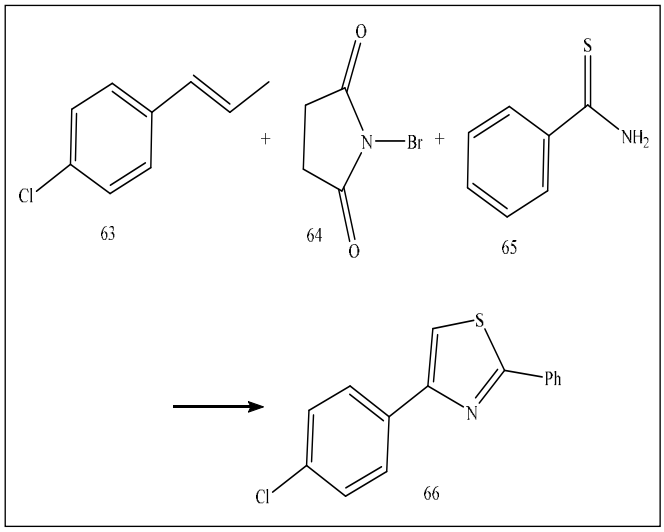

Fig. 23: Synthesis of 4-(4-chlorophenyl)-2-phenylthiazole[46]

2,4-Diphenylthiazole

In a round bottom flask morpholino(phenyl) methanethione compound **67** (1.0 mMol), 2-bromo-1-phenylethan-1-one compound **68** (1.15 mMol), NH_4OAc (1.6 mMol) and TEAI (tetraethylammonium iodide) (0.1 mMol) were added and heated at 110 ^{0}C, the heating continued for 2h. After that, the reaction mixture was cooled and followed by addition EtOAc & hexane (1:4). The crude precipitate was filtered, then recrystallized from ethanol. The compound **69** was formed (Fig. 24)[47].

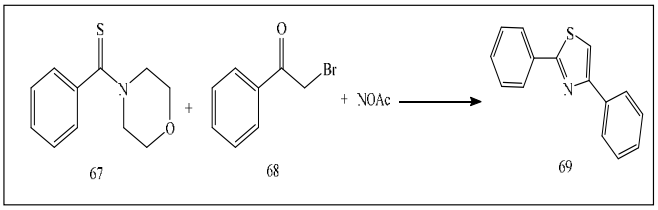

Fig. 24: Synthesis of 2,4-diphenylthiazole[47]

4-Chloropyrrolo[2',1':2,3]thiazolo[5,4-*d*] pyrimidine

The mixture of 4,6-dichloropyrimidin-5-amine (compound **70** 0.01M) with NaSEt (0.01 M) in methanol (30 mL) was refluxed for 3h at 65 ^{0}C. The compound **71** was produced. To form the pyrrole ring, compound **71** was heated with 2,5 dimethoxy-tetrahydrofuran in AcOH at 120 ^{0}C for 20 min to obtain compound **72**. The compound **72** was treated with m-CPBA to oxidize sulfide and give compound **73**. To cyclization compound **73** were added TFA and TFAA at 0 ^{0}C and stirred for 45 min to give the desired compound **74** (Fig. 25)[48].

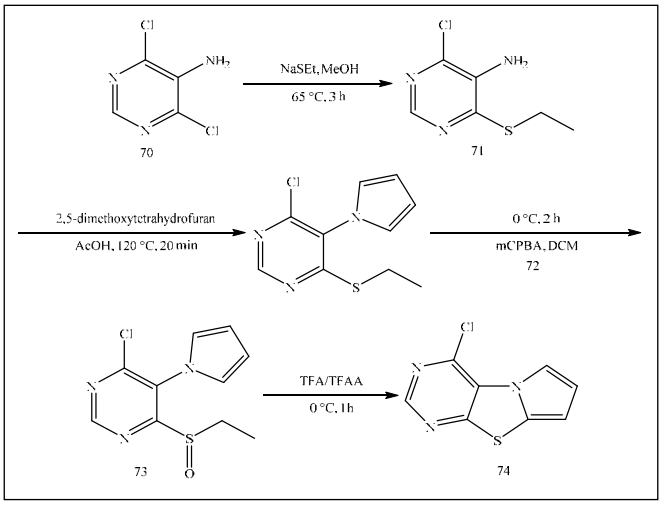

Fig. 25: Synthesis of 4-chloropyrrolo[2',1':2,3] thiazolo[5,4-*d*]pyrimidine[48]

