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A REVIEW: SYNTHESIS SCHEMES OF ANTIMICROBIAL AND ANTICANCER THIAZOLE DERIVATIVES

Harmandeep Kaur*
Harinder Kaur
Amit Chawla
U.S. Baghel
R.K. Dhawan

Khalsa College of Pharmacy, Amritsar, India.

ABSTRACT

Heterocyclic compounds comprise the major family of organic compounds. Thiazole derivatives are an important class of heterocyclic compounds. The extensive synthetic possibilities of these heterocyclic due to the presence of several reaction sites. Thiazoles and their derivatives have attracted continuing interest over the years because of their varied biological activities and are enormously essential with wide range of synthetic, pharmaceutical, and industrial applications. Approximately 90% of new drugs contain heterocyclic moieties. So far, modifications of thiazole ring have proven highly effective with improved potency and lesser toxicity. The high therapeutic properties of these heterocycles have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents.

Key words: Thiazole derivatives, Antimicrobial activity, Anticancer activity

INTRODUCTION

Thiazole is aromatic, heterocyclic organic compound that have five membered molecular ring structures C_3H_3NS.[1] Thiazole was first described by Hantzch and Weber in 1887. Prop confirmed its structure in 1889. The numbering of thiazole starts from sulphur atom. [2] Numerous reports have appeared in the literature which highlights their chemistry and pharmacological uses. [3,4,5] There is larger Pi-electron delocalization in thiazoles as compared to corresponding oxazoles and hence have greater aromaticity which is evidenced by the chemical shift of the ring protons in proton NMR spectroscopy indicating strong diamagnetic current. [6] Mostly researches have maintained their interest in nitrogen and sulphur containing heterocyclic compounds through decades of historical development of organic synthesis. [6, 7] In the continuation of our drug research program[8-15], the present work is aimed towards the construction of novel heterocyclic compounds of anticipated utility as anticancer agents. Design of new lead structures employed as antitumor agents is one of the most urgent research areas in contemporary medicinal chemistry. Cancer is a second leading cause of death. [17] and is characterized by the uncontrolled proliferation of cells, which may be rapid or slow depending on the particular cancer. It poses a searious human health problem despite much progress in understanding its biology and pharmacology. [18] Thiazole derivatives have been reported to posse's broad spectrum of pharmacological activities like anticancer[19], antidiabetic[20], CNS depressant[21], analgesic[22], antifilarial[23], antifungal and antibacterial[24], anthelmintic and antitumoral[25] activites. Mostly thiazole derivatives are known to posses intresting biological properties that show anticancer and antimicrobial activities.

Address for correspondence

Harmandeep Kaur*
Khalsa College of Pharmacy, Amritsar, India.

SCHEMES AND SYNTHESIS OF THIAZOLE DERIVATIVES

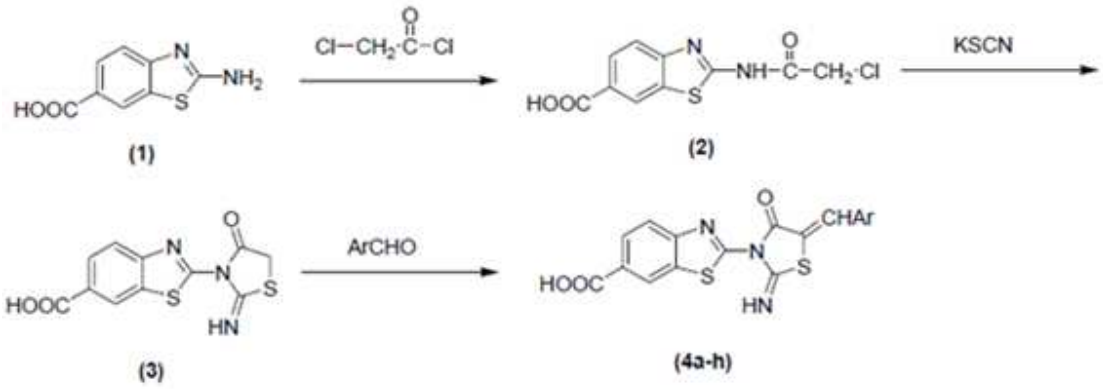
A. Antimicrobial activity:

Various methods for the synthesis of compound having antimicrobial activity:

1. Method for the synthesis of 2-[5-(arylidene)- 2-imino-4-oxo-thiazolidi- 3yl]benzothiazole-6-carboxylic acid (4a-h)

The condensation of chloroacetyl chloride in the presence of anhydrous K_2CO_3 as base and chloroform as solvent with 2-amino-benzothiazole-6-carboxylic acid **(1)** gives 2-(2- chloroacetyl amino) benzothiazole- 6- carboxylic acid **(2)**. On reaction with KSCN in refluxing acetone yield 2-(2-imino-4- oxo-thiazolidin-3-yl) benzothiazole-6-carboxylic acid **(3)**. Condensation of 2-(2-imino-4- oxo-thiazolidin-3-yl) benzothiazole-6-carboxylic acid with various aromatic aldehydes afford a series of compound 2-[5-(arylidene)-2-imino-4-oxo-thiazolidin-3yl]benzothiazole-6-carboxylic acid.i.e. 2-[5-(2-Chlorobenzylidene)-2-imino-4-oxo-thiazolidin-3-yl]benzothiazole-6-carboxylic acid **(4a)**, 2-[5-(4-Chlorobenzylidene)-2-imino-4-oxo-thiazolidin-yl]benzothiazole-6-carboxylic acid **(4b)**, 2-[5-(4-Hydroxybenzylidene)-2-imino-4-oxo-thiazolidin-3yl]benzothiazole-6-carboxylicacid **(4c)**, 2-[5-(3-Bromobenzylidene)-2-imino-4-oxo-thiazolidin-3yl]benzothiazole-6-carboxylic acid **(4d)**, 2-[2-Imino-5-(4-methoxybenzylidene)-4-oxo-thiazolidin-3-yl]benzothiazole-6-carboxylicacid **(4e)**, 2-[2-Imino-5-(3-nitrobenzylidene)-4-oxo-thiazolidin-3-yl]benzothiazole-6-carboxylic acid **(4f)**, 2-[2-Imino-5-(4-

nitrobenzylidene)-4-oxo-thiazolidin-3-yl]benzothiazole-6-carboxylic acid **(4g)**, 2-(5-Benzylidene-2-imino-4-oxo-thiazolidin-3-yl)benzothiazole-6-carboxylic acid **(4h)**.[26,27]



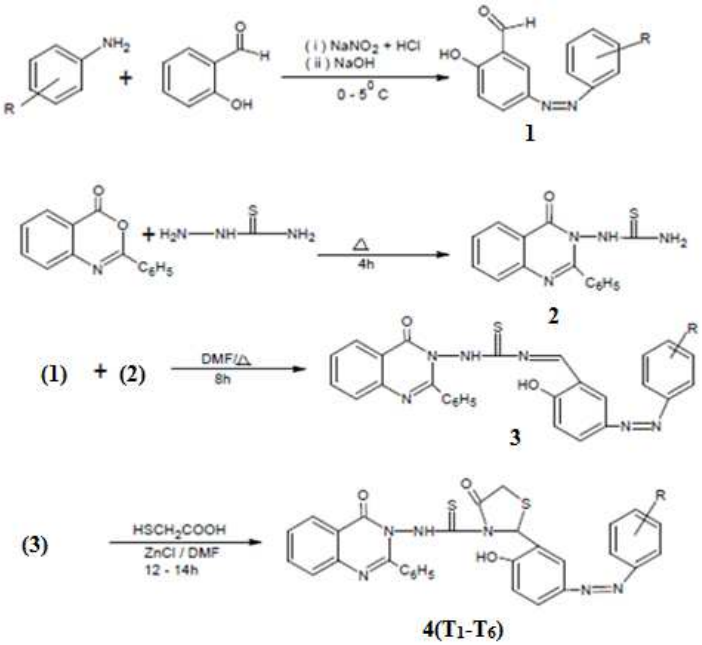
Structures of the compounds 4a-h, their melting points and yields of synthesis

Compound	Substituent Ar	M.P. ^{0}C	Yield %
4a	2-ClC_6H_4	255-257	61
4b	4-ClC_6H_4	248-250	59
4c	4-OHC_6H_4	244-246	69
4d	3-BrC_6H_4	278-280	58
4e	4-$OCH_3C_6H_4$	251-253	55
4f	3-$NO_2C_6H_4$	266-268	65
4g	4- $NO_2C_6H_4$	273-275	68
4h	C_6H_5	238-240	63

Scheme 1: Synthesis of 2-[5-(arylidene)- 2-imino-4-oxo-thiazolidin 3yl]benzothiazole-6-carboxylic acid (4a-h)

2. Method for the Synthesis of 2-(2 -hydroxy-5 (substitutedphenyldiazyl)-N-[(4-oxo -2-phenylquinazoline 3(4H) – yl)]-4-oxo 1, 3thiazolidine-1-carbothioamide 4(T1–T_6)

For the synthesis of titled compounds, substituted 1^0 amine were dissolved in aq. HCL acid and stirred at 0^0-5^0c. To cold solution, sodium nitrite was added drop wise to constantly stirred reaction mixture.



