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Recent Progress in Phenothiazine Derivatives and its Biological Significance: A Review

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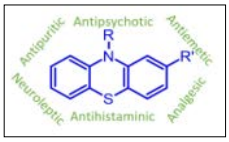
ABSTRACT

Phenothiazines are class of organic compounds that have become exceedingly important due to their varied biological and significant chemical properties. Phenothiazine and its derivatives have prominent place in pharmacology and biomedicine. In last couple of decades' significant attention has been paid on synthesis of phenothiazine derivatives and their subsequent screening towards widespread pharmacological activities.



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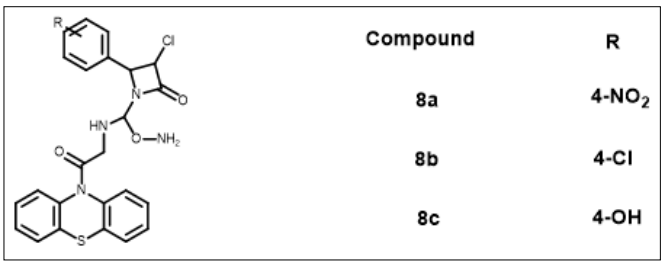
Introduction

Phenothiazine and its derivatives are known for their pharmacological importance. Up to now over 7000 phenothiazine derivatives have been synthesised and investigated for wide spectrum of pharmacological/ biological activities [1a]. This class of organic compounds has become exceedingly important due to their varied biological and significant chemical properties. Phenothiazine and its derivatives have prominent place in pharmacology and biomedicine [1b]. In last couple of decades' significant attention has been paid on synthesis of phenothiazine derivatives and their subsequent screening towards widespread pharmacological activities. Now a day's combination of two or more pharmacophores into single molecule is considered as a promising approach to design and synthesize a pertinent compound with diverse biological activities, interacting with specific or multiple targets [1c]. Phenothiazine moiety is extremely significant scaffold for drug development, owing to tremendous large variety of pharmacological activities. In this review, recent development in the field of phenothiazine derivatives and emphasized on their biological activities has been discussed. Prominent phenothiazine derivatives and their biological activities are highlighted.

Antibacterial Activity

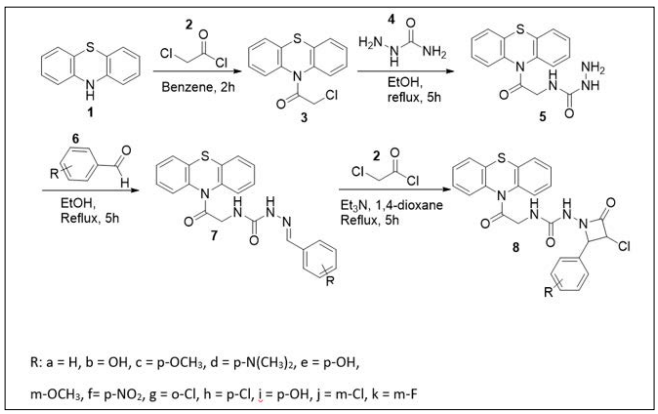
A. Rajasekaran et al. has synthesized a series of eleven novel phenothiazine derivatives and all these synthesized derivatives were screened in vitro antimicrobial activity, among all these compounds, compound 8a, 8b and 8c showed significant anti-bacterial activity against gram-negative organisms Pseudomonas aeruginosa and Vibreo cholera [1d].



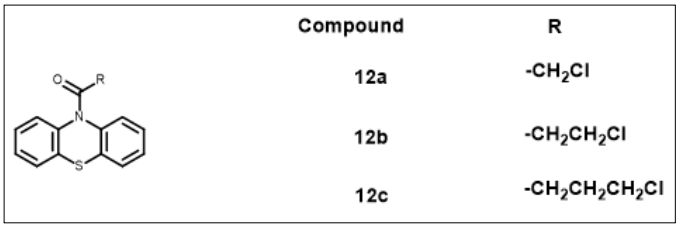
Compound	R
8a	4-NO_2
8b	4-Cl
8c	4-OH

Synthesis includes reaction of Phenothiazine with chloroacetyl chloride in benzene followed by treatment with semicarbazide to obtain semicarbazide derivative 5. It is further converted to Schiff's base 7 using various aromatic aldehydes which is further condensed with chloroacetyl chloride to obtain substituted azitidinones 8. (Scheme 1).

Scheme 1:

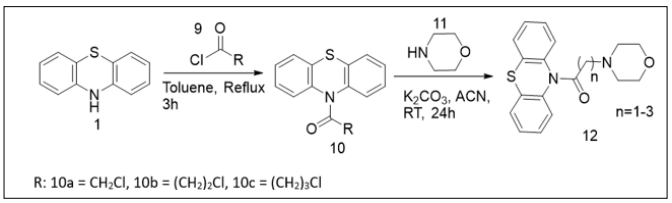


P. Chandrashekara et al. has synthesized a series of chloro based N-Phenothiazine derivatives and its morpholine derivatives. All synthesized derivatives were evaluated for their anti-bacterial activity against two gram-positive bacterial species namely, Bacillus subtilis and staphylococcus aureus, by disc diffusion technique method using nutrient agar medium, among all the compounds, compound 12a, 12b and 12c showed potent anti-bacterial activity [2].

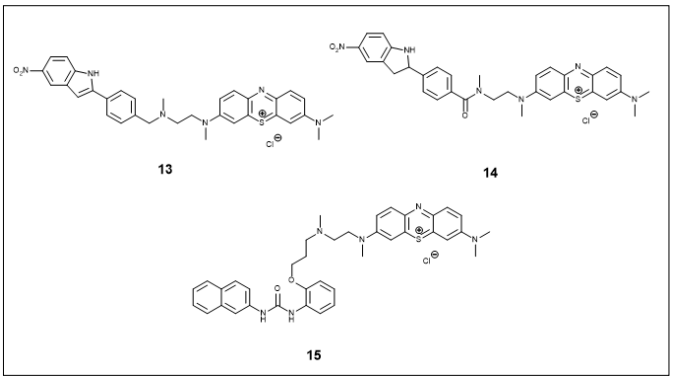


A simple two step synthesis consists of acetylation of phenothiazine using literature method followed by treatment of N-acetyl phenothiazine with potassium carbonate and morpholine to obtain three candidates of interest 12 (Scheme 2).

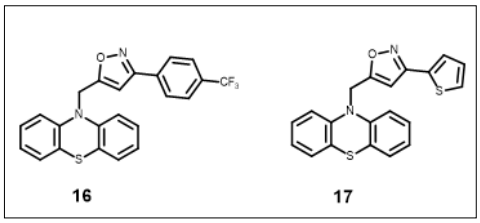
Scheme 2:



A. Rineh et al. has synthesized phenothiazine derivatives which are methylene blue linked with efflux pump inhibitors INF55 Compound 13 and 14 and INF271 (A biphenyl urea, compound 15; these hybrid compounds reduced survival of Escherichia coli and Acinetobacter baumannii as demonstrated by antibacterial photodynamic inactivation in vitro and in vivo compared with treatment in presence or absence of methylene blue [3]. Synthetic schemes for these compounds has not been provided in the literature by authors.

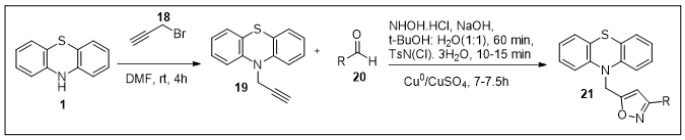


V. Guguloth et al. has synthesized fifteen novel Isoxazole phenothiazine derivatives, all these synthesized derivatives have been evaluated for their anti-bacterial activity. Among all the compounds, compound containing 4-trifluoromethyl group on phenyl ring 16 and compound containing thiophene moiety 17 exhibited superior activity against gram-positive and gram-negative bacteria [4].