2-Aminothiazole derivatives using nano chitosan as a catalyst

A mixture of compound **75** (2.0 mMol), thiourea **76** (3.0 mMol), I_2 (2.0 mMol) and nano chitosan **77** (0.03g) in the presence ethanol was refluxed. The end of the reaction was monitored by TLC (ethyl acetate/petroleum ether 1:4). After the reaction was completed, the catalyst was removed by filtration and solvent was evaporated. The solid obtained was dissolved in hot water and followed by heating with ether and ammonia three times. The product was recrystallized from EtOH to form pure compound **78** (Fig. 26)[49].

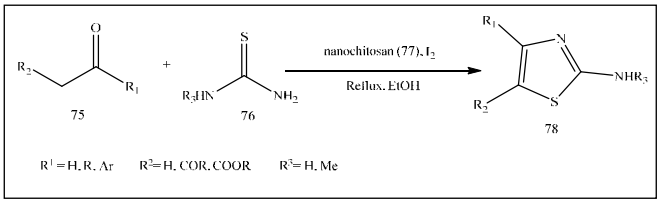

Fig. 26: Synthesis of 2-aminothiazole derivatives using nano chitosan as a catalyst[49]

5-(2′ -Indolyl) thiazole

A mixture of compound **79** (2.0 mMol) and compound **80** 3-tosyloxypentane-2,4-dione (2.0 mMol) in EtOH was irradiatied for 10 min at 78 ^{0}C by MW power (100 w). The TLC showed that the thioamide was formed. After that, (2.1 mMol) phenylhydrazine was added and irradiated by MW at the same temperature for 10 min. After adding two drop ply-phosphoric acid, irradiation was then continued at 78 ^{0}C for 15 min. The reaction mixture was diluted with water and extracted two-times with ethyl acetate (10 mL). The organic layer was dried by anhydrous $NaSO_4$, then the mixture was concentrated under vacuum. Purification

of the product was by silica gel column chromatograph using hexane-ethyl acetate to get the desired compound **81** (Fig. 27)[50].

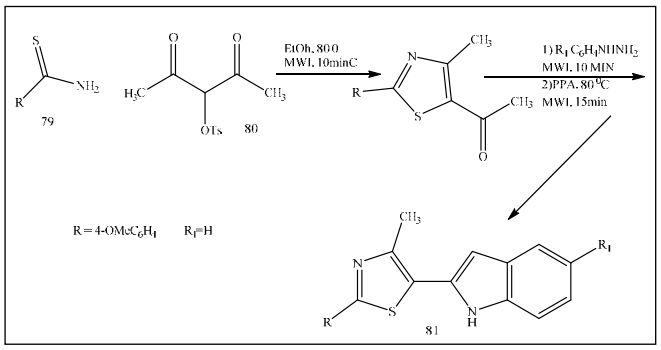

Fig. 27: Synthesis of 5-(2′-indolyl) thiazole[50]

2-(2-Fluorophenyl)-4-(trifluoromethyl)thiazole-5-carboxylate

To the solution of compound **82** (35 mMol) in ethanol (100 mL) was added compound **83** (35 mMol) and refluxed for 24h. After the reaction was over, the solvent was removed under vacuum. The coloured mixture was allowed to stand until white crystals were formed. The solid crystals of compound 84 were formed (Fig. 28)[51].

