Fayoum University
Faculty of Science
Chemistry Department

Synthesis of Some Interesting Heterocyclic Compounds Containing Pyrimidine Moiety

By

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Synthesis of Some Interesting Heterocyclic Compounds Containing Pyrimidine Moiety

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M. Sc., Organic Chemistry, 2018

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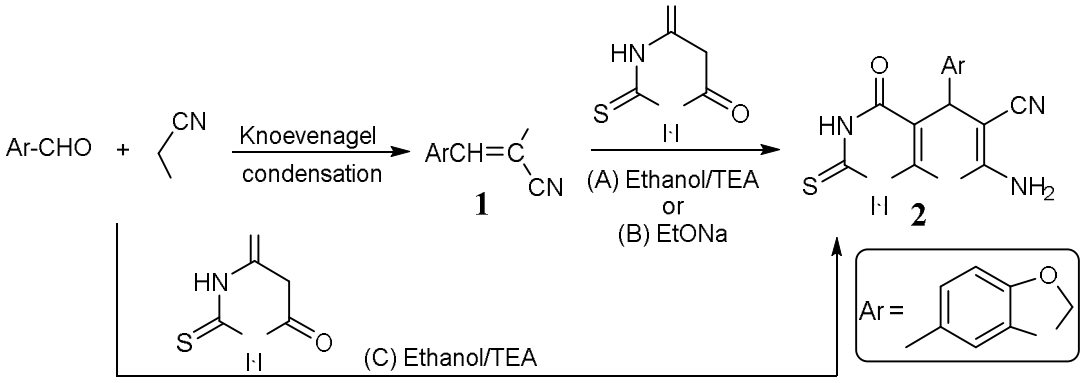
This thesis includes synthesis of 7-amino-5-(benzo[*d*][1,3]dioxol-5-yl)-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile **(2)** and 7-amino-5-(benzo[*d*][1,3]dioxol-5-yl)-6-imino-2-thioxo-1,2,3,5,6,7-hexahydro-4*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidin-4-one **(10**). Also, it studies the behavior of these compounds towards different chemical reagents to produce some heterocyclic compounds having expected antimicrobial activities.

