Part –V: Utilities of Active Methylene Compounds and Heterocycles Bearing Active Methyl or having an Active Methine in the Formation of Nitrogenous Heterocycles Having oxygen or sulfur atom

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Abstract

Most of the common and novel synthesized active methylene compounds as well as heterocycles bearing active methyl or having methine site were used in the syntheses of wide variety of five-, six- and seven-membered azaheterocyclic systems having oxygen or sulfur atom in their structures in addition to some oxygenated heterocycles such as pyrans. Many synthetic approaches were used for the preparation of target heterocyclic systems such as cyclocondensation reactions, ring opening-ring closure, cycloaddition, acid-, base-catalyzed reaction, intermolecular cyclization and self-condensation as well as ring–chain tautomerism has been reviewed in this paper.

Keywords: Active methylene, Isoxazles, Thiazoles, Oxadiazoles, Thiadiazoles, Thiazines, Pyrans, Oxazepines, Thiazepines

Introduction

Common and novel synthesized active methylene compounds are useful as a versatile synthetic building block for a variety of functional and pharmacologically active substances. Motivated by this fact and during the last three decades, our work was focused on the use of common and novel synthesized acyclic active methylene compounds as well as heterocycles that having active methyl and methine groups in the formation of some Five-, Six-, and Seven-Memberd azaheterocyclic systems having oxygen or sulfur atom in their structures and evaluated their biological activities.

1. Synthesis of Five-Memberd nitrogenous heterocycles with oxygen or sulfur atom

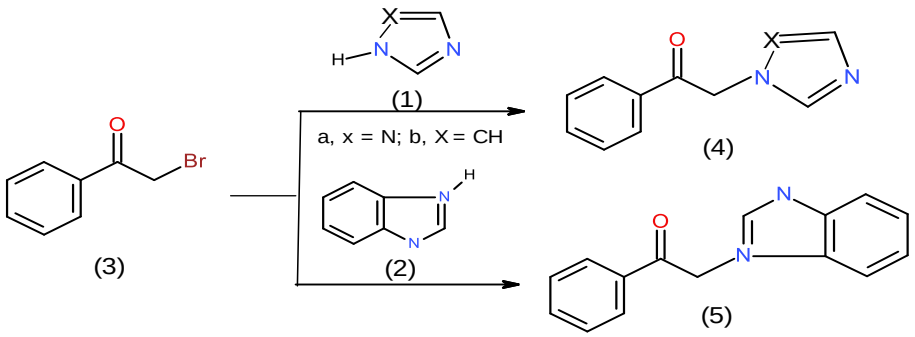
Some important five-memberd nitrogenous heterocycles with oxygen or sulfur atom such as isoxazles, thiazoles, oxadiazoles and thiadiazoles as well as thiophene and benzofuran were prepared with the help of the common and novel synthesized acyclic or cyclic active methylene compounds as well as heterocycles having active methyl or methine site in their structures.

1.1. Isoxazole formation

Isoxazole rings are found in some natural products such as ibotenic acid. They also form the basis of drugs including the COX-2 inhibitor valdecoxib, lactamase-resistant antibiotic such as cloxacillin and flucloxacillin. The synthetic androgenic steroid danazol also has an isoxazole ring (Crossley & Browne, 2010). Diverse applications associated with isoxazole moiety led us to develop various synthetic approaches for the formation of them. Most of the newly synthesized isoxazoles afforded through the interaction of hydroxylamime with some prepared compounds, these are:

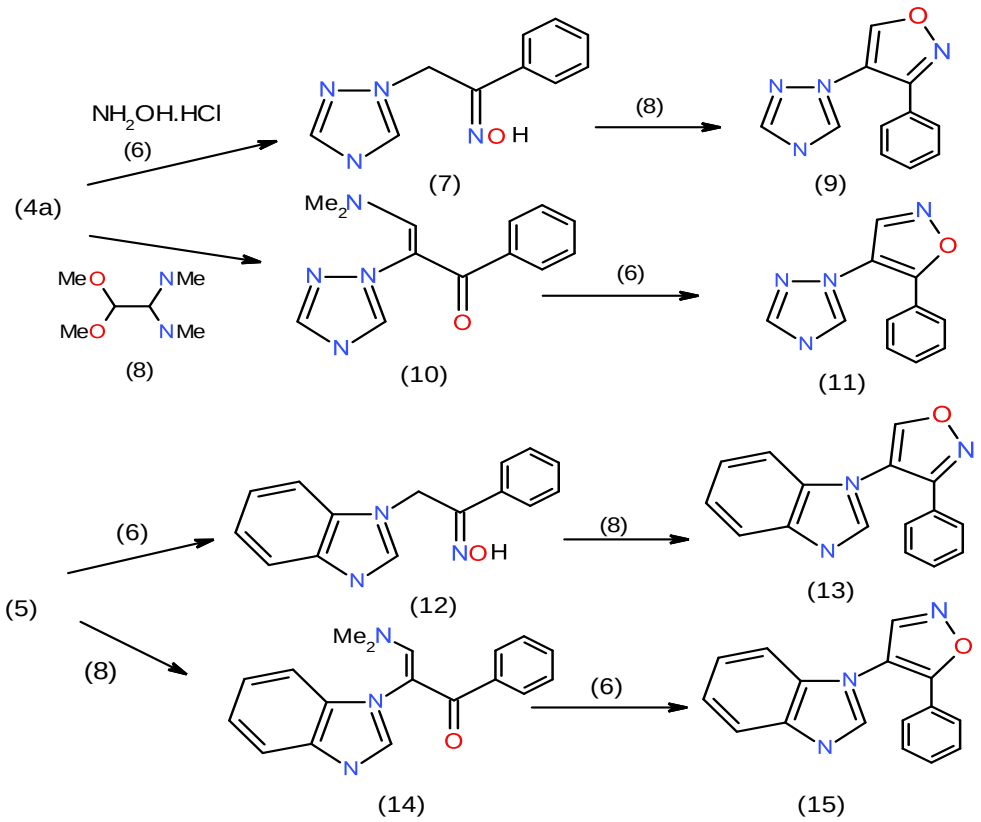
1.1.1. Acetophenone derivatives

Alkylation of 1,2,4-triazole (**1a**), imidazole (**1b**) and benzimidazole (**2**) with phenacyl bromide (**3**) led to the formation of three active methylene compounds, 1,2,4-triazolylacetophenone **(4a),** imidazolylacetophenone **(4b)** and benzimidazolylacetophenone **(5)**, respectively (Mohamed Abdel-Megid, Elnagdi, & Negm, 2002) (Scheme 1).



Scheme 1: formation of azolyl acetophenones

Two isomertic isoxazolylazoles were obtained from azolylacetophenones **4** and **5**. Thus, when 1,2,4-triazolylacetophenone (**4a**) condensed with hydroxylamine hydrochloride (**6**), the oxime **6** was produced, which underwent cyclocondensation reaction on treating with dimethylformamide dimethylacetal (DMFDMA) (**8**) to afford isoxazoletriazole **9.** Whereas its isomeric form **10** was formed via the reaction of the enaminone **9,** obtained from condensation of **4a** with DMFDMA, with hydroxylamine hydrochloride (Mohamed Abdel-Megid et al., 2002). Similar behavior on benzimidazolylacetophenone (**5**) took place and the two isomeric isoxazolylbenzimidazoles (**13**) and (**15**) were obtained (Scheme2).

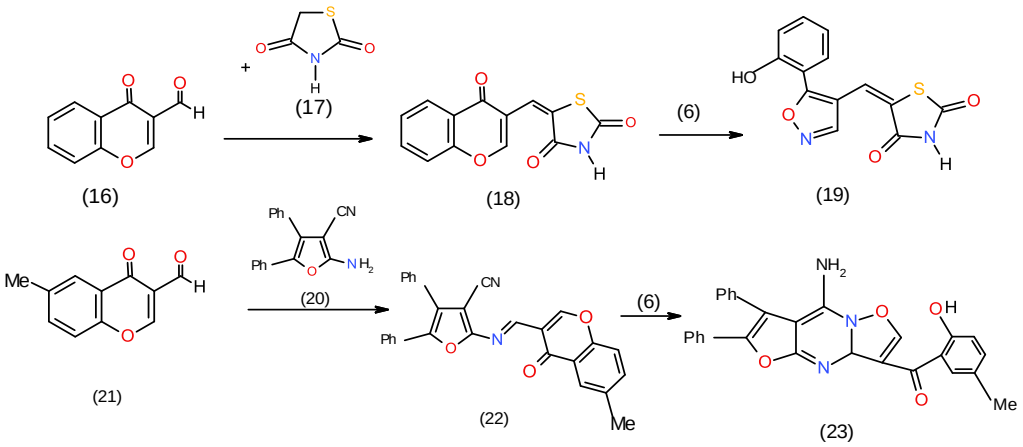


Scheme 2: Formation of azolyl isoxazole derivatives

1.1.2. Chromone derivatives

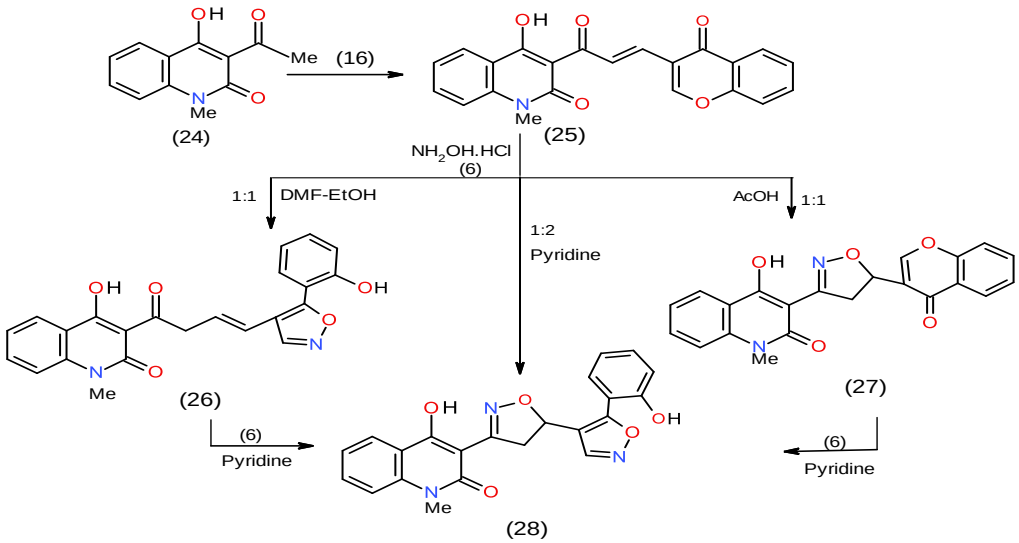
Interestingly, it has been found that the C-2 of chromone is an active site with methine and when it attached by a nitrogenous nucleophile such as hydroxyl amine ring-opening of the ɤ-pyron followed by ring closure reaction took place giving rise to the target isoxazole. Thus, Knoevenagel condensation of 3-formylchromone (**16)** with thiazolidine-2,4-dione (**17**) furnished 3-chromenyl- methylidenethiazolidinedione **18,** which reacted with an equimolar amount of hydroxylamine hydrochloride (**6**) in ethanolic sodium hydroxide solution to yield 4-

isoxazolylmethylidene- thiazolidinedione **19** (Ibrahim, Abdel-Hamed, & El-Gohary, 2011). Also, when 2-(6-methyl4-oxochromeny-3-yl) methylideneamino-4,5-diphenylfuran-3-carbonitrile **(22**), obtained from the condensation of 2-aminofurancarbonitrile (**20**) with 6-methyl-3-formylchromone (**21**), was allowed to react with hydroxylamine hydrochloride (**6**) in boiling pyridine–water mixture, a nitrogen bridge-head triheterocyclic system having isoxazole ring in its structure **23** was produced by the same manner explained for the compound having chromone nucleus (M. Abdel-Megid, Elkazak, Seada, & Farouk, 2010). (Scheme 29).



