Fayoum University
Faculty of Science
Chemistry Department

Synthesis and Biological Evaluation of Some Fused Pyran and Pyrimidine Derivatives

By
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Synthesis and Biological Evaluation of Some Fused Pyran and Pyrimidine Derivatives

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M. Sc., Organic Chemistry, 2019

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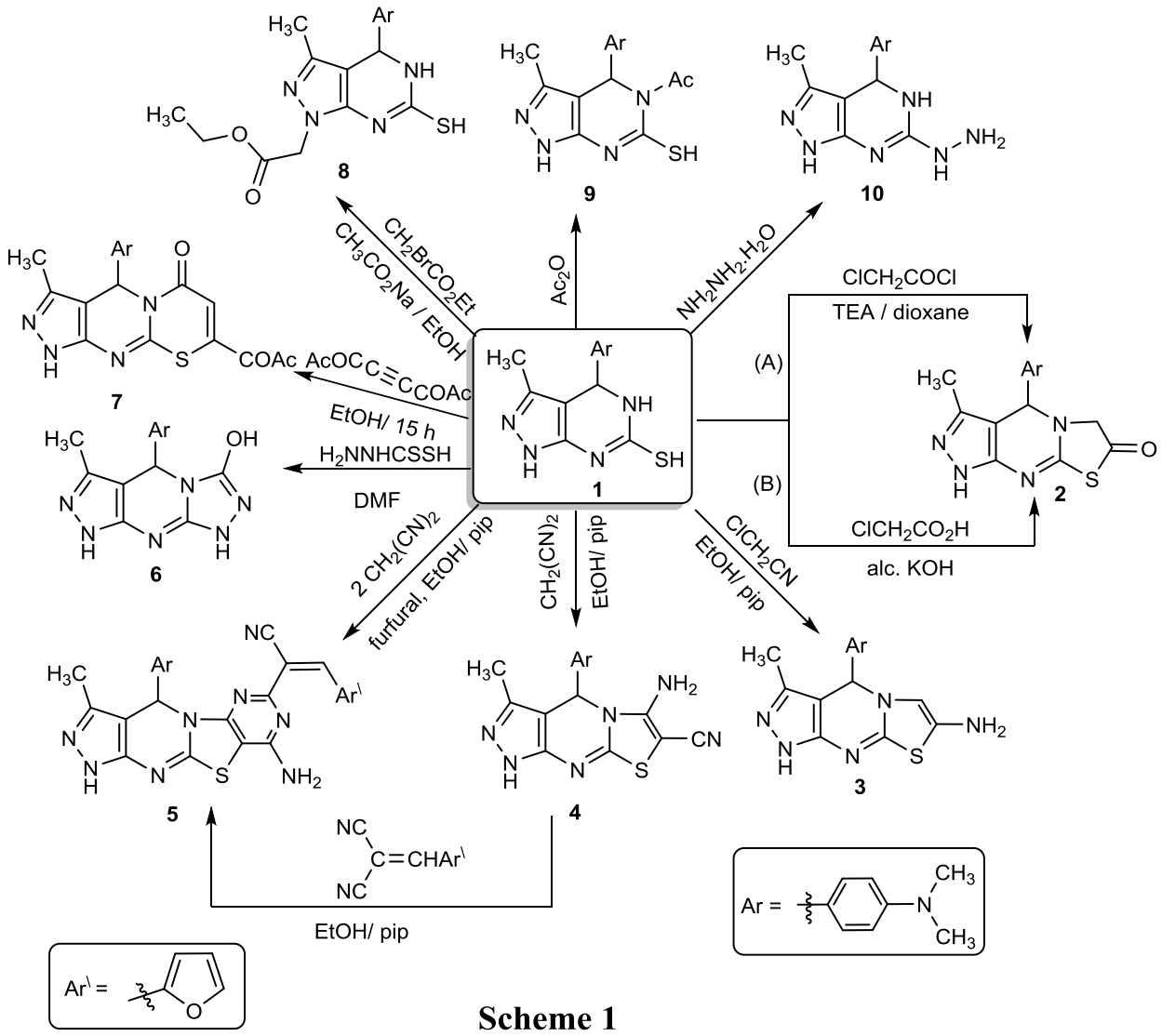
summary

In this thesis the synthesis of 4-(4-(dimethylamino)phenyl)-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiol **1**, 4-(6-hydrazinyl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-*N*,*N*-dimethylaniline **10** and 6-amino-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile **24** were reported. Subsequently, the behavior of these compounds towards different chemical reagents was studied to produce new heterocyclic compounds having expected antimicrobial activities.