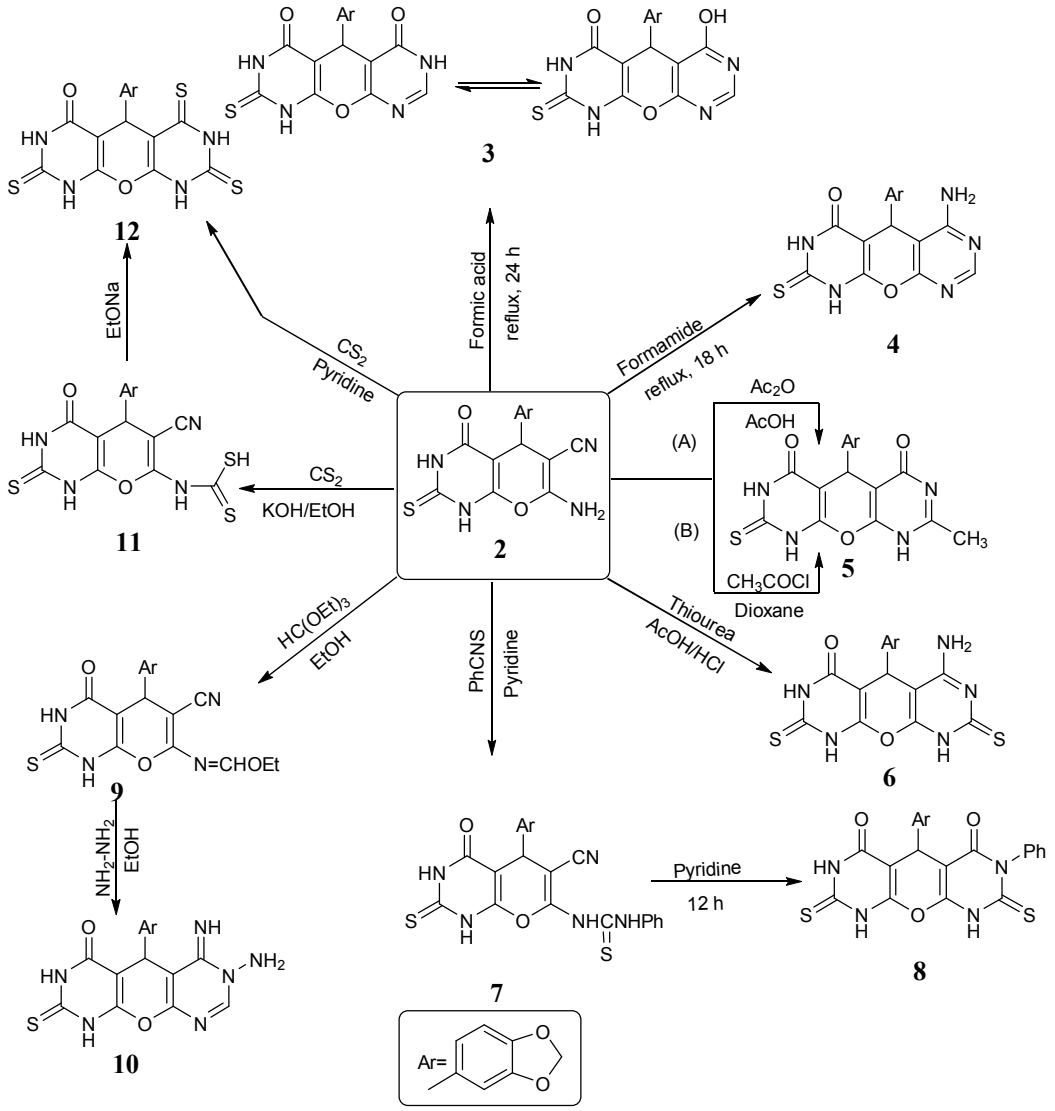
Studies on 7-amino-5-(benzo[*d*][1,3]dioxol-5-yl)-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (2).