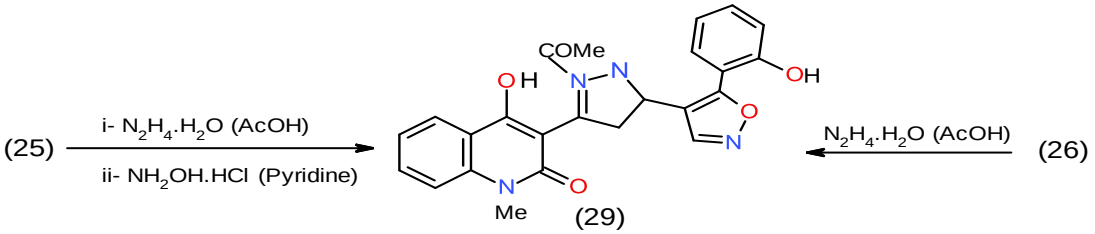
Scheme 3: Formation of substituted and fused isoxazoles

The addition of hydroxyl amine to the enone **25,** which formed by condensation of 3-formylchromone (**16**) with 3-acetylquinolone (**24**) is depend on reaction medium and molar ratio. When compound **25** was subjected to react with equimolar amount of hydroxylamine hydrochloride (**6**) in boiling DMF-ethanol mixture, the isoxazolyl derivative **26** was produced but when the reaction was carried out in glacial acetic acid it proceeds in a completely different manner and isoxazolylquinolone **27** was obtained. The reaction of both **26** and **27** with hydroxylamine hydrochloride in boiling pyridine gave the biisoxazolylquinolone **28** which could be also obtained by reaction of compound **25** with excess with hydroxylamine (1:2 ratio) hydrochloride in boiling pyridine (Abass, Abdel-Megid, & Hassan, 2007) (Scheme 4).



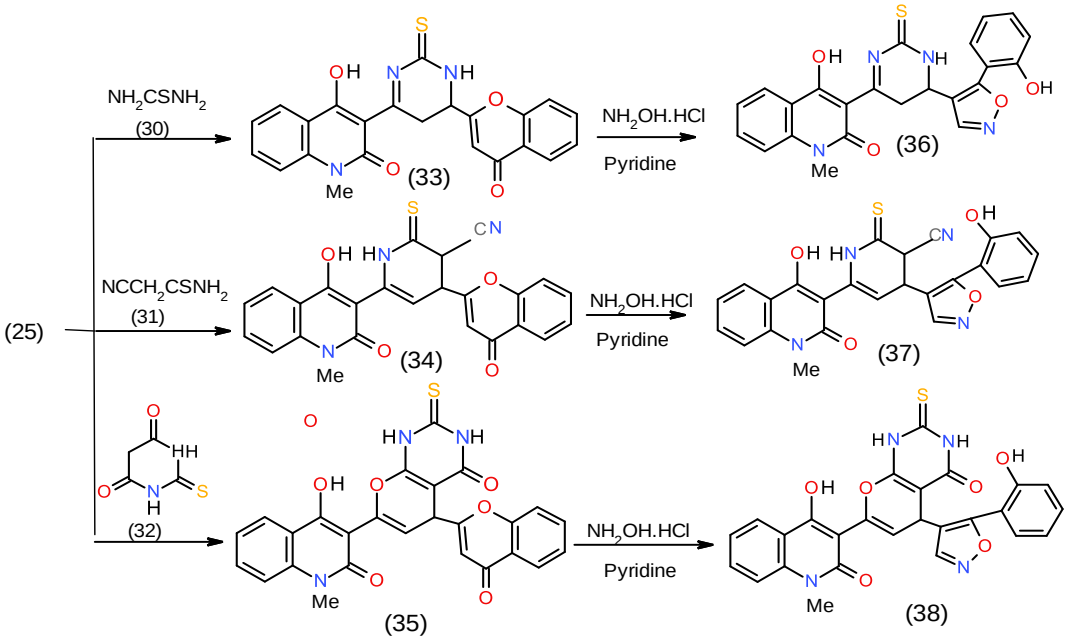
Scheme 4: Formation of bi-isoxazolyl quinolinones

Moreover, treatment the enone **25** with hydrazine hydrate in glacial acetic acid followed by addition of hydroxylamine hydrochloride in dry pyridine afforded pyrazolylisoxazolylquinoli- none **29,** which can be also obtained on addition of hydrazine hydrate to **26** in glacial acetic acid (Abass et al., 2007) (Scheme 5).



Scheme 5 Formation of pyrazolylisoxazolyl quinolinone

Addition of thiourea (**30**), cyanothioacetamide **(31)** and 2-thiobabarbituric acid (**32**) to α, β-unsaturated carbonyl center of compound **25** in boiling ethanol containing piperidinium acetate yielded, pyrimidinethione **33**, thioxopyridinecarbonitrile **34** and pyranopyrimidinethione **35**, respectively. Isoxazoles carrying pyrimidinethione **36,** pyridinecarbonitrile **37** and pyrano- pyrimidinethione **38** were produced when hydroxylamine hydrochloride (**6**) reacted with **33, 34** and **35**, respectively (Abass et al., 2007) (Scheme 6).

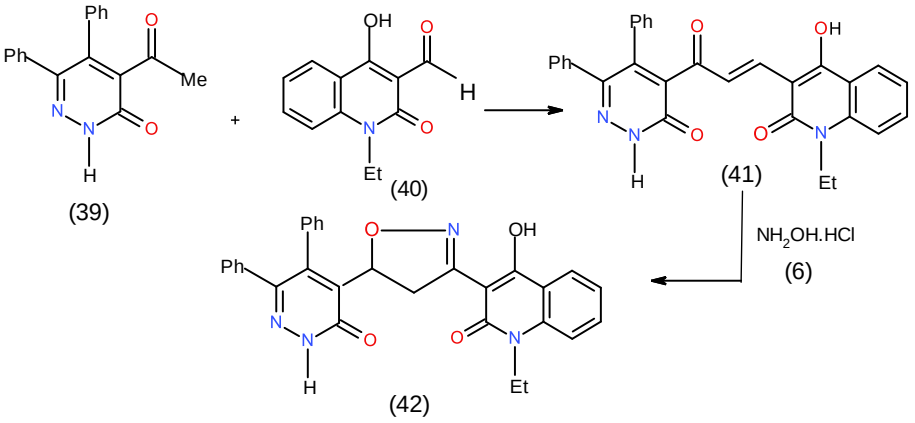


Scheme 6: Formation of isoxazole from chromone derivatives

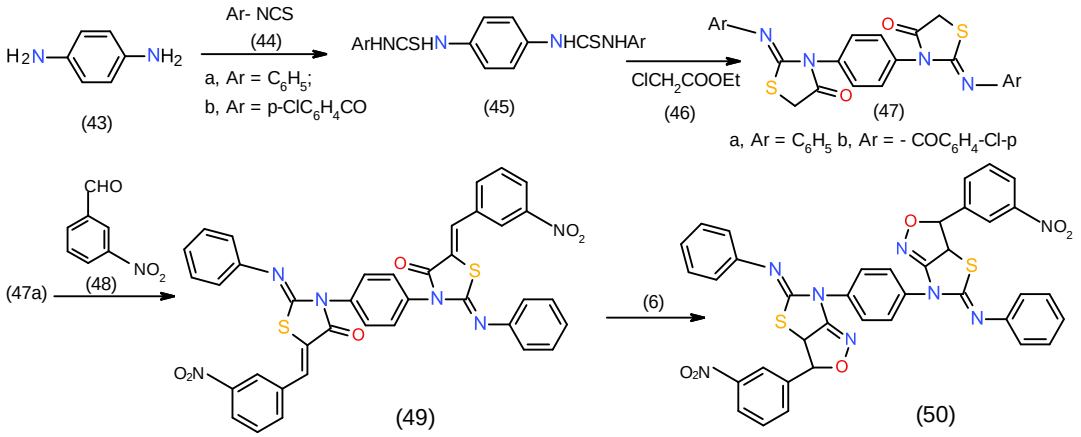
1.1.3. Synthesized enone does not have chromone

A novel diheterocyclic enone **41** was synthesized from the condensation of 4-acetylpyridazinone **39** with 3-formylquinolone **40** was prepared and used as starting material for thr synthesis isoxazole and other heterocyclic systems . Thus, pyridizinylquinolyinylisoxazole **42** obtained by treating the enone **41** with hydroxylamine hydrochloride (6) (M. Abdel-Megid, 2006) (Scheme 7).

On the other hand, when p-phenylenediamine (**43**) was subjected to react with both phenyl isothiocyanate (**44a)** and p-chlorobenzoyl isothiocyanate (**44b**), the respective p-bisthiourido derivatives **45a, b** was formed. Treatment of **45a, b** with ethyl chloroacetate (**46**) afforded the bis-thiazolidinone **47a, b.** Condensation of **47a** with m-nitrobezaldehyde (**48)** yielded the cylic enone **49**. The action of hydroxylamine hydrochloride upon **49** gave p-bis(isoxazolothiazolidine) phenylenes (**50**) (M. Abdel-Megid & M.A.A. Awas, 2002) (Scheme 8)**.**

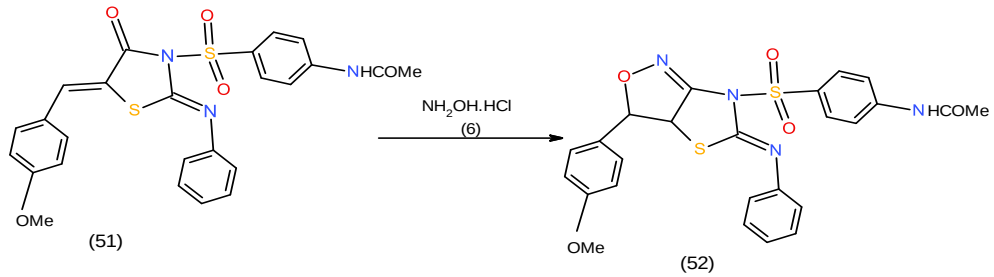


Scheme 7: Formation of biheterocyclylisoxazole



Scheme 8: Formation of p- bis-isoxazolothiazolidinyl phenylene

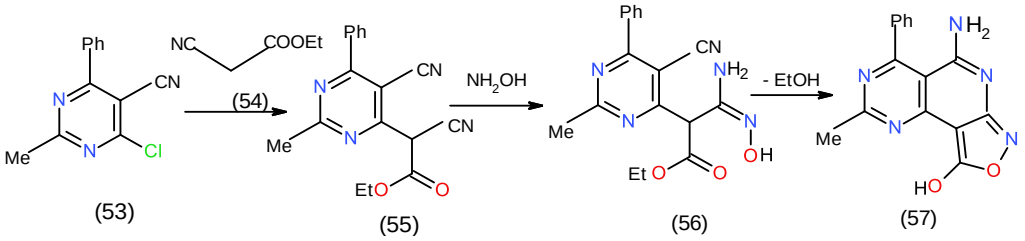
Moreover, cyclocondensation of hydroxylamine hydrochloride (6) with 5-Arylidene-2-phenyliminothiazolidinone **51,** in boiling ethanol (Gabr, Abdel-Megid, Awas, & Abdel-Fatah, 2010) afforded thiazoloisoxazole derivative **52** (Scheme 9).



Scheme 9: formation of thiazoloisoxazole

1.1.4. Ethyl cyanoacetate derivative

Treatment of chloropyrimidinecarbonitrile **53** with ethyl cyanoacetate **54** afforded the ethyl cyanoacetate derivative **55.** The action of hydroxylamine hydrochloride upon **55** in refluxing ethanol led to the formation of the oxime **56**, which underwent ring closure on heating with sodium ethoxide to give pyrimidopyridoisoxazole **57** (M. Abdel-Megid, 1995) (Scheme 34).



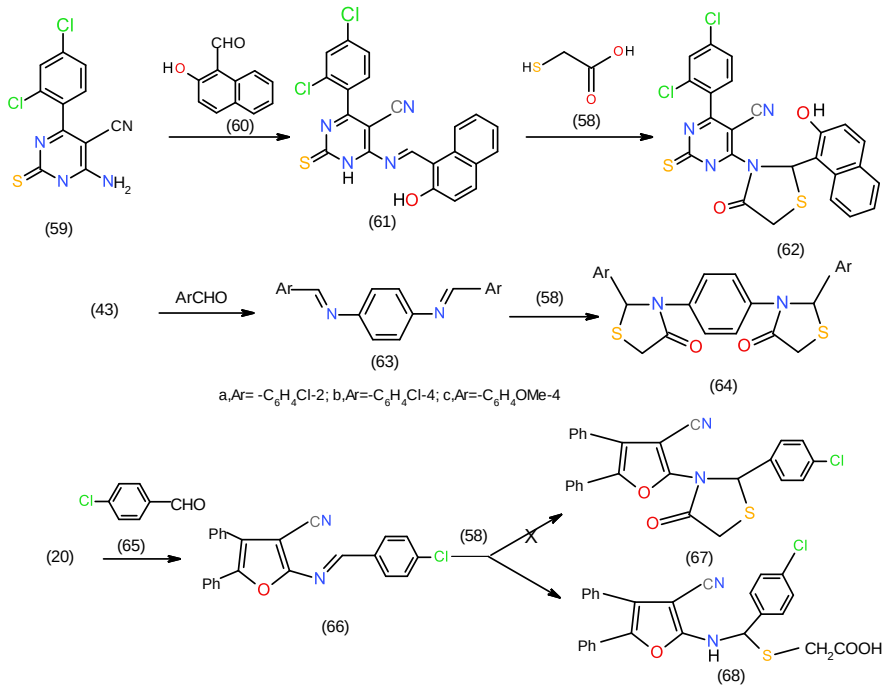
Scheme 10: Formation of isoxazolylpyridopyrimidine

1.2. Thiazole formation

Recently, various synthetic strategies for thiazolidinone derivatives as well as their biological significance were summarized in a review (Kaur Manjal et al., 2017). The 1,3-thiazolidin-4-ones possess wide range of pharmacological activities such as anti-cancer, anti-diabetic, anti-microbial, anti-viral, anti-inflammatory (Lakhan & Singh, 1991) and anti-convulsant. In view of the varied physiological activities of thiazolidiones (el-Feky & Abd el-Samii, 1995), it was of interest to synthesized thiazole derivatives of a potential biological activities using active methylene compound such as thioglycollic acid (**58**), haloacetic acid or its ethyl ester (**46**) and phenacyl bromide (**3**).