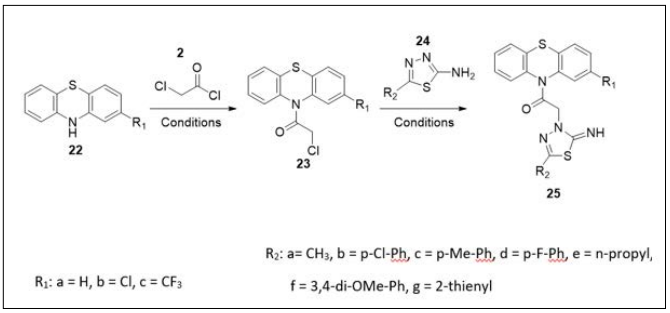
Synthesis of 16 and 17 started with reacting propargyl bromide with phenothiazine in presence of potassium tert-butoxide to obtain 19. Further, varius aromatic aldehydes were converted to their aldoxime derivatives, converted them into their respective nitrile oxides using chloramine trihydrate and then treated them with phenothiazine derivative in presence of Cu (I) catalysts to obtain desired Isoxazole-phenothiazine hybrids 21 in high yields. (Scheme 3).

Scheme 3:



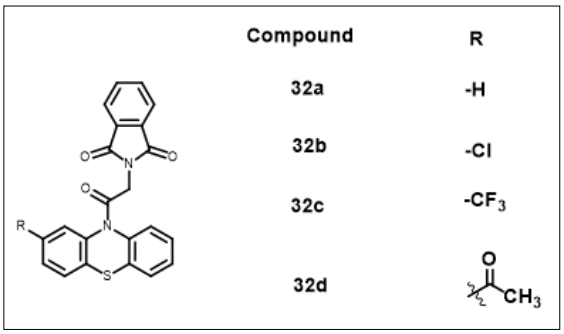
1. J. Ramprasad et al. have reported phenothiazine-thiadiazole hybrids. All the synthesized compounds were evaluated for their anti-bacterial activity by using disc diffusion method. These compounds were screened against three bacterial strains viz. Staphylococcus aureus, Pseudomonas aeruginosa and Escherichia coli, using ciprofloxacin as the standard drug. Compound 25a and 25b showed significant inhibition activity against all three bacterial strains [5].

Scheme 4:



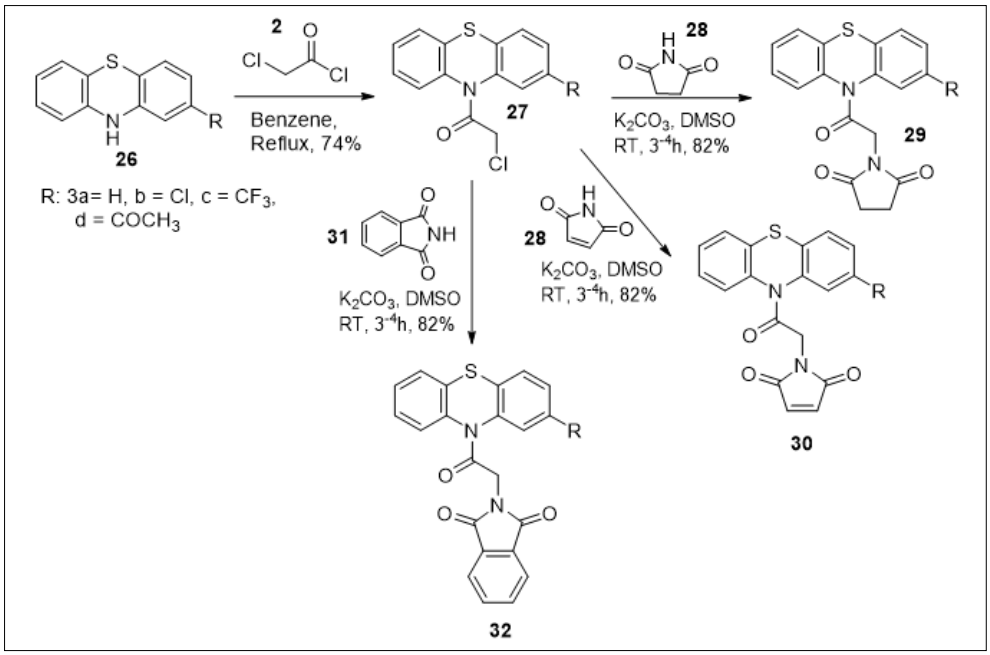
Antifungal Activity

T. Bansode et al. synthesized some new N-acyl substituted phenothiazines, all synthesized compounds were screened for their antifungal activity against Aspergillus niger, Aspergillus flavus, Aspergillus fumigatus, Candida albicans in DMSO by serial plate dilution method, among all these compounds, compound 32a, 32b, 32c and 32d showed good antifungal activity [6].

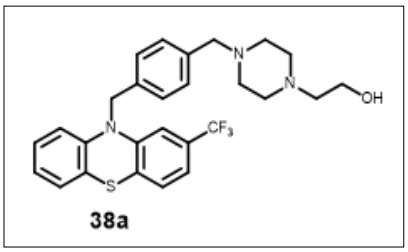


The N-acyl derivatives of phenothiazines (27) were synthesized by acylation of Phenothiazine under standard conditions followed by treatment with different imides in presence of K_2CO_3 to obtain target compounds 29, 30 and 32 with excellent yields. The reaction sequence is outlines in scheme 5.

Scheme 5:

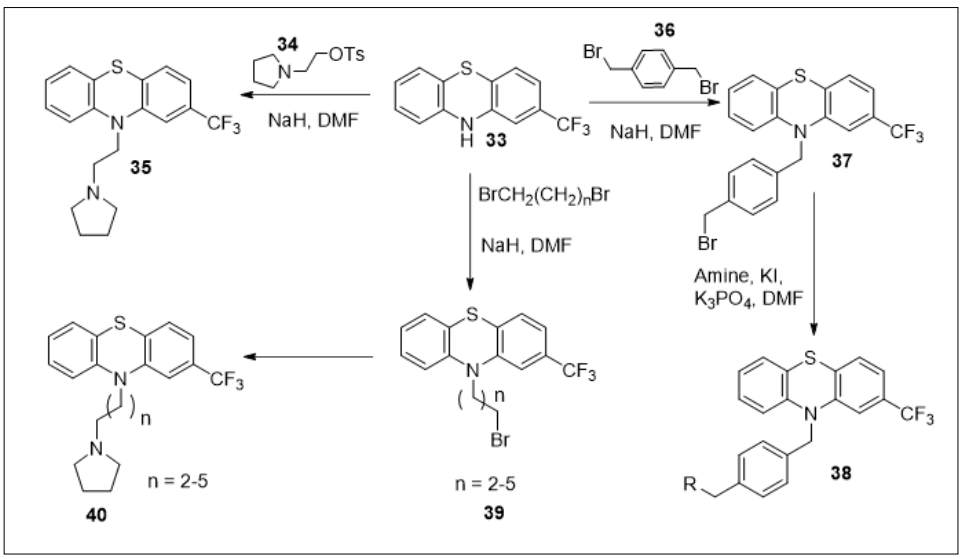


M. Montoya et al. synthesized a novel series of compounds and all these compounds were evaluated for antifungal activity against Cryptococcus neoformans and Candida albicans strain SC5314 and among all the compounds, compound 38a found most potent for antifungal activity [7].