R-H, m-NO_2, p-NO_2, m- OCH_3, p-OCH_3, p-Cl

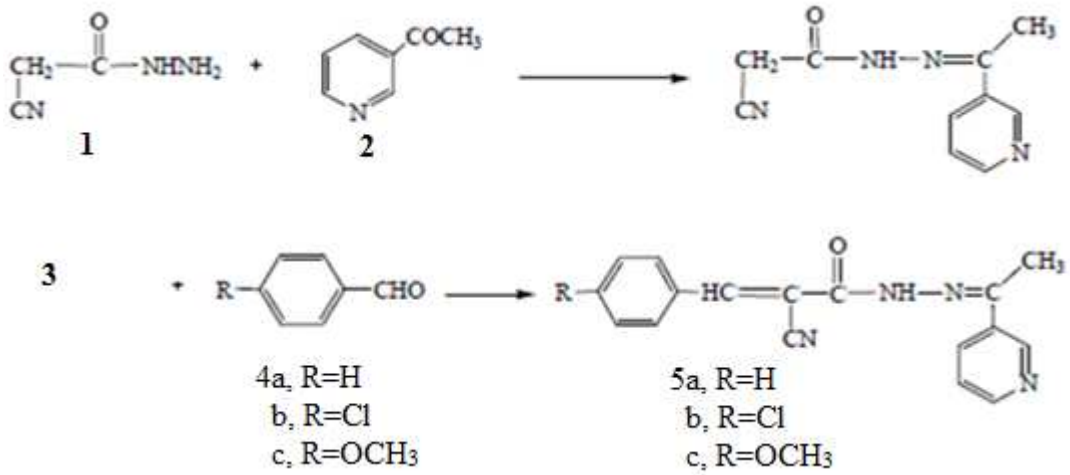
Scheme 2: Synthetic route of novel compounds

The diazotized solution was immediately added in small portion to salicylaldehyde with constant stirring substituted 2-hydroxyl 5-(phenyldiazenyl) benzaldehyde **(1)** formed. Quinazoline derivative of thiosemicarbazide **(2)** was prepared by reacting benzoylated anthranilic acid and thiosemicarbazide in the presence of ethanol. The reaction of equimolar quantities of **(1)** and **(2)** in the presence of DMF resulted in the formation of 1-(2-hydroxyl-5-(substituted phenyl) diazylbenzaldehyde-3-(4-oxo-2-phenyl quinazolin-3(4H)-yl) thiourea (**3**). The compounds **4(T_1-T_6)** i.e. 2-(2-hydroxy-5(phenyldiazyl)-N-[(4-oxo-2-phenylquinazolin 3(4H)-yl)]-4-oxo-1,3 thiazolidin-1-carbothiamide **(T_1)** , 2-(2-hydroxy-5(4-nitro phenyldiazyl)-N-[(4-oxo-2-phenylquinazolin 3(4H)-yl)]-4-oxo-1,3 thiazolidin-1-carbothiamide **(T_2)** , 2-(2-hydroxy-5(3-nitro phenyldiazyl)-N-[(4-oxo-2-phenylquinazolin 3(4H)-yl)]-4-oxo-1,3 thiazolidin-1-carbothiamide **(T_3)** , 2-(2-hydroxy-5(4-methoxy phenyldiazyl)-N-[(4-oxo-2-phenylquinazolin 3(4H)-yl)]-4-oxo-1,3 thiazolidin-1-carbothiamide **(T_4)** ,2-(2-hydroxy-5(3-methoxy phenyldiazyl)-N-[(4-oxo-2-phenylquinazolin 3(4H)-yl)]-4-oxo 1,3 thiazolidin-1-carbothiamide **(T_5)**, 2-(2-hydroxy-5(4chloro phenyldiazyl)-N-[(4-oxo-2-phenlquinazolin 3(4H)-yl)]-4-oxo 1,3 thiazolidin-1-carbothiamide **(T_6).**[28]

B. Anticancer activity:

1 (a). General method for the synthesis of 5(a), 5(b), 5(c)

The reaction of cyanoacetyl hydrazine **(1)** with 3-acetyl pyridine **(2)** in 1,4-dioxane to form hydrazide-hydrazone derivatives i.e. 2-cyano-N'-(1-(pyridine-3yl) ethylidene) acetohydrazide **(3)**.

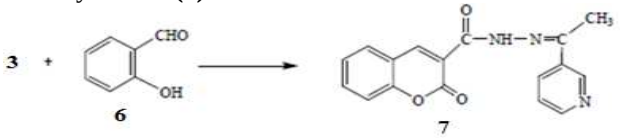


Scheme 1(a): Synthesis of Hydrazide-Hydrazone derivatives (5a-c)

Thus the reaction hydrazide- hydrazone derivatives **(3)** with either benzaldehyde **4(a)**, 4-chlorobenzaldehyde **4(b)**, 4-methoxybenzaldehyde **4(c)** gave the corresponding benzal derivatives i.e. 2-cyano-N'-(1-pyridin-3-yl) ethylidene) acrylohydrazide **5(a)**, 3-(4-chlorophenyl)-2-cyano-N'-(1-(pyridine-3-yl)-ethylidene) acrylohydrazide **5(b)**, 2-cyano-3-(4-methoxyphenyl)- N'-(1-(pyridin-3-yl)ethylidene) acrylohydrazide **5(c)**. [29]