Pyrano[2,3-*d*]pyrimidine derivative **(2)** was obtained *via* different routes (Scheme 1).



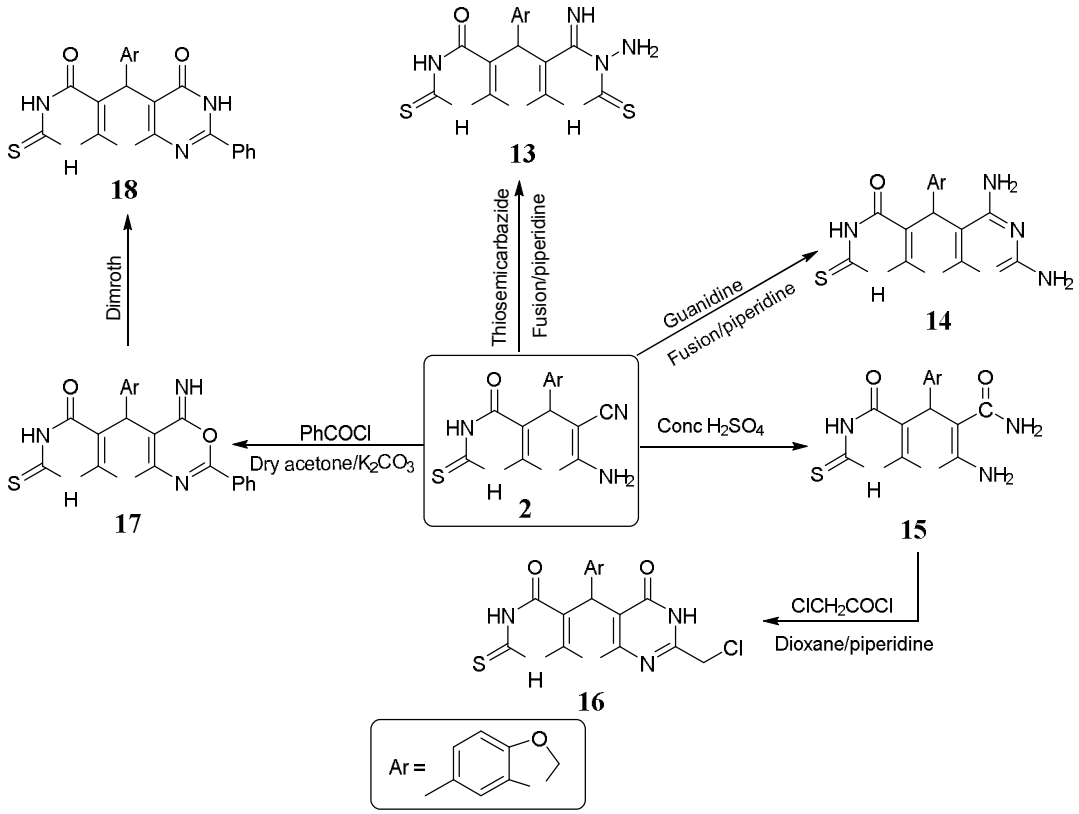
(Scheme 1)