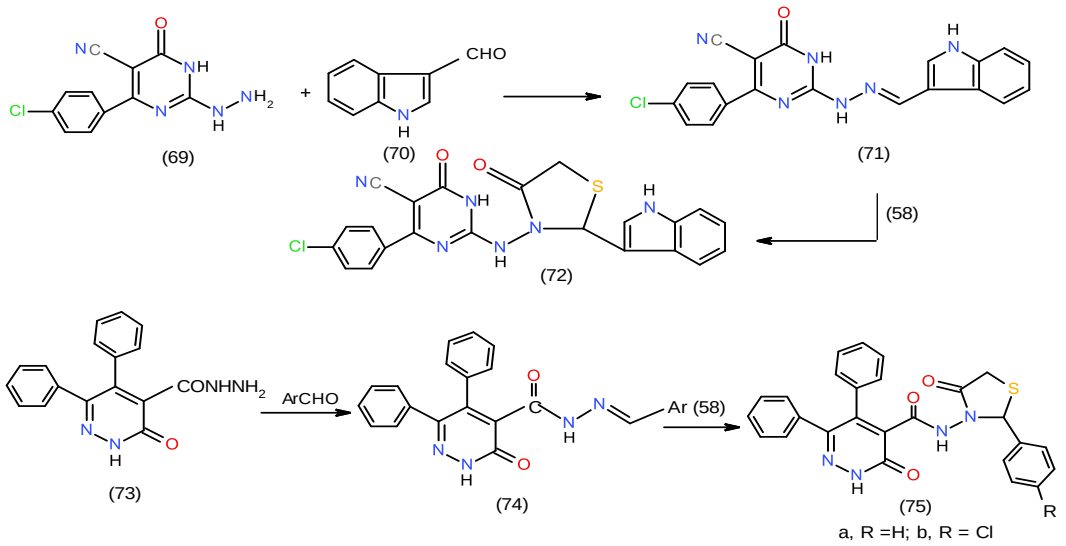
1.2.1. Thioglycollic acid

Thioglycollic acid (**58**) is often called mercaptoacetic acid. It contains both a thiol (mercaptan) and carboxylic acid functional groups in addition to active methylene center. Cycloaddition of thioglycollic acid to C=N of arylideneamino group afforded the target thiazolidinone. Thus, condensation of 4-aminopyrimidinecarbonitrile (**59**) with 1-formyl-2-naphthol (60) yielded 4-arylideneaminopyrimininethione **61,** which submitted to react with thioglycollic acid **(58)** to afford thioxopymidinylthazolidinone **62** (M. Abdel-Megid, Abdel-Rahman, & Ali, 1998). Also, condensation of p-phenylenediamine (**43**) with some aromatic aldehydes furnished the respective p-bis(arylidineamino)phenylenes **63a-c**, which underwent cycloaddition with thioglycollic acid in dry solvent to give p-bis(arylthiazol- idinyl)phenylenes **64 a-c,** respectively (M. Abdel-Megid & M.A.A. Awas, 2002). The action of thioglycollic acid (**58**) in dry dioxane upon p-chlorobenzylideneaminofuran **67**, which obtained from the condensation of 2-amino- furancarbonitrile **20** with p-chlorobenzaldehyde **65** not gave the target thiazolidinone **67** but compound **68** was obtained (M. Abdel-Megid, Elkazak, et al., 2010) (Scheme 11).



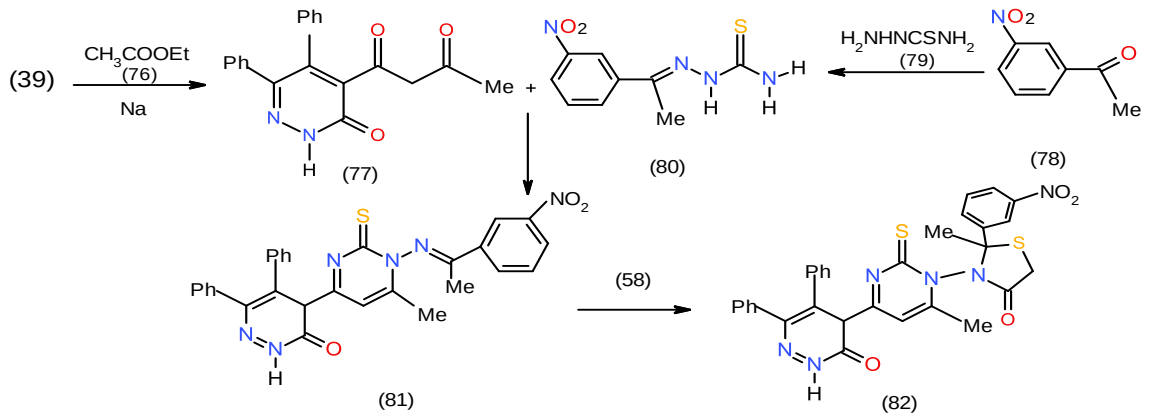
Scheme 11: Addition of Thioglycollic acid on arylideneamino derivatives

Furthermore, the same action was observed in case of arylidene hydrazide or arylidene carbohydrazide. Therefore, 2-hydrazinopyimidine **69** with 3-formylindole (**70**) gave the hydrazone **71,** which on reacting with thioglycollic acid (**58**) in dioxane yielded indolylthiazol- idinylaminopyrimidine **72** (M. Abdel-Megid, Awas, Seada, Elmhdy, & Elsayed, 2010). Also, cycloaddition of thioglycollic acid (**58**) on arylidene- carbohydrazides **74a, b** obtained from condensation of **73** with aromatic aldehydes afforded the corresponding thiazolidenone derivatives **75a, b** (M. Seada, Fawzy, Jahine, Abd El-Megid, & Saad, 1989) (scheme 12).



Scheme 12: Thiazolidinone formation

Synthesized active methylene compound namely, pyridazinyl-butan-1,3-dione **77** was obtained from the reaction of 4-acetylpyridazinone **39** with ethyl acetate (**76**) under clasein condensation (M. Abdel-Megid, Gabr, Awas, & Abdel-Fatah, 2009). Reaction of compound **77** with acetophenonethiosemicarbazone **80** prepared by the condensation of p-nitroacetophenone (**78**) with thiosemicarbazide (**79)** afforded thioxopyrimidinylpyridazinone **81**. Addition of thioglycollic acid (**58**) to **81** in dry benzene cyclocondensation took place giving rise to thiazolidinylpyrimidinylpyridazinone **82** (M. Abdel-Megid et al., 2009) (Scheme 13).

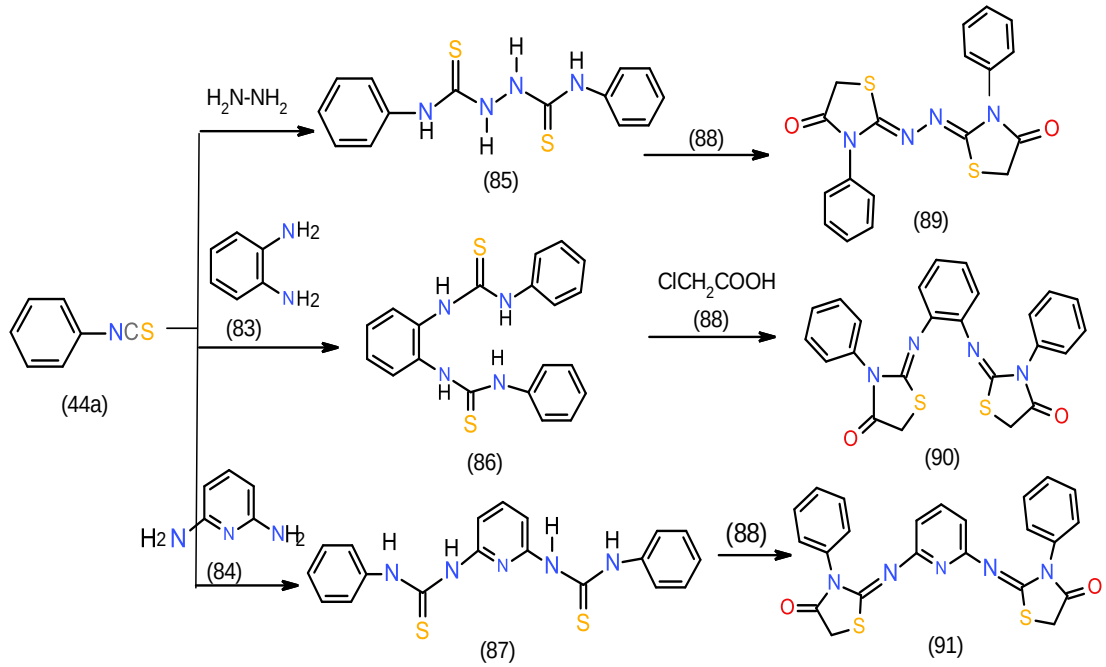


Scheme 13: Formation of thiazolidinylpyrimidinylpyridazinone

1.2.2. Haloacetic acid and its ethyl ester.

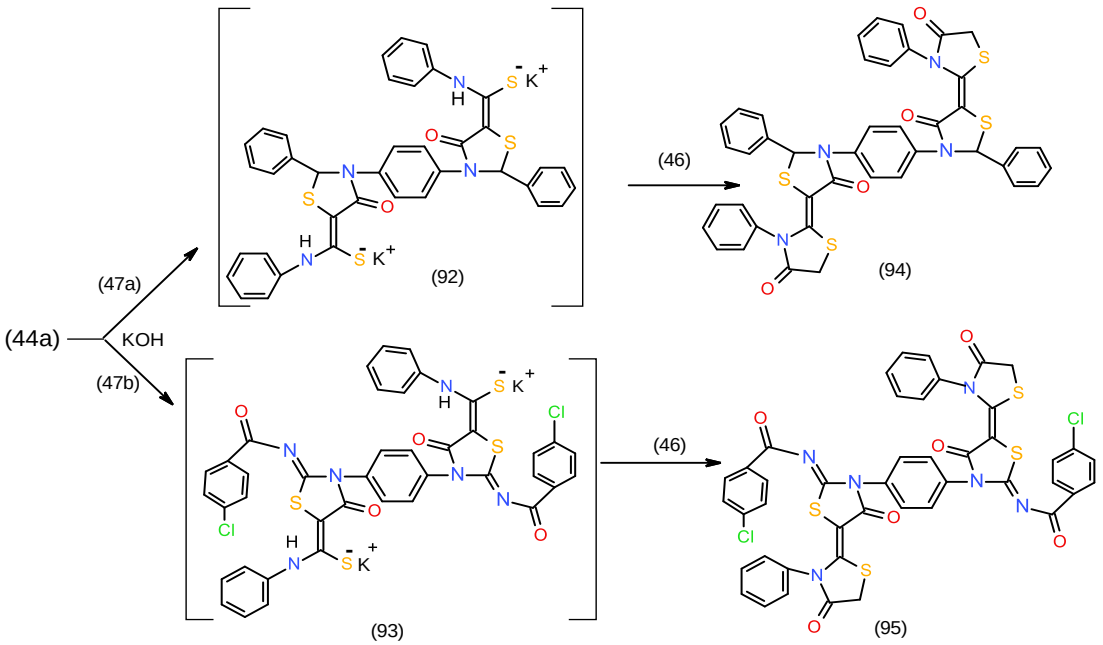
Addtion of isothiocyanate to amines or to active methylene center afforded thiourea derivatives, which underwent cyclocondensation with haloacetic acid and its ethyl ester to yield the target thiazolidinones, Thus, addition of phenyl isothiocyanate (**44a**) to hydrazine hydrate, o-phenylene- diamine (**83**) and 2,6-diaminopyridine (**84**) afforded bis(N-phenyl) thiourea (**85**), 1,2-bis(N-phenylthioureido) benzene (**86**) and 2,6-

bis(N-phenylthioureido) pyridine (**87**), respectively (Seada M., Abdel-Rahman M. R., & Abdel-Megid M., 1993). When the monochloroacetic acid (**88**) was allowed to react with bis(N-phenyl) thioureas **85-87**, the corresponding bis thiazolidinone derivatives **89-91** were obtained (M. Seada et al., 1989) (scheme 38).