1(b). Method for the synthesis of oxo-N'-(1-(pyridine-3-yl) ethyliene)-2H-chromene-3- carbohydrazide (7)

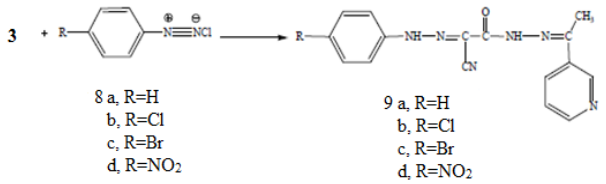
On the other hand, the reaction of compound **(3)** with salicyaldehyde **(6)** gave the coumarin derivative i.e. oxo-N'-(1-(pyridine-3-yl) ethyliene)-2H-chromene-3-carbohydrazide **(7)**.



Scheme 1(b): Synthesis of oxo-N'-(1-(pyridine-3-yl) ethyliene)-2H-chromene-3- carbohydrazide (7)

1(c). Method for the synthesis of Phenylydrazone derivatives (9a-d)

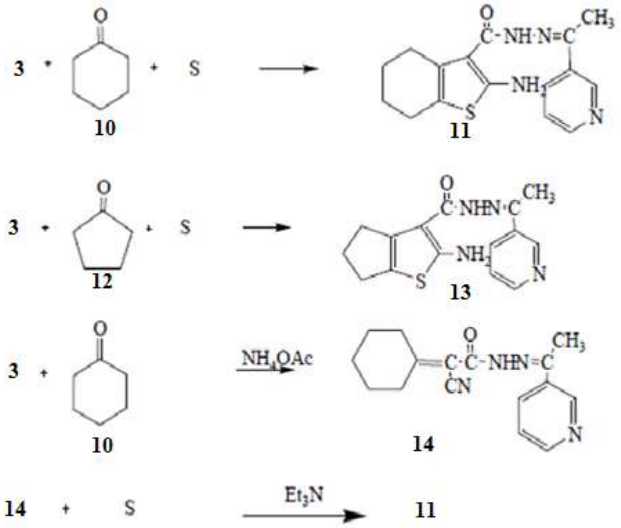
The reactivity of the active methylene group present in compound **(3)** towards diazonium salts. Thus, the reaction of **(3)** with either benzene diazonium chloride **8(a)**, 4-cholro benzene diazonium chloride **8(b)** , 4-bromo benzene diazonium chloride **8(c)** , 4-nitro benzene diazonium chloride **8(d)** gave the hydrazone derivatives i.e. 2-cyano-2(2-phenyl hydrazinylidene)-N'-[1-(pyridine-4yl)ethylidene] acetohydrazide **9(a)**, 2-[2-(4-chlorophenyl) hydrazinylidene]-2-cyano-N'-[1-(pyridine-4-yl) ethylidene] acetohydrazide **9(b)**, 2-[2-(4-bromophenyl) hydrazinylidene]- 2- cyano-N'-[1-(pyiridin-4-yl) ethylidene] acetohydrazide **9(c)**, 2-cyano-2-[2-(4-nitrophenyl) hydrazinylidene]-N'-[1-(pyridine-4-yl) ethylidene] acetohydrazide **9(d)**. [29]



Scheme 1(c): Synthesis of Phenylydrazone derivatives (9a-d)