Studies on 4-(4-(dimethylamino)phenyl)-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine-6-thiol (1)

Compound **1** was reacted with chloroacetyl chloride or monochlroacetic acid to afford thiazolo[3,2-*a*]pyrimidine derivative **2**. Also, fused pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidine derivatives **3** and **4** were attainable *via* refluxing compound **1** with either chloroacetonitrile or malononitrile in ethanol and a few drops of piperidine. In addition, compound **4** was reacted with furfurylidene malononitrile to afford pyrazolo[3,4-*d*]thiazolo[3,2-*a*:4,5-*d'*]dipyrimidine derivative **5**, which was also be obtained from the four multicomponent reaction of compound **1** with 2 mol of malononitrile and furfural. The nucleophillic addition reaction between compound **1** and *N*-amino dithiocarbamic acid gave pyrazolo[3,4-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivative **6**. Furthermore, reaction of compound **1** with dimethyl acetylenedicarboxylate furnished pyrazolo[3,4-*d*][1,3]thiazino[3,2-*a*]pyrimidine derivative **7**. The behavior of compound **1** towards ethyl bromoacetate afforded pyrazolo[3,4-*d*]pyrimidin-1-yl)acetate derivative **8**. Treatment of compound **1** with acetic anhydride furnished compound

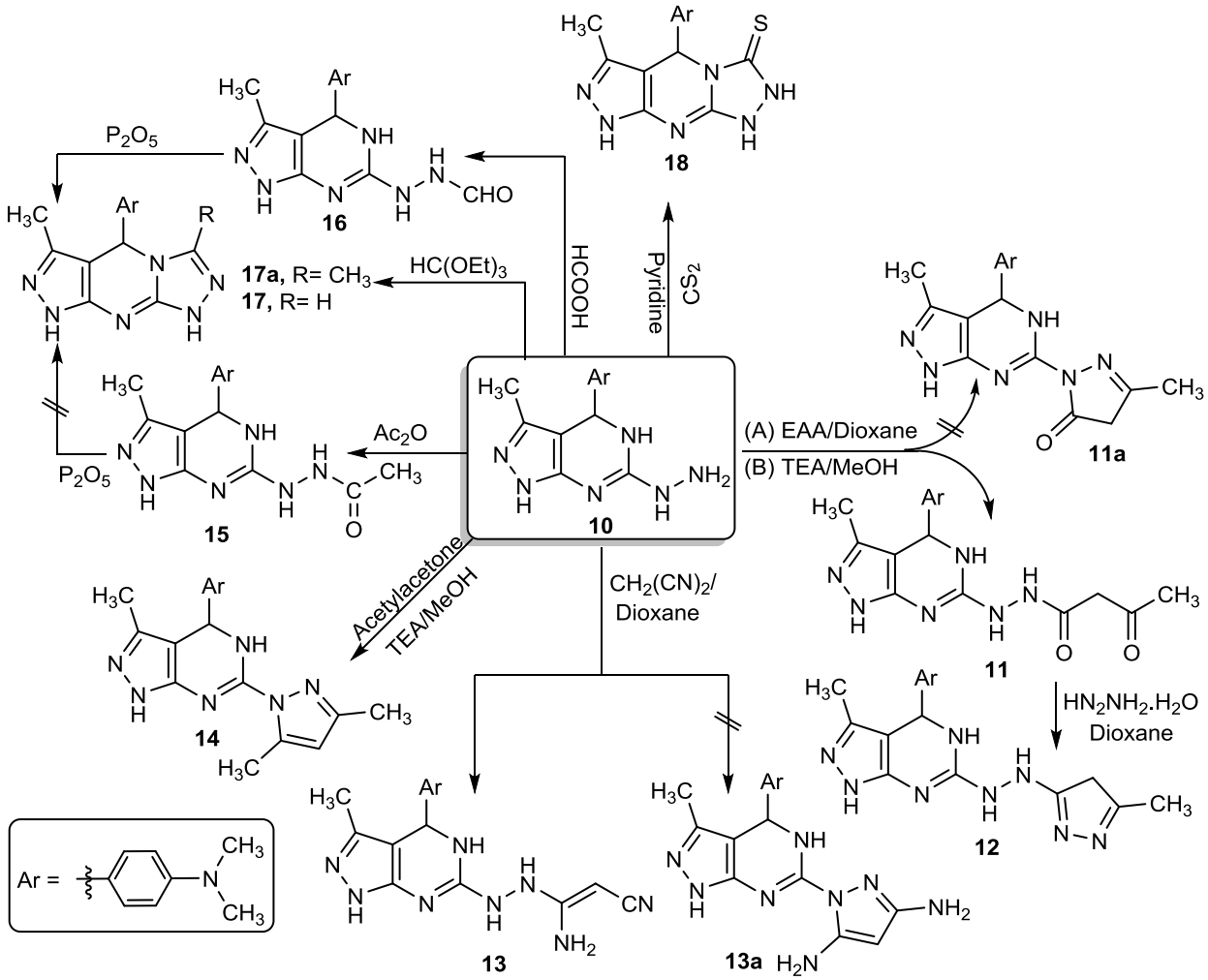
9, while refluxing compound **1** in hydrazine hydrate for 20 h gave Hydrazinyl derivative **10** (Scheme 1).



