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Synthesis and Biological Evaluation of some Novel Phthalazine Derivatives

By

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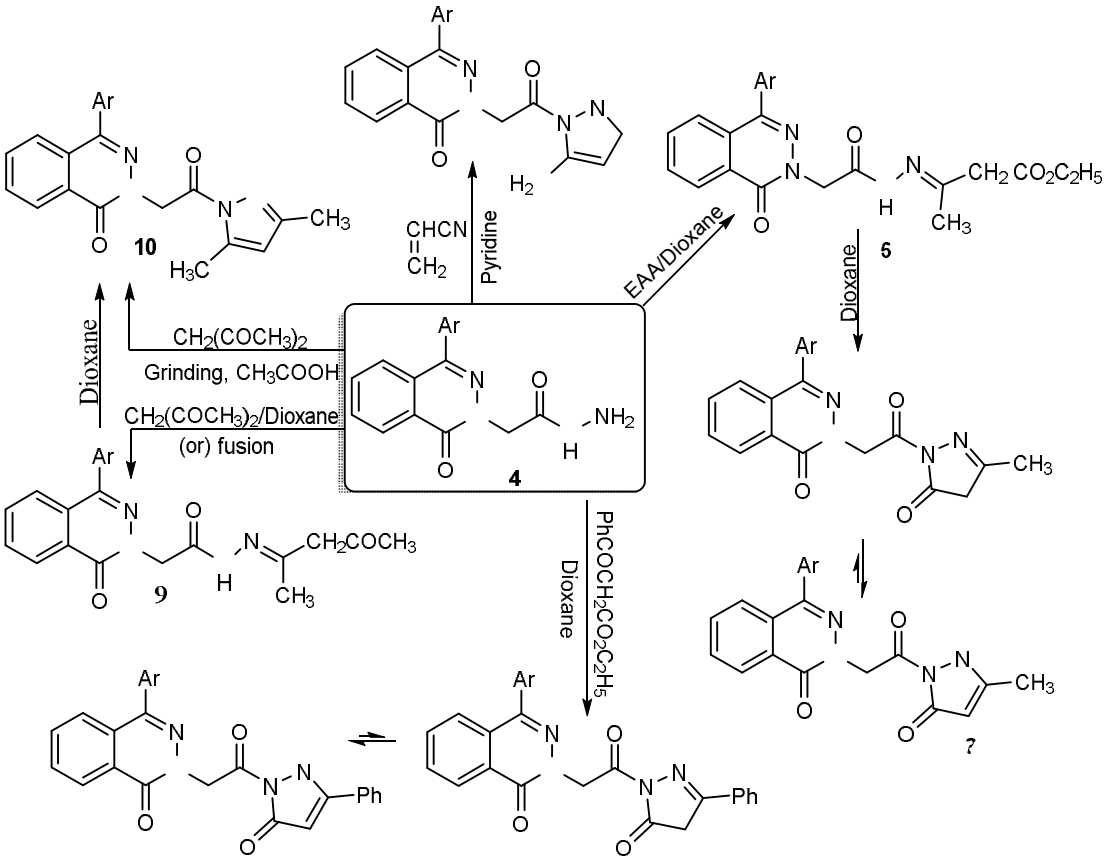
Synthesis and Biological Evaluation of some Novel Phthalazine Derivatives

In this thesis the synthesis of 2-(4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetohydrazide **(4)**, 4-(3,4-dimethylphenyl)-2-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)phthalazin-1(2*H*)-one **(23)**, ammonium 2-(2-(4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetyl)hydrazine-1-carbodithioate **(28)**, and 4-(3,4-dimethylphenyl)-1-oxophthalazine-2(1*H*)-carbothiohydrazide **(37)** were utilized as precursors to construct a novel series of phthalazinones bearing various valuable function groups in excellent yields *via* several simple and promising approaches.

Synthesis and reactions of 2-(4-(3,4-Dimethylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetohydrazide (4)