1 (d). Method for the synthesis of tetrahydro benzo[b] thiophene derivative

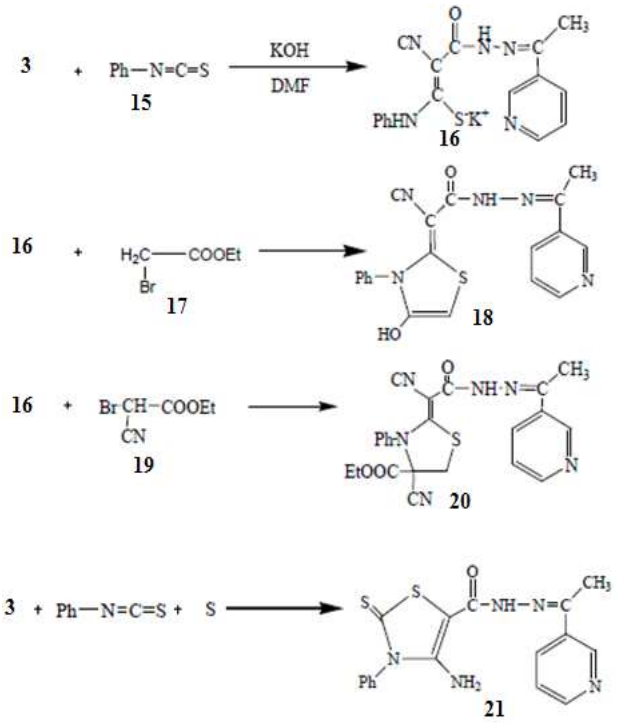
Moreover, the reaction of compound **(3)** with cyclohexanone **(10)** and elemental sulfur in the presence of triethylamine led to the formation of 4,5,6,7-tetrahydro benzo[b] thiophene derivative i.e. 2-Amino-4,5,6,7-tetrahydro-N'-[1-(pyridin-3yl) ethylidene) benzo[b] thiophene-3-carbohydrazide **(11)**. On the other hand, the reaction of compound **(3)** with cyclopentanone **(12)** and sulfur gave the cyclopentene[b] thiophene derivative **(13)**. Thus , the reaction of compound **(3)** with cyclohexanone in the presence of ammonium acetate in an oil bath at 140^0c gave the knoevenagel condensation product 2-cyano-2-cyclohexylidene-N'-(1-(pyridine-3yl)ethylidene) acetohydrazide **(14)**. The later reacted with elemental sulfur in the presence of triethylamine to produce the same tetrahydro benzo[b] thiophene derivative i.e. 2-Amino-4,5,6,7-tetrahydro-N'-[1-(pyridin-3yl) ethylidene) benzo[b] thiophene-3-carbohydrazide **(11)** .[29]



Scheme 1(d): Synthesis of tetrahydro benzo[b] thiophene derivative

1(e). Genral methods for the synthesis of Thiazole derivatives (18,20,21)

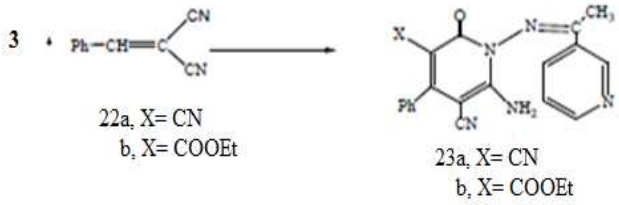
Thus compound **(3)** reacted with phenyl isothiocynate **(15)** in DMF/KOH solution at room temperature to give the intermediate Pot. Sulphide salt **(16)**. Heterocyclization of 16 with α-haloketone like ethyl bromoacetate **(17)** gave thiophene derivative i.e. 2-(4-hydroxy-3-phenyl thiazol-2(3H)-ylidene)-2-isocyano-N'-(1-(pyridine-3-yl)ethylidene) acetohydrazide **(18)**. In the similar way, the reaction of **(16)** with ethyl bromocyanoacetate **(19)** gave thiazole derivative (2-Z) ethyl-2(1-(pyridine-3-yl) ethylideneaminocarbamoyl) (cyano) methylene)-4-cyano-3-phenylthiazolidine-4-carboxylate **(20)**. Furthermore, compound 3 reacted with phenyl isothiocyanate and elemental sulfur in 1,4-dioxane containing triethylamine to give thiazole derivative i.e. 4-Amino-2,3 dihydro-3-phenyl-N'-(1-(pyridine-3-yl)ethylidene)-2-thioxothiazolo-5-carbohydrazide **(21)** .[29]



Scheme 1(e): Synthesis of Thiazole derivatives (18,20,21)

1(f). Method for the synthesis of 23(a,b)

Thus, the reaction of 3 with either 2-benzylidene malonitrile 22(a) or ethyl 2-cyano-3-phenylacrylate 22(b) gave the pyridine derivatives 1-(1-phenylethylideneamino)- 6-amino-1,2-dihydro-2-hydroxy-4-phenylpyridine-3-carboxylate 23(a) and ethyl-1-(1-

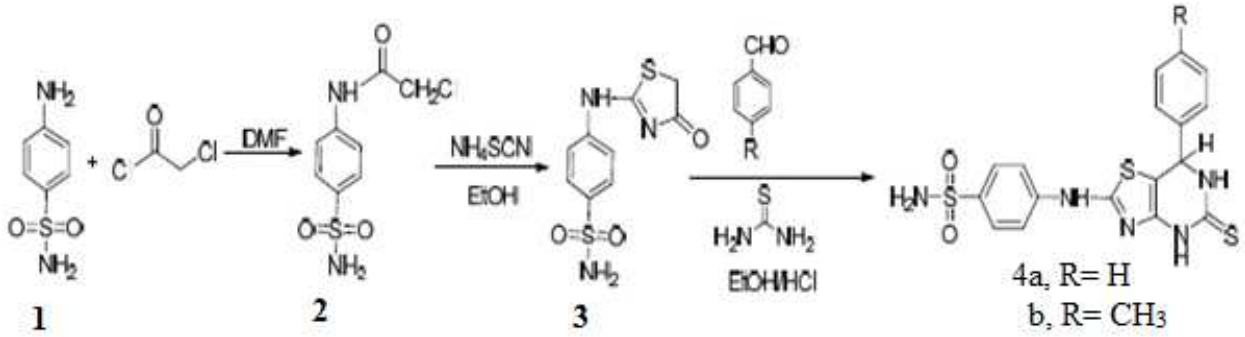


Scheme 1(f): Synthesis of 23(a-b)