Scheme 1

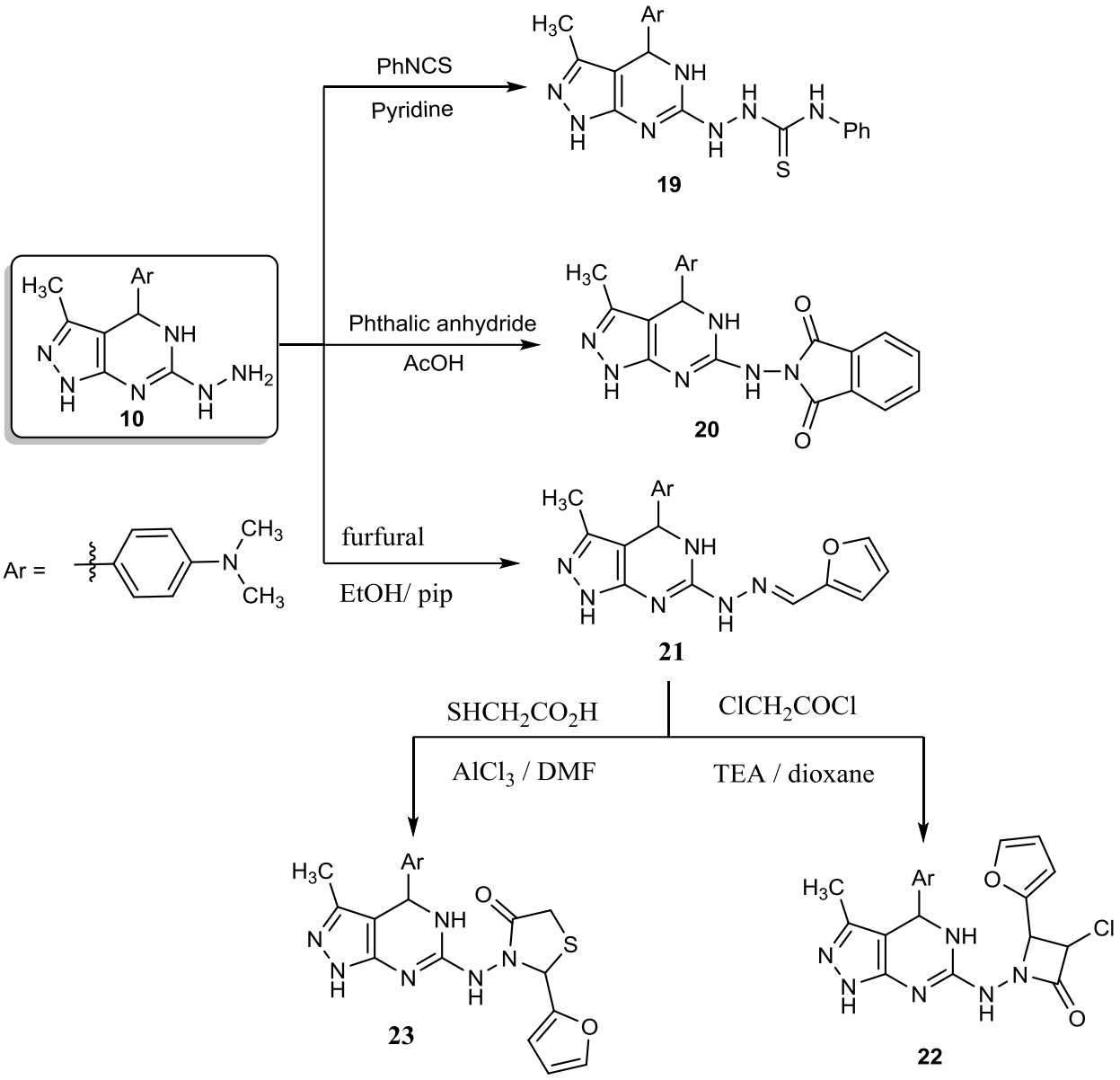
Studies on 4-(6-hydrazinyl-3-methyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)-*N*,*N*-dimethylaniline (10)