Pyranopyrimidine derivative **2** reacted with formic acid to afford pyranodipyrimidinone derivative **3**, while the interaction between derivative **2** and formamide furnished pyranodipyrimidinone derivative **4**. Also, condensation of **2** either with acetic anhydride in glacial acetic acid, or acetyl chloride in dioxane gave pyranodipyrimidinone derivative **5**. In addition, compound **2** was refluxed with thiourea in presence of glacial acetic acid to yield pyranodipyrimidinone derivative **6**. Refluxing a mixture of derivative **2** and phenyl isothiocyanate in pyridine produced phenylthiourea derivative **7**, which on cyclization by refluxing in pyridine for another 12 h gave pyranodipyrimidinone derivative **8**. Treatment of compound **2** with triethyl orthoformate in refluxing ethanol afforded formimidate derivative **9**. After that, derivative **9** was allowed to reflux with hydrazine hydrate in boiling ethanol to give the cyclic compound **10**. Interaction of pyranopyrimidine derivative **2** with carbon disulfide in ethanolic KOH furnished carbamodithioic acid derivative **11**, which was cyclized using the strongly alkaline sodium ethoxide solution to give compound **12**. Also, the cyclic compound **12** could be prepared directly *via* the condensation between pyranopyrimidine derivative **2** and carbon disulfide in pyridine (Scheme 2).