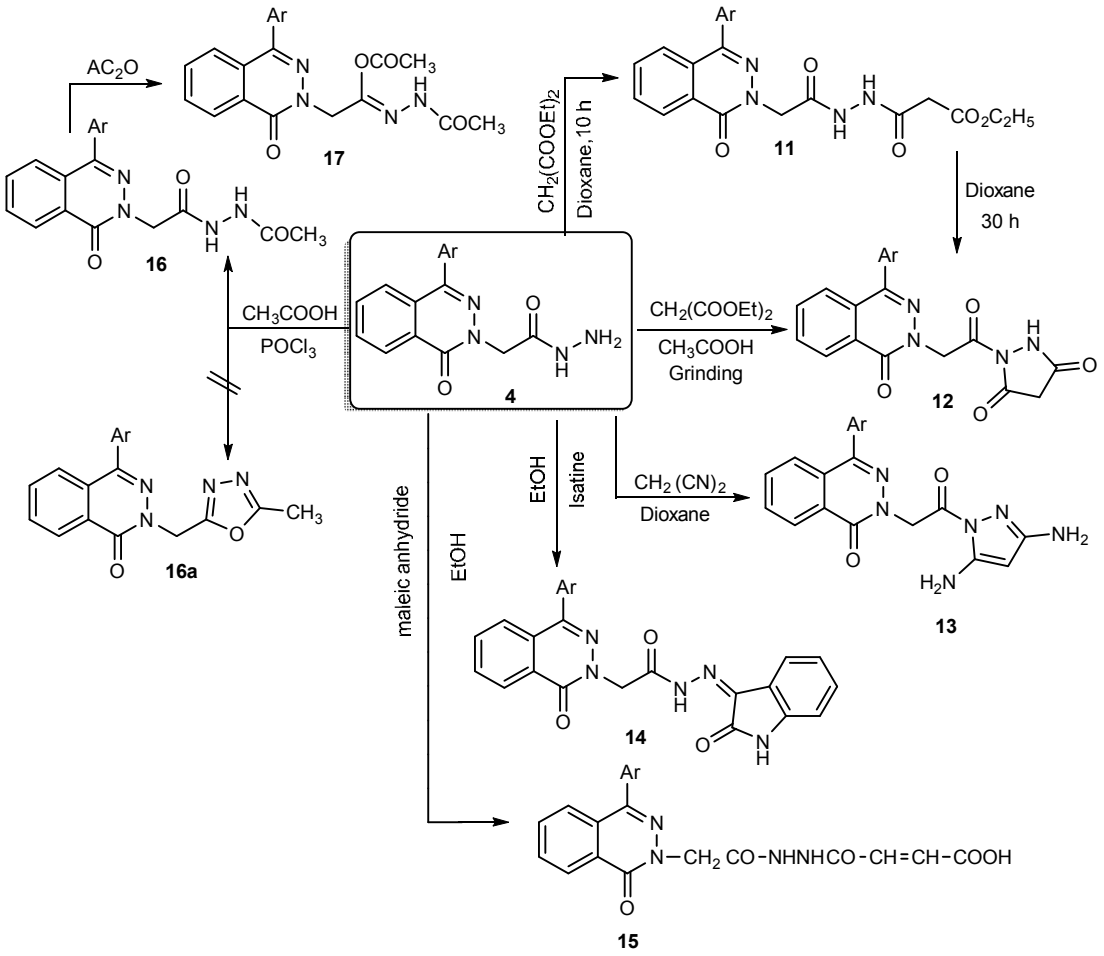
The reaction of acetohydrazide derivative **4** with acrylonitrile in pyridine gave rise to a new 2,3-dihydro-1*H*-pyrazole derivative **5**. In another attempt to build up more heterocycles attached to phthalazine acetohydrazide derivative **4**, it was allowed to reflux with ethyl acetoacetate in dioxane. Surprisingly, and after 10 h, only the acyclic derivative **6** was isolated. Additionally, compound **6** was chemically proven when a subsequent cyclization was accomplished and 4-(3,4-dimethylphenyl)-2-(2-(3-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl)-2-oxoethyl)phthalazin-1(2*H*)-one (**7**) was attained *via* refluxing the acyclic isolated intermediate **6** in dioxane for an extra 30 h. Likewise, another 5-*exo-trig* ring closure was observed, and a new dihydropyrazolone ring was attained through the reaction of phthalazine acetohydrazide derivative **4** with ethyl benzoylacetate in boiling dioxane for 30h . In many attempts to develop better reaction profiles, various reaction conditions were explored to synthesize pyrazole derivative **10**. Phthalazine acetohydrazide derivative **4** was allowed to reflux with acetylacetone in dioxane for 10 h to have access to 2-(4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1*H*)-yl)-*N*'-(4-oxopentan-2-ylidene)acetohydrazide (**9**). An alternative pathway to assemble compound **9** was also developed by the fusion of acetohydrazide **4** with acetylacetone and few drops of piperidine at 200 ^{o}C for only 30 min. The cyclization of the isolated intermediate **9** to the target pyrazole derivative **10** took place through the prolonged heating of **9** in dioxane or *via* grinding of acetohydrazide derivative **4** with acetylacetone in the presence of a few drops of acetic acid at room temperature for only 30 min (Scheme1).