The behavior of hydrazinyl derivative **10** towards active methylene compounds namely, ethyl acetoacetate, malononitrile, and acetyl acetone afforded compounds **11**, **13**, and **14** respectively. Also, refluxing the acyclic compound **11** with hydrazine hydrate in dioxane afforded compound **12**. Acetohydrazide derivative **15** was accessible through the reaction of compound **10** with acetic anhydride. The acetohydrazide derivative **15** was allowed to reflux with phosphorous pentaoxide in dry toluene to give the cyclic derivative **17a**, however no cyclization product was observed and, instead, the original compound **15** was recovered unchanged. Refluxing compound **10** with formic acid gave formohydrazide derivative **16**, which was refluxed with phosphrous pentaoxide in dry toluene to afford pyrazolo[3,4-*d*][1,2,4]triazolo[4,3-*a*]pyrimidine derivative **17**. Also, compound **17** was asserted chemically through the reaction between compound **10** and triethyl orthoformate. Also, treating a solution of compound **10** in pyridine with carbon disulphide afforded pyrazolotriazolopyrimidine derivative **18** (Scheme 2).



Scheme 2

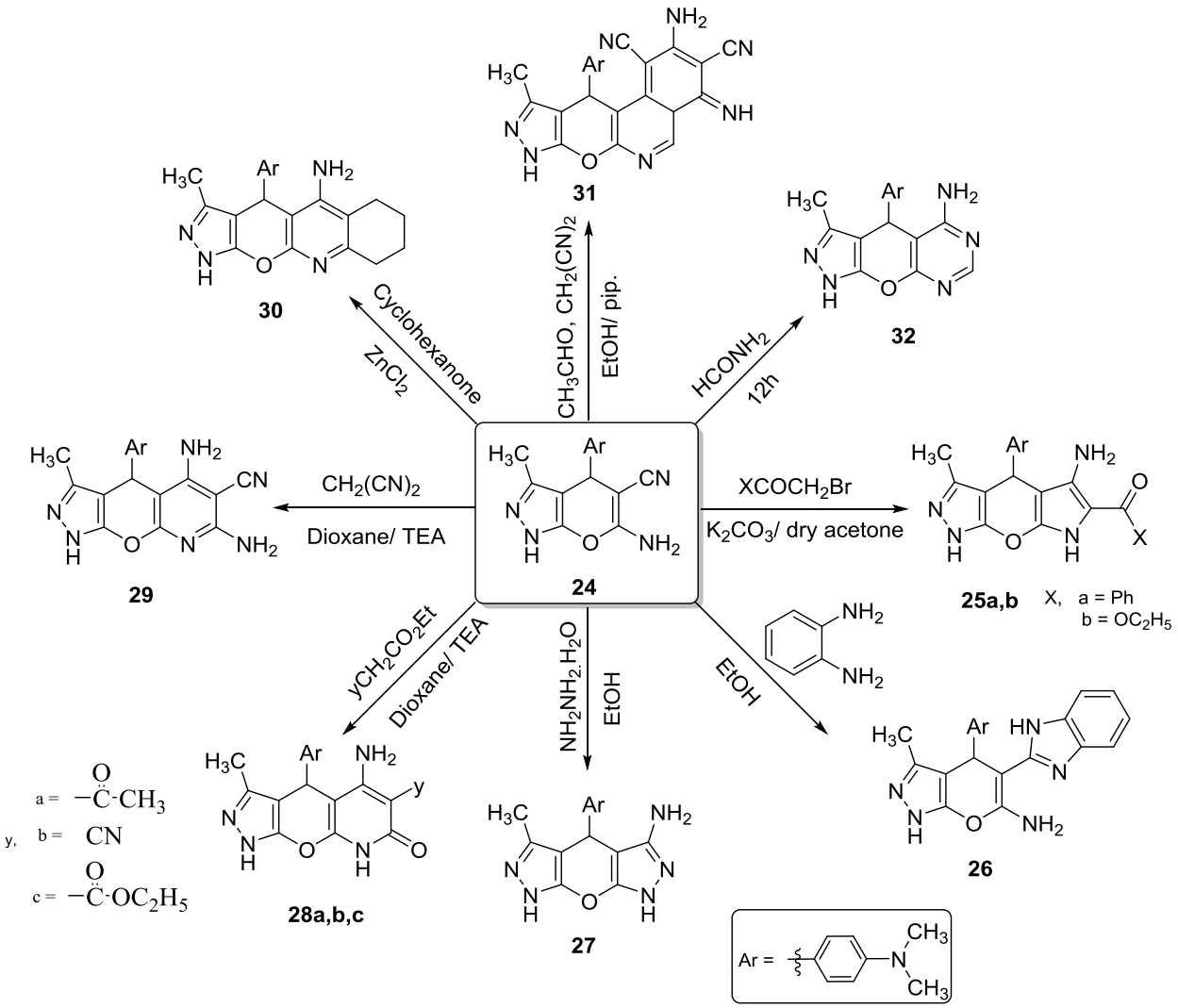
Reaction of hydrazinyl derivative **10** with phenyl isothiocyanate in pyridine submitted **19**. Additionally, behavior of compound **10** with phthalic anhydride in glacial acetic acid furnished compound **20**. Schiff's base **21** was achieved by the fusion of compound **10** with furfural and a few drops of piperidine. In addition, Schiff's base **21** was allowed to reflux with chloroacetyl chloride and triethyl amine to give the corresponding azetidinone derivative **22**. Furthermore, a cycloaddition reaction occurred between Schiff's base **21** and thioglycolic acid to afford the corresponding thiazolidinone derivative **23** (Scheme 3).