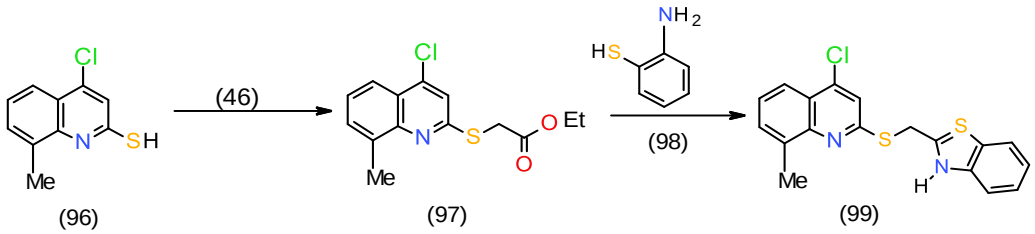
Scheme 14: Formation of bis-thiazolidinones

Moreover, the tetra-thiazolidinones **94** and **95** were formed via the action of phenyl isothiocyanate (**44a**) upon **47a, b** in the presence of DMF-KOH mixture followed by addition of ethyl chloroacetate (**46**). The formation of both **94** and **95** probably formed through the non-isolable intermediates **92** and **93** respectively (M. Abdel-Megid & M.A.A. Awas, 2002) (Scheme 15).



Scheme 15: Formation of tetra-thiazolidinones

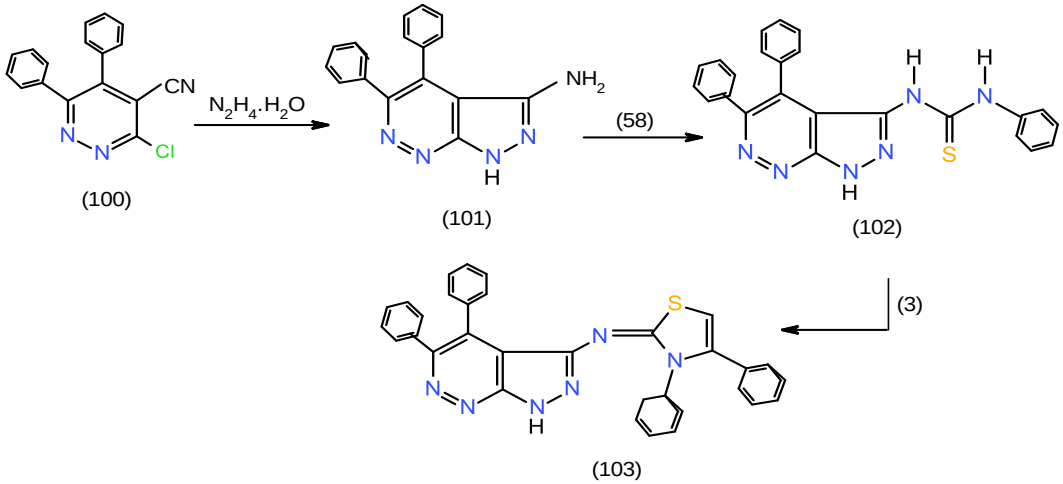
Also, alkylation of sulfanylquinoline derivative **96** with ethyl chloroacetate (**46**) furnished ethyl quinolinylthioacetate **97**, which reacted with o-aminothiophenol (**98**) to furnish benzothiazolyl-methylthioquinoline (**99**) (Ismail, Abdel-Megid, & Hassa, 2004) (Scheme 16).



Scheme 16: Formation of benzothiazole derivative

1.2.3. Phenacyl bromide

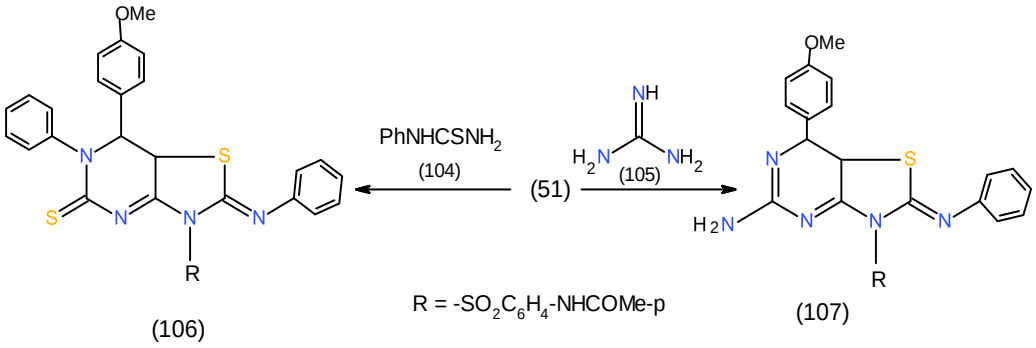
Hydrazonolysis of 3-chloropyridazinecarbonitrile **100** with hydrazine hydrate afforded 3-amino-pyrazolopyridazine **101**. Addition of phenyl isothiocyanate (**58**) to **101** yielded 1,3-disubstituted thiourea (**102**), which converted to diphenylthiazole derivative **103** by the action of phenacyl bromide (**3**) (M. Seada et al., 1989) (Scheme 17).



Scheme 17: Formation of diphenylthiazole derivative

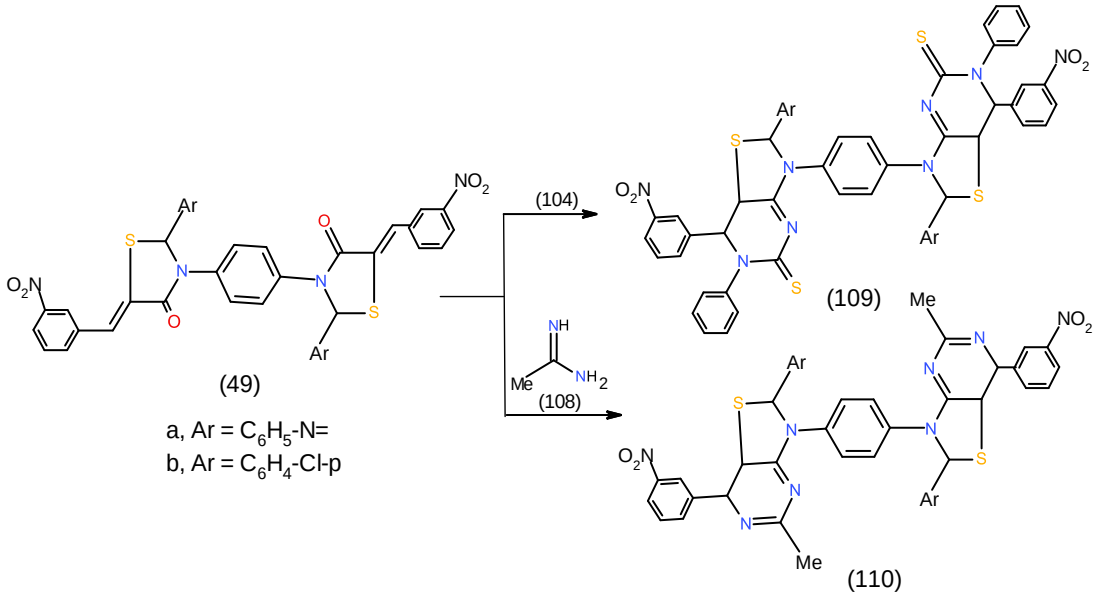
1.2.4. Formation of thiazolopyrimidine and related compounds

A series of thiazolopyrimidine derivatives was designed and synthesized in our lab. Thus, the action of N-phenylthiourea (**104**) and guanidine hydrochloride (**105**) upon 5-arylidene- thiazolidinone **51** in boiling dimethyl formamide furnished thiazoloprimidinethione **106** and aminothiazoloprimidine **107** (M. Seada, Abdel-Megid, & El-Deen, 1993) (Scheme 18).



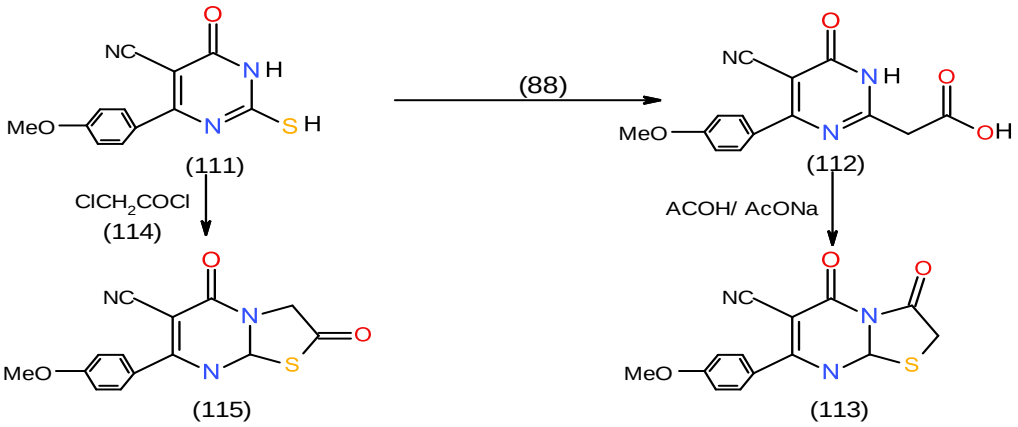
Scheme 18: Formation of thiazolopyrimidines

Similarly, the cyclic enones **49a, b** reacted with N-phenylthiourea (**104**) and acetamidine hydrochloride (**108**) in DMF to afford the respective bis (pyrimidothiazolin3-yl) phenylenes **109a, b** and **110 a, b** (M. Abdel-Megid & M.A.A. Awas, 2002) (Scheme 19).



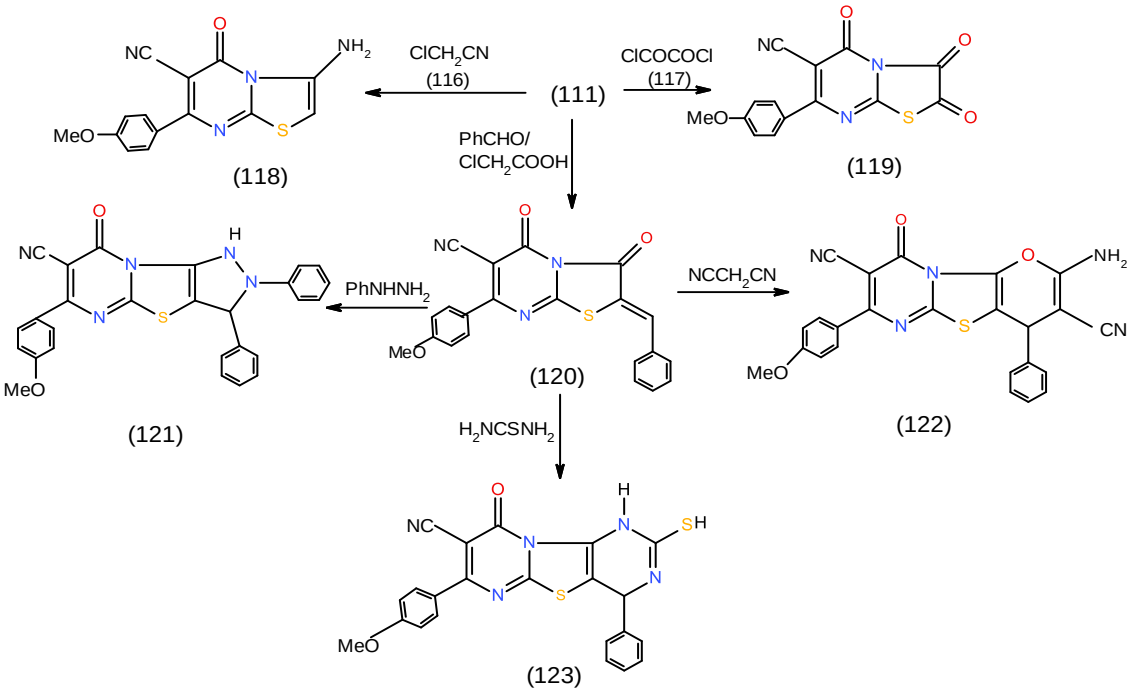
Scheme 19: Formation of bis (pyrimidothiazolin3-yl) phenylenes

Furthermore, alkylation of 2-sulfanylpyromidinecarbonitrile (**111**) with chloroacetic acid (**88**) produced 2-carboxymethylthiopurimidine (**112**). Boiling of **112** in acetic anhydride, sodium acetate and glacial acetic acid mixture afforded the thiazolopyrimidine (**113**), whereas its isomeric form **115** was obtained on reacting **111** with chloroacetyl chloride (**114**) (M. H. Abdel-Megid, Awas, Seada, El-Mahdy, & Elsayed, 2009) (Scheme 20).