Scheme 1

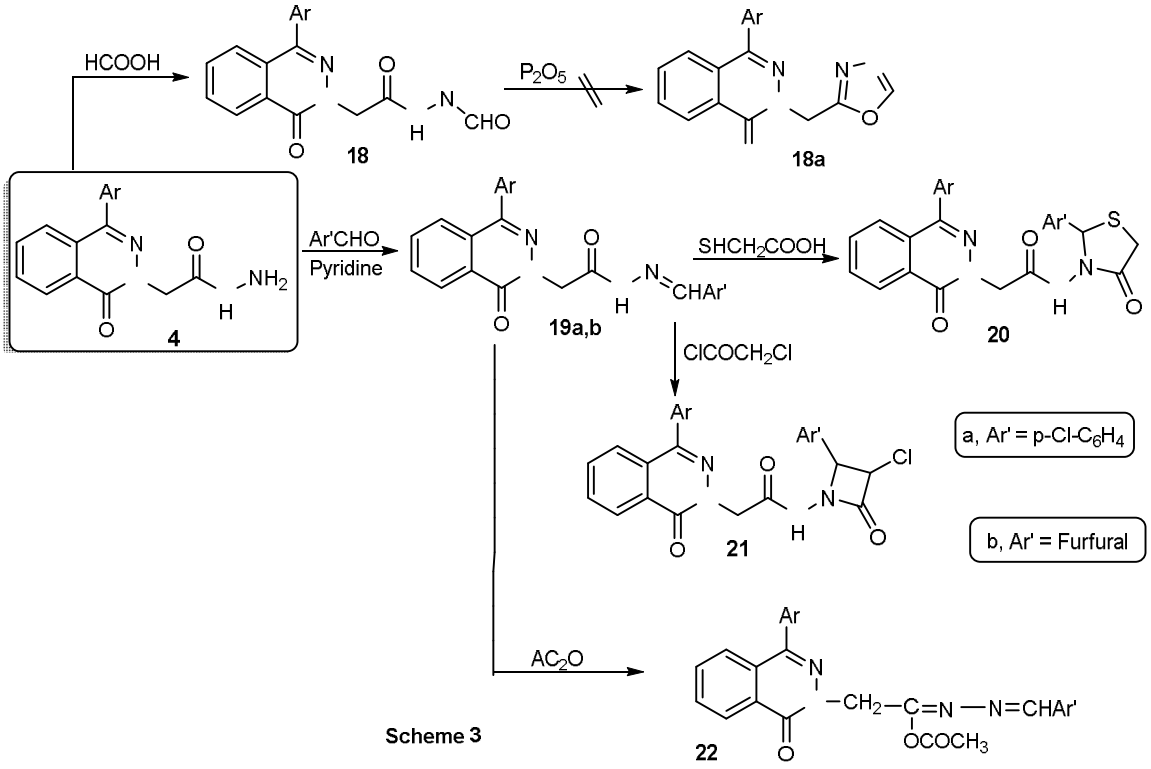
Refluxing our acetohydrazide scaffold **4** with diethyl malonate in dioxane for 10 h to obtain the isolable ethyl 3-(2-(2-(4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetyl)hydrazineyl)-3-oxopropanoate (**11)** and then cyclizing the isolated intermediate **11** by refluxing in dioxane for an extra 30 h, or *via* grinding of acetohydrazide derivative **4** with diethyl malonate in the presence of a few drops of acetic acid at room temperature for only 30 min gave rise to pyrazolidine-3,5-dione derivative **12**. The exploration of the reactivity of active methylene nucleophiles on acetohydrazide scaffold **4**, the latter compound was allowed to react with malononitrile in dioxane to submit the cyclization product 3,5-diamino-1*H*-pyrazol derivative **13**. Additionally, a condensation reaction was observed, and oxoindolin derivative **14** was isolated when phthalazine acetohydrazide derivative **4** was treated with isatin. Refluxing acetohydrazide scaffold **4** with maleic anhydride in ethanol to obtain the acyclic product [4-(2-(2-(4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetyl)hydrazineyl)-4-oxobut-2-enoic acid (**15)** was isolated. The reaction of phthalazine acetohydrazide derivative **4** with acetic acid in the presence of phosphorous oxychloride didn't afford the expected cyclized oxadiazol derivative **16a**, but rather an *N*-acetylation reaction occurred at the terminal amino of acetohydrazide derivative **4** to afford the *N'*-acetyl acetohydrazide **16** as the sole product. In

another attempt to have an access to the desired cyclization product **16a**, *N'*-acetyl acetohydrazide derivative **16** was allowed to reflux with acetic anhydride; however, no cyclization reaction was observed. Alternatively, *O*-acylation reaction was reported, and the corresponding diacetyl derivative **17** was attained as the only product (Scheme 2).