PhNCS
Pyridine
19
Phthalic anhydride
AcOH
20
furfural
EtOH/ pip
21
10
Ar =
SHCH2CO2H
AlCl3 / DMF
ClCH2COCl
TEA / dioxane
23
22

Scheme 3

Studies on 6-amino-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile (24)

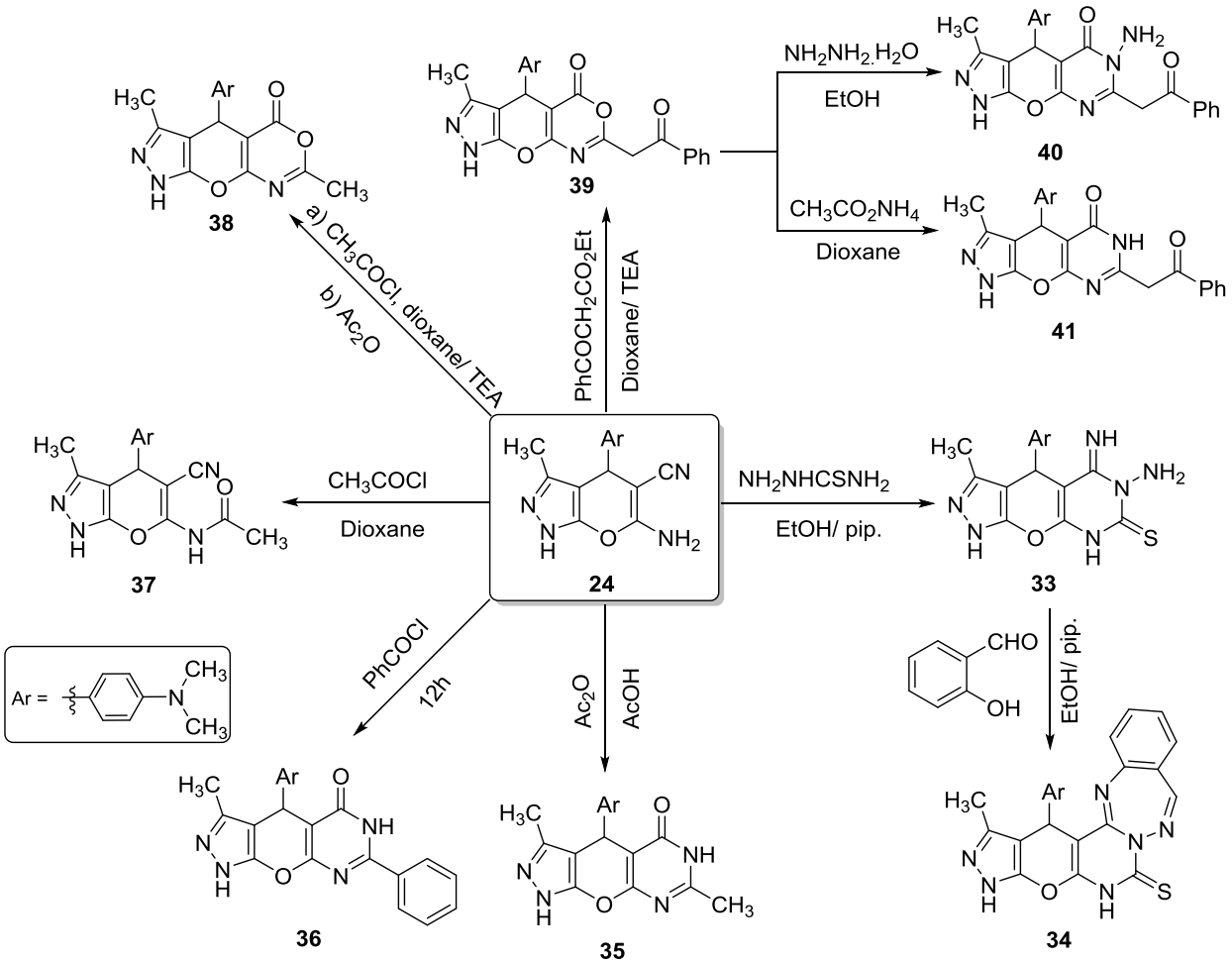
Alkylation of compound **24** with phenacyl bromide or ethyl boromoacetate in dry acetone afforded **25a,b**. the new synthetic benzo[*d*]imidazole derivative **26** was achieved through the interaction between compound **24** and *o*-phenylene diamine in ethanol. Refluxing compound **24** in hydrazine hydrate gave pyrano[2,3-*c*:6,5-*c'*]dipyrazole derivative **27**. An additional pathway for building up polyfunctionally fused pyrans was achieved *via* the treatment of compound **24** with assorted active methylene compounds namely, ethyl acetoacetate, ethyl cyanoacetate, and diethylmalonate in dioxane and triethylamine afforded aminopyridinone derivative **28a,b,c**. In the same manner, diaminopyridine derivative **29** was isolated when compound **24** was refluxed with malononitrile in dioxane and triethylamine. Condensation between compound **24** and cyclohexanone in the presence of Lewis acid such as anhydrous zinc chloride afforded pyranoquinoline derivative **30**, condensation of compound **24** with acetaldehyde and malononitrile afforded isoquinoline derivative **31**, while condensation of compound **24** and formamide furnished fused pyranopyrimidine derivative **32** (Scheme 4).