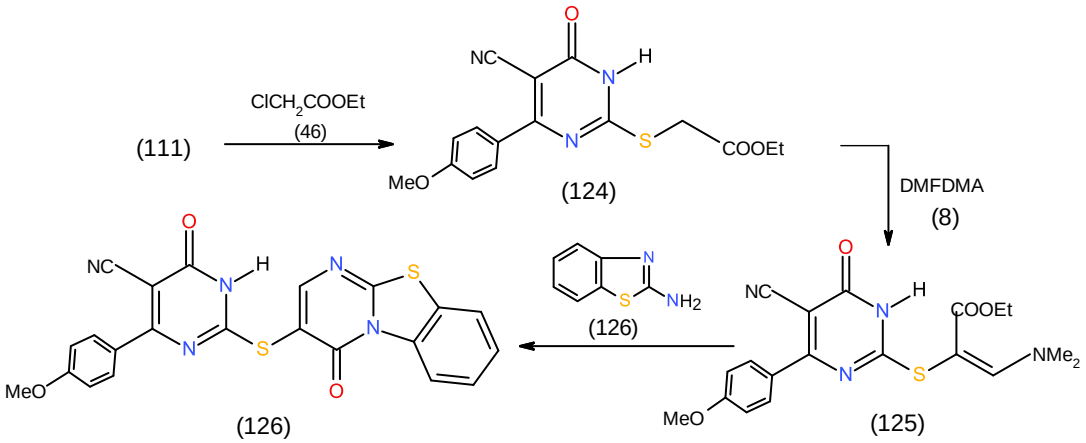
Scheme 20: Formation of thiazolopyrimidines

Furthermore, alkylation of **111** with chloroacetonitrile (**116**) and dioxalyl chloride (**117**) afforded 3-aminothiazolopyrimidine **118** and trioxothiazolopyrimidine **119**, respectively. Treatment of **111** with benzaldehyde and monochloroacetic acid (**88**) yielded 2-benzylidenethiazolopyrimidine **120**. Action of phenyl hydrazine, malononitrile and thiourea upon **120** furnished pyrazolo- thiazolopyrimidine **121**, pyranothiazolopyrimidine **122** and pyrimidothiazolopyrimidine **123** (M. H. Abdel-Megid et al., 2009) (Scheme 21).



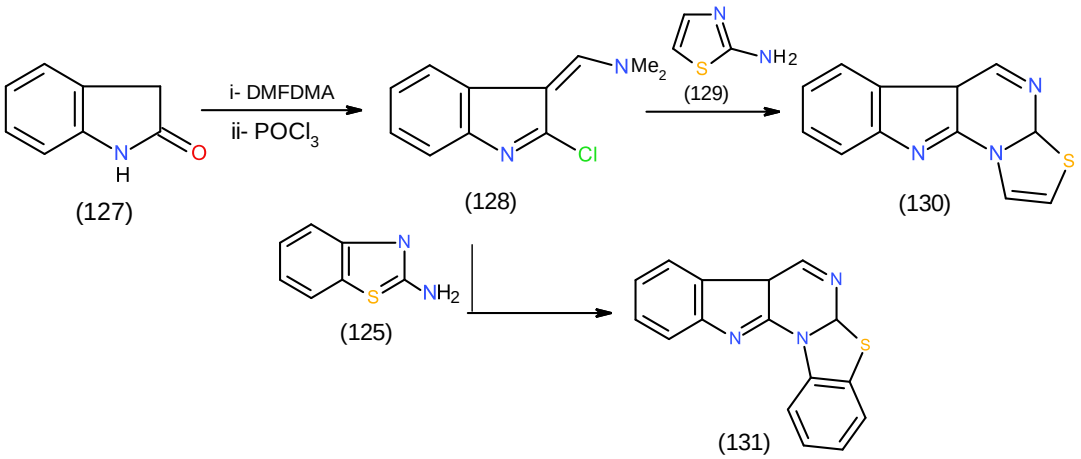
Scheme 21: Formation of thiazolopyrimidinecarbonitrile derivatives

Also, alkylation of compound **111** with ethyl chloroacetate (**46**) then reaction the product (**124**) with DMFDMA (**8**) afforded the enaminone **125,** which subjected to react with 2-aminobenzothiazole (**126**) in boiling acetic acid to give diheterocyclylthioether **127** having benzothiazolopyrimidine in its structure (M. H. Abdel-Megid et al., 2009) (Scheme 22).



Scheme 22: Formation of benzothiazolopyrimidine

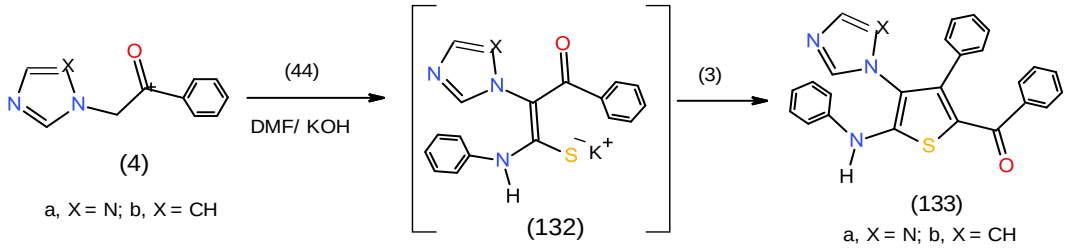
On the other hand, condensation of 2-indinone (**127**) with DMFDMA (**8**) and treatment the product with phosphorous oxychloride afforded 2-chloroindole derivative **128,** which converted into indolothiazolopyrimidine (**130)** when it reacted with 2-aminothiazole (**129)**. The action of 2-aminobenzothiazole **(125**) upon **128** was studied and giving rise to polyfused thiazolopyrimidine derivative **131** (M. Abdel-Megid, 2006) (Scheme 23).



Scheme 23: Formation of indolothiazolopyrimidines

1.3. Formation of thiophene

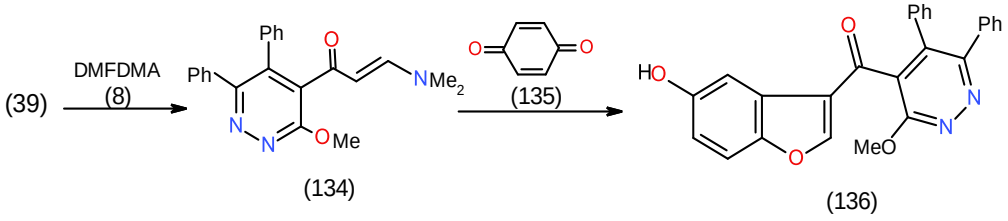
Thiophenes are classically prepared by the reaction of 1,4-diketones, diesters, or dicarboxylates with sulfidizing reagents such as P_4S_{10} such as in the Paal-Knorr thiophene synthesis. Specialized thiophenes can be synthesized similarly using Lawesson's reagent as the sulfidizing agent, or via the Gewald reaction, which involves the condensation of two esters in the presence of elemental sulfur (Joule & Mills, 2013). A new method was used in our work when azolylacetophenones **4a, b** reacted with phenyl isothiocyanate (**44**) to afford in situ an adduct (**132**) that could not be isolated in pure form. However, when it treated with phenacyl bromide (**3**), the azolylthiophene derivatives **133a, b** was obtained (M. Abdel-Megid, 2003) (Scheme 24).



Scheme 24: Formation of substituted thiophene

1.4. Benzofuran formation

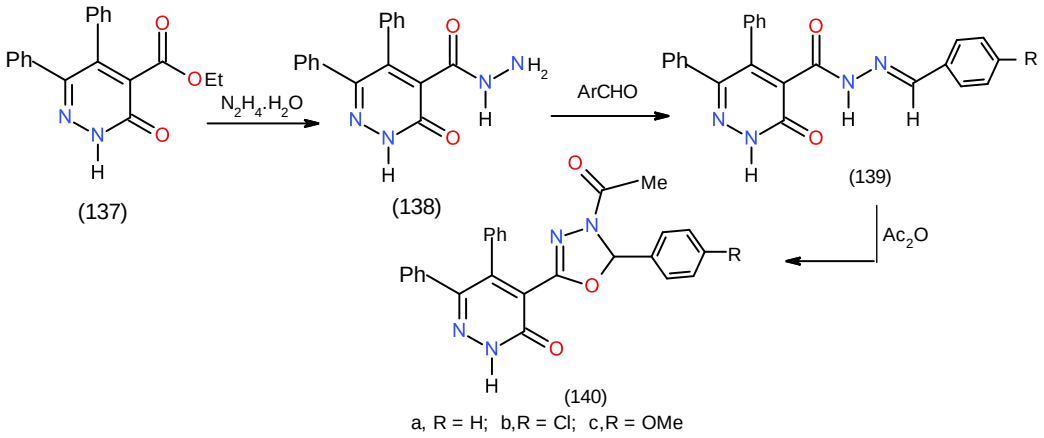
Benzofuran and its derivatives are widely used for industrial purposes and also exhibit a broad range of biological activities. A recent review compiles examples synthetic methodologies used for the preparation of benzofurans are described (Kishor, 2017) but did not include the novel method that was done in our laboratory, where benzofuran derivative **136** synthesized by treatment of 1,4-benzoquinone (**135**) with the enaminone **134,** obtained on condensation of acetylpyridazine (**39**) with DMFDMA (**8**) in glacial acetic acid (M. Abdel-Megid, 2007) (Scheme25).



Scheme 25: Formation of pyridazinyl benzofuryl ketone

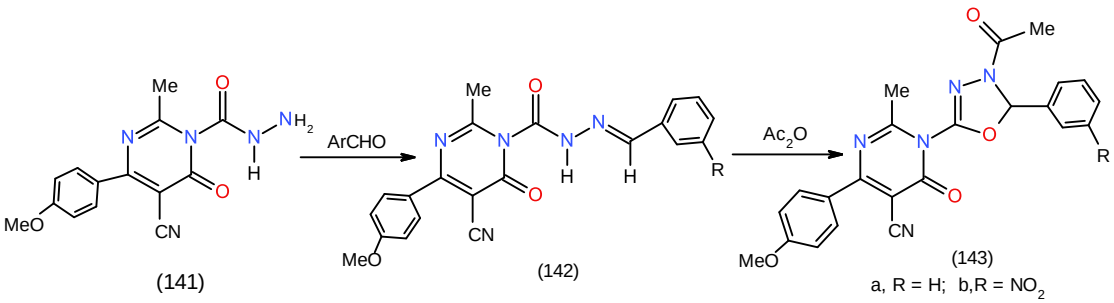
1.5. Formation of oxadiazoles

1,3,4-oxadiazole and its isomers are all known and appear in variety of pharmaceutical drugs including raltegravir, butalamine, fasiplon, oxolamine, and pleconaril (Joule & Mills, 2013).This facts encourage us to prepare them in our laboratory. Therefore, hydrazonolysis of 4-carbethoxypyridazinone **137** with hydrazine hydrate afforded 4-carboxyhydrazidepyridazinone **138**, which on condensation with aromatic aldehydes gave the correspondding arylidenehyrazides **139a-c**. Compound **139** underwent ring closure on refluxing it in acetic anhydride yielding the respective 1,3,4-oxadiazoles **140a-c** (M. Seada et al., 1989) (Scheme 27).



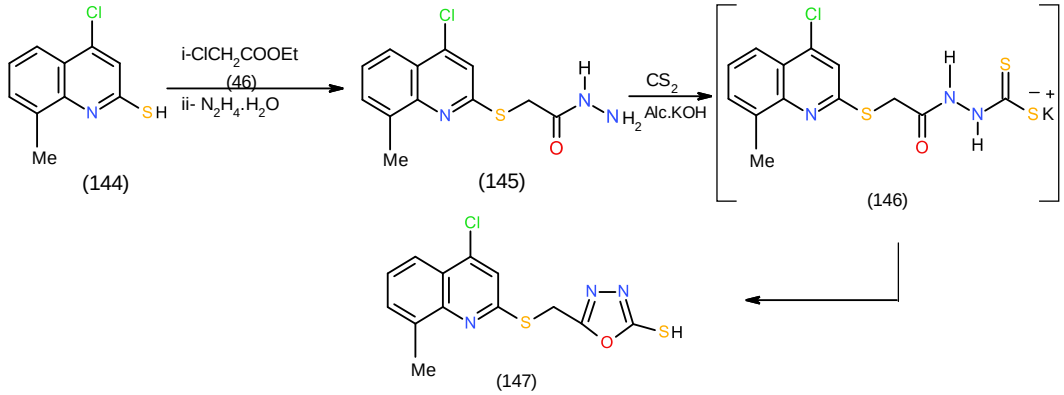
Scheme 26: Intramolecular cyclization of arylidenehyrazides

Similarly, condensation of acetohydrazide **141** with aromatic aldehydes gave the respective arylidenehyrazides **1462a, b** in which the side chain underwent intramolecular cyclization on refluxing with acetic anhydride yielding the corresponding 1,3,4-oxadiazoles **143a, b** (M. Abdel-Megid, 1997) (Scheme 27).