Scheme 2

In order to have access to more assorted heterocycles attached to parent scaffold, phthalazine acetohydrazide derivative **4** was refluxed with formic acid to obtain *N'*-formyl acetohydrazide **18**, thereafter **18** was refluxed with phosphorous pentaoxide in dry toluene to obtain the oxadiazol derivative **18a**.Unfortunately, no cyclization was observed, and the acyclic *N*'-formyl acetohydrazide **18** was recovered unchanged even after 24 h. Schiff's bases **19a,b** were acquired in a good yield *via* a condensation reaction between acetohydrazide derivative **4** with different aromatic aldehydes of namely *p*-chlorobenzaldehyde or furfural in pyridine. A new thiazolidine ring was assembled and thiazolidinyl acetamide derivative **20** was accessible through thia addition type on azamethine moiety then a subsequent *5-exo-trig* ring closure reaction. Furthermore, valuable 2-azetidinone ring was attached to scaffold compound **4** through a cycloaddition reaction of chloroacetyl chloride with a solution of Schiff's base **19a** in dioxane and triethylamine. Additionally, when the hydrazone **19b** was allowed to react with acetic anhydride; however, no cyclization reaction was observed. Alternatively, *O*-acylation reaction was reported, and acetohydrazonic anhydride **22** was attained as the only product (Scheme 3).

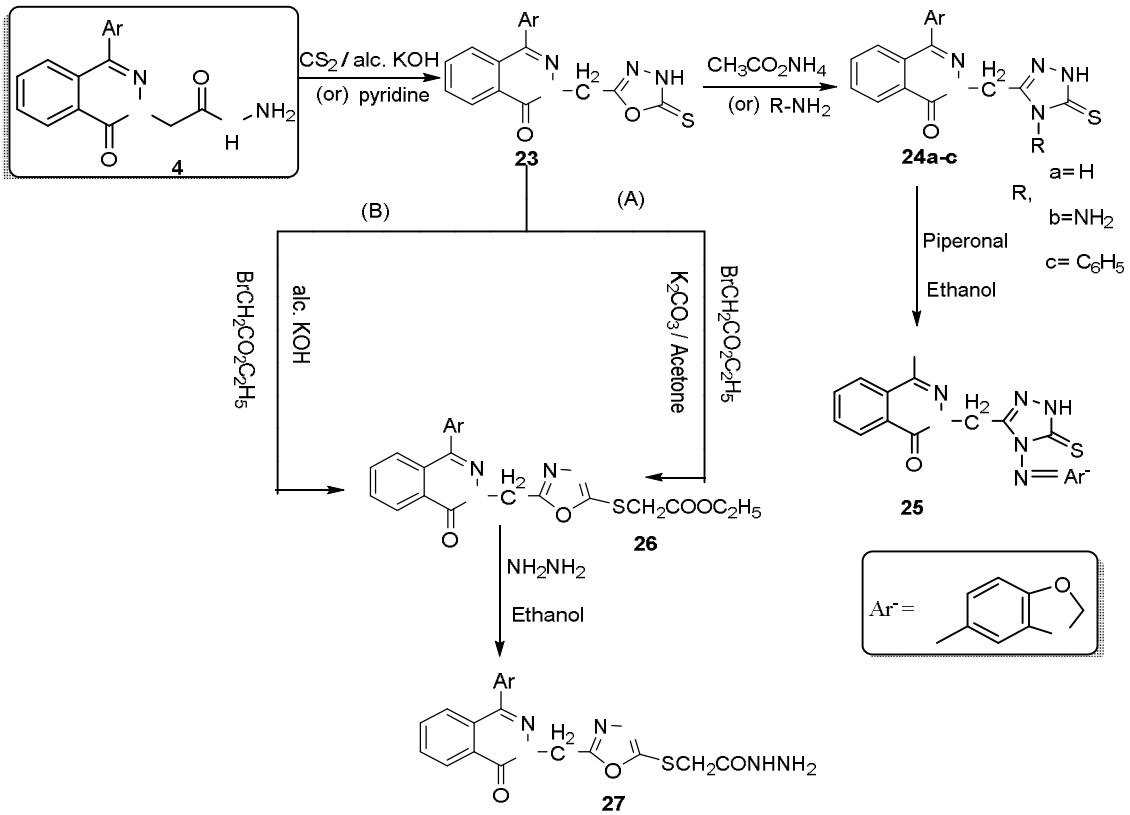


Scheme 3

Synthesis and reactions of 4-(3,4-dimethylphenyl)-2-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methyl)phthalazin-1(2*H*)-one (23)

Another suggested pathway for building up a new oxadiazol derivative was achieved *via* the treatment of a compound **4** in alcoholic potassium hydroxide or pyridine with carbon disulphide to afford oxadiazol derivative **23**. The behavior of oxadiazol derivative **23** towards assorted nitrogen nucleophiles, namely ammonium acetate, hydrazine hydrate and aniline was thoroughly investigated. Thus, the interaction of oxadiazol derivative **23** with

ammonium acetate, hydrazine hydrate and aniline produced the corresponding triazol derivatives **24a-c**. Additionally, Schiff's base **25** was acquired in a good yield *via* a condensation reaction between triazol derivative **24b** and piperonal in ethanol. The behavior of compound **23** towards ethyl bromoacetate as alkylating agents, was explored in which oxadiazol derivative **23** was allowed to react with ethyl bromoacetate in presence of ethanolic solution of potassium hydroxide or potassium carbonate in dry acetone to furnish 1,3,4-oxadiazol-thioacetate **26**, a better reaction profile and yield were observed in case of refluxing in ethanolic KOH. The structure of the ester **26** was established chemically *via* the interaction with hydrazine hydrate and afforded 1,3,4-oxadiazol-thioacetohydrazide **27** (Scheme 4).