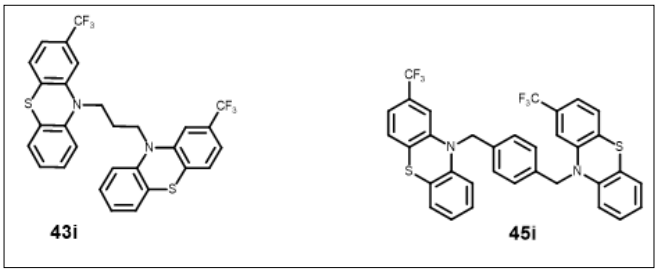
A series of analogues were synthesized starting from 2-(trifluormethyl)-10H-phenothiazine (33). Direct alkylation with 2-N-pyrrolidinylethyl tosylate furnished 35. Analogs with other chains were obtained using an approach where an alkylation is carried out with dibromo alkane followed by displacement with pyrrolidines (Scheme 6).

Scheme 6:



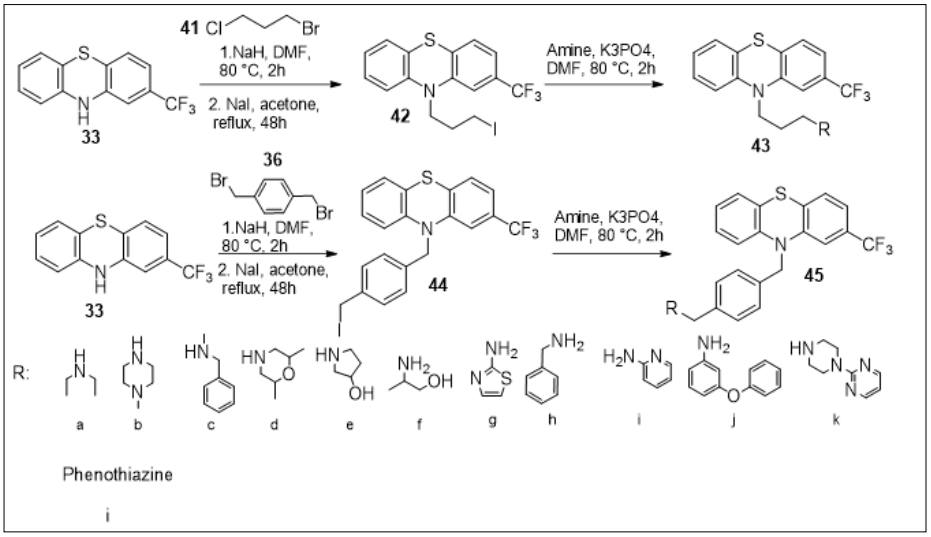
Antitubercular Activity

P. Madrid et al. synthesized analogs of the psychotropic phenothiazines. All synthesized phenothiazines were examined as antitubercular agents against Mycobacterium tuberculosis H37Rv and found that two bis-phenothiazine compounds 43i and 45i were potent for antitubercular activity [8].

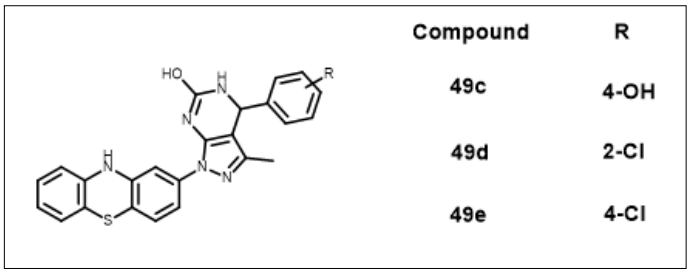


Substituted phenothiazines were alkylated using di-halo alkyl halides or dihalo benzyl bromides and then converted to alkyl/aryl iodides 42/44, which upon displacement by various amines provided the desired target compounds 43 and 45. However, it was observed that the self-condensation of Phenothiazines (bis-phenothiazines) with alkyl or aryl linker proved to be potent compared to other candidates 43i and 45i (Scheme 7).

Scheme 7:

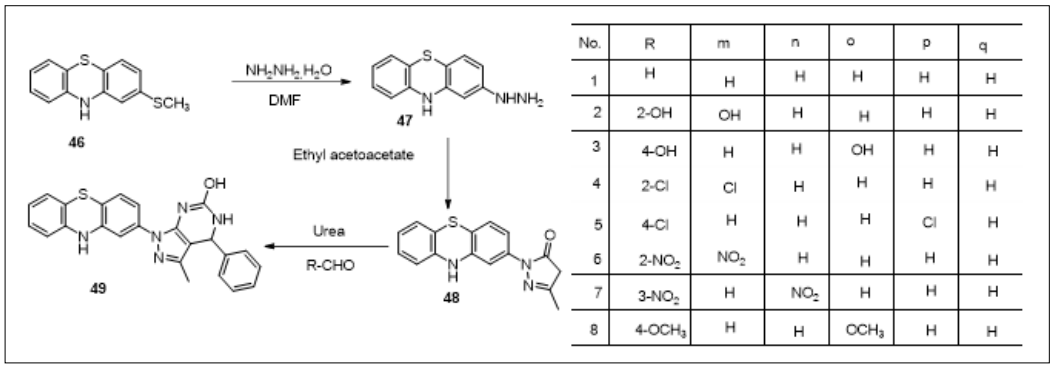


A. Trivedi et al. synthesized novel 2-hetrocycle-substituted phenothiazines with a pyrazolo [3,4-d] pyrimidine nucleus by using the Biginelli multi-component cyclo-condensation reaction (Scheme 8). All the synthesized compounds were evaluated for their antitubercular activity against Mycobacterium tuberculosis H37Rv. Among all the compounds, compound **49a**, **49b** and **49c** were found to be particularly active against Mycobacterium tuberculosis H37 Rv strain [9].



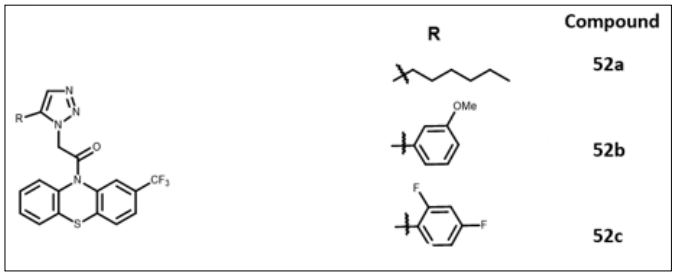
2-methylthiophenithiasine 46 and hydrazine hydrate were refluxed for eight hours to obtain hydrazinophenithiazine 47 which upon treatment with ethyl acetoacetate in 30% sodium hydroxide furnished pyrazole derivative. The pyrazole derivative of phenothiazine is then subjected to Biginelli reaction with Urea and Substituted aromatic aldehydes to obtain target compound 49 (Scheme 8).

Scheme 8:



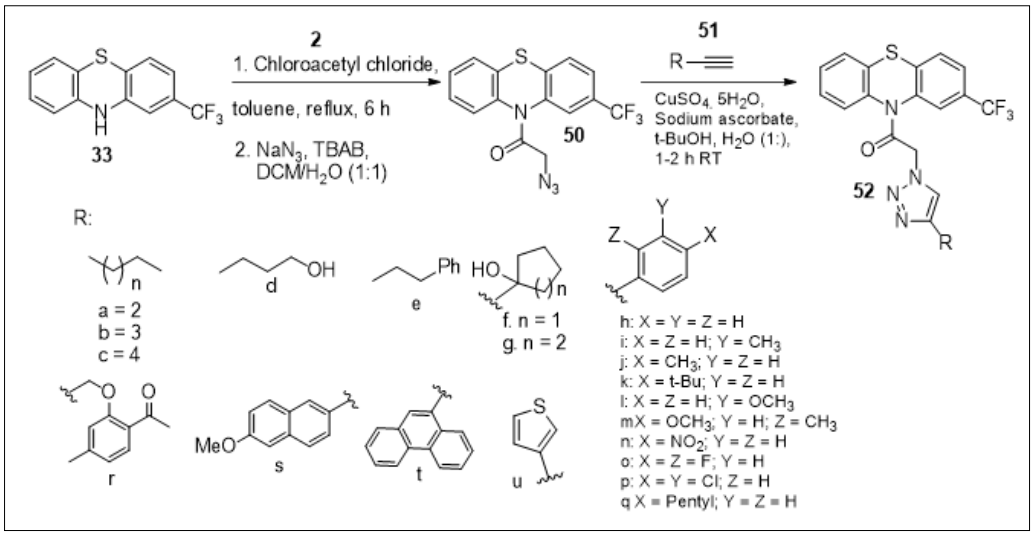
No.	R	m	n	o	p	q
1	H	H	H	H	H	H
2	2-OH	OH	H	H	H	H
3	4-OH	H	H	OH	H	H
4	2-Cl	Cl	H	H	H	H
5	4-Cl	H	H	H	Cl	H
6	2-NO_2	NO_2	H	H	H	H
7	3-NO_2	H	NO_2	H	H	H
8	4-OCH_3	H	H	OCH_3	H	H