Scheme 27: Formation of oxadiazolylpyrimidines

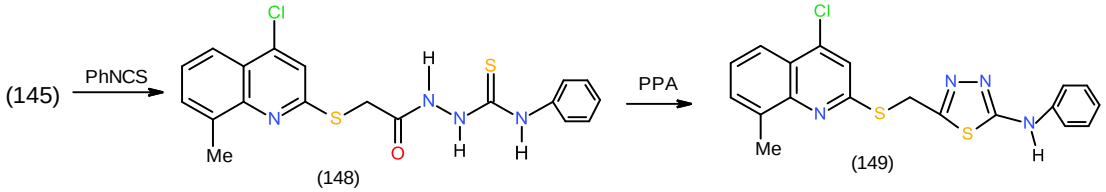
On the other hand, alkylation of 2-sulfanylquinoline (**144**) with ethyl chloroacetate (**46**) then reaction the product with hydrazine hydrate afforded the acid hydrazide (**145**). Refluxing of **145** with carbon disulfide in alcoholic potassium hydroxide solution yielded 1,3,4-oxadizole derivative **147** was produced. The formation of **147** may be formed as a product of cyclization of the non-separated intermediate **146** (Ismail et al., 2004) (Scheme 28).



Scheme 28: Formation of 1,3,4-oxadiazole

1.6. Formation of 1,3,4-thiadizoles

Treatment of **145** with phenyl isothiocynate yielded the thiosemicarbazide derivative **148**, which on refluxing in poly phosphoric acid (PPA) intramolecular cyclization took place forming 1,3,4-thiadiazole derivative **149** (Ismail et al., 2004) (Scheme 29).



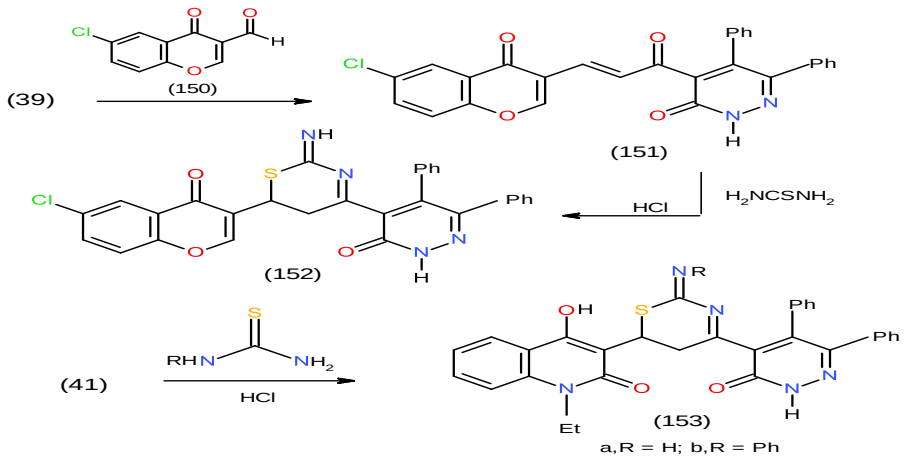
Scheme 29: Formation of 1,3,4-thiadiazole

2. Synthesis of Six-Membered heterocycles

Thiazine is one of the most important six-membered nitrogenous heterocycles with sulfur atom and pyran is an oxygenated heterocyclic compounds. Both of them could be prepared using common and novel synthesized acyclic or cyclic active methylene compounds as well as heterocycles having active methyl or methine site in their structures.

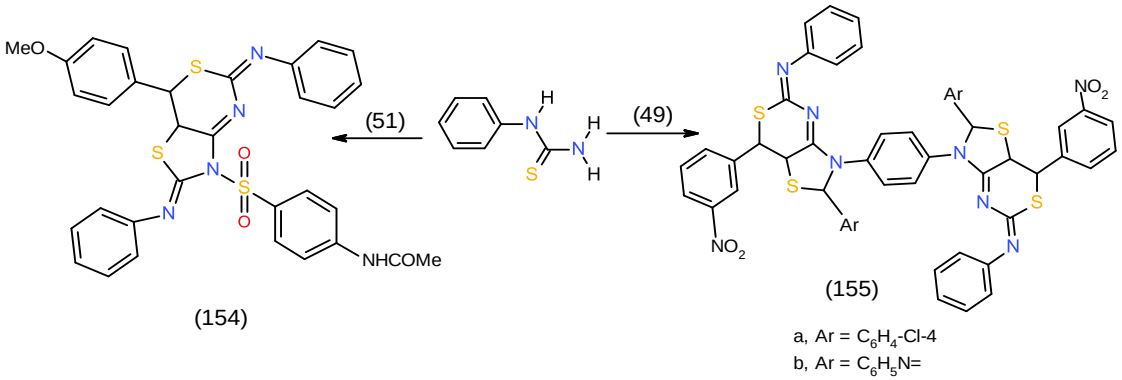
2.1. Formation of 1,3-thiazines

Extensive studies have been performed on the synthesis and reactivity of 1,3-thiazines and their benzo derivatives (Weinreb & Orr, 2008). We have been found that most of the synthesized 1,3-thiazines in our laboratory arise from the interaction between thiourea with acyclic and cyclic enones in acid medium. Thus, the action of thiourea upon biheterocylic enones **151** obtained by condensation of acetylpyridazine **39** with 6-chloro-3-formylchromone (**150**) afforded 4,6-dihetrocycy-1,3-thiazines **152.** Similarly**,** treatment the enone **41** with thiourea and N-phenylthiourea yielded 1,3-thiazine derivative **153a, b,** respectively (Gabr et al., 2010) (Scheme 30).



Scheme 30: Formation of 4,6-diheterocyclyl-1,3-thiazines

By the same manner, the cyclic enones **51** and **49a, b** reacted with N-phenylthiourea in ethanol containing few drops of hydrochloric acid yielded the respective thiazolothiazine derivatives **154** and **155a, b** (M. Abdel-Megid & M.A.A. Awas, 2002)[7,17] (Scheme 31).



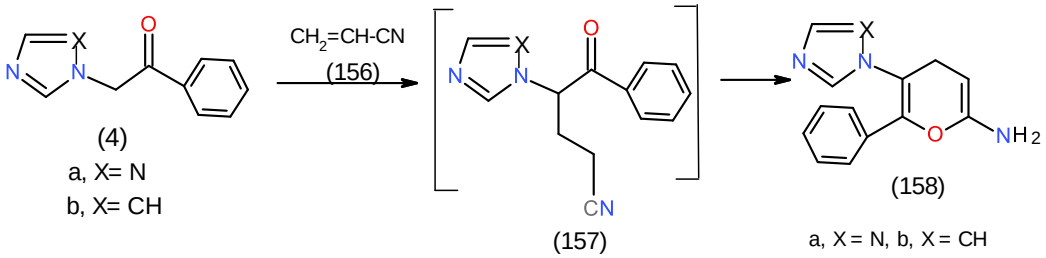
Scheme 31: Formation of thiazolo1,3-thiazines

2.2. Pyran Formation

Pyran derivatives are widely found in nature, α-pyrone and γ-pyrone mainly exist in plants. Benzopyran (chromene), chromone, coumarin, flavonoid, isoflavone and anthocyanin can be regarded as pyran derivatives. Among the stable members of this family is tetrahydropyran, sugars often occur in pyranose forms containing the tetrahydropyran ring (Brimble, Gibson, & Sperry, 2008). In our work, we used the enones and enaminones for the preparation either substituted or fused pyran derivatives.

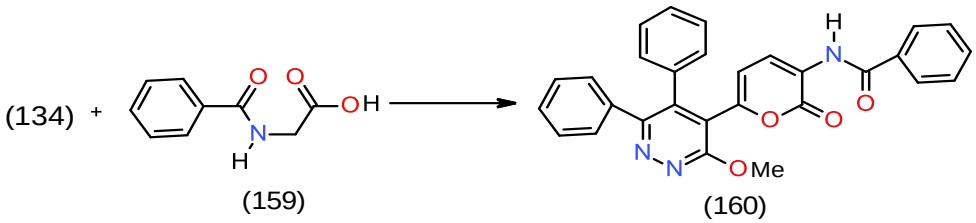
2.2.1. Formation of substituted pyrans.

In cyanoethylation of the azolylacetophenones **4a, b** with acrylonitrile (**156**) in pyridine-water mixture the product obtained did not show CN absorption band in IR spectra. This means that cyanoethylation took place giving intermediate **157**, which on intramolecular cycloaddition gave 3-azolylpyrans **158a, b** (M. Abdel-Megid, 2003) (Scheme 32).



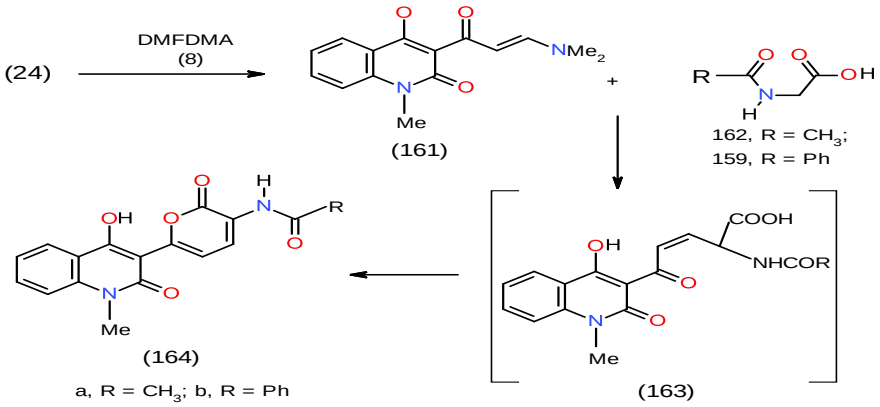
Scheme 32: Formation of azolylpyrans

Treatment of the enaminone **134** with hippuric acid (**159)** in refluxing acetic anhydride yielded the pyrone derivative **160** (M. Abdel-Megid, 2007) (Scheme33).



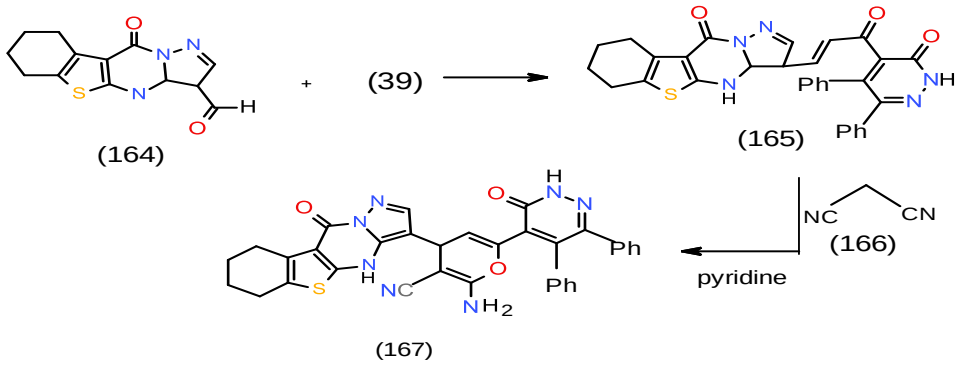
Scheme 33: Formation of pyridazinlpyron

Also, boiling of aceuric acid **162** and hippuric acid (**159)** in acetic anhydride with the enaminone **161,** obtained by condensation of acetylquinolone **24** with DMFDMA (**8**) furnished pyranyl- quinolinone **164a, b,** respectively through the non-separable intermediate **163**(Abass et al., 2007) (Scheme 34).