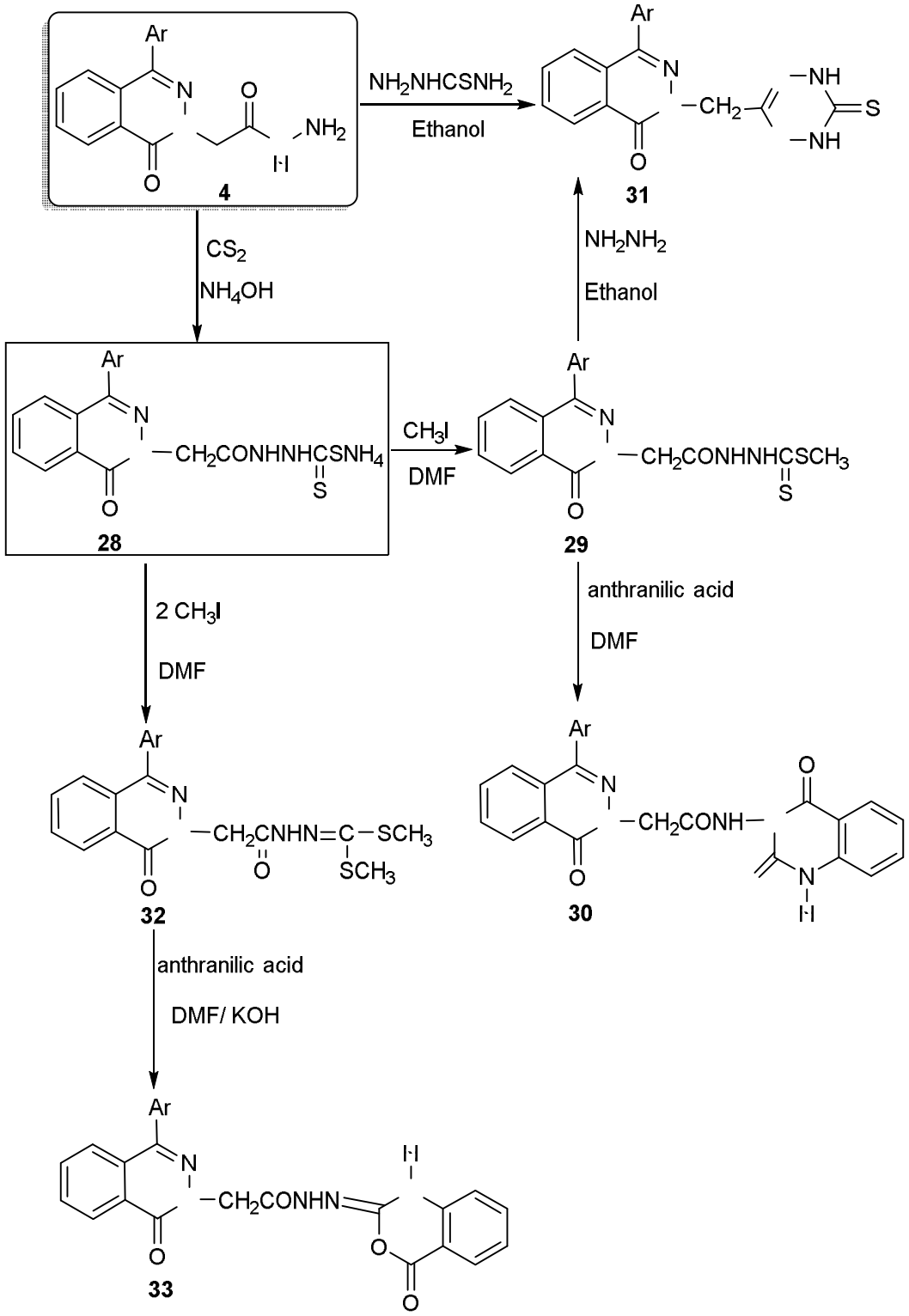


Scheme 4

<u>Synthesis and reactions of ammonium 2-(2-(4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetyl)hydrazine-1-carbodithioate (28)</u>