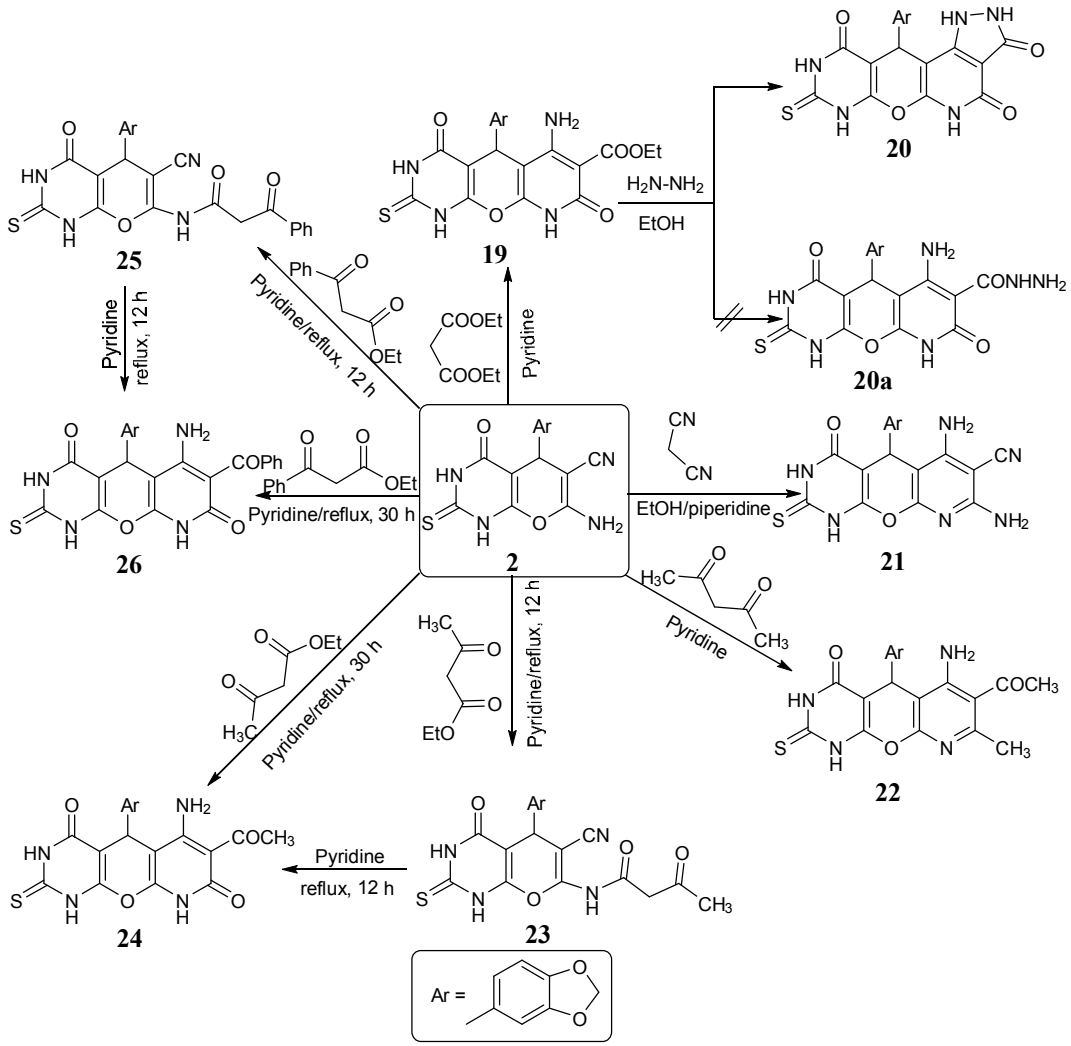
(Scheme 2)

Additionally, fusion of pyranopyrimidine derivative **2** with thiosemicarbazide in presence of a few drops of piperidine submitted compound **13**, while treatment of **2** with guanidine in in presence of a few drops of piperidine furnished derivative **14**. Moreover, addition of compound **2** into sulfuric acid (96%) in ice bath followed by stirring for 4 h at room temperature afforded derivative **15**, which further refluxed with chloroacetyl chloride in dioxane to produce pyrano[2,3-*d*:6,5-*d*']dipyrimidinedione derivative **16**. Interestingly, treatment of derivative **2** with benzoyl chloride in dry acetone containing anhydrous potassium carbonate gave oxazine intermediate **17**, which was transformed into the final product **18** by Dimroth rearrangement (Scheme 3).