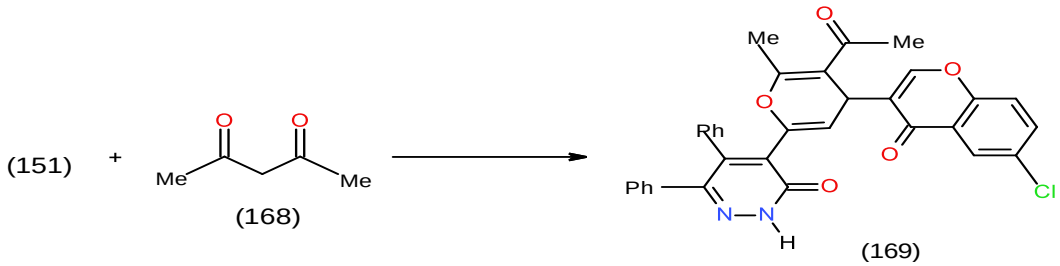
Scheme 34: Formation of oxoquinolinylpyrons

The biheterocyclic enone **165** performed by condensation of formyl derivative **164** with 4-acetyl- pyridazinone **39,** was subjected to react with malononitrile (**166**) in boiling pyridine afforded 4,6-disubstituted aminopyrancarbonitrile **167** (El-mahdy, El-Kazak, Abdel-Megid, Seada, & Farouk, 2009)(Scheme 35).



Scheme 35: Formation of aminopyrancarbonitrile

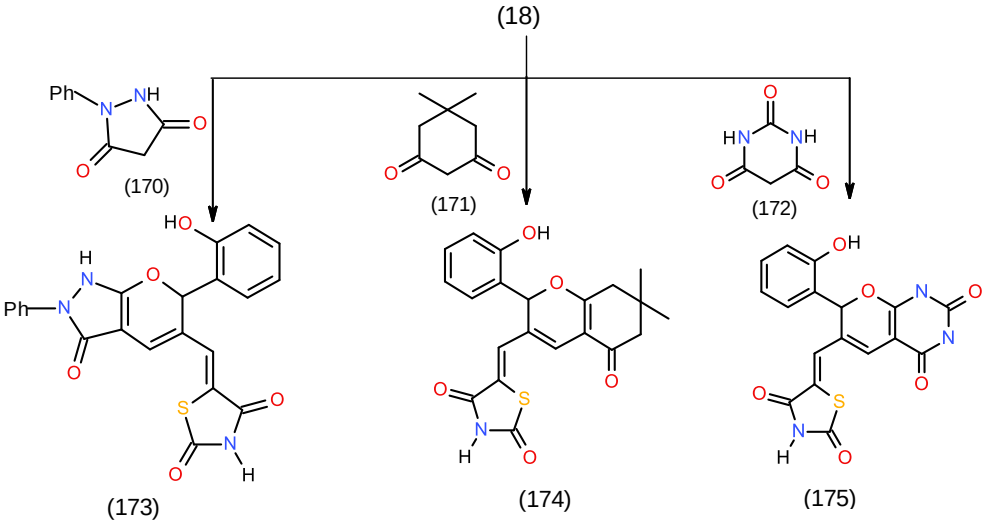
Also, when the biheterocyclyl enone **151** refluxed with acetyl acetone (**168**) in ethanol containing few drops of piperidine yielded the pyridazinylpyran **169,** where the reaction proceeds via nucleophilic carbanion attack at β-position of the α, β-unsaturated center followed by cyclocondensation (Gabr et al., 2010) (Scheme 36).



Scheme 36: Formation of chromenylpyridazinyl pyran

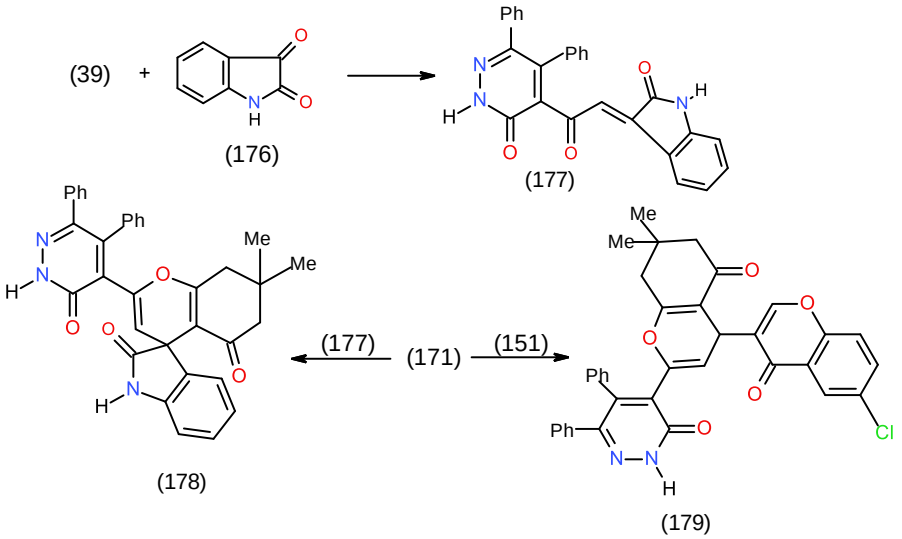
2.2.2. Formation of fused pyrans.

Nucleophilic attack by carbanion of cylic active methylene compounds at active methine site of ɤ-pyran nucleus, ring opening–ring closure reactions took place producing the target condensed pyran. Therefore, refluxing of the enone **18** with 1-phenylpyrazolidine (**170**), 5,5-dimethyl- cycohexane-1,3-dione (**171**) and barbituric acid (**172**) in boiling sodium ethoxide afforded pyrazolopyran **163,** 5-(chromenylmethylidene)thiazolidinone **174** and pyranopyrimidine derivative **175,** respectively (Ibrahim et al., 2011) (Scheme 37).



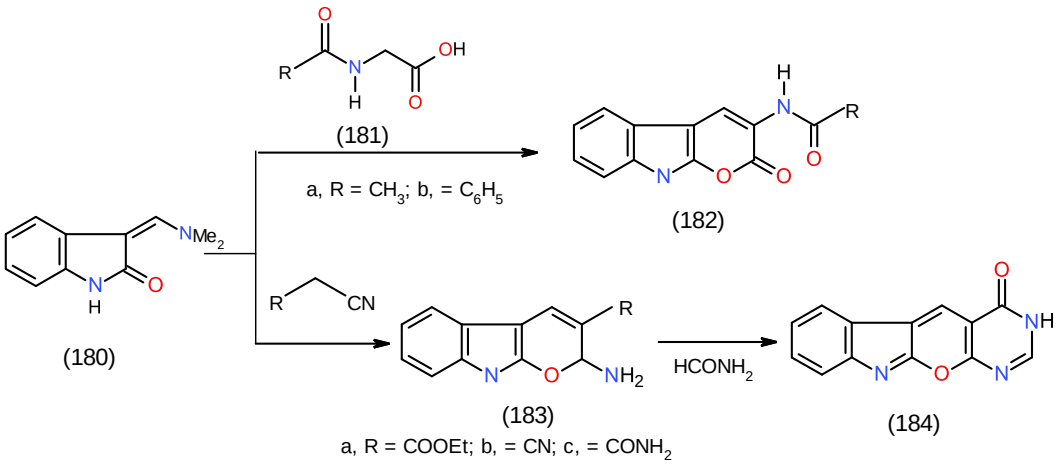
Scheme 37: Formation of some condensed pyrans

Also, condensation of acetylpyridazine **39** with isatin (**176**) yielded the enone **177.** The effect of 5,5-dimethylcycohexane-1,3-dione (**171**) upon the enones **177** in boiling ethanol containing catalytic amount of triethyl amine giving rise to spiro chromenylindole derivative **177** (Gabr et al., 2010)**.** similarly, diheterocyclyl chromene **178** was prepared by the action of compound **171** upon the enone **151** under the same reaction conditions (Scheme 38).



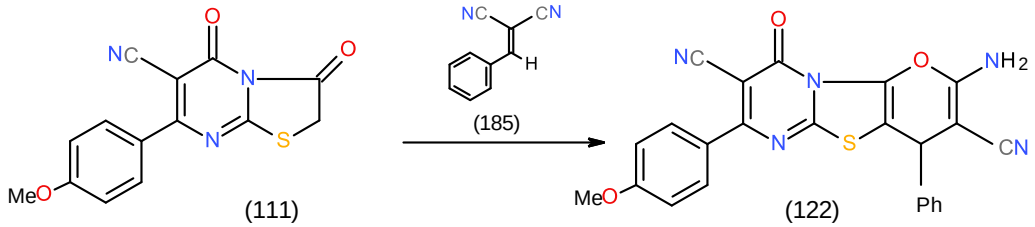
Scheme 38: Formation of tetrahydrochromene

Furthermore, the condensation of indonone **127** with DMFDMA (**8**) afforded the enaminone (**180**). Reaction of compound **180** with N-acetyl and N-benzoyl glycine **181a, b** in boiling acetic anhydride, acetamidopyran-2-one **182a** and benzamidopyran-2-one **182b** were obtained, respectively. Also, compound **180** reacted with some active methylene compounds namely, ethyl cyanoacetate, malononitrile and cyanoacetamide in acetic acid to yield pyranoindol derivatives **183a-c**. In addition, fusion of **183a** with formamide gave pyrimidopyranoindole **184** (M. H. Abdel-Megid et al., 2009) Scheme 39).



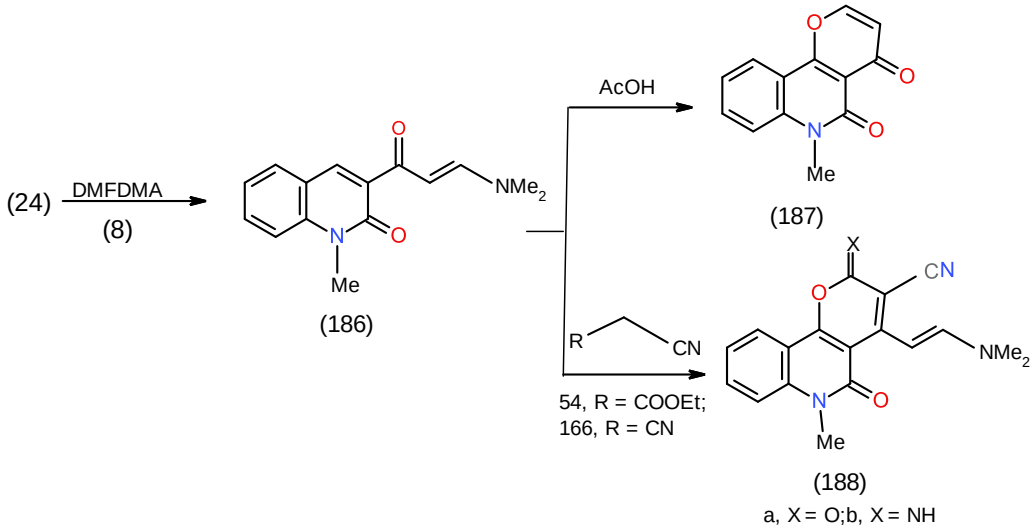
Scheme 39: Formation of pyranoindole derivatives

Pyranothiazolopyrimidinone **122** could be also obtained by treatment of **111** with α-cyano cinnamonitrile **(185),** the condensed product of malononitrile with benzaldehyde (M. Seada et al., 1993) (Scheme 40).



Scheme 40: Formation of pyranothiazolopyrimidinone

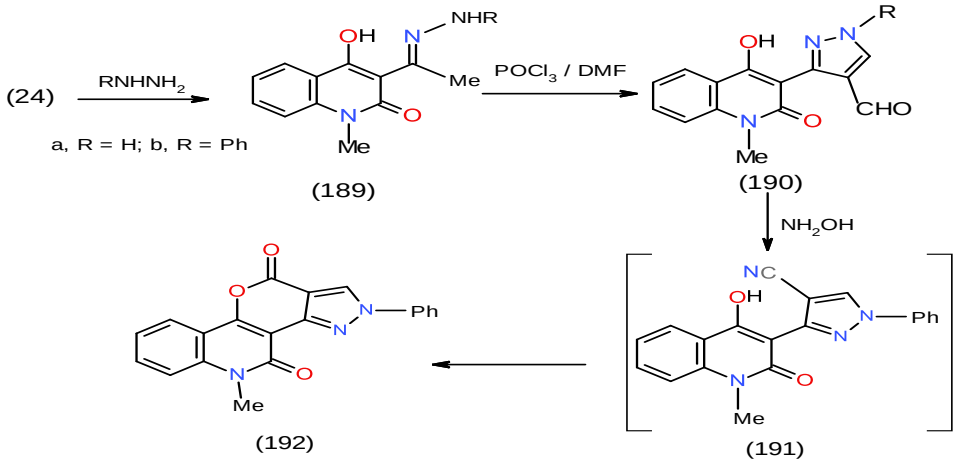
On the other hand, condensation of acetylquinolone **24** with DMFDMA (8) furnished the enaminone **186**. Heating the enaminone **186** in glacial acetic acid, intramolecular cyclization took place giving rise to pyranoquinolinone derivative **187** whereas, treatment of **186** with active methylene compounds such as ethyl cyanoacetate (**54**) and malonomitrile (**166**) in basic medium afforded the pyranoquinolinone **188 a, b,** respectively (Abass et al., 2007) (Scheme 41).