Phenylethylideneamino)-6-amino-5-cyano-1,2-dihydro-2-hydroxy-4-phenylpyridine-3-carboxylate **23(b)**. [29]

2(a). Method for the synthesis of thiazolopyrimidine derivatives (4a,b)

The sulphonamide **(1)** reacted with chloroacetyl chloride furnished, 2-chloro-N-(4-sulfamoyl phenyl) acetamide **(2)** which was reacted with ammonium thiocynate in ethanol under reflux to give a strategic starting material 4-(4-oxo-4,5 dihydrothiazole-2yl amino) benzene sulfonamide **(3)**.[29]

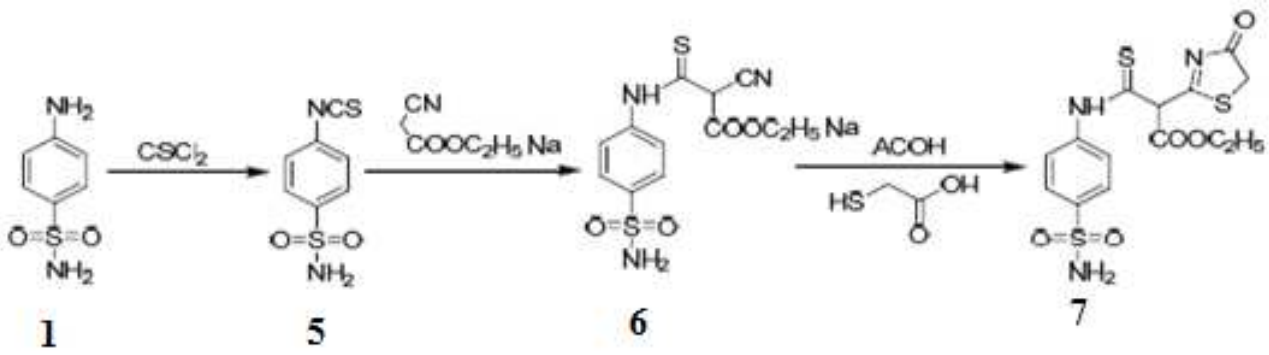


Scheme 2(a): Synthesis of thiazolopyrimidine derivatives (4a-b)

By interaction of compound (3) with thiourea and aromatic aldehyde in ethanol containing few drops of HCl through cyclization the thiazolopyrimidine derivatives i.e. 4-(7-phenyl-5-thioxo-4,5,6,7-tetrahydrothiazolo[4,5-d] pyrimidin-2-yl amino) benzenesulfonamide 4(a) and 4-(5-thioxo-7-p-tolyl-4,5,6,7-tetrahydrothiazolo [4,5-d] pyrimidin-2yl amino) benzenesulfonamide 4(b) were obtained via Bignelli reaction [30].

2(b). Method for the synthesis of ethyl 2-(4-oxo-4,5-dihydrothiazol-2-yl)-3-(4-sulfamoyl phenylamino)-3-thioxopropanoae (7)

The treatment of sulphonamide (1) with thiophosgene to get the starting material 4-isothiocyanatobenzene sulfonamide (5). Reaction of compound (5) with ethylcyanoacetae sodium salt yielded ethyl 2-cyano-3-(4-sulfamoylphenylamino)-3-thioxopropanoate (6).