(Scheme 3)

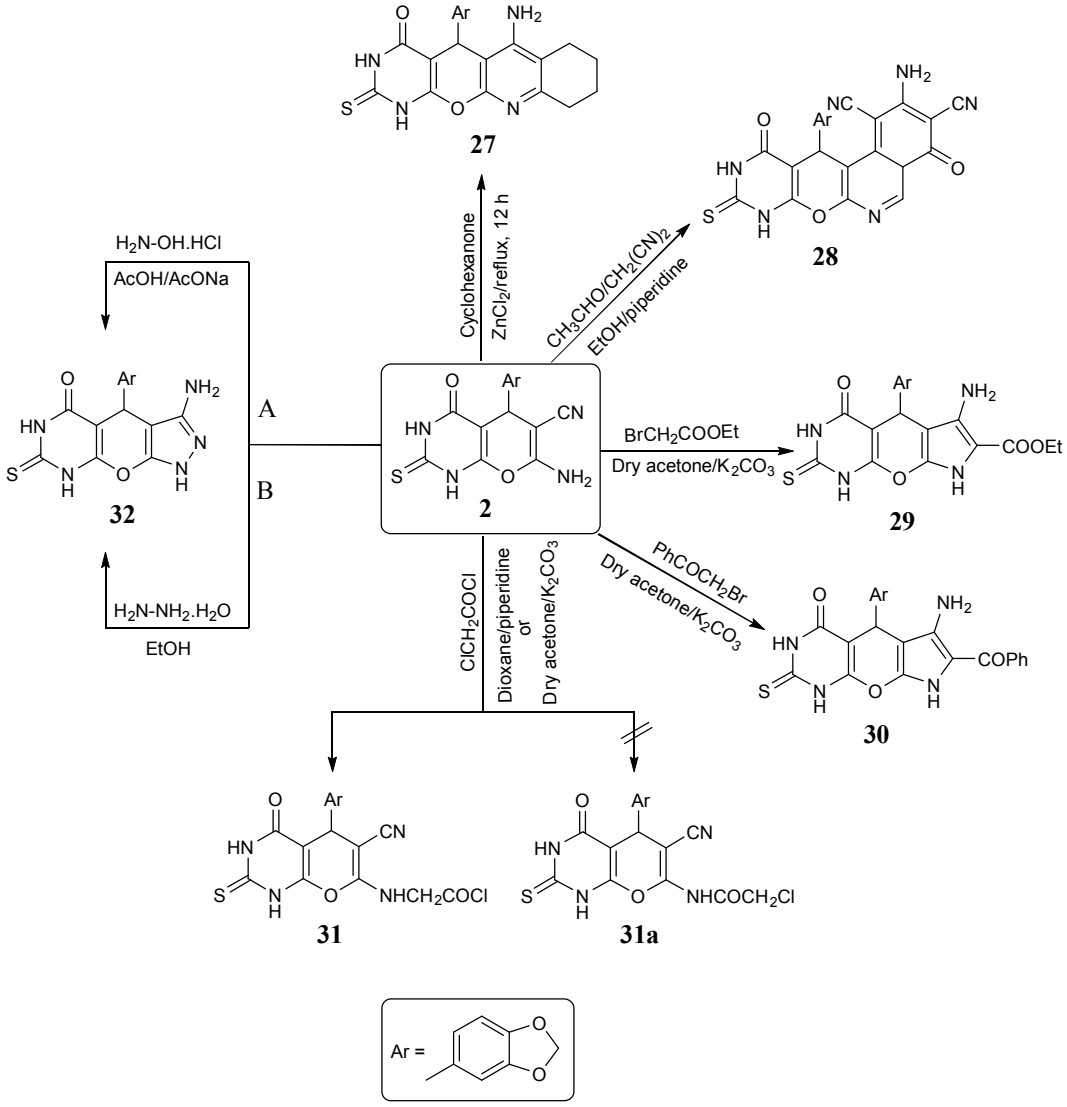
The high functionality of pyranopyrimidine derivatives prompted us to study the effect of active methylene compounds on compound **2**. Synthesis of polyfunctionally fused pyridine was achieved by treatment of compound **2** with diethyl malonate to afford pyridopyranopyrimidine derivative **19**. Later, compound **19** was allowed to react with hydrazine hydrate in refluxing ethanol to afford derivative **20** rather than **20a**. Also, treatment of compound **2** with malononitrile gave pyridopyranopyrimidine derivative **21**. Also, reaction of pyranopyrimidine derivative **2** with acetyl acetone in pyridine directly furnished the cyclic compound **22**. Moreover, treatment of compound **2** with ethyl acetoacetate in pyridine afforded the acyclic compound **23**. After that, the isolable intermediate **23** was further refluxed in pyridine for additional 12 h to get the cyclic compound **24**. Also, the cyclic compound **24** could be prepared directly *via* the condensation between pyranopyrimidine derivative **2** and ethyl acetoacetate in pyridine under reflux for 30 h. Furtheremore, reaction of compound **2** with ethyl benzoylacetate in pyridine under reflux for 12 h gave the acyclic compound **25**. After that, the isolable intermediate **25** was further refluxed in pyridine for additional 12 h to get the cyclic compound **26**. Also, the cyclic compound **26** could be prepared directly *via* the condensation between pyranopyrimidine derivative **2** and ethyl benzoylacetate in pyridine under reflux for 30 h (Scheme 4).