Scheme 41: Formation of pyranoquinolones

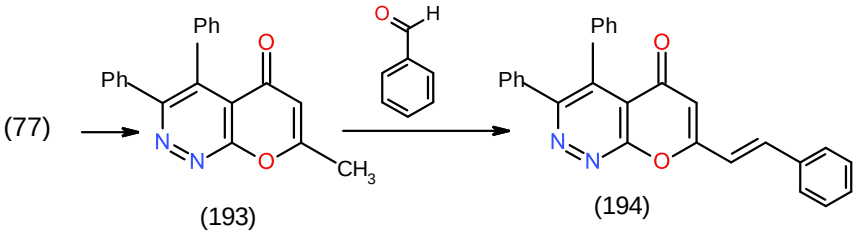
Moreover, condensation of acetylquinolinone **24** with hydrazine hydrate and phenylhydrazine afforded the respective hydrazones **189a, b** ,which subjected to react with Vilsmeier-Haack reagent ($POCl_3$-DMF) to give the

formylpyrazoles **190 a, b**. Condensation of formylpyrazole **190b** with hydroxylamine hydrochloride in glacial acetic acid did not gave the expected oxime or the intermediate carbonitrile **191,** in which the hydroxyl group was added to CN forming iminopyranoquinolone, which in turn hydrolyzed to produce pyrazolopyranoquinolinone **192** (Abass et al., 2007) (Scheme 42).



Scheme 42: Formation of pyrazolopyranoquinolinone

Furthermore, when pyridazinyl-butan-1,3-dione (**77**) treated with concentrated sulfuric acid, ring closure took place giving rise to pyranopyridazinone derivative **193.** The presence of methyl group at position-7 was deduced from its ability to condense with benzaldehyde yielding styrylpyranopyridazine **194** (M. Abdel-Megid et al., 2009) (Scheme43)

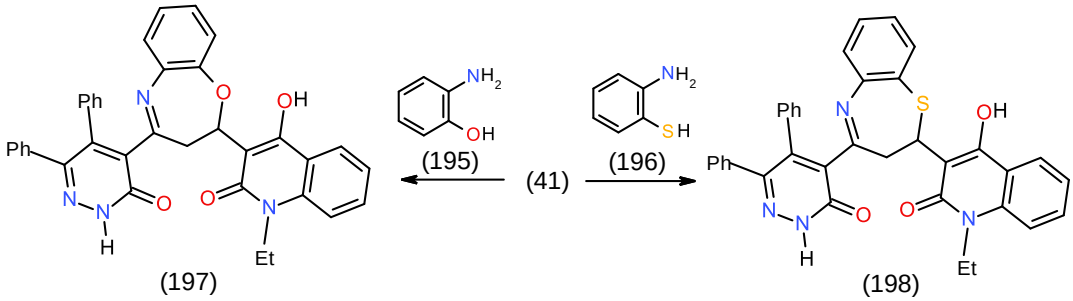


Scheme 43: Formation of pyranopyridazine

3. Synthesis of Seven-Membered heterocycles

3.1. Formation of thiazepines and oxazepines

Benzodiazepines resulted in the synthesis of heterocycle-fused diazepine derivatives with potential pharmacological activity. Pyridoazepines are recognized to be active in the central nervous system and have a comparable activity to the well-known benzodiazepines. This makes the synthesis and the study of pyridodiazepines, pyridooxazepines and pyridothiazepines an important research topic (Muylaert, Jatczak, Mangelinckx, & Stevens, 2016). Although these structures have a great similarity with benzodiazepines (M. Abdel-Megid, Abass, & Hassan, 2007), Thus, the action of o-aminophenol (**195**) and o-aminothiophenol (**196**) upon the enone **41** afforded the correspondding benzoxazepine **197** and benzothiazepine **198** (M. Abdel-Megid & Ismail, 2002) (Scheme 44).



Scheme 44: Formation of benzoxazepine and thiazepine

Conclusion

In this study effort to optimize the synthetic procedures for the preparation of various bioactive heterocycles. Herein, we explain how active acyclic and cyclic methylene compounds as well as heterocyclic having active methyl or methine sites were used to synthesize wide varieties of heterocyclic systems by choosing certain starting materials and different synthesizing reagents. This study will help researchers in the fields of organic and medicinal chemistry to design and implement new procedures for the constructions of novel biological components

References

Abass, M., Abdel-Megid, M., & Hassan, M. (2007). Substituted Quinolinones, Part 12: Heterocyclization Reactions of 3-(3-Chromonyl)acryloylquinolinone with Some Bifunctional Nucleophiles. Synthetic Communications, 37(2), 329-352. doi: 10.1080/00397910601033930

Abdel-Megid, M. (1995). Synthesis of some new polynuclear heterocycles derived from ethyl α-[5-cyano 2-methyl-6-phenylpyrimidin-4-yl] cyanoacetate. Indian Journal of Heterocyclic Chemistry, 4, 269-272.

Abdel-Megid, M. (1997). ChemInform Abstract: Synthesis of Some Heterobicyclic Compounds Bearing 4-Anisyl-5-cyano-2- methyl-6-oxopyrimidin-1-yl Moiety. ChemInform, 28(35). doi: 10.1002/chin.199735039

Abdel-Megid, M. (2003). Reactivity of Functionally Substituted Azoles Towards Electrophiles. Novel Synthesis of Thienylazoles and Phenylazoles. Synthetic Communications, 33(1), 153-160. doi: 10.1081/scc-120015571

Abdel-Megid, M. (2006). A versatile molecule for the synthesis of some new polynuclear bioactive heterocyclic systems. International Journal of Chemistry, 16(3), 149-157.

Abdel-Megid, M. (2007). A New Route for the Synthesis of Substituted Pyridazines. Synthetic Communications, 37(18), 3211-3218. doi: 10.1080/00397910701547847

Abdel-Megid, M., Abass, M., & Hassan, M. (2007). Substituted quinolinones. Part 13 a convenient route to heterocyclization reactions with 3-substituted 4-hydroxyquinolin-2(1H)-one. Journal of Heterocyclic Chemistry, 44(2), 315-322. doi: 10.1002/jhet.5570440206

Abdel-Megid, M., Abdel-Rahman, T. M., & Ali, U. F. (1998). Synthesis of some aminopyrimido[4,5-d]pyrimidinethiones and related compounds with their effect of cellobiase activity. Mansoura Science Bulletin (A, Chemistry), 25(2), 17-35.

Abdel-Megid, M., Awas, M. A. A., Seada, M. H., Elmhdy, K. M., & Elsayed, M. M. (2010). Synthesis and Mollucicidal Activity of Some New Bicyclic and Polycyclic Pyrimidine Derivatives.

Abdel-Megid, M., Elkazak, A. M., Seada, M., & Farouk, O. (2010). Heterocyclization Reactions of 2-Arylideneamino-4,5-Diphenylfuran-3-Carbonitriles. Journal of Applied Sciences Research, 6(12), 2133-2138.

Abdel-Megid, M., Elnagdi, M. H., & Negm, A. M. (2002). Studies with 1-functionally substituted alkyl azoles: Novel synthesis of functionally substituted azolylbenzimidazoles and functionally substituted azolyl-1,2,4-triazoles. Journal of Heterocyclic Chemistry, 39(1), 105-108. doi: 10.1002/jhet.5570390115

Abdel-Megid, M., Gabr, Y., Awas, M. A. A., & Abdel-Fatah, N. M. (2009). Synthesis of some new hetarylpyranopyridazines, cinnolines, and hetarylpyridazine derivatives. Chemistry of Heterocyclic Compounds, 45(11), 1354-1364. doi: 10.1007/s10593-010-0433-1

Abdel-Megid, M., & Ismail, M. M. (2002). Synthesis of bioactive aza-heterocyclic systems derived from novel biheterocyclic enone. International Journal of Chemistry, 12(40), 287-296.

Abdel-Megid, M. H., Awas, M. A. A., Seada, M. H., El-Mahdy, K. M., & Elsayed, M. M. (2009). A Convenient Synthesis of Some New Bioactive Diheterocylic Thioether and Thiazolopyrimidine Derivatives. Acta Chem. Solv., 56, 852-859.

Brimble, M. A., Gibson, J. S., & Sperry, J. (2008). 7.08 - Pyrans and their Benzo Derivatives: Synthesis. In A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven & R. J. K. Taylor (Eds.), Comprehensive Heterocyclic Chemistry III (pp. 419-699). Oxford: Elsevier.

Crossley, J. A., & Browne, D. L. (2010). An Alkynyliodide Cycloaddition Strategy for the Construction of Iodoisoxazoles. The Journal of Organic Chemistry, 75(15), 5414-5416. doi: 10.1021/jo1011174

el-Feky, S. A., & Abd el-Samii, Z. K. (1995). Synthesis and antiinflammatory properties of some novel thiazolidinones and imidazolidinones derived from 4-(3-phenyl-4(3H)-quinazolinon-2-yl)-3-thiosemicarbazone. Die Pharmazie, 50(5), 341-343.

El-mahdy, K., El-Kazak, A., Abdel-Megid, M., Seada, M., & Farouk, O. (2009). Synthesis, Characterization and Biological Evaluation of some New Thieno[2,3-d]Pyrimidine Derivatives. JOURNAL OF ADVANCES IN CHEMISTRY, 5(1), 581-591. doi: 10.24297/jac.v5i1.937

Gabr, Y., Abdel-Megid, M., Awas, M. A., & Abdel-Fatah, N. M. (2010). Synthesis of Some New Pyridazinylspirohetarylindoles and Hetarylpyridazine Derivatives. Heterocycles, 81(2), 395 - 406. doi: 10.3987/COM-09-11845

Ibrahim, M. A., Abdel-Hamed, M. A.-M., & El-Gohary, N. M. (2011). A new approach for the synthesis of bioactive heteroaryl thiazolidine-2,4-diones. Journal of the Brazilian Chemical Society, 22, 1130-1139.

Ismail, M. M., Abdel-Megid, M., & Hassa, M. M. (2004). Some Reactions of 2- and 4-Substituted 8-Methylquinolin-2(1)-ones and their Thio Analogue. Chemical Paper, 58(2), 117-125.

Joule, J. A., & Mills, K. (2013). Heterocyclic Chemistry (Fifth ed.): John Wiley & Sons.

Kaur Manjal, S., Kaur, R., Bhatia, R., Kumar, K., Singh, V., Shankar, R., . . . Rawal, R. K. (2017). Synthetic and medicinal perspective of thiazolidinones: A review. Bioorganic Chemistry, 75, 406-423. doi: https://doi.org/10.1016/j.bioorg.2017.10.014

Kishor, R. (2017). Review on Synthetic Routes for Synthesis of Benzofuran-Based Compounds Kishor R More. Journal of Chemical and Pharmaceutical Research, 9(5), 210-220.

Lakhan, R., & Singh, R. L. (1991). Synthesis and evaluation of 2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones and their 5-arylidene derivatives as potential fungicides. Journal of Agricultural and Food Chemistry, 39(3), 580-583. doi: 10.1021/jf00003a029

M. Abdel-Megid, & M.A.A. Awas. (2002). A FACILE SYNTHESIS OF P-BIS(4-THIAZOLIDINON-3-YL)PHENYLENES AND RELATED SYSTEMS AND RELATED SYSTEMS. Heterocyclic Communications, 8(2), 161. doi: https://doi.org/10.1515/HC.2002.8.2.161

Muylaert, K., Jatczak, M., Mangelinckx, S., & Stevens, C. (2016). Synthesis of pyrido-annelated diazepines, oxazepines and thiazepines. Current Medicinal Chemistry, 23(42), 4784-4823.

Seada, M., Abdel-Megid, M., & El-Deen, I. M. (1993). Synthesis and biological activities of some new thiazolidinones. Indian Journal of Heterocyclic Chemistry, 3, 81-86.

Seada, M., Fawzy, M. M., Jahine, H., Abd El-Megid, M., & Saad, R. R. (1989). Synthesis and Biological Activities of Some New Pyridazine Derivatives. Journal of the Chinese Chemical Society, 36(3), 241-249. doi: 10.1002/jccs.198900036

Seada M., Abdel-Rahman M. R., & Abdel-Megid M. (1993). Synthesis of some more 1,3-disubstituted-2,3-dihydro-2-thioxo-4,6-(1H,5H) pyrimidinediones and related analoges. Indian Journal of Heterocyclic Chemistry 3, 9-14.

Weinreb, S. M., & Orr, R. K. (2008). 8.07 - 1,2-Thiazines and their Benzo Derivatives. In A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven & R. J. K. Taylor (Eds.), Comprehensive Heterocyclic Chemistry III (pp. 513-566). Oxford: Elsevier.