**Faculty of Science**
**Chemistry Department**

# Synthesis and Characterization of Some New Azoles and Azines Functionalized with Active Centers for Biological Applications

**By**

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**A thesis submitted for the degree of Ph.D. of science in chemistry**

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**Chemistry Department**
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**Synthesis and Characterization of Some New Azoles and Azines Functionalized with Active Centers for Biological Applications**

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## ABSTRACT

The purpose of this original work is to prepare novel biologically active compounds through the following three parts:

**Part I**: Synthesis of new pyrazoles and pyridines with trimethoxyphenyl scaffold as Combretastatin analogues was archived *via* reaction of (*E*)-3-(dimethylamino)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one with active nitriles, β-ketoester, 1,3-diketones, heterocyclic amines and hydrazonyl halides. Molecular docking and anticancer screening of the newly compounds were described against HePG-2, HCT-116, MCF-7 and PC3 cancer cell lines.

**Part II**: A new series of compounds containing thiazole nucleus with dimethoxyphenyl scaffold as Rhodanine analogues have been synthesized from the reactions of the thiosemicarbazones with a series of α-halocarbonyl compounds. The new synthesized compounds were

evaluated for their antimicrobial activities against fungal and yeast strains.

**Part III**: A new series of 3-cyanopyridines with the dimethoxyphenyl scaffold were prepared from the reaction of 3-(4-bromophenyl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one with active nitriles. The newly prepared 2-thioxo-1,2-dihydropyridine-3-carbonitrile was used for the preparation of new series of condensed thienopyridines.

**Keywords:** Acetophenone derivatives**,** enaminones, hyrdrozonyl halides, thiosemicarbazones, azoles, azines and biological activity.

## SUMMARY

The purpose of this original work is to synthesize novel biologically active compounds as drugs analogues through the following three parts.

**Part 1: Synthesis, Anticancer Screening and Molecular docking studies of New Heterocycles with Trimethoxyphenyl Scaffold as Combretastatin Analogues**

The starting material f

or this study; (*E*)-3-(dimethyl amino)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one **2** was prepared by refluxing 1-(3,4,5-trimethoxyphenyl)ethanone **1** with dimethyl formamide-dimethyl acetal (DMF-DMA) in dry xylene (**Scheme I**).

Treatment of the enaminone **2** with active nitriles namely, benzoyl acetonitrile and ethyl cyanoacetate in acetic acid and in the presence of ammonium acetate afforded the corresponding substituted pyridine derivatives **4** and **5** respectively (**Scheme I)**.

Refluxing acetyl acetone, ethyl acetoacetate or ethyl benzoyl acetate with enaminone **2**, in glacial acetic acid and in the presence of ammonium acetate, yielded the

corresponding tri-substituted pyridine derivatives **6, 7** and **8**, respectively (**Scheme I**).

However, enaminone **2** reacted with, 4*H*-1,2,4-triazol-3-amine and/or 2-aminobenzimidazole, in refluxing glacial acetic acid to afford the corresponding fused azolopyrimidines **9** and **10**, respectively**.** Furthermore, the enaminone **2** reacted with 6-amino-2 thioxopyrimidin-4-one **11**, in boiling acetic acid to give thioxopyrido[2,3-*d*] pyrimidinone **12 (Scheme II)**.

Treatment of the enaminone **2** with *C*-acetyl-*N*-arylhydrazonoyl chlorides **15a-c** and (*C*-ethoxycarbonyl)-*N*-arylhydrazonoyl chlorides **15d,e** in dry benzene, with triethylamine yielded the tri-substituted pyrazoles **16a-e** as sole product in each case **(Scheme II)**.

On the other hand, hydrazinolysis of the newly synthesized tri-substituted pyrazole **16d** with hydrazine hydrate under reflux temperature afforded the corresponding pyrazolo[3,4-*d*]pyridazine derivative **17 (Scheme II)**.

The anticancer activity of new synthesis compounds were screened with respect to four cancer cell lines, including; HePG-2, HCT-116, MCF-7 and PC3 and the results

revealed that 12 compounds have low activity on the 4 human cancer cell lines less. However Compounds **2,4 and 7** showed remarkable anticancer activity.

**Part 2: Synthesis and Antimicrobial activity of New Thiazolidine-Based Heterocycles as Rhodanine Analogues**

In this part of study, 3,4-dimethoxyacetophenone thiosemicarbazones **20a,b** were prepared from the reaction of 3,4-dimethoxyacetophenone **18** with the thiosemicarbazides **19a,b** in the presence of sodium acetate, in refluxing ethanol (**Scheme III**).

The thiosemicarbazones **20a,b** were treated with the *α*-haloesters namely; ethyl bromoacetate and ethyl-2-bromoprpionate, in ethanol and in the presence of equivalent amount of sodium acetate, to afford the corresponding substituted thiazole derivatives **21** and **22a,b,** respectively (**Scheme III**).

In a similar manner, the thiosemicarbazones **20a,b** were treated with chloroacetone and phenacyl chloride to afford the corresponding substituted thiazole derivatives **23a,b** and **24**, respectively (**Scheme III**). However,

treatment of the thiosemicarbazide derivatives **20a,b** with *C*-acetyl-*N*-arylhydrazonoyl chlorides **15a-c** in ethanol and in the presence of catalytic amount of triethylamine to yield the azo-thiazole derivatives **25a-e** (**Scheme III**). On the contrary, treatment of the thiosemicarbazide derivatives **20a,b** with *C*-ethoxycarbonyl-*N*-arylhydrazonoyl chlorides **15d,e** afforded the corresponding substituted thiazoles **27a-c** (**Scheme III**).

All the synthesized compounds were tested against a penal of Gram +ve and Gram –ve bacteria, yeast and fungi. All of the tested compounds showed a neglectable activity against either Gram +ve and Gram –ve bacteria but some compounds showed considerable highly inhibitory effect against two fungal strains. The results showed that five of the most active compounds **22b**, **23b**, **25d**, **25e** and **27b** contain 3-ethylthiazole scaffold which may lead to enhance the antifungal activity.

**Part 3: Design, synthesis and structural elucidation of new pyridine and thienopyridine derivatives**

In this part of study, the chalcone **29** was refluxed in an alcoholic solution (methanol or ethanol) of malononitrile, in the presence of an equivalent amount of

base (piperidine or NaOH) to afford the corresponding unexpected cyanopyridine derivatives **30a,b** (**Scheme IV**). On the other hand, the chalcone **29** was reacted with 2-cyanothioacetamide in ethanol, in the presence of triethyl amine to give cynopyridinethione derivative **32** (**Scheme IV**).

Treatment of the 2-mercaptonicotinonitrile **32** with the 2-chloro-*N*-arylacetamide derivatives **33a-c** namely, 2-chloro-*N*-phenylacetamide, 2-chloro-*N*-(4-fluorophenyl) acetamide or 2-chloro-*N*-(*p*-tolyl)acetamide in refluxing ethanol and in the presence of few drops of triethyl amine, afforded the corresponding 2-(*N*-aryl)-carboxamido-methylthiopyridine derivatives **34a-c**, respectively, which underwent cyclized by boiling in sodium ethoxide to give 2-(*N*-aryl)-carboxamidomethyl-thienopyridine **35a-c.** However, compounds **35a-c** obtained directly from the reaction of compound **32** with 2-chloro-*N*-arylacetamide derivatives **33a-c**, in refluxing sodium ethoxide solution (**Scheme IV**).

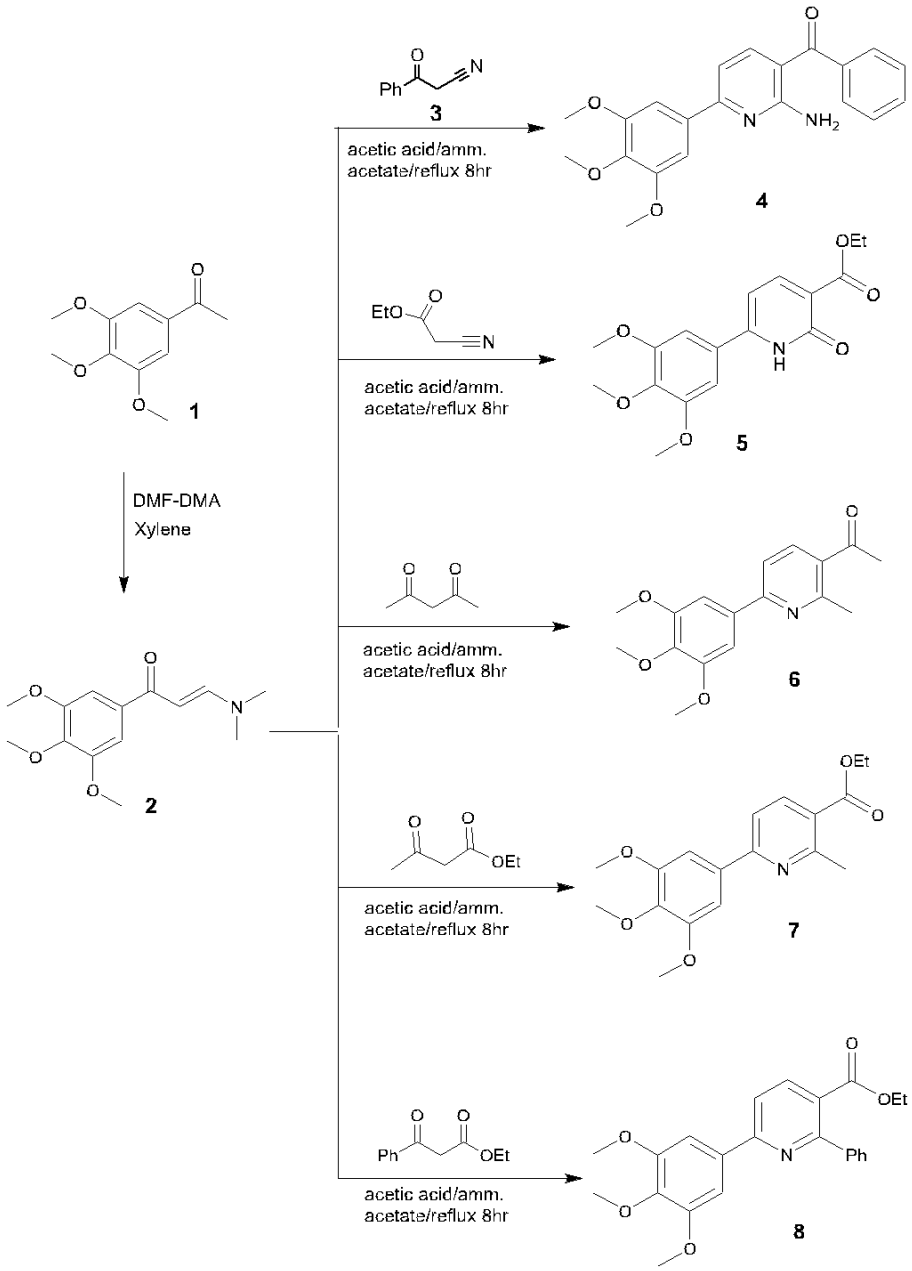
The synthetic potentiality of the pyridinethion **32** was investigated through their reactions with several reagents such as ethyl chloroacetate, phenacyl chloride and chloroacetone to afford the corresponding *S*-alkylated

derivatives **36a-c**, respectively, which underwent cyclization by boiling in sodium ethoxide solution to afford **37a-c**. However, thieno[2,3-*b*]pyridine derivatives **37a-c** could be synthesis directly by action of sodium ethoxide on pyridinethion **32** with α-halo carbonyl compounds (**Scheme IV**).