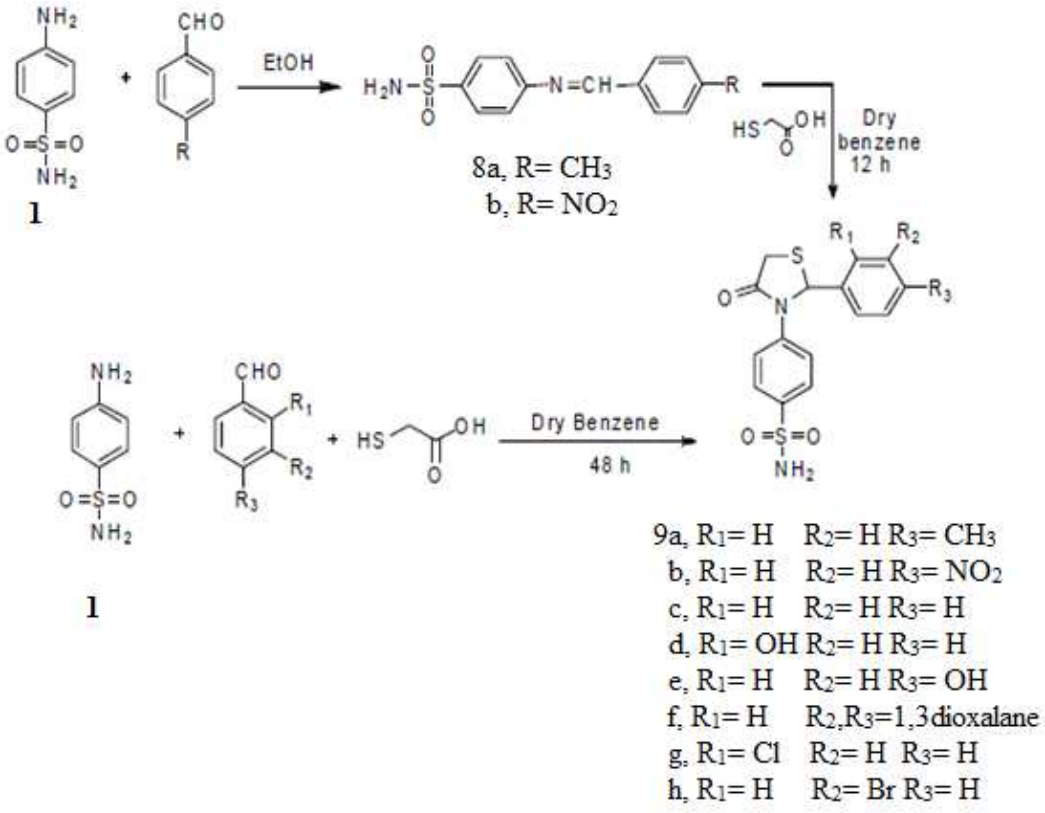


Scheme 2(b): Synthesis of ethyl 2-(4-oxo-4,5-dihydrothiazol-2-yl)-3-(4-sulfamoyl phenylamino) -3-thioxopropanoae (7)

which upon reflux with thioglycolic acid in the presence of acetic acid yielded the corresponding ethyl 2-(4-oxo-4,5-dihydrothiazol-2-yl)-3-(4-sulfamoyl phenylamino)-3-thioxopropanoae (7) [30].

2(c). Method for the synthesis of thiazolidinone derivatives 9(a-h)

The formation of 4-oxothiazolidine i.e. 4-(4-oxo-2-p-tolylthiazolidin-3-yl) benzenesulfonamide 9(a), 4-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl) benznesulfonamide 9(b) was obtained by two step reaction through the formation of schiff's base, by refluxing sulfanilamide with corresponding aldehyde in absolute ethanol.

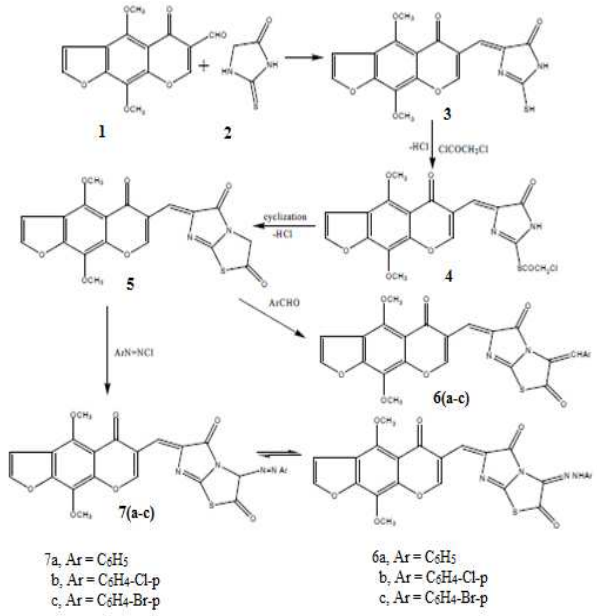


Scheme 2(c): Synthesis of thiazolidinone derivatives 9(a-h)

The formation of thiazolidinones i.e. 4-(4-oxo-2-p-tolylthiazolidin-3-yl) benzenesulfonamide 9(a), 4-(2-(4-nitrophenyl)-4-oxothiazolidin-3-yl) benzenesulfonamide 9(b), 4-(4-oxo-2-phenyl thiazolidin-3-yl) benzenesulfonamide 9(c), 4-(2-(2-hydroxy phenyl)-4-oxothiazolidin-3-yl) benzenesulfonamide 9(d), 4-(2-(4-(hydroxyphenyl)-4-oxothiazolidin-3-yl) benzenesulfonamide 9(e), 4-(2-(Benzo[d][1,3] dioxol-5-yl)-4-oxothiazolidin-3-yl) benzenesulfonamide 9(f), 4-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl) benzenesulfonamide 9(g), 4-(2-(3-Bromophenyl)-4-oxothiazolidin-3-yl) benzenesulfonamide 9(h) was continued by refluxing the schiff's base with thioglycolic acid in dry benzene for additional 12h. In addition, one pot reaction can be conducted via refluxing sulfanilamide (1) with the required aldehyde and thioglycolic acid in dry benzene for 48h[30].