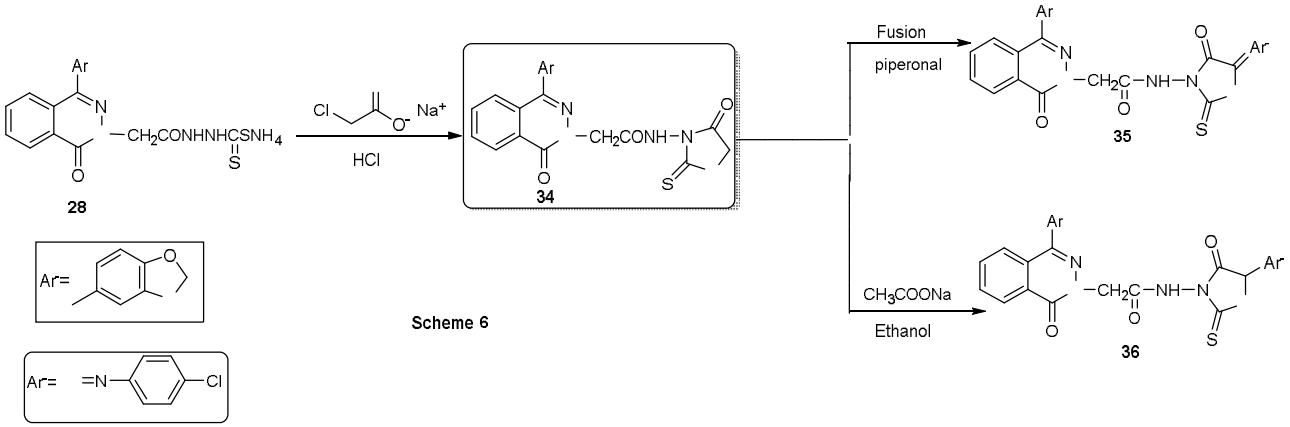
The treatment of acetohydrazide **4** solution in ammonium hydroxide with carbon disulfide to obtain ammonium carbodithioate derivative **28**. Compound **28** was reacted with methyl iodide in refluxing DMF produced mono methyl derivative **29**. The later compound **29** was proven chemically when a subsequent cyclization reaction was achieved *via* refluxing mono methyl compound **29** with anthranilic acid in DMF for 6 h to submit 1,4-dihydroquinazolin derivative **30**. Interestingly, reaction of monomethyl compound **29** with hydrazine hydrate in ethanol submitted 1,2,4,5-tetrazin phthalazin-1(2*H*)-one (**31**). The tetrazin compound **31** was also proven chemically through synthesizing it utilizing a second method in which acetic acid hydrazide **4** was allowed to reflux with thiosemicarbazide to yield targeted compound **31**. In exploration of the effect of methyl iodide as alkylating agents on carbodithioate derivative **28**, the later compound was allowed to react with 2 mol methyl iodide in DMF to yield

compound **32**. Attempts were effort to cyclize the dimethyl compound **32** by refluxing with anthranilic acid in presence of solution of potassium hydroxide to furnish benzo[*d*][1,3]oxazinacetohydrazide **33** (Scheme 5).