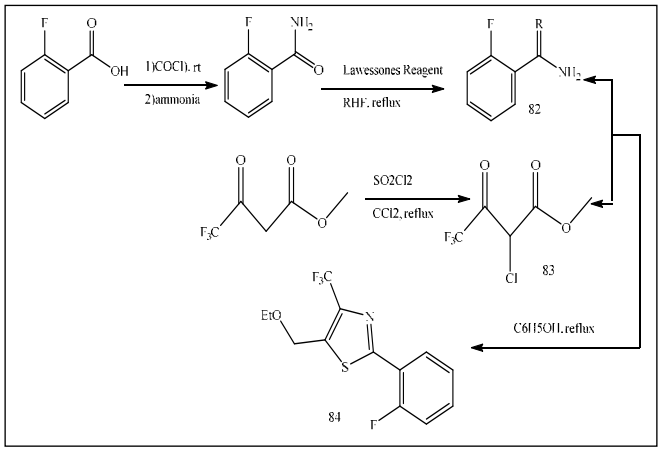

Fig. 28: Synthesis of 2-(2-fluorophenyl)-4-(trifluoromethyl)thiazole-5-carboxylate[51]

(E)-2-2[2-(2-Nitrobenzylidene)hydrazinyl]-4-phenylthiazole-3-ium bromide

A mixture of 2-(1-substituted methylidene) hydrazinecarbonthioamide compound **85** (1.0 mMol) and 1-aryl-2-bromoethanone compound **86** (1.0 mMol) in absolute EtOH (30 mL) was refluxed for 1h. After that, the reaction mixture was cooled to room temperature. The precipitate formed was filtered, washed with ethanol and recrystallized with EtOH to obtain pure crystals of compound **87** (Fig. 29)[52].

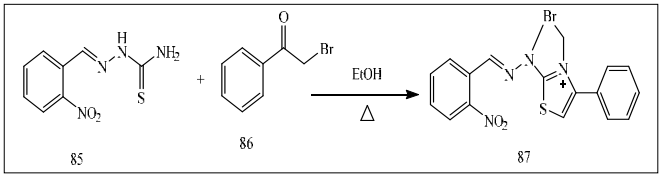

Fig. 29: Synthesis of *(E)*-2-2[2-(2-nitrobenzylidene) hydrazinyl]-4-phenylthiazole-3-ium bromide[52]

(*R*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-2-(*S*-1-(tert-butyldiphenylsilyloxy)ethyl)-4,5-dihydrothiazole-4-carboxamide

To the solution of compound, **88** (0.65 mMol) in dichloromethane (10 mL) was added N, N'-diisopropylethylamine (1.28 mMol) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (0.64 mMol), and stirred for 15 min at room temperature. After that, compound **89** (0.16 mMol) and triphenylphosphine (1.28 mMol) were added and then refluxed for 24h. The solvent was removed under low pressure. The solid product was purified by silica-gel (EtOAc/hexane 1:2) to get compound **90** (Fig. 30)[53].

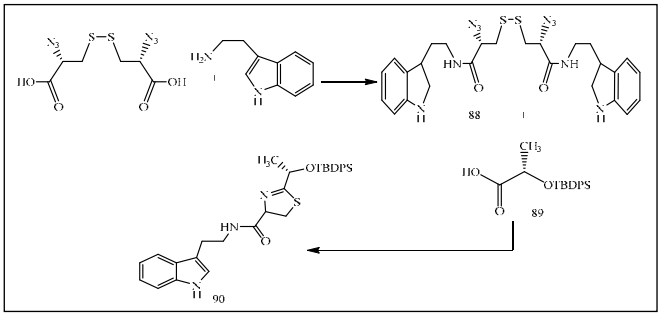

Fig. 30: Synthesis of *(R)*-*N*-(2-(1*H*-indol-3-yl)ethyl)-2-(*S*-1-(tert-butyldiphenylsilyloxy)ethyl)-4,5-dihydrothiazole-4-carboxamide[53]