(Scheme 4)

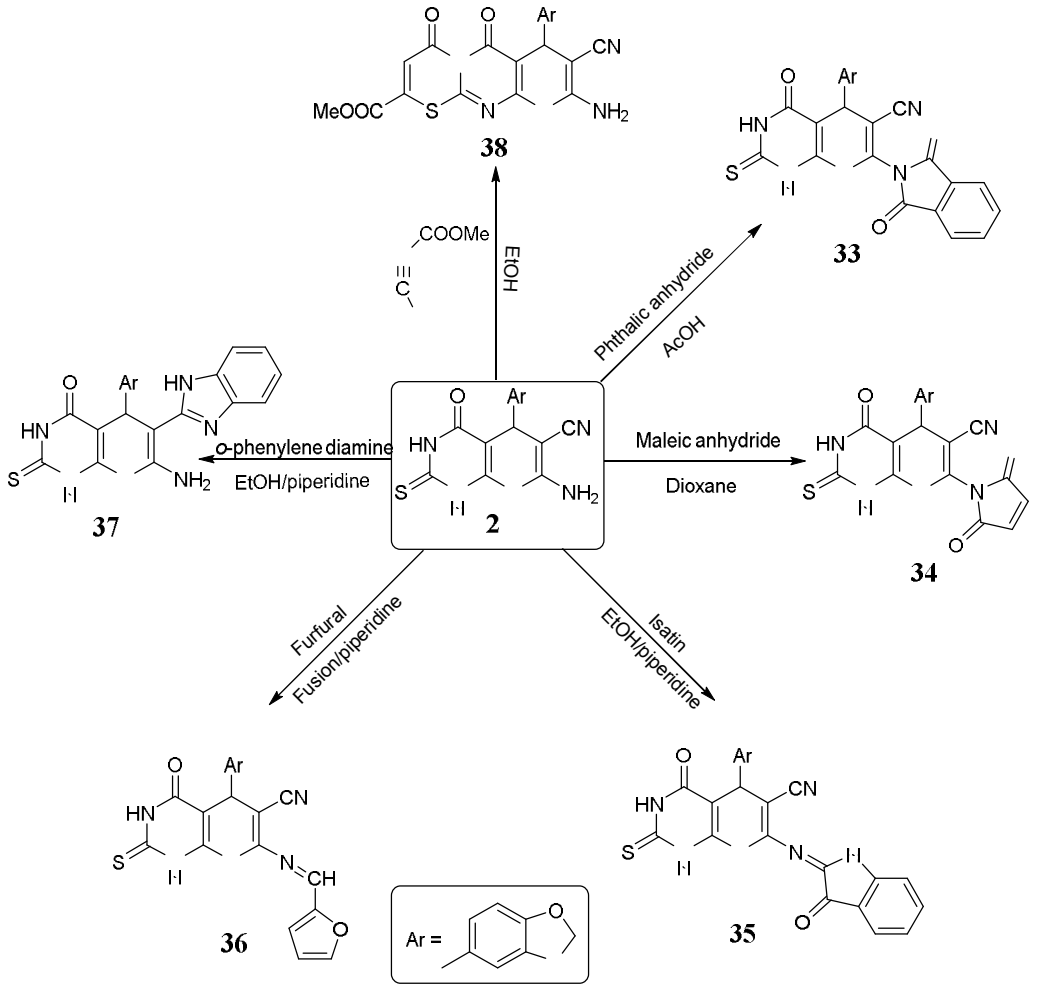
Moreover, pyranopyrimidine derivative **2** was treated with cyclohexanone in presence of lewis acid such as anhydrous zinc chloride under dry conditions for 12 h to furnish pyrimidopyranoquinolinone derivative **27**. In addition, condensation of **2** with a solution of acetaldehyde and malononitrile in absolute ethanol and a few drops of piperidine afforded pyrimidopyranoisoquinoline-1,3-dicarbonitrile derivative **28**. The synthetic strategy for building up a pyrrole ring fused to pyranopyrimidine moiety was achieved by alkylation of pyranopyrimidine derivatives with α-halo acetic acid derivatives, then cyclization of the alkylated product in basic medium. Therefore, treatment of pyranopyrimidine derivative **2** with ethyl bromoacetate in dry acetone containing anhydrous potassium carbonate furnished pyrrolopyranopyrimidine derivative **29**. Also, treatment of derivative **2** with phenacyl bromide in dry acetone containing anhydrous potassium carbonate afforded pyrrolopyranopyrimidinone derivative **30**. Interestingly, compound **2** was allowed to react with chloroacetyl chloride in different basic medium conditions to submit the acetylated product **31a**. Surprisingly, the alkylated compound **31** was obtained instead of **31a**. Herein, pyrazolopyranopyrimidinone derivative **32** could be obtained by refluxing a mixture of compound **2** either with hydroxylamine