Scheme 5

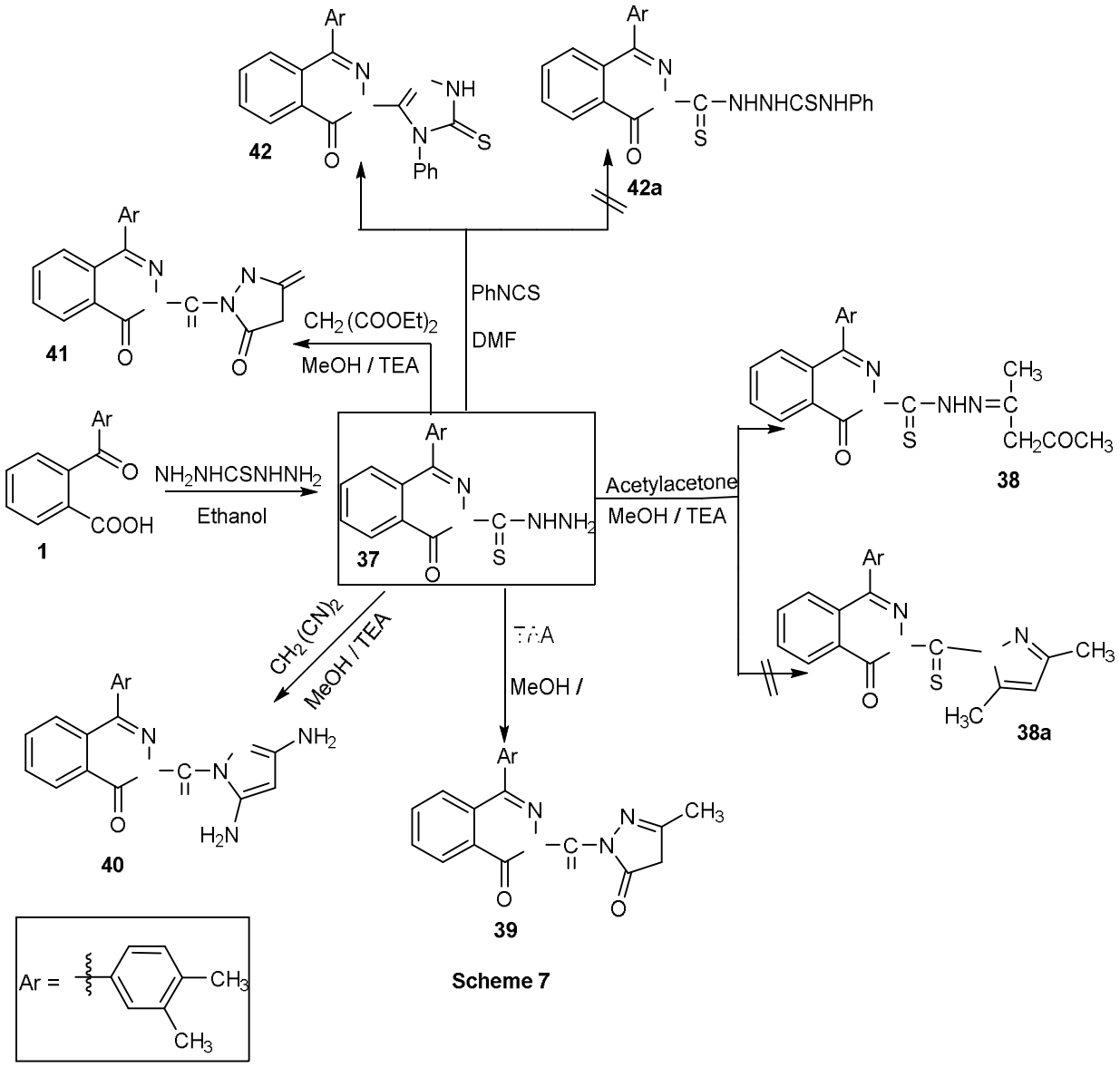
In another attempt to build up more heterocycles attached to key compound **28**, it was allowed to reflux with sodium chloroacetate in basic medium followed by acidification by conc. HCl gave 4-oxo-2-thioxothiazolidin derivative **(34)**. Additionally, the presence of active methylene in 4-oxo-2-thioxothiazolidin **34** encourages us to assemble arylidine derivatives. Compound (**35**) was acquired *via* the fusion of 4-oxo-2-thioxothiazolidin **34** with piperonal and few drops of piperidine. The reaction of 4-oxo-2-thioxothiazolidin **34** with *p*-chlorobenzene diazonium chloride to yield *N*-(5-((4-chlorophenyl)diazenyl)-4-oxo-2-thioxothiazolidin-3-yl)-2-(4-(3,4-dimethylphenyl)-1-oxophthalazin-2(1*H*)-yl)acetamide (**36**) (Scheme 6).



Scheme 6

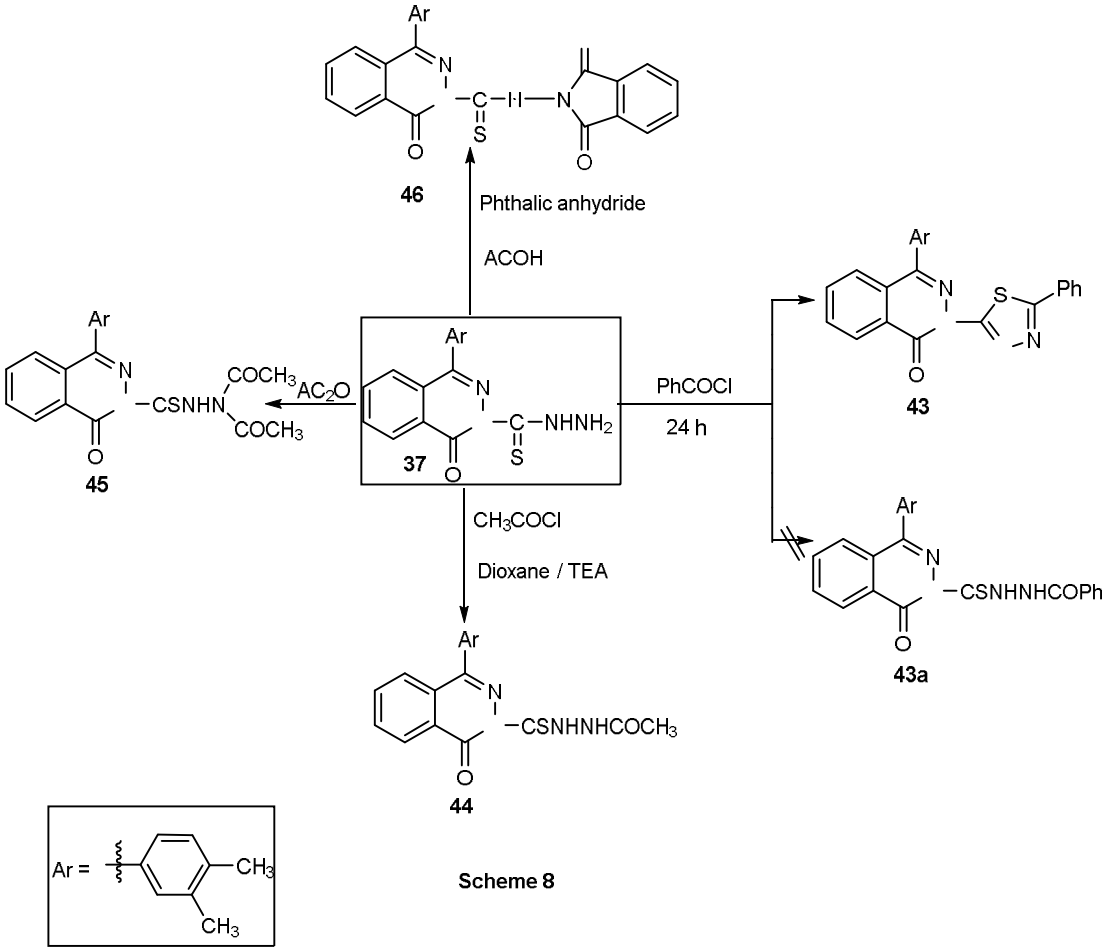
Synthesis and reactions of 4-(3,4-dimethylphenyl)-1-oxophthalazine-2(1*H*)-carbothiohydrazide (37)

Carbothiohydrazide derivative **(37)** was readily available through a condensation reaction between *o*-benzoyl benzoic acid **1** and thiocarbonohydrazide in boiling ethanol. Interestingly, the cyclized compound 2-(3,5-dimethyl-1*H*-pyrazole-1-carbonothioyl)-4-(3,4-dimethylphenyl)phthalazin-1(2*H*)-one **(38a)** was expected to be the final product of the reaction between carbothiohydrazide **37** and acetylacetone, but rather an condensation reaction occurred at the terminal amino of carbothiohydrazide **37** to submitt the 4-(3,4-dimethylphenyl)-1-oxo-*N*′-(4-oxopentan-2-ylidene)phthalazine-2(1*H*)-carbothiohydrazide **(38)** as the sole product. Importantly, in case of refluxing compound **37** with ethylacetoacetate in methanol and few drops of TEA the desired cyclization product 4,5-dihydro-1*H*-pyrazolone derivative **(39)** was observed. In another attempt to build up more heterocycles attached to our carbothiohydrazide derivative **37**, the latter compound was allowed to react with malononitrile in methanol and few drops of TEA to submit the cyclization product 3,5-diamino-1*H*-pyrazole derivative **(40)**. Likewise, pyrazolidine-3,5-dione **41** was attained through the reaction of our key compound **37** with diethyl malonate in boiling methanol for 6h. A solution of carbothiohydrazide derivative **37** in DMF was refluxed with phenyl isothiocyanate for 24 h to produce 2-(4-(3,4-dimethylphenyl)-1-oxo-1,2-dihydrophthalazine-2-carbonothioyl)-*N*-phenylhydrazine-1-carbothioamide **(42a)**. Surprisingly, the cyclization product 4-(3,4-dimethylphenyl)-2-(4-phenyl-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)phthalazin-1(2*H*)-one **(42)** was obtained instead of expected compound **42a** (Scheme 7).



Scheme 7

The solution of carbothiohydrazide derivative **37** was refluxed with benzoyl chloride for 24 h to yield *N*'-(4-(3,4-dimethylphenyl)-1-oxo-1,2-dihydrophthalazine-2-carbonothioyl)benzohydrazide was expected, **(43a)**. But, the cyclization product 4-(3,4-dimethylphenyl)-2-(5-phenyl-1,3,4-thiadiazol-2-yl)phthalazin-1(2*H*)-one **(43)** was obtained instead of **43a**. Compound **44** was accessible through the reaction of carbothiohydrazide derivative **37** with acetyl chloride in presence of few drops of triethylamine. Likewise, the same behavior was observed in case of treating carbothiohydrazide derivative **37** with acetic anhydride and gave the diacetyl derivative **45**. Interestingly, a condensation reaction was observed, and dioxoisoindolin derivative (**46**) was isolated when carbothiohydrazide derivative **37** was treated with phthalic anhydride (Scheme 8).



Scheme 8

The structure of newly-synthesized phthalazines derivatives were confirmed by chemical methods, analytical and spectral date (IR, H^1NMR, C^{13}NMR, and M.S spectrum).

Finally, the antimicrobial activity of newly-synthesized phthalazines were screened against different microbial strains; namely, Gram-negative and Gram-positive bacteria utilizing Amoxicillin as a standard drug.