Disubstituted 2- aminothiazole

In a round bottom flask charged with ethyl aceto acetate, compound **91**(1.0 mMol), urea or thiourea compound **92** (1.0 mMol), N-bromosuccinimide (1.0 mMol) and diethylstilbestrol (0.5 mL) were added and the mixture was stirred at 60 ^{0}C until completion of the reaction. After that, the solid product was filtered,

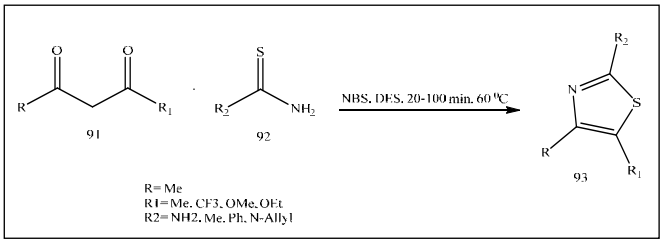

Fig. 31: Synthesis of disubstituted 2-aminothiazole[54]

washed with water and recrystallized from diethyl ether or ethanol to give compound **93** (Fig. 31)[54].

3-Alkyl-2-(aryl imino)-4-cyclopropyl-5-(20-fluorophenyl)-thiazole derivatives

A mixture of 2-bromo-2-(2-fluorophenyl)-1-cyclopropylethanone compound **94** (1.0 mMol), alklisothiocyanate **95** (1.0 mMol) and arylamine **96** (1.0 mMol) was added to the round bottom flask containing ethanol (10 mL), after that was added PVP (polyvinyl pyridine (0.2 mMol). The reaction mixture was stirred for some time to complete the reaction. The end of the reaction was monitored by TLC. The solid product formed at the completion of the reaction was filtered, then recrystallized with ethanol and water (1:1) to produce pure compound **97** (Fig. 32)[55].

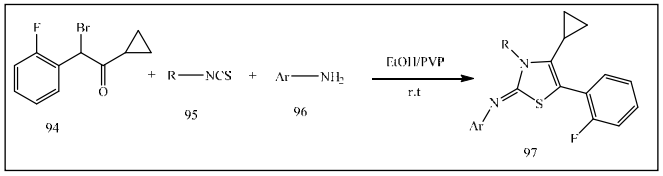

Fig. 32: Synthesis of 3-alkyl-2-(aryl imino)-4-cyclopropyl-5-(20-fluorophenyl)-thiazole derivatives[55]

(4-Amino-2-(methylthio)thiazol-5-yl)(morpholino) methanone

To the solution of compound **98** (2.93 mMol) in acetone (20 mL) was a added compound **99** (4.40 mMol) and stirred for 2h at room temperature. After that was added 1,8-diazabicyclo[5.4.0]undec-7-ene (5.84 mMol) at 0 ^{0}C and stirred continued for 1h at room temperature. The reaction treated with mixture was ethyl acetate, then washed, and dried with anhydrous magnesium sulfate. The solvent was removed under vaccum and the residue purified by column chromatography (hexane/ethylacetate 1:1) to get compound **100** (Fig. 33)[56].

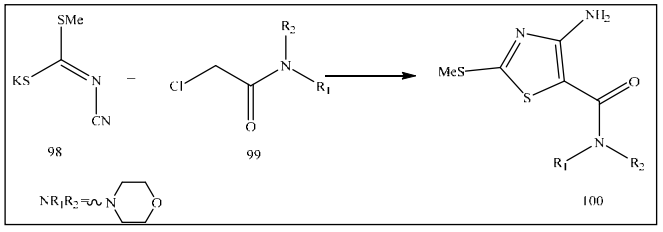

Fig. 33: Synthesis of (4-amino-2-(methylthio)thiazol-5-yl) (morpholino)methanone[56]

5-Bromo-4-phenylthiazol-2-amine

To the solution of bromine (2.84 mMol) in AcOH (glacial) (2 mL) was slowly added the solution of H_2SO_4 and 2-amin-4-phenyl-1,3-thiazole (2.84 mMol). The reaction mixture was stirred at room temperature for 18h. The mixture was treated with diethyl ether to form a precipitate. The crude precipitate was dissolved in 25mL hot water and the pH was adjusted to 11 with ammonium hydroxide. The fresh precipitate was filtered to obtain compound **101** (Fig. 34)[57].