D. Addla et al. synthesized a series of novel 2-(trifluoromethyl) phenothiazine-1,2,3-triazoles. All the 22 synthesized compounds were screened for in-vitro anti-mycobacterial activity against Mycobacterium tuberculosis H37Rv. Primarily, three compounds (24, 25) and (26) were found to be the most potent (MIC:6.25 µg/mL) antitubercular agents with good selectivity index (with lower toxicity) [10].

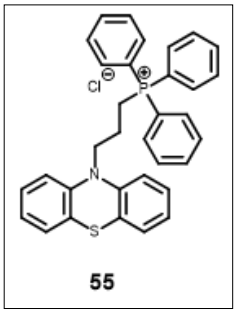


Starting point of the synthesis was preparation of key intermediate 2-azido-1-(2-(trifluoromethyl)-10H-phenothiasine-10-yl) (50) which was obtained from treatment of chloroacetyl chloride with trifluoromethyl phenothiazine which is sequentially treated with sodium azide to furnish 50. 50 is further subjected to Huisgen's (3+2) cycloaddition reaction with various alkynes to obtain triazole hybrids 52 in excellent yields (Scheme 9).

Scheme 9:



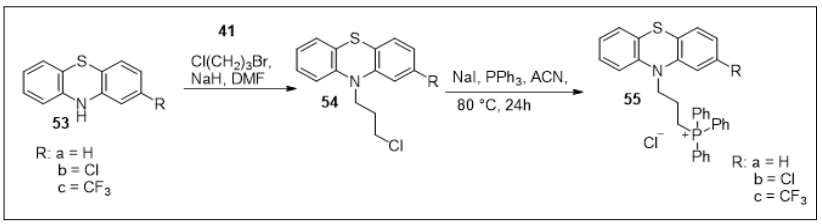
E. Dunn et al. synthesized a series of alkyltriphenylphosphonium (alkyl TPP) cations, Among the all-synthesized compounds, compound 55 showed inhibition of Mycobacterium tuberculosis growth at 0.5 µg/mL. compound 55 was targeting energetic processes (i.e. NADH oxidation and oxygen consumption), occurring in the mycobacterial membrane. This shows the enormous potential of alkyl TPP cations to improve the delivery and therefore efficacy of bioactive agents targeting oxidative phosphorylation in the mycobacterial membrane [11].



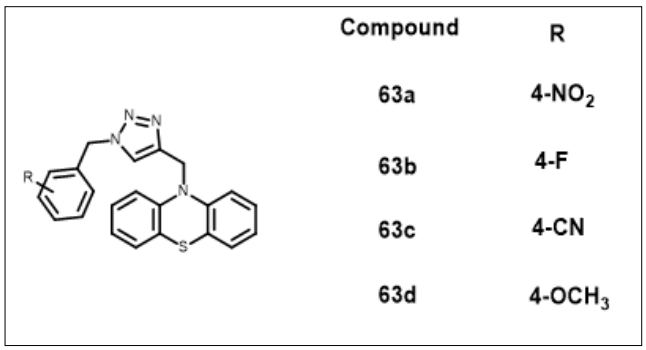
55

Desired compound 55 was prepared, starting form reaction of Phenothiazine and 1-bromo-3-chloropropane resulting in formation of 10-(3-chloropropyl)-10H-phenothiazine (54) which is then further treated with sodium iodide and Triphenyl phosphine provided the desired compound 55 (Scheme 10).

Scheme 10:



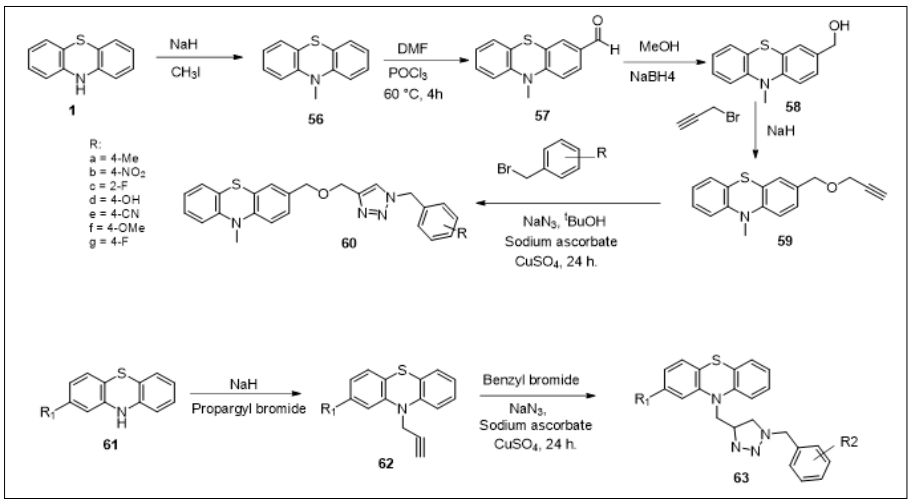
R. Reddyrajula et al. reported synthesis of 36 new phenothiazine hybrid molecules containing 1,2,3-triazole moiety. All the synthesized compounds were screened for in-vitro growth inhibition activity against Mycobacterium tuberculosis H37Rv strain (ATCC-27294) and Pyrazinamide, Ciprofloxacin and Streptomycin were used as the reference drugs. Among the tested compounds, four compounds namely 63a-d showed potent anti-tubercular activity with MIC of 1.6 µg/mL against Mycobacterium tuberculosis H37Rv strain [12].



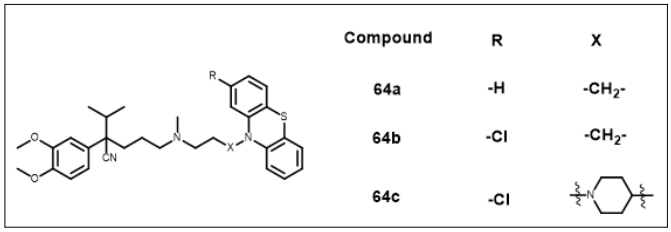
Compound	R
63a	4-NO_2
63b	4-F
63c	4-CN
63d	4-OCH_3

The general strategy applied for the synthesis of target compound involves Huisgen's 1,3-dipolar cyclo-addition reaction where, 10-methyl-3-((prop-2-yn-1-yloxy)methyl)-10H-pehnothiazine 59 prepared through literature procedures is treated with substituted aryl bromides in presence of sodium azide and sodium ascorbate to furnish target compounds 60 and 63 (Scheme 11).