Scheme 4

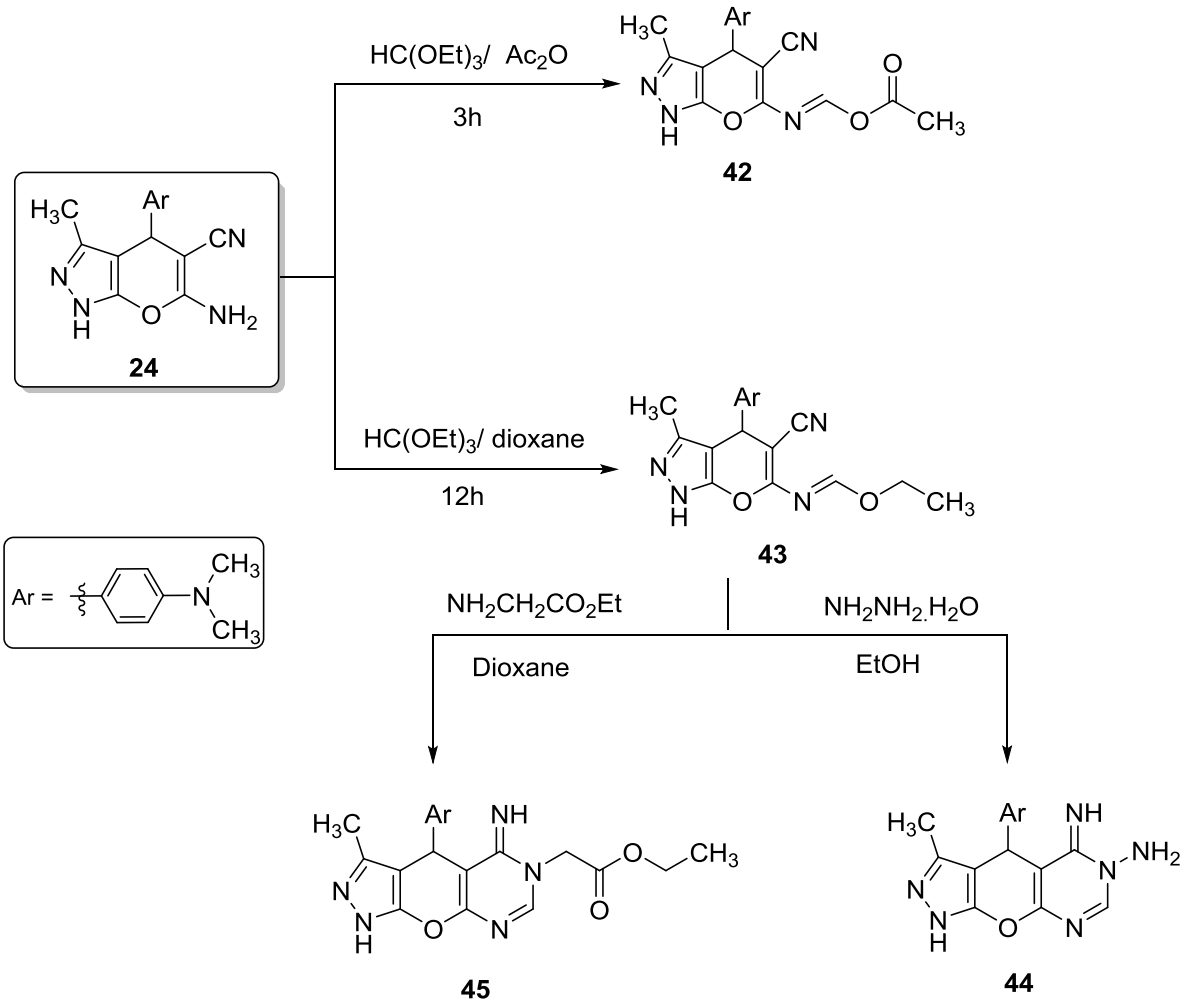
Furthermore, fused pyrimidine derivative was achieved from the reaction between compound **24** and thiosemicarbazide to afford pyrimidine thione derivative **33**, which reacted with salicyldehyde to give corresponding benzotriazepine derivative **34**. Acetylation of compound **24** with acetic anhydride in glacial acetic acid afforded pyrimidinone derivative **35**. Reaction of compound **24** with benzoyl chloride gave phenylpyrimidinone derivative **36**. Moreover, the behavior of compound **24** with acetyl chloride in presence of dioxane afforded the acyclic derivative **37**. Also, compound **24** was reacted either with acetyl chloride in

presence of dioxane and a few drops of triethylamine, or acetic anhydride to yield oxazine derivative **38**. The reaction of compound **24** with ethyl benzoylacetate in presence of dioxane and a few drops of triethylamine afforded oxazine derivative **39**, which was converted into *N*-aminopyrimidine derivative **40** *via* refluxing with hydrazine hydrate. Also, compound **39** was fused with ammonium acetate to give pyrimidine derivative **41** (Scheme 5).



Scheme 5

Compound **24** was condensed with triethyl orthoformate in acetic anhydride to submit formimidic anhydride derivative **42**, while refluxing compound **24** with triethyl orthoformate in dioxane afforded the methylformimidate derivative **43**. Compound **43** was refluxed with *N*-nucleophiles such as hydrazine hydrate and ethyl glycinate to give compound **44** and **45**, respectively (Scheme 6).



Scheme 6

All of the newly synthesized compounds were:

- Confirmed from elemental analysis and spectral data.
- Tested *in vitro* against a variety of bacteria to study their anti-bacterial activity.