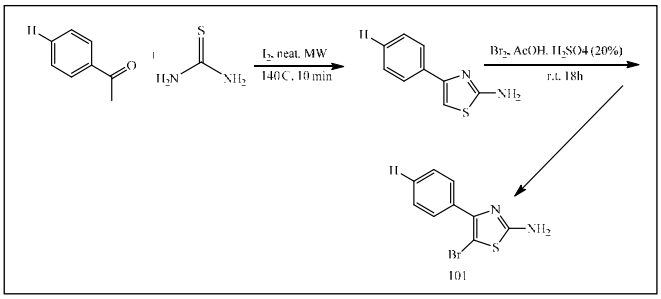

Fig. 34: Synthesis of 5-bromo-4-phenylthiazol-2-amine[57]

4-((Hydroxyiminomethyl)-1-(2-oxo-2-(4-phenylthiazol-2-ylamino)ethyl) pyridinium chloride

4-Pyridinealdoxime compound 102 (2.6 mM) dissolved in 25 mL acetonitrile, taken in a round bottom flask and stirred at room temperature. Compound 103 (3.2 mM) was dissolved in 20mL dry acetonitrile and then slowly added to the first solution. After that, at room temperature, the mixture was stirred for 3h and refluxed for 4h. The solid product was filtered, washed with acetonitrile and then with hot acetone. The solid product was dried and recrystallized from acetone/methanol (2:1). Compound 104 was formed[58] (Fig. 35).

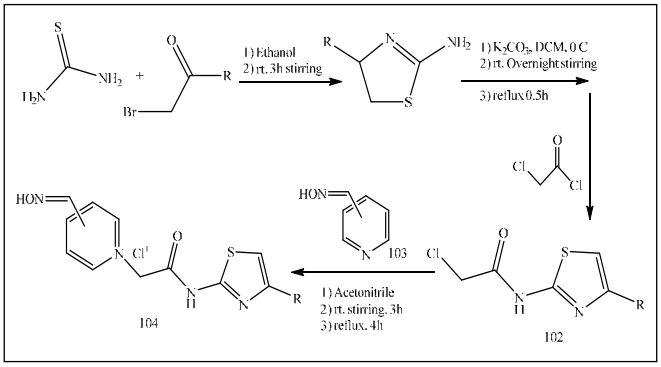

Fig. 35: Synthesis of 4-((hydroxyiminomethyl)-1-(2-oxo-2-(4-phenylthiazol-2-ylamino)ethyl) pyridinium chloride[58]

Ethyl 2-[2-(allylamino)thiazol-4-yl]acetate

A mixture of sodium methoxide (which was prepared from 0.1 mol sodium in 60 mL methanol), compound **105** (0.05 M) and ethyl 5-chloro-4-oxopentanoate compound **106** (0.055 M) was refluxed for 13h. After the residue was formed, the solvent was removed and the residue was dissolved in H_2O and hydrochloric acid was used to

neutralize to pH 7 to 8. The desired compound **107** was extracted from chloroform, then dried and recrystallized with Et_2O (Fig. 36)[59].