3(a). Method for the synthesis (3E,6Z)-3-(aryl-hydrazone)-6-[(4,9-dimethoxy-5-oxo-5Hfuro[3,2-g]chromen-6-yl)methylene]imidazo[2,1-b]thia-zole-2,5(3H,6H)-dione derivatives (7a-c)

The condensation of of 4,9 dimethoxy-5-oxo-5H-furo[3,2-g] benzopyran-6-carboxylate **1** [31,32]with 2-thio-4-imidazolinone **2** to give (4Z)-2-mercapto-4-[(4,9 dimethoxy-5-oxo-5-H-furo[3,2-g] chromen-6-yl)methylen]-1-H-imidazol-5-(4H)-one **3**. Treatment of 3 with α-chloroacetyl chloride gave S-(4Z)-4, 5-dihydro-4-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl) methylen]-1H-imidazol-2-yl-2-chloro-ethanethioate **4**. When compound **4** was heated with acetic anhydride, cyclization took place, and (6Z)-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl) methylen] imidazo [2,1-b] thiazole-2,5 [3H,6H]-dione **5** was obtained via loss of HCL.

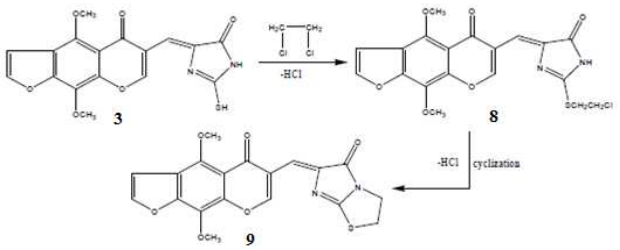


Scheme 3(a): Synthesis (3E,6Z)-3-(aryl-hydrazone)-6-[(4,9-dimethoxy-5-oxo-5Hfuro[3,2-g]chromen-6-yl)methylene]imidazo[2,1-b]thia-zole-2,5(3H,6H)-dione derivatives (7a-c)

Moreover, compound **(5)** having an active methylene group was condensed with aromatic aldehydes (benzaldehyde,chlorobenzaldehyde, bromobenzaldehyde) in glacial acetic acid in the presence of fused sodium acetate at 140^0c to give (3E,6Z)-3-benzylidene)-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl) methylen] imidazo [2,1-b] thiazole-2,5-[3H,6H]-dione **6(a)**, (3E,6Z)-3-(7-chlorohepta-2,4,6-trinylidene)-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl) methylen] imidazo [2,1-b] thiazole-2,5-[3H,6H]-dione **6(b)**, (3E,6Z)-3-(7-bromohepta-2,4,6-trinylidene)-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl) methylen] imidazo [2,1-b] thiazole-2,5-[3H,6H]-dione Compound **5** reacted in sodium hydroxide solution with aromatic diazonium compounds to give (6Z)-3-(2-phenyldiazenyl)-6-[(4,9-dimethoxy-5-oxo-5H-furo [3,2-g]-chromen-6-yl)methylen)imidazo [2,1-b] thiazole-2,5[3H,6H]-dione **7(a)**, (6Z)-3-(2-(6-chlorohexa-1,3,5-triynyl) diazenyl)-6-[(4,9-dimethoxy-5-oxo-5H-furo [3,2-g]-chromen-6-yl)methylen)imidazo [2,1-b] thiazole-2,5[3H,6H]-dione **7(b)**, (6Z)-3-(2-(6-bromohexa-1,3,5-triynyl) diazenyl)-6-[(4,9-dimethoxy-5-oxo-5H-furo [3,2-g]-chromen-6-yl)methylen)imidazo [2,1-b] thiazole-2,5[3H,6H]-dione **7(c)**. [31,32,33]

3(b). Method for the synthesis of compound 9

The work was further extended to investigate the behaviour of **3** with 1,2 dichloroethane to give (4Z)-2-(2-chloroethylthio)-4-[(4,9-dimethoxy-5-oxo-5H furo[3,2-g] chromen-6-yl) methylene]-1H-imidazol-5(4H)-one **8.**



Scheme 3(b): Synthesis of compound 9

Which upon crystalization with acetic anhydride gave (6Z)-2,3-dihydro-6-[(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl)methylen]imidazo[2,1-b] thiazol-5(6H)-one **9** by elimination of HCl [31,32,33].

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