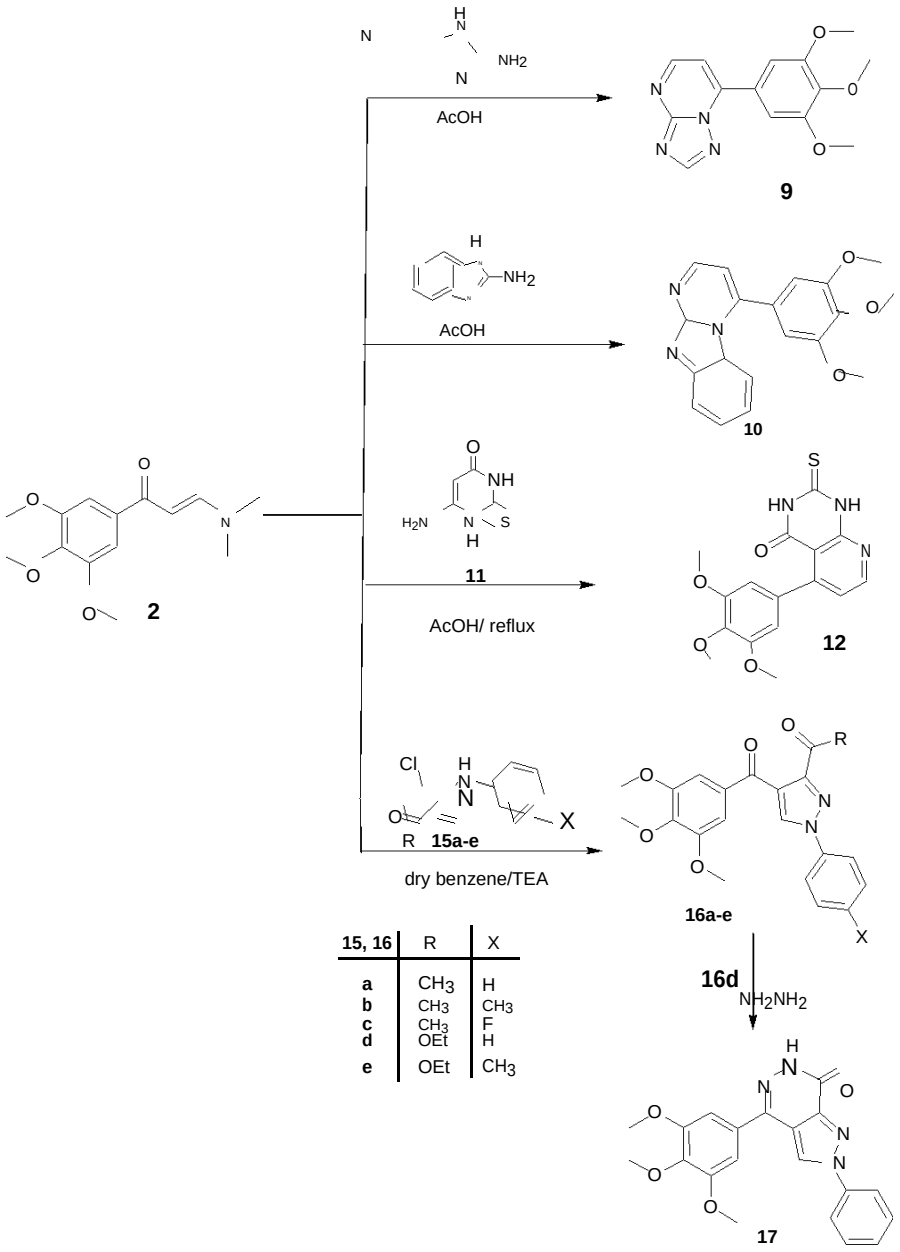
Additionally, 2-mercaptonicotinonitrile **32** was reacted with methyl iodide to give *S*-methyl derivative **38** and with chloroacetonitrile to give the *S*-alkylated derivative **39** which cyclized in boiling sodium ethoxide solution to afford compound **40** (**Scheme V**).

the reactivity of the thiopyridine derivative **32** towards (C-ethoxycarbonyl)-*N*-arylhydrazonoyl chlorides **15d** was examined by refluxing it in ethanol, in the presence of an equivalent amount of triethyl amine which yielded open structure compound **42** (**Scheme V**).

The structures of all the synthesized compounds were substantiated on the basis of from the correct analytical and spectroscopic data including IR, $^{1}$HNMR, $^{13}$CNMR and MS.


Ph
3
acetic acid/amm.
acetate/reflux 8hr
NH2
4
EtO
OEt
5
1
DMF-DMA
Xylene
6
OEt
7
Ph
OEt
8
2

**Scheme I**




| 15, 16 | R | X |
|---|---|---|
| a | $CH_3$ | H |
| b | $CH_3$ | $CH_3$ |
| c | $CH_3$ | F |
| d | OEt | H |
| e | OEt | $CH_3$ |

**Scheme II**