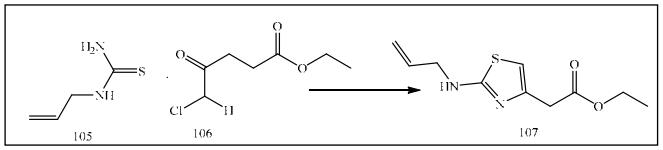

Fig. 36: Synthesis of ethyl 2-[2-(allylamino)thiazol-4-yl] acetate[59]

2-(3-Isobutylindeno[1,2-c]pyrazol-1(4*H*)-yl)-4-phenylthiazole

Appropriate solution of indenopyrazole **108** (1.0 mMol), $(CH_2OH)_2$ (15 mL), hydrazine hydrate (H_6N_2O) (1 mL) and potassium hydroxide (0.5 mL). was refluxed for 5h at 200 ^{0}C. After that the mixture was poured into ice water. The solid obtained was filtered, washed, dried and recrystallized with $CHCl_3$ to form compound **109** (Fig. 37)[60].

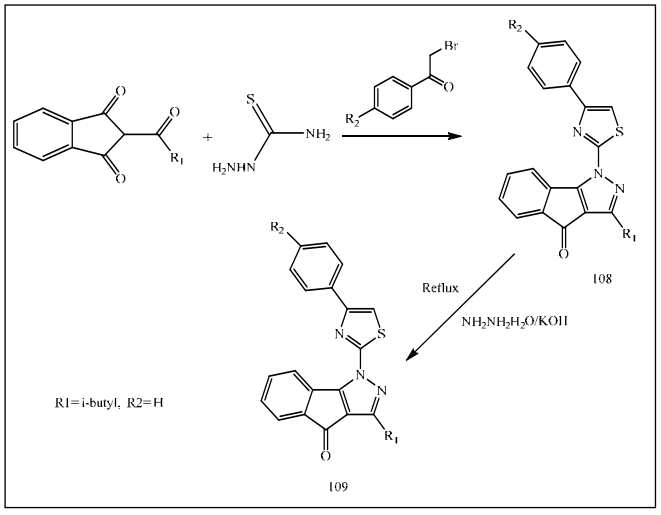

Fig. 37: Synthesis of 2-(3-Isobutylindeno[1,2-c]pyrazol-1(4*H*)-yl)-4-phenylthiazole[60]

4-Methyl-5-phenylthiazol-2-amine

In a round bottom flask a mixture containing 2-methyl-2-nitro-3-phenyloxirane compound **110** (0.5 mMol), thiourea compound **111** (0.5 mMol), sodium methoxide (1.0 mMol) and methanol (3 mL) was stirred for 6h at room temperature. The reaction was completed and methanol was removed under vacuum. The residue was dissolved in a mixture of ethyl acetate and water. The organic layer was washed, dried with sodium sulfate and concentrated. Silica gel chromatography (MeOH/DCM) used to purify the product compound **112** (Fig. 38)[61].

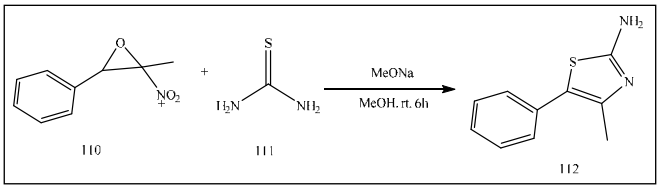

Fig. 38: Synthesis of 4-methyl-5-phenylthiazol-2-amine[61]

CONCLUSION

Thiazoles have a unique structural configuration with good properties, hence it has great significance in medicine. Thiazoles have an unassailable position in pharmaceutical chemistry and continue to be of great interest for those who are working in this field. The numerous procedures describe here may well be useful to synthesise various new compounds containing thiazole moiety that might be better in term of efficiency and lower toxicity. Research activities on the thiazole moiety for various illnesses whose treatment are interesting continues. Consequently, in the previous literature that thiazole ring encompassing heterocyclic structure takes extensive medical applications. The review of thiazole derivatives shows a variety of research appears in the recent past and gives ideas for future design of new drugs.

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