hydrochloride in glacial acetic acid containing a catalytic amount of anhydrous sodium acetate, or hydrazine hydrate in ethanol (Scheme 5).



(Scheme 5)

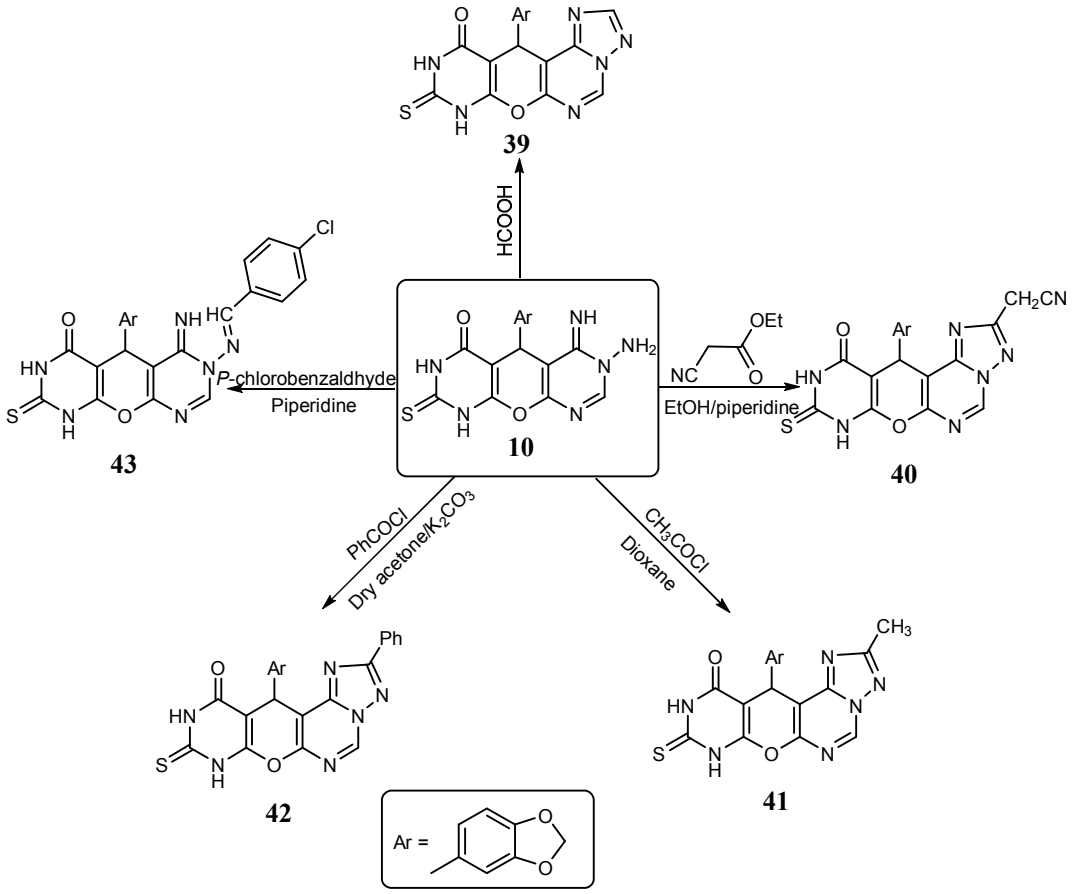
Refluxing a mixture of derivative **2** with phthalic anhydride in glacial acetic acid gave pyranopyrimidine derivative **33**. Interestingly, compound **2** was allowed to react with maleic anhydride in dioxane to afford pyranopyrimidine derivative **34**. The reaction of compound **2** with isatin in ethanol and a few drops of piperidine furnished derivative **35**. For the synthesis of Schiff's base, a mixture of compound **2** and furfural was fused in oil bath in presence of a few drops of piperidine to afford compound **36**. Reaction of compound **2** with *o*-phenylenediamine in absolute ethanol and a few drops of piperidine yielded compound **37**. Additionally, reaction of compound **2** with dimethyl acetylenedicarboxylate in refluxing ethanol for 12 h furnished methyl 9-amino-7-(benzo[*d*][1,3]dioxol-5-yl)-8-cyano-4,6-dioxo-4*H*,6*H*,7*H*-pyrano[2',3':4,5]pyrimido[2,1-*b*][1,3]thiazine-2-carboxylate **(38)** (Scheme 6).



(Scheme 6)

Studies on 7-amino-5-(benzo[*d*][1,3]dioxol-5-yl)-6-imino-2-thioxo-1,2,3,5,6,7-hexahydro-4*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidin-4-one (10).

The high functionality of pyranodipyrimidine derivatives prompted us to study the effect of acidic medium and some nucleophiles on compound **10** to construct more polyfunctionally fused and attached heterocycles. For instance, refluxing a mixture of derivative **10** with formic acid afforded triazolopyranodipyrimidinone derivative **39**. Moreover, the effect of ethyl cyanoacetate on compound **10** in refluxing ethanol and a few drops of piperidine furnished triazolopyranodipyrimidinyl acetonitrile **40**. In the same context, treatment of **10** with acetyl chloride in dioxane afforded triazolopyranodipyrimidinone derivative **41**. Additionally, reaction of derivative **10** with benzoyl chloride and anhydrous potassium carbonate in dry acetone gave triazolopyranodipyrimidinone derivative **42**. Finally, Schiff's base was obtained by fusion of compound **10** with *p*-chlorobenzaldehyde in presence of a few drops of piperidine in oil bath to produce pyranodipyrimidinone derivative **43** (Scheme 7).



(Scheme 7)

<u>All the newly synthesized compounds were:</u>

- Confirmed by spectral and micro-analytical data.

- Tested *in vitro* against various types of bacteria to study their anti-bacterial activity.