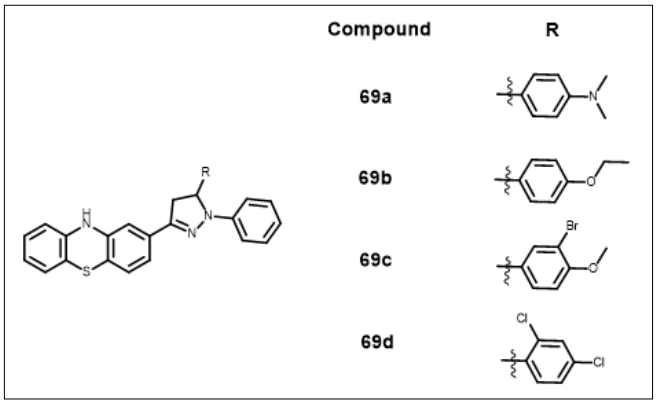
Scheme 11:



Malkeet kumar et al. synthesized novel hybrid efflux pump inhibitors which are phenothiazine derivatives. All these derivatives were tested in vitro and in macrophages individually and in combination with the anti-TB drugs, Rifampicin (RIF) and Isonicotinic acid hydrazide (INH), to determine their potentiating potential. Compounds 64a-c showed promising anti-tubercular activity individually and in combination with the anti-TB drugs [13].

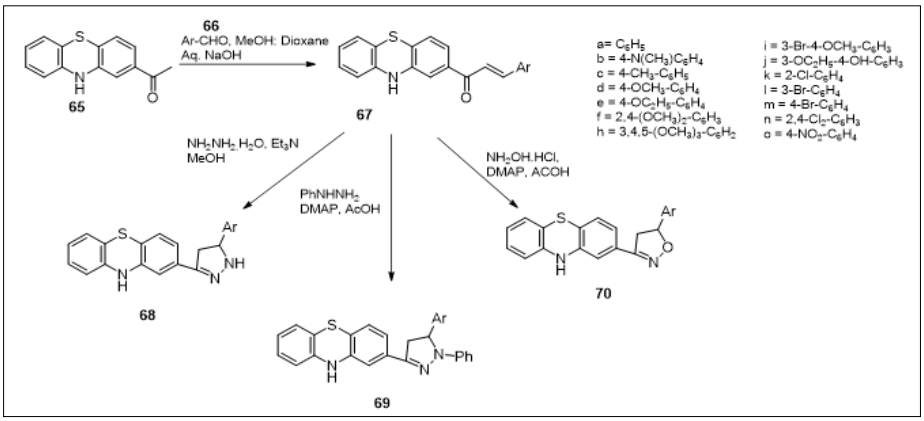


R. Pemmadi et al. synthesized around 60 novel hybrid phenothiazine analogs. All synthesized compounds were screened preliminary for anti-TB activity against pathogenic strains of M. tuberculosis H37Rv (ATCC 27294), using Microplate Alamar Blue Assay (MABA). Among the 60 synthesized compounds **69a-d** showed potent in vitro anti TB activity with MIC 6.25 µg/mL and selectivity index > 10 [14].



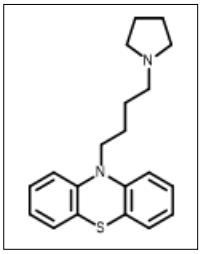
2-acetyl phenothiazine (65) was treated with aryl aldehydes under aldol conditions to obtain phenol-thiazinylchalcones (67). These intermediates were further treated with hydrazine hydrate, phenyl hydrazide and hydroxyl amine to obtain three different scaffolds 68, 69 and 70 (Scheme 12).

Scheme 12:



Antimalarial Activity

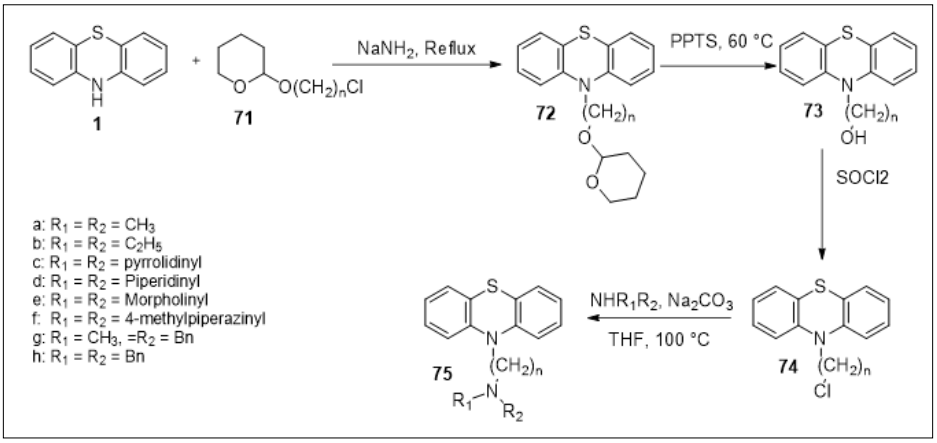
J. Guan et al. synthesized a series of new chemo-sensitizers (modulators) which were derivatives of phenothiazines. All the synthesized compounds were evaluated against chloroquine -resistant Plasmodium falciparum, compound 75c showed superior activity than



than verapamil which is one of the best known chemosensitizers with fractional inhibitory concentration (FIC) index 0.21, against verapamil 0.51 which is more than twice as active as verapamil [15].

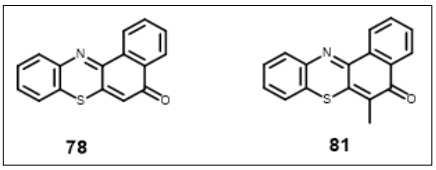
Phenothiazine was reacted with THP protected 4-chloro-1-butanol and 6-chloro-1-hexanol. THP protection was removed and hydroxy group was replaced by substituted amines to furnish desired compounds 75.

Scheme 13:



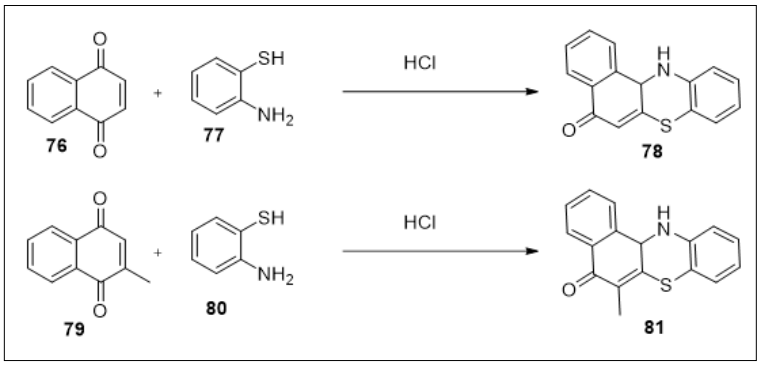
Antiviral Activity

I. Mucsi et. al. evaluated Benzo [a] phenothiazine derivatives for their antiviral activities alone and in combination with Aciclovir (ACV) in Vero cells using yield reduction assay. Among the tested compound It was found that, the antiviral effect of ACV on wild type HSV-2 strain was potentiated when ACV was combined with compound 78 and 81 [16a].



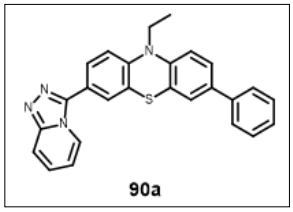
2-aminothiophenol (77) is treated with 1,4-napthoquinone (76) in acidic conditions to produce 5H-benzo[a]phenothiazine-5-one through dehydrogenation and dehydration [16b].

Scheme 14:



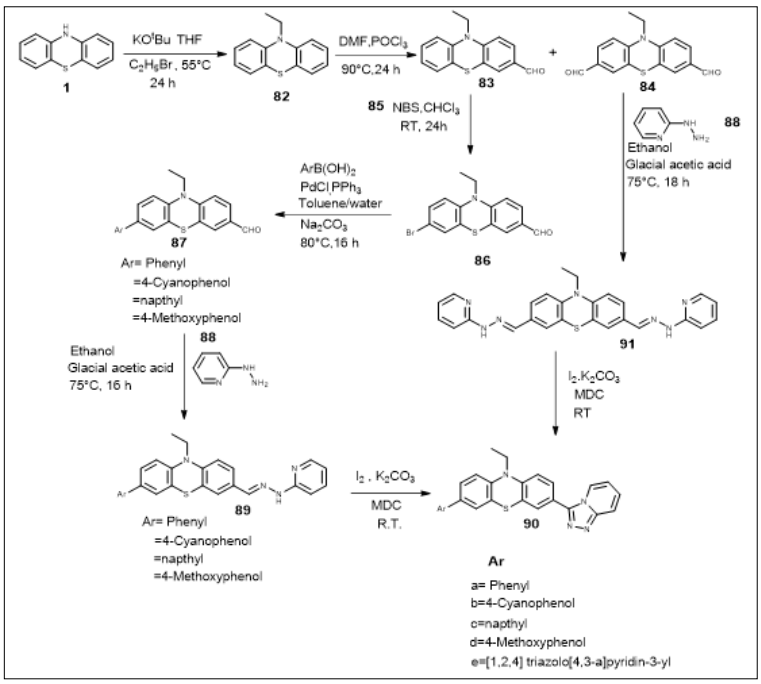
Anticancer Activity

T. Sachdeva et al has synthesized a series of novel phenothiazine based triazolopyridine derivatives. All the synthesized compounds were evaluated against human breast cancer carcinoma including MDA-MB-231, MDA-MB-468, MCF7 SKBR3 and T47D. Among all the compounds tested compound 90a showed considerable cytotoxicity and apoptotic induction effect against human breast cancer cells [17].

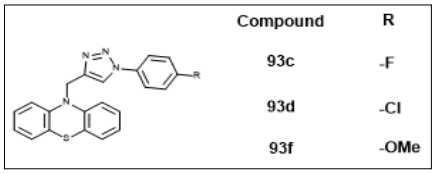


N-alkylation of phenothiazine in presence of potassium tert-butoxide and ethyl bromide afforded the compound 82 which was subjected to Vilsmeir-Haack reaction which resulted in the mixture of products mono- and di-formylated viz. 83 and 84. Bromination of 83 was carried out with NBS to obtain 86 which is further coupled to aryl boronic acid to obtain precursor 87. Similarly, condensation of 84 and Aryl boronic acid produced precursor 91. Both precursors were treated with pyridyl hydrazine to achieve the final target compounds.

Scheme 15:

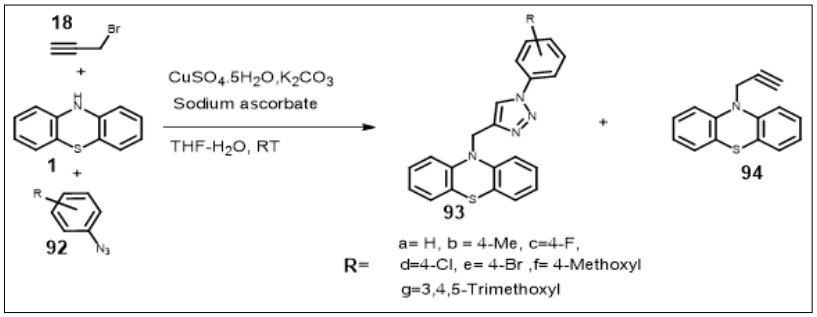


N. Liu et al synthesized a series of novel phenothiazine-1,2,3-triazole analogues. All these synthesized compounds evaluated for their antiproliferative activity against stomach (MGC-803), oesophagus (EC-109), prostate (PC-3), breast (MCF-7) and liver cancer (HepG-2) cell lines. Among all the tested compounds, compound 93c, 93d and 93f showed potent inhibitory activity against all selected cell lines [18].

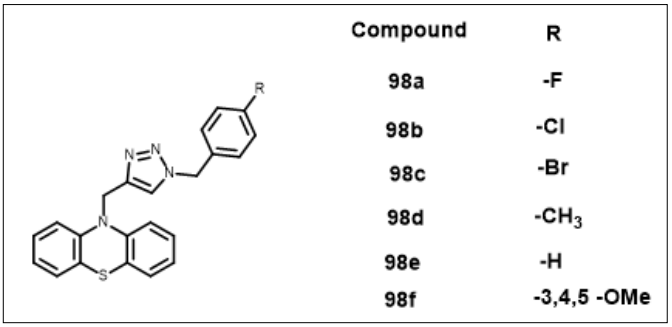


10H-Phenothiazine was reacted with propargyl bromide and azide derivatives to afford Phenothiazine-1,2,3-triazole 93 in presence of potassium carbonate and sodium ascorbate. This one step synthesis provides 72-86% yields (Scheme 16).

Scheme 16:

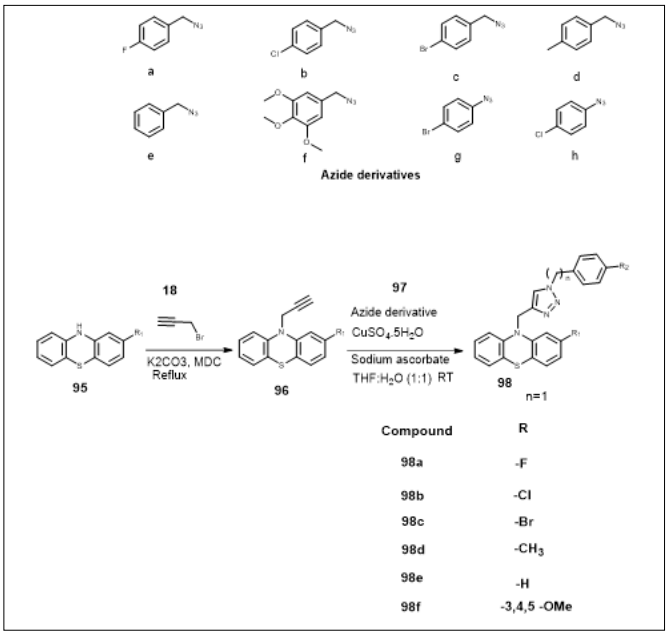


1. J. Zhang et al synthesized a series of novel phenothiazine-1,2,3-triazole derivatives and evaluated their anticancer activity in vitro against three selected cancer cell lines (MDA-MB-468, MDA-MB-231 andMCF-7). Among these derivatives, compound 98a-f showed anti-cancer activity, among all these compound 98f showed the most excellent anti-cancer activity [19].

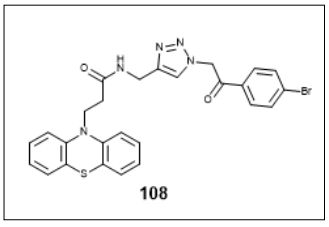


Phenothiazine was treated with propargyl bromide to provide 96 in presence of potassium carbonate. Intermediate 96 was then treated with aromatic azides using sodium ascorbate and copper sulphate in THF: water to furnish desired compounds 98 (Scheme 17).

Scheme 17:



D. Belei et al. synthesized a series of novel phenothiazine 1,2,3 -triazole derivatives. The activity of all synthesized derivatives was evaluated on human FTase. Among all the tested derivatives, compound 108 has Farnesyltransferase inhibitory effects led to reduction of proliferation on most of the cancer cell lines. This is showing that mixing the phenothiazines and 1,2,3 motif in a single compound structure can led to new scaffolds in the field of farnesyltransferase inhibitors [20].

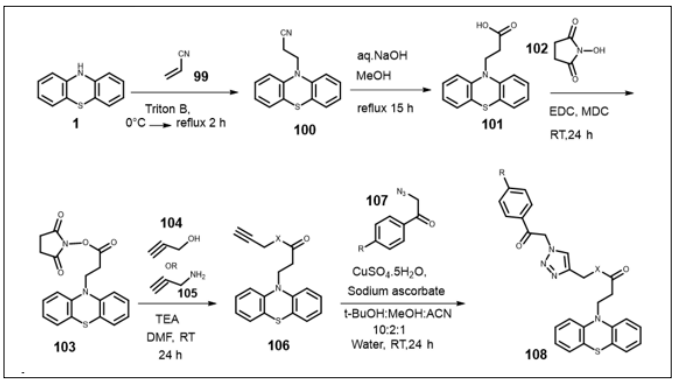


In Scheme 18.1: starting acid **101** was obtained by condensation of Phenothiazine with acrylonitrile in presence of triton B then by hydrolysis of nitrile 101 was obtained. Acid **101** is then couple with N-hydroxy Succinimide leading to an activated ester and then treatment with propargyl amine furnished acetylenic amide **106**. It was treated with alpha-azido ketones using biphasic phase transfer system to obtain **108**.

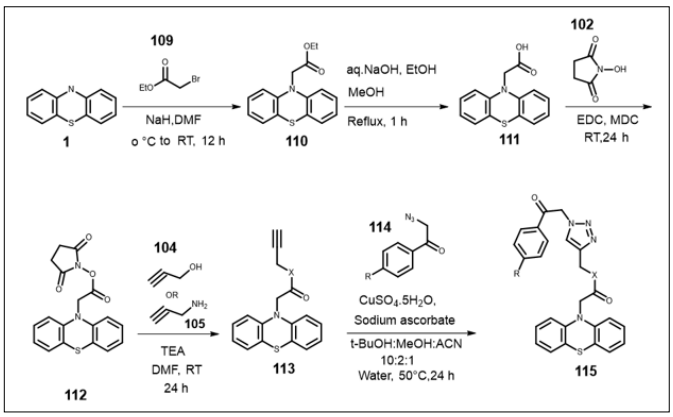
In Scheme 18.2; the starting acid is prepared by treatment of Phenothiazine with ethyl bromoacetate in DMF followed by saponification of ester with aq. Sodium hydroxide. Coupling of the carboxylic acid with N-Hydroxy Succinimide led to activated ester and then reaction with propargyl amine furnished acetylenic amine. Click reaction with alpha-azidoketones furnished the desired triazole compound **113** and same reaction sequence with propargyl alcohol furnished triazole compounds **115**.

In Scheme 18.3; Substituted phenothiazine's were treated with chloroacetyl chloride followed by sodium azide to obtain **118**. This was then condensed with **119** to obtain triazole compounds **120** using copper sulphate and sodium ascorbate. (Scheme 17.1-3).

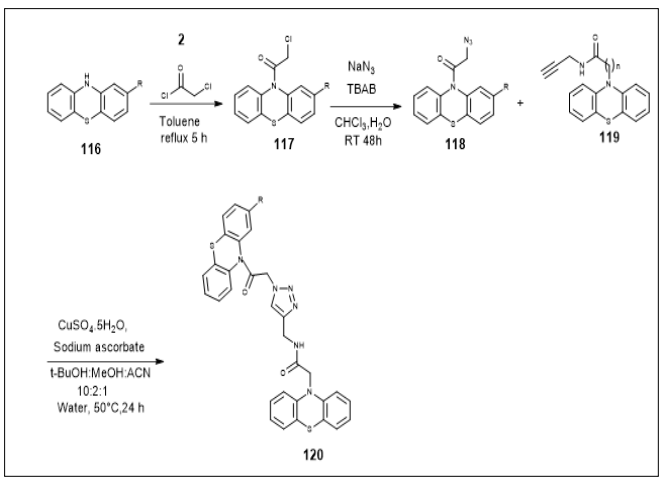
Scheme 18.1:



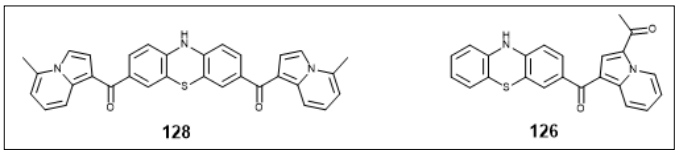
Scheme18.2:



Scheme 18.3:

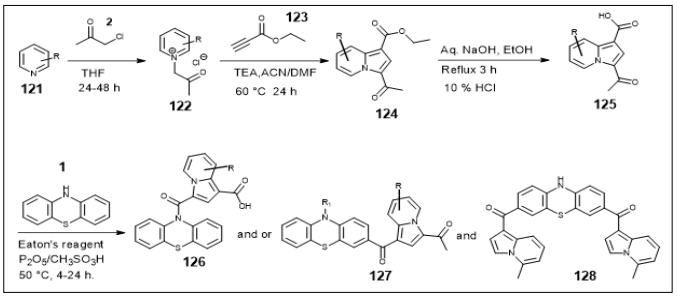


I. Moise et al. synthesized a series of Indolizine Phenothiazine derivatives. All the compounds were evaluated on tubulin polymerization and human FTase. This screening utilized 60 different human tumor cell lines representing leukemia, melanoma and cancers of the lung, colon, brain, ovary, breast, prostate, and kidney cancers. Among the all tested derivatives compound 126 and 128 potent antitumor activity [21].

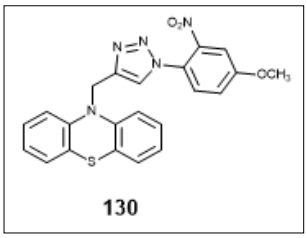


Synthesis was initiated with formation of Pyridinium salts 122 using commercially available pyridines with chloroacetone in THF. In further steps, salts 122 were subjected to 1,3-dipolar cycloaddition reaction with ethyl propiolate in presence of triethylamine in order to create Indolizine ring. Further, the esters were hydrolyzed and the carboxylic acids were treated in presence of Eaton's reagent with Phenothiazine and N-methylphenothiazine to obtain three different targets 126, 127 and 128 (Scheme 19).

Scheme 19:

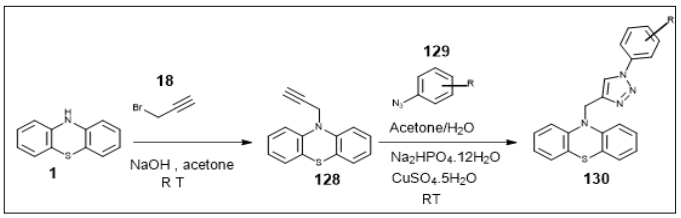


N. Liu et al. synthesized two novel series of 1,2,3-triazole-phenothiazine and di-thiocarbamate-phenothiazine hybrids by molecular hybridization strategy. All the synthesized derivatives were evaluated for their anti-proliferative activity against three gastric cancer cell lines (MKN28, MGC-803 and MKN45). Compound 130 showed most potent inhibitory activity. Importantly, compound 130 was revealed as a novel tubulin polymerization inhibitor and an orally active antitumor agent [22].

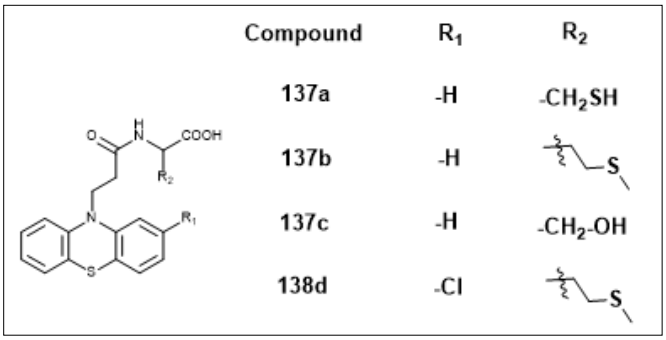


In a two-step synthesis, triazole hybrids were synthesized using Phenothiazines treated with propargyl bromide followed by click reaction with aromatic azides to obtain title compound 130 (Scheme 20).

Scheme 20:

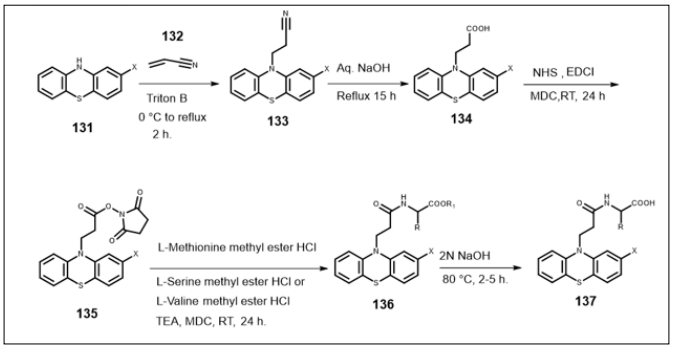


G. Dumitriu et al. synthesized phenothiazine derivatives bearing different amino acids. All these derivatives were evaluated on human FTase. Among all the tested derivatives, compounds 137a-d showed promising inhibitor of human farnesyltransferase [23].

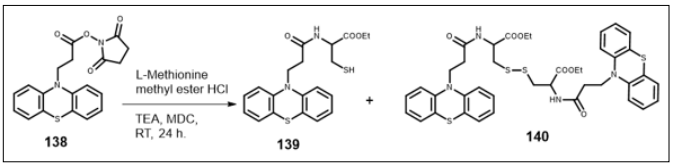


Phenothiazine was treated with acrylonitrile under Michael addition conditions to obtain 133 which was hydrolyzed to furnish carboxylic acid 134. 134 was activated to it's corresponding NHS ester followed by treatment with amino acids to obtain target compounds 139 (Scheme 21.1). In case of L-cysteine moiety, dimer 140 formation was observed along with the monomers (Scheme 21.2). To explore the importance of three carbon atom chain between phenothiazinic nitrogen and the methionyl residue, a triazolyl unit was incorporated in the synthesis. Phenothiazine was initially reacted with 1-bromo-3chloropropane using sodium hydride. It was further treated with sodium azide to obtain 142. Triazole unit was furnished by click reaction with ethyl propiolate. Saponification followed by amino acid coupling furnished the desired compounds 146 (Scheme 21.3).

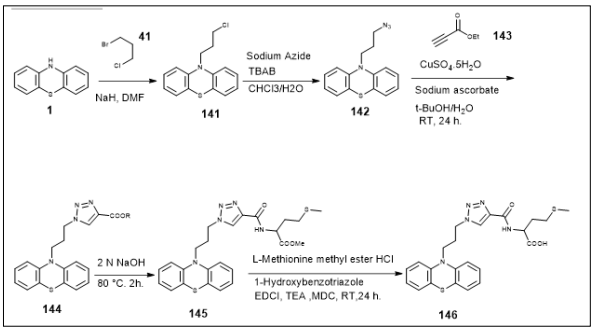
Scheme 21.1:



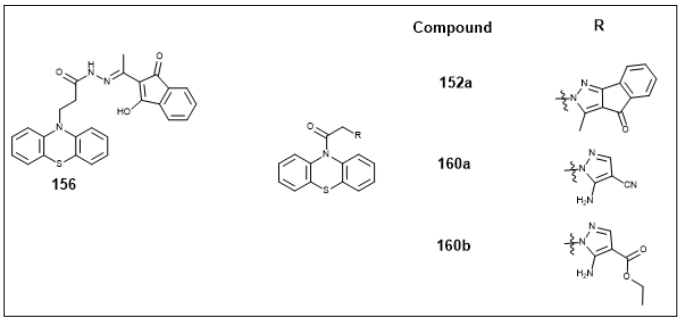
Scheme 21.2:



Scheme 21.3:

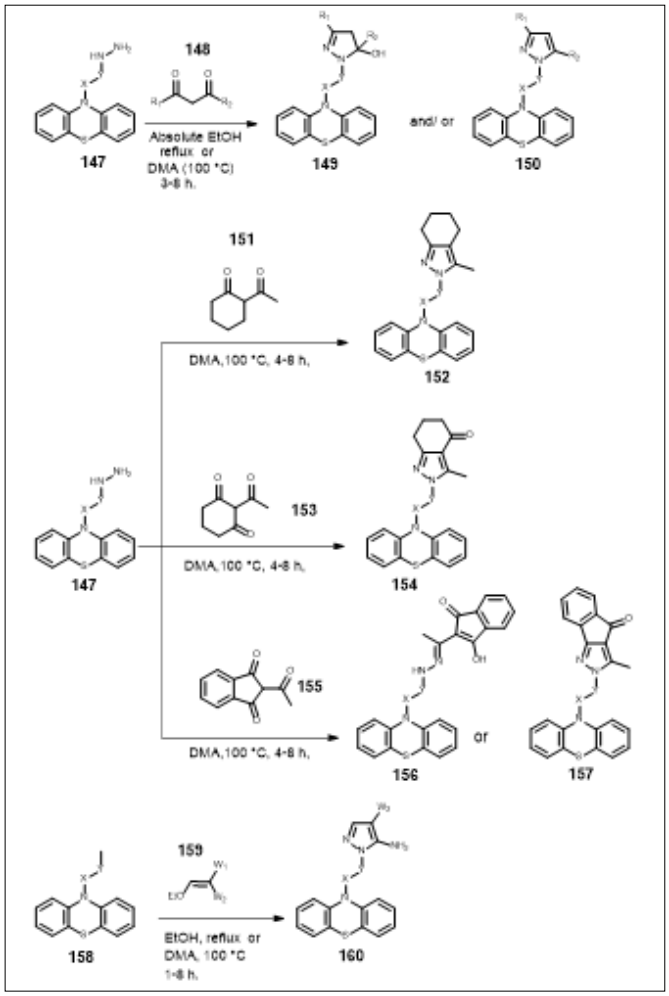


L. Atudosie et al synthesized a series of new phenothiazine derivatives bearing a pyrazole unit. The synthesized compounds were evaluated on human FTase at a single high dose. Among all the tested derivatives, compounds 152a, 160a and 160b showed promising inhibitor of human farnesyltransferase [24].

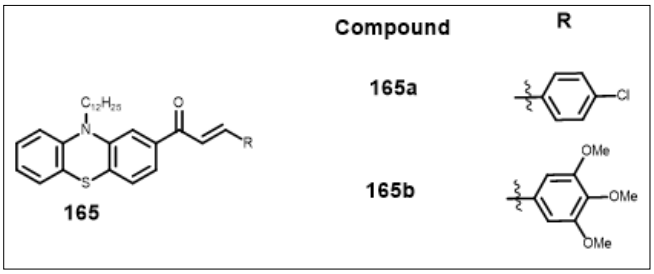


Acyl hydrazine's were treated with alkyl hydrazine and 1,3-diketones to furnish pyrazole and or di-hydropyrazoles in a single step synthesis (Scheme 22).

Scheme 22:

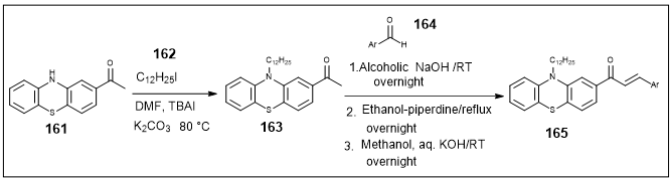


A. Asiri et al synthesized novel chalcone-based phenothiazine derivatