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Approaches for the synthesis, chemical modification and biological properties of *N*-acylphenothiazines

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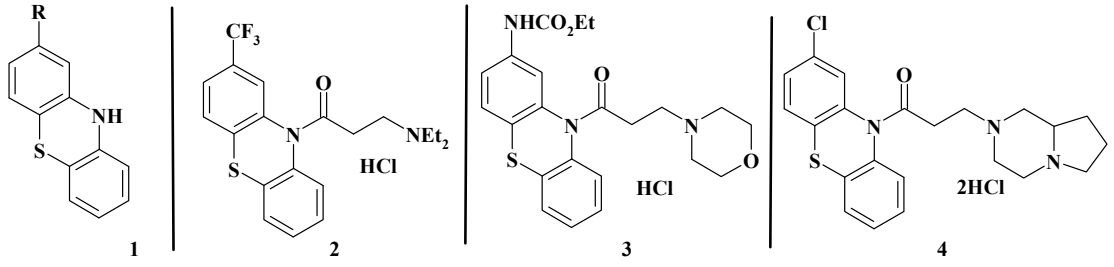
A B S T R A C T

In this review we systematized the theoretical and experimental data concerning the versatile approaches for the synthesis of N-acylphenothiazines. The aim of the study was to compile the literature reported worldwide in the past 20 years. This article also reviewed the analysis of pharmacological activities of these heterocycles as one of the promising chemotherapeutic objects for the modern bioorganic and medicinal chemistry. It has been hypothesized that the enormous biological potential of these moieties is due to the radical nature in the acyl moiety. Therefore, the present review will be a good contribution to the literature and will provide the platform for the medicinal chemistry researchers to carry out more studies aiming the N-acylphenothiazine moieties as the novel chemotherapeutic agents.

1. Introduction

Among the class of heterocyclic compounds, phenothiazine and its derivatives **1** occupy a considerable place in medicinal chemistry, which is associated with the great practical importance, especially the significant biological activity of the mentioned compounds. Phenothiazines were reported to possess anticholinergic, antihypertensive, anthelmintic and, most significantly the neuroleptic activity.[1,2] It is also reported that a number of phenothiazine derivatives were applied in pharmacology.[3] Among the N-acylphenothiazines, drugs are also known. These are such drugs as fluoroacyzine 2, etmozin 3 and nonachlazine 4.



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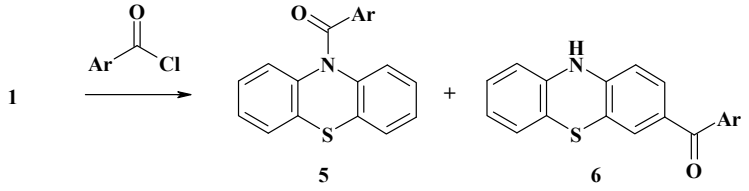
The presented review is an attempt to summarize a huge volume of data on *N*-acylphenothiazines being a widely studied class of molecules used in the modern organic and medicinal chemistry.

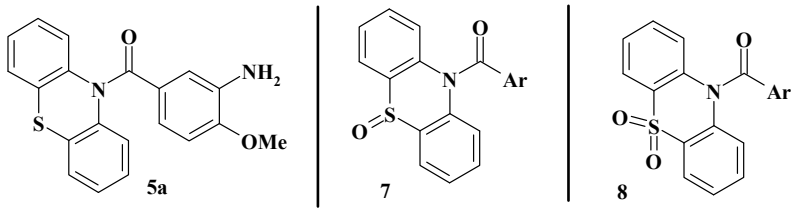
2. Acylphenothiazines based on heterocyclic acids

The acylation of phenothiazine **1** by using aromatic acid acyl chlorides was investigated in works.[4-6] As a result, a series of *N*-acylphenothiazines were obtained (**Scheme 1**). These compounds were synthesized by reacting 10*H*-phenothiazine with suitably substituted benzoyl chlorides in toluene at 90°C, without base. These derivatives demonstrated essential activity against cell proliferation and tubulin polymerization, comparable to fenstatin.



Scheme 1.

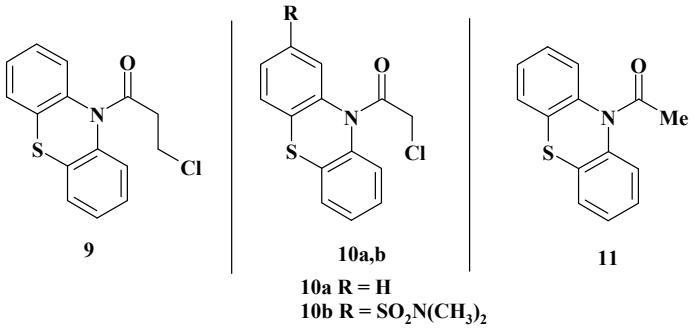
(3-Amino-4-methoxy-phenyl)-phenothiazin-10-yl-methanone (**5**) was proved to be the most potent compound in the series. The mechanism of action of the above mentioned compounds tributes to the ability to interact with colchicine binding site of the tubulin molecule. A similar effect was observed for (5-oxo-5*H*-5lambda*4*-phenothiazin-10-yl)-aryl-methanone **7** and (5,5-dioxo-5*H*-5lambda*6*-phenothiazin-10-yl)-aryl-methanone **8** [6] **(Scheme 2**).



Scheme 2.

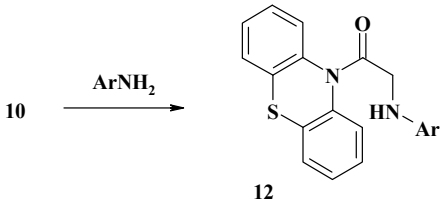
In the work[7] it was shown that compounds with general formula **5** were the inhibitors of butyrylcholinesterase and acetylcholinesterase. Similar effect was observed for *N*-acylphenothiazines obtained by means of aliphatic carboxylic acids.[8] Two dis-similar mechanisms for the binding of these compounds to butyrylcholinesterase and acetylcholinesterase have been described. Phenothiazines inhibites butyrylcholinesterase by the mechanism involving interaction between the phenothiazine cyclic system and aromatic residues in the active site cleft. Some phenothiazines also inhibites acetylcholinesterase by the interaction of the carbonyl group with the cleft of the active site. Such specific and potent butyrylcholinesterase inhibitors can potentially be applied in the treatment of dementia, such as Alzheimer's disease.

The authors performed the acylation of phenothiazine using chloroacetic acid and 3-chloropropionic acid.[9] Thus, *N*-acylphenothiazines were obtained, that were reported to possess antiprotozoal properties against the flagellated forms of Leishmania. The antifungal activity of these compounds was aimed by Sarmyen et al.[10] In this work, it was shown that 3-chloropropionic acid derivative **9** did not exhibit activity. At the same time, it was also revealed that 2-chloro-1-phenothiazin-10-yl-ethanone **10a** was active against various yeast and mold strains. Due to the activity observed in compound **9**, other *N*-acyl derivatives **10b** and **11** have been obtained and studied and the finding revealed that none of these compounds were active against the tested strains (**Scheme 3**).



Scheme 3.

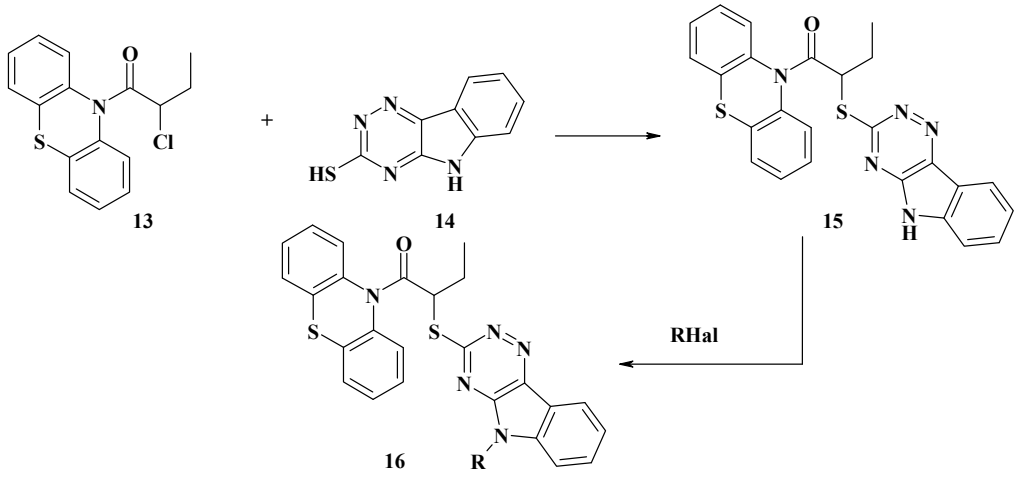
Chloroacetamides **10** were used in the synthesis of arylaminoacetyl phenethiazines **12** (**Scheme 4**). The specified transformation occurs by interaction of different aryl amines with simple experiment protocol to obtain new phenathiazine analogues in good yield.[11] Antioxidant activity of the synthesized compounds was assessed using two *in vitro* methods, namely, the analysis of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging and the analysis of a human low density lipoproteins (LDL) oxidation inhibition. Thus, a number of highly active compounds with antioxidant properties have been found.[11]



Scheme 4.

3. Acylphenothiazines based on aliphatic and aromatic acids

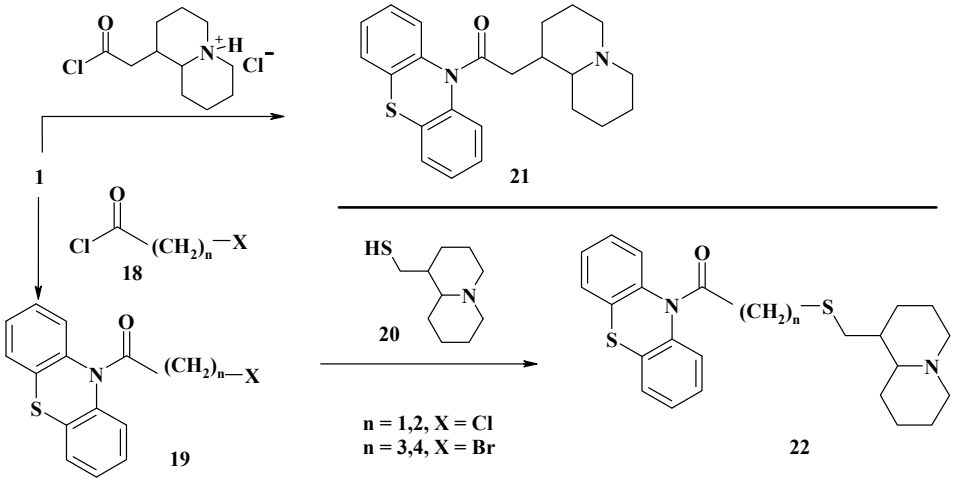
During *in silico* screening and biological trials, the authors reported[12–14] that the identified compound **15** (**scheme 5**), which was named Inauchzin (INZ) as a representative of a new class of small molecules that efficiently activate p53 and can induce p53-dependent apoptosis in cancer human cells without causing genotoxic stress. The authors also synthesized a number of analogs like **16** (**scheme 5**), which were observed to inhibit p53.



Scheme 5.

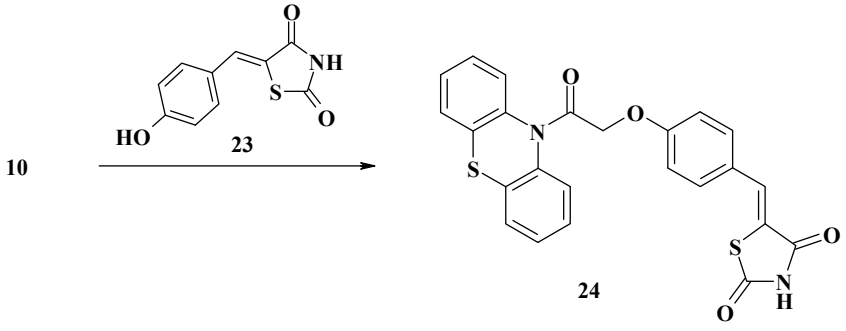
In the studies[15-17] compound **21** was obtained starting from epigomolupine noilchloride hydrochloride **17** and phenothiazine **1**. The reaction was carried out under normal conditions. At the

same time, compound **22** was obtained by reacting phenothiazine **1** with the corresponding-haloalkanoyl chloride **18** followed by the reaction of *N*-(ώ-halogen)alkanoylphenothiazine **19** with thiolupinine (**Scheme 6**). The required compounds were obtained with about 40% yield in acetonitrile. The same experimental conditions were used to obtain higher homologues. The obtained compounds demonstrated very good affinity for M1 and M2 receptors, with nanomolar Ki values, which for the most active compounds *N*-[(ώ-lupinylthio)propionyl / butyryl]phenothiazines were comparable to those for pirenzepine and methoctramine, respectively. The obtained compounds **21** and **22** were also appeared as cholinesterases inhibitors.[15]



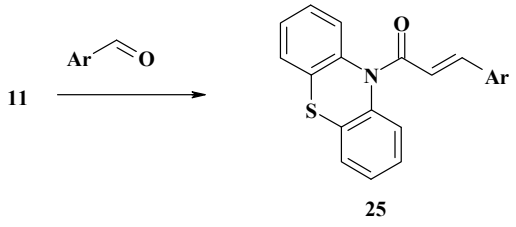
Scheme 6.

Chloroacetylphenothiazine **10** was also applied in the alkylation of 5-(4-hydroxy)benzylidene-2,4-thiazolidinedione **23**. As a result, compound **24**, which exhibited the antitumor properties, was obtained (**Scheme 7**).[17]



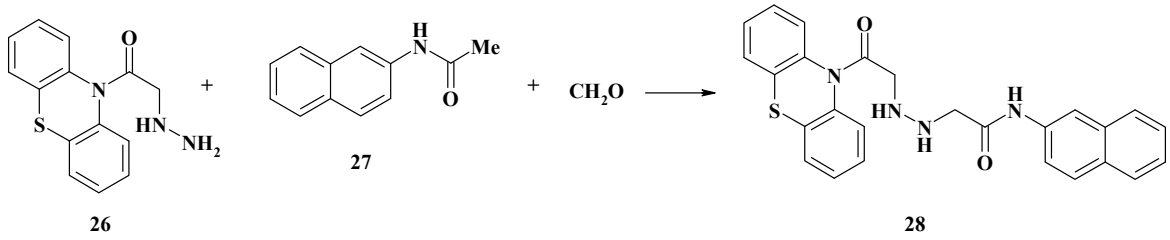
Scheme 7.

Cinnamyl phenothiazines **25** were reported to possess the antimicrobial properties against *B. subtillis*, *E. coli*, *A. niger*, and *C. albicans*. They were yielded by the reaction of acetyl phenethiazine with aromatic aldehydes as mentioned in (**Scheme 8**).[18] Mentioned above compounds were obtained by Claisen-Schmidt reaction, i.e., by treating *N*-acyl phenothiazine with methanolic KOH (40%) and various aldehydes, which gave above 90% yield.



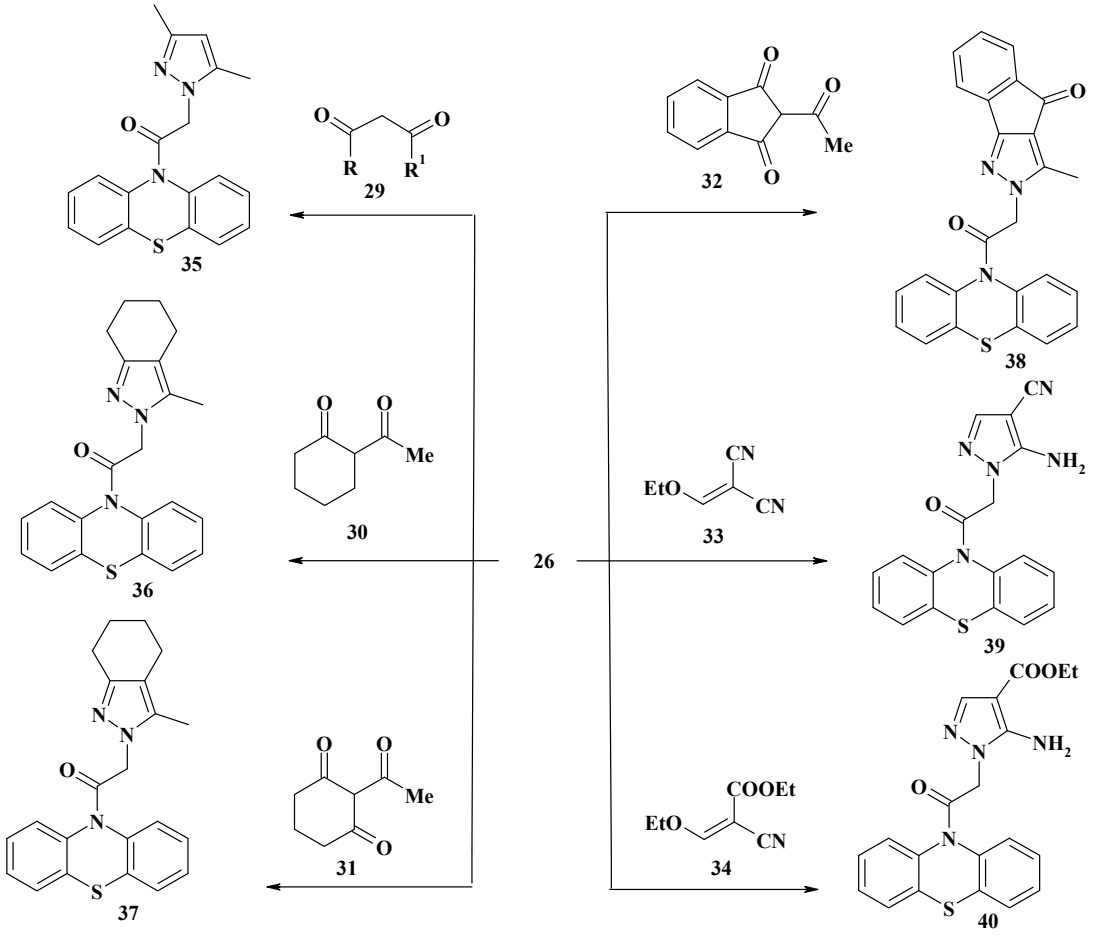
Scheme 8.

By the means of Mannich reaction in between hydrazinoacetylphenothiazine **26** and 2-acetaminonaphthalene **27**, the compound **28** was obtained (**Scheme 9**).[19] The reaction took place in an alcoholic environment in the presence of formaldehyde. The authors also studied the anti-inflammatory investigations and observed to possess a moderate anti-inflammatory effect.



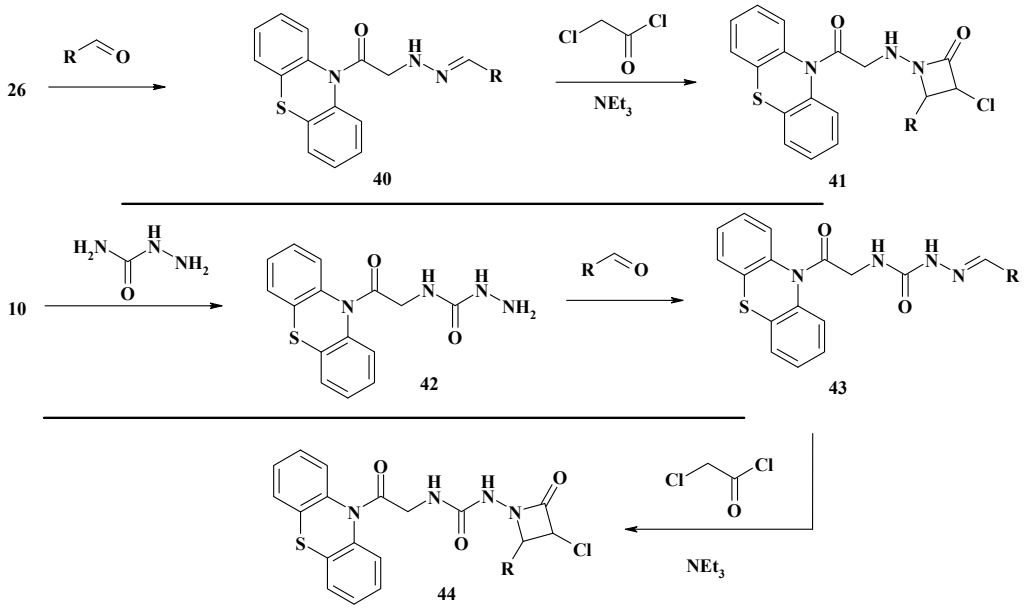
Scheme 9.

Hydrazinoacetyl phenethiazinone **26** was used in the reaction with various diketones, as well as with ethoxymethylidenecyanoacetic ether (**Scheme 10**).[20] The condensation of compound **26** with acyclic 1,3-diketone afforded corresponding pyrazole. In this work importance of the pyrazole ring nature was considered and structural variations were obtained by reacting compound **26** with cyclic di- and triketones **30–32** in order to give tetrahydroindazoles and indenopyrazoles. Thus, reaction of compound **26** with cyclic diketone **30** or with triketone **31** led to 25–65% of 4,5,6,7-tetrahydroindazolederivatives. Condensation of the compound **26** with triketone **32** in DMA at 100°C afforded the cyclized indenopyrazole as unique product, in 71% yield. The compounds **39**, **40** were prepared by reaction of the required compound **26** with 2-cyano-3-ethoxyacrylonitrile **33** or 2-cyano-3-ethoxyacry-late **34** in boiling ethanol or in DMA at 100°C. The resulting compounds were found to have the ability to inhibit the farnesyltransferase protein.



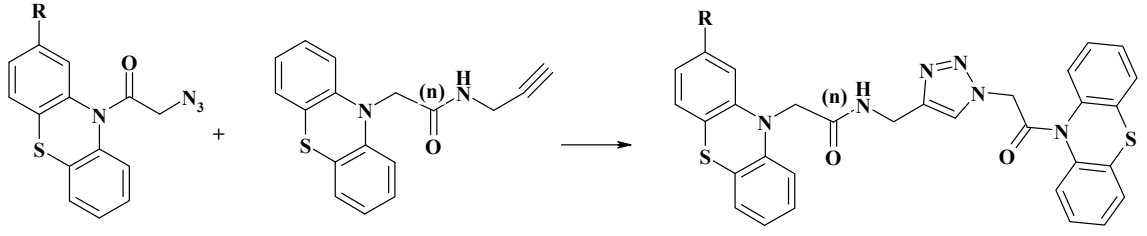
Scheme 10.

A series of new azetedinone derivatives **41** and **44** were synthesized by cyclocondensation of various Schiff bases of the phenothiazine series **40** and **43** with chloroacetyl chloride in the presence of triethylamine (**Scheme 11**).[21,22] The cyclocondensation of Schiff bases with chloroacetyl chloride in triethylamine revealed with fairly high yields in a relatively short reaction time and easy work-up procedures. These conditions enable this method to be applicable for the synthesis of 2-azetidinone based heterocyclic. The antimicrobial, antioxidant and antitumor[21,22] activities were examined for the obtained compounds.



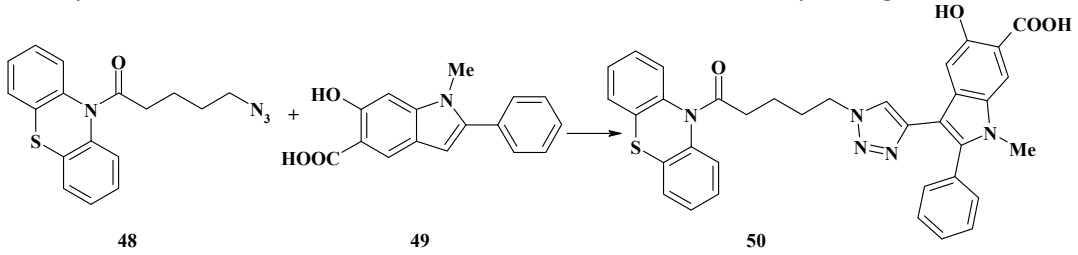
Scheme 11.

Triazole-phenothiazine conjugates **47**[22] which also have the ability to inhibit the farnesyltransferase protein, were obtained by means of Husgen cycloaddition according to **Scheme 12**.



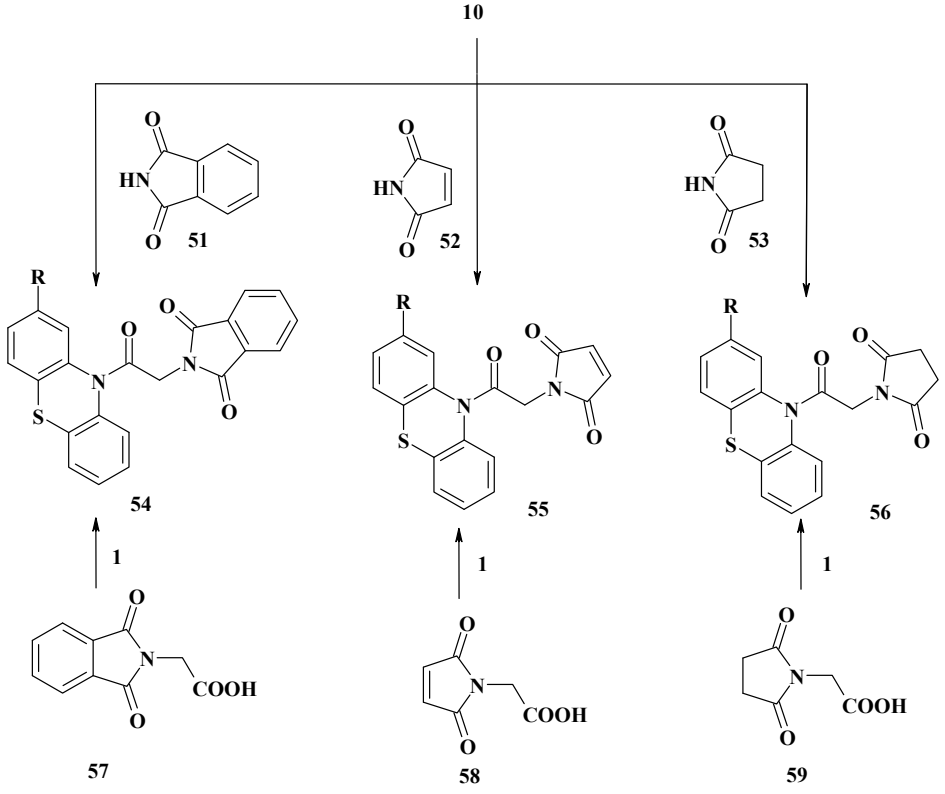
Scheme 12.

Husgen cycloaddition **(Scheme 13**) was also used to synthesize compound **50**, which inhibited SHP2 (SRC oncogenic domain containing tyrosine phosphatase-2 protein).[23] The Huisgen cycloaddition is a 1,3-dipolar cycloaddition between an azide and a terminal or internal alkyne to give a 1,2,3-triazole.



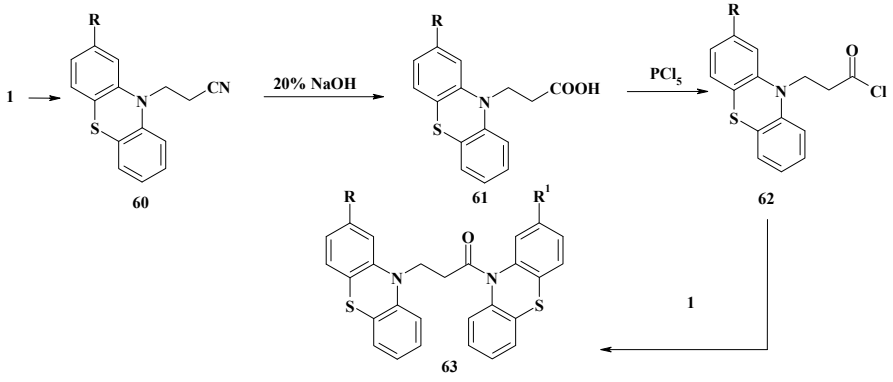
Scheme 13.

N-acyl derivatives of phenothiazines **54-56** were synthesized by two different methods.[24] In the first method, compounds **10** were treated with imides **51-53** in the presence of anhydrous K_2CO_3 at room temperature, and in the second, phenothiazines **1** were treated with acid chlorides **57-59** in xylene at 120 °C. The sequence of reactions is shown in **Scheme 14**. These compounds have been investigated for their antifungal activity against *Aspergillus niger (NCIM № 617)*, *Aspergillus flavus (NCIM № 524)*, *Aspergillus fumigatus (NCIM № 902)*, *Candida albicans (NCIM № 300)*. Compounds were found to be active at a concentration of 10 mg/ml against *A. niger, A. velus, A. fumigatus and C. albicans*.



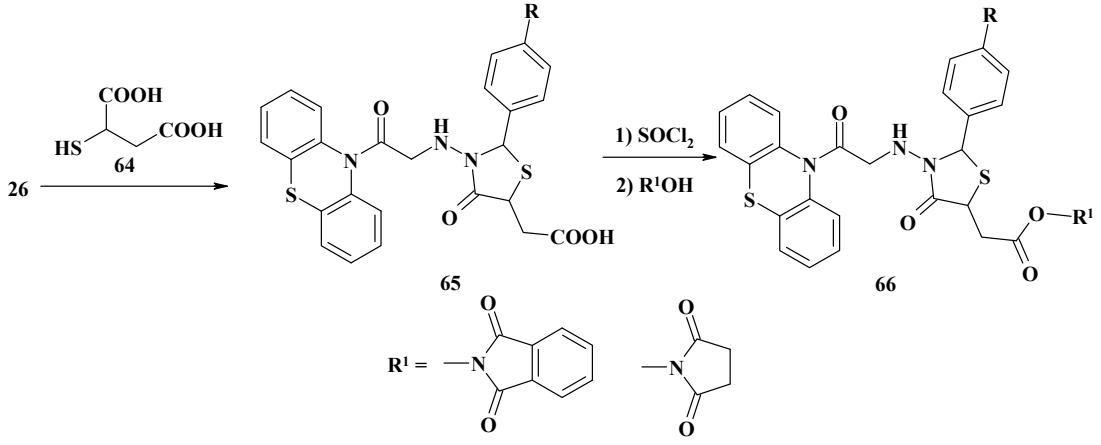
Scheme 14.

The same researchers obtained bisphenothiazine derivatives **63** by acylation of phenothiazines **1** with 3-(10*H*-phenothiazin-10-yl) propionic acid chlorides **62.**[25] The initial acids **61** were synthesized by hydrolysis of nitriles **60**, which, in turn, were obtained by cyanoethylation of phenthiazines **1** (**Scheme 15**). The corresponding acids were converted into acid chlorides by using PCl_5 and coupled with various phenothiazines to afford. For compounds **63**, antimicrobial activity against the aforementioned strains of bacteria and fungi was also investigated. As a result, the compounds have been identified to exhibit comparable activity with ampicillin and fluconazole.



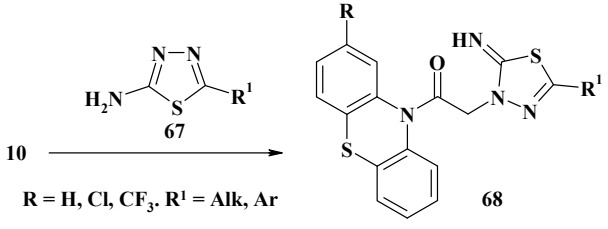
Scheme 15.

Aiming the pharmacological potential of thiazolidinones and phenothiazines, compounds **66** were synthesized containing both the moieties.[26] Based on phenothiazine **1**, the authors obtained hydrazones **26**, which then underwent cyclization upon treatment with mercaptosuccinic acid **64** in the presence of anhydrous zinc chloride. As a result, [2-aryl-4-oxo-3-[{2-oxo-2- (phenothiazin-10-yl)ethyl}amino]-1,3-thiazolidin-5-yl]ethanoic acids **65** were synthesized, which were then converted into the corresponding acid chlorides under the action of thionyl chloride, the treatment of which with *N*-hydroxyphthalimide or *N*-hydroxysuccinimide leaded to the formation of phthalimido or succinimido[2-aryl-4-oxo-3-[{2-oxo-2-(phenothiazin-10-yl) ethyl} amino]-1,3-thiazolidin-5-yl]ethanoates **66** (**Scheme 16**). The antibacterial and antifungal activities of compounds **66** were investigated, and they all showed considerable inhibition to the bacterial and fungal growth.



Scheme 16.

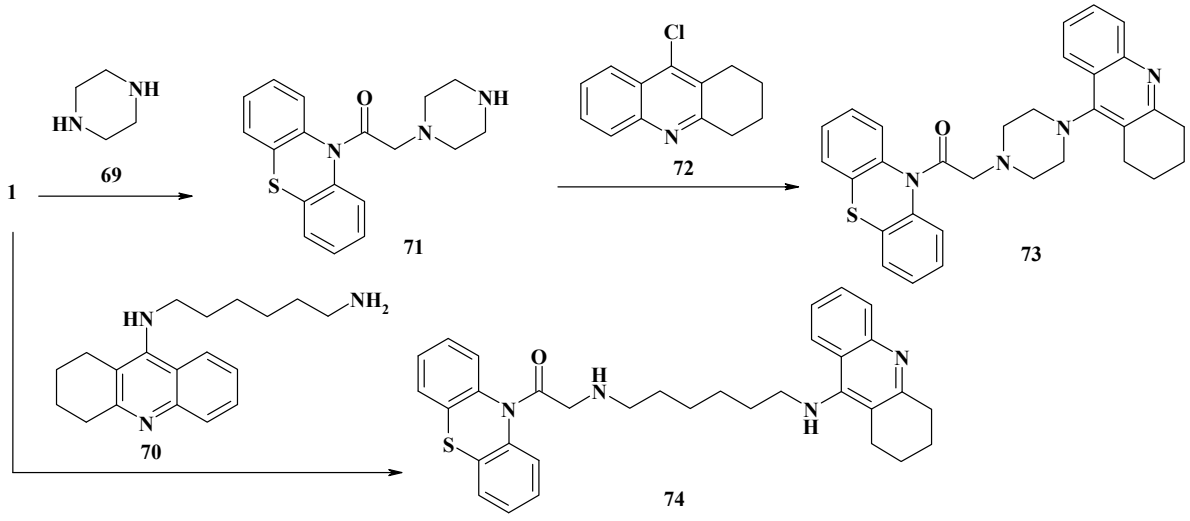
1,3,4-thiadiazole-phenothiazine conjugates **68** combinatorial library was obtained by the authors of the work.[27] To obtain the compound 68, the reaction of 2-amino-1,3,4-phenothiazoles **67** alkylation with chloroacetyl derivatives **10** was performed as per the protocol mentioned in (**Scheme 17**). The target compounds were synthesized in ethanol under reflux conditions. The obtained compounds were then assessed for biological potential against the strains of mycobacterium tuberculosis H37Rv. The structure-activity relationship demonstrated that an alkyl (methyl/n-propyl) or substituted (4-methyl/4-Cl/4-F) phenyl groups on the 1,3,4-thiadiazole ring enhance the inhibition activity of the compounds. The cytotoxicity study revealed that none of the active molecules are toxic to a normal Vero cell line, thus proving the lack of general cellular toxicity.



Scheme 17.

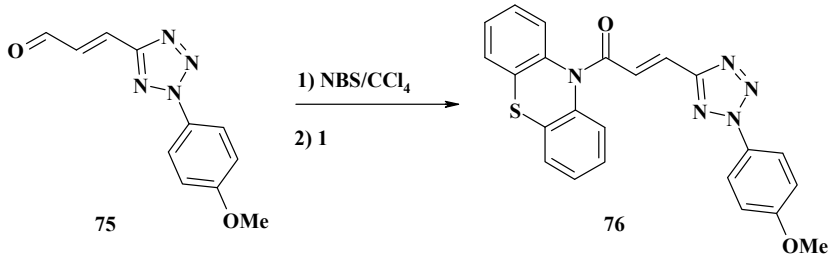
Several tacrine-phenothiazine hybrids **73** and **74** were obtained in according to the method described in the link [28] (**Scheme 18**), which inhibited acetylcholinesterase and tau-protein involved in Alzheimer's disease. The synthesis procedure of compound **73** is interaction of chloroacetylphenothiazine with excessive piperazine in the presence of K_2CO_3/KI, 1-(10*H*-phenothiazin-10-yl)-2-(piperazin-1-yl) ethanone. Next the intermediate was converted to the desired compound **73**. The target compounds **74** were synthesized in CH_2Cl_2 or CH_3COCH_3 under reflux conditions. Reducing temperature or shortening the time was negative on the conversion of reactant and product yields. In addition, the type

of solvents and bases had certain impact on the composition of the products. Among all the series members, compound **74** revealed to be the most potent compound with an IC50 of 89 nM.



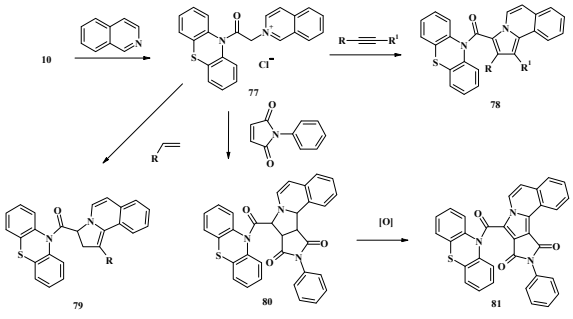
Scheme 18.

The synthesis of acyl derivative **76** was described in the study.[29] The synthesis was achieved by the interaction of phenothiazine **1** with the corresponding acid bromide, which was synthesized *in situ*, the bromination of (E)-3-(2-(4-methoxyphenyl)-2*H*-tetrazol-5-yl)acrylaldehyde **75** using *N*-bromosuccinimide lead to the production of **76** (**Scheme 19**). The biological assessment of the prepared compounds revealed that the compounds possessed significant inhibitory effects against P-gp. 5.

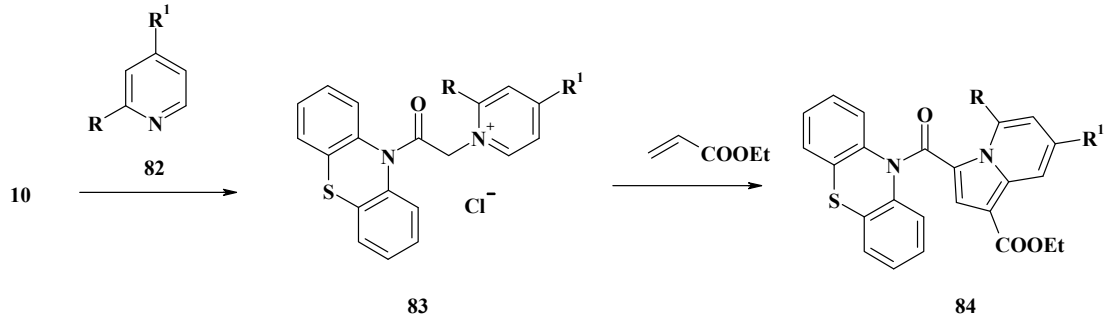


Scheme 19.

Baku et al. developed a simple and effective approach to various benzoindolizine derivatives of *N*-acylphenothiazines **78-81**.[30] The compound **77** was generated from the condensation of isoquinoline with N-(2-chloroacetyl)phenothiazine **10**. It was subsequently exposed to an array of acetylenic and olefinic dipolarophiles. It was observed that the reaction proceeded equally well with both the acetylenic and olefinic compounds (**Scheme 20**).

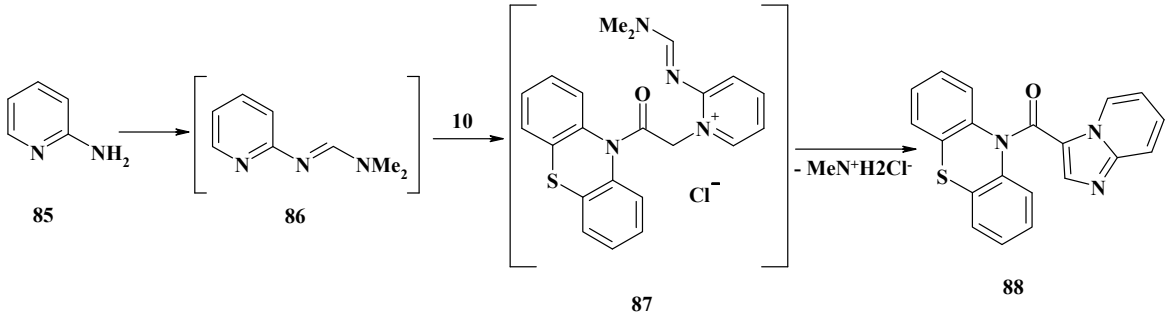


Scheme 20.



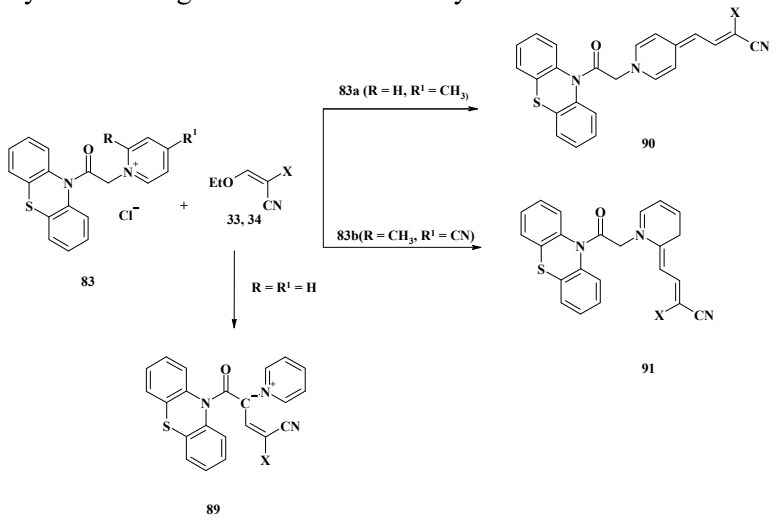
Scheme 21.

The synthesis of imidazo[1,2-*a*]pyridine **88** was carried out by the alkylation of amidine **86** with compound **10**, that was followed by the cyclization of the resulting cycloimonium salt **87** and elimination of dimethylamine hydrochloride[5] (**Scheme 22**). The intermediate compound **86** was obtained by the condensation reaction of 2-aminopyridine **85** with DMF/DMA.



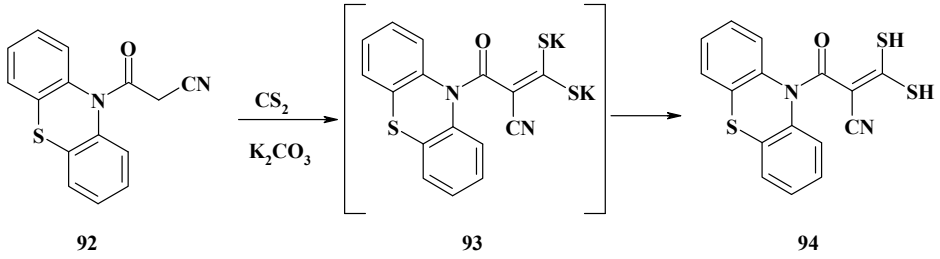
Scheme 22.

The compounds **84** and **88** were found to exhibit very moderate tubulin polymerization inhibition at a concentration of 10^{-4} M with values of 31-48%. Pyridinium salts **83** reacted with trisubstituted alkenes (2-cyano-3-ethoxyacrylonitrile **33** and ethyl 2-cyano-3-ethoxyacrylate **34** to yield disubstituted compounds **89**.[31] While performing the same reaction with picoline salts **83a** (R = H, R^1 = CH_3) and **83b** (R = CH_3, R^1 = H), unexpectedly red compounds **90, 91** were obtained as the only reaction products (**Scheme 23**). The compounds **90** appeared to be the significant inhibitors of human farnesyl transferase. It was concluded that the phenothiazine ring replacement with a diethylamine fragment in these compounds may lead to a significant loss of activity.



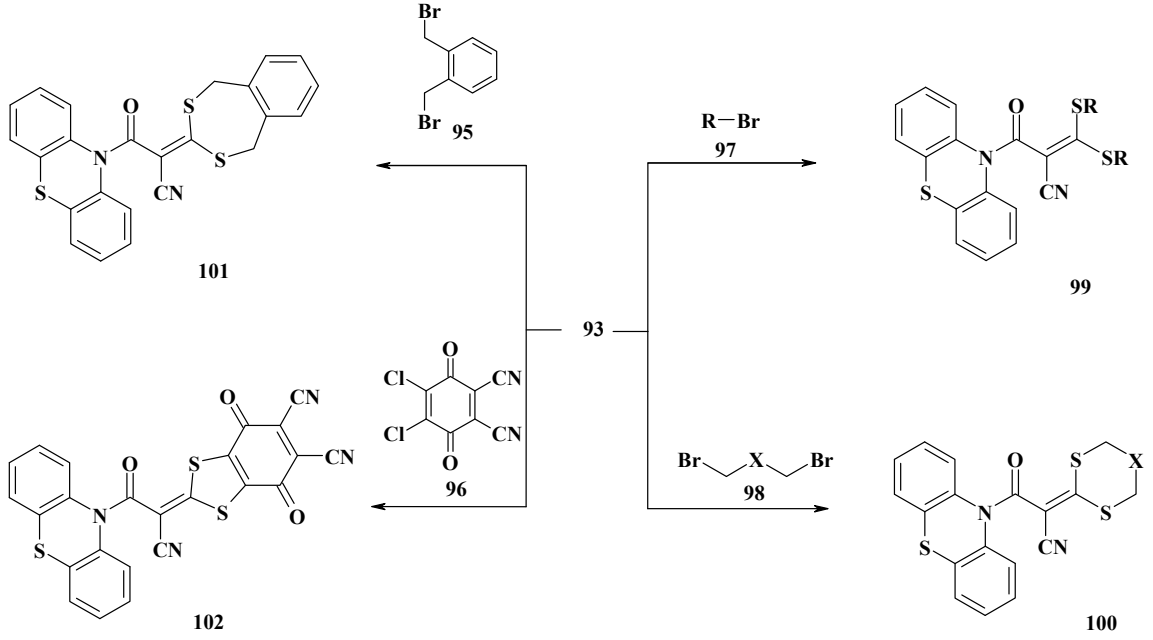
Scheme 23.

In the work reported by Fadda et al.[32] behavior of 3-oxo-3-(10*H*-phenothiazin-10-yl)propanenitrile (**92**) toward some bifunctional reagents as a facile and appropriate route to synthesize some heterocyclic compounds containing phenothiazine moiety was described. The cyanoacetamide **92** was synthesized by means of the phenothiazine **1** with a mixture of cyanoacetic acid and acetic anhydride reaction. At the same time its reaction with carbon disulfide yielded the intermediate **93**, which reacted *in situ* with diluted hydrochloric acid to yield 3,3-dimercapto-2-(10*H*-phenothiazine-10-carbonyl) acrylonitrile **94** (**Scheme 24**).



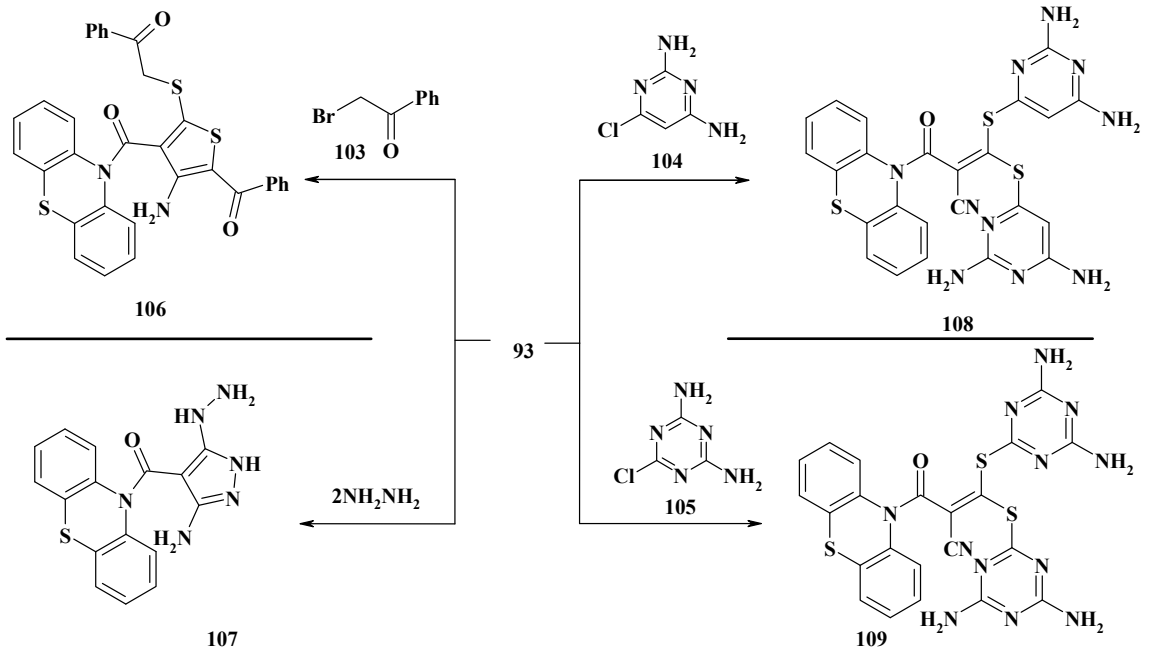
Scheme 24.

The reaction with alkylating reagents **95-98** was studied for the synthesis of compound **93**.[32] As a result; the derivatives 99-102 were obtained through the protocol mentioned in **Scheme 25**. The intermediate **93** reacted with different haloalkanes namely, 1-chlorododecane, 1-chlorohexadecane, 1,3-dibromopropane and 1,5-dibromopentane in a stirring mixture of acetone and N,N-dimethylformamide (1:2) containing anhydrous potassium carbonate as a base to obtain derivatives **99** and **100** respectively. Furthermore, the reaction of intermediate **93** with equimolar amount of dihaloalkanes under the same reaction conditions afforded compounds **101** and **102**.



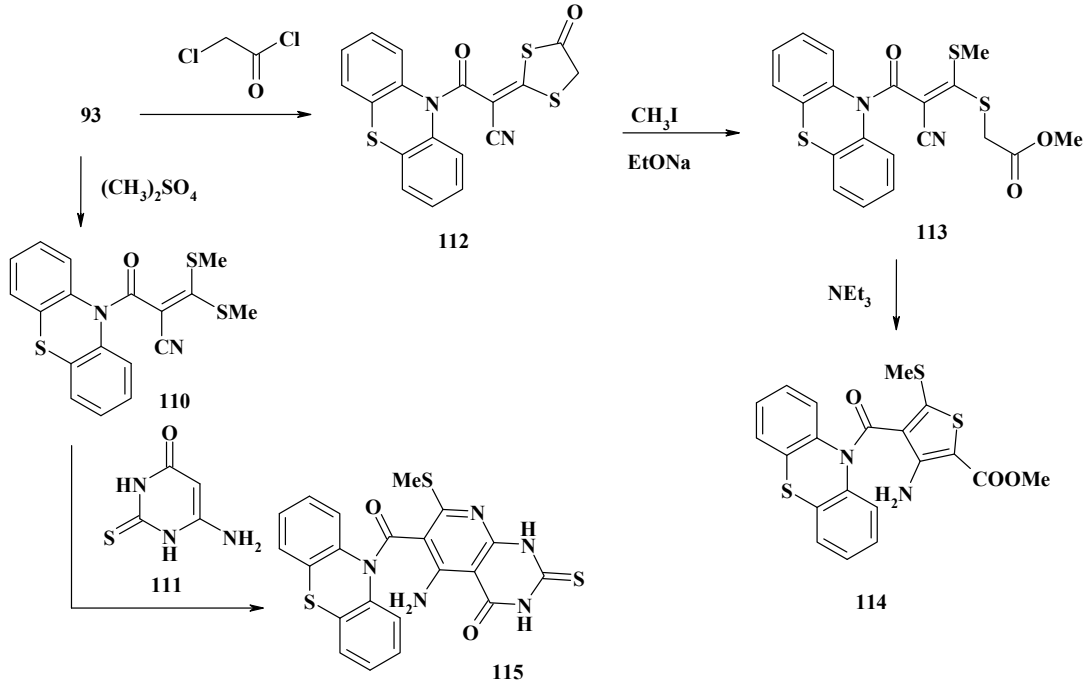
Scheme 25.

In addition to the above mentioned sheme, the reaction of the intermediate **93** with two moles of 6-chloropyrimidine-2,4-diamine **104**, 6-chloro-1,3,5-triazine-2,4-diamine **105**, phenacyl bromide **103** in a mixture of acetone and *N*,*N*-dimethylformamide (1:2) containing anhydrous potassium carbonate as a base, new phenothiazine derivatives **106**, **108**, **109** were obtained. The reaction of **93** with hydrazine yielded to the formation of compound **107**[32] (**Scheme 26**).



Scheme 26.

When compound **93** interacted with chloroacetyl chloride in a stirred mixture of acetone and *N*, *N*-dimethylformamide (1:2) containing anhydrous potassium carbonate, compound **112** was obtained under the similar conditions. When treated with methyl iodide in the presence of sodium ethoxide, acyclic compound **113** was formed, which underwent cyclization to give compound **114** (**scheme 27**). In addition, the intermediate compound **93** reacted with dimethyl sulfoxide to form the S-alkyl derivative **110**, which was heated with 6-aminothiouracil **111** in refluxing *N*,*N*-dimethylformamide to form pyridopyrimidine derivative **115**[32] (**scheme 27**).



Scheme 27.

For the synthesized compounds **99-102**, **106-109** and **111-115**, *in vitro* antibacterial activity was performed against gram-positive bacteria *(S. aureus* and *B. subtilis*) and gram-negative bacteria *(E. coli* and *P. aeruginosa*). The compounds were also evaluated for their *in vitro* antifungal potential against *Candida albicans* and *F. oxysporum strains*. The results revealed that most of the tested compounds exhibited significant inhibitory effects on the growth of the studied strains of bacteria and fungi. In general, most of the investigated compounds showed better potential against gram-positive than gram-negative bacteria.

3. Conclusions

Class of phenothiazines is the parent molecule of a multitude of drugs that have enjoyed varied and extensive use throughout medical and veterinary practice, possessing wide range of pharmacological activities. The major achievements in their study have been related to anticholinergic, antihypertensive, anthelmintic and, most significantly the neuroleptic activity. The present review was aimed to systematize the versatile approaches for the synthesis of N-acylphenothiazines, chemical modifications, structure elucidation and pharmacological applications. In particular, the existing methods of *N*-acylphenothiazines synthesis were divided into 2 sections: 1) Acylphenothiazines based on aliphatic and aromatic acids; 2) Acylphenothiazines based on heterocyclic acids. The review included the extract of the studies in the past twenty years that were performed globally, specifically on the synthesis and biological assessment of N-acylphenothiazines. Given the data presented in the article, *N*-acylphenothiazine scaffolds are the powerful tool in medicinal chemistry and the present study will prompt researchers to perform more studies aiming N-acylphenothiazines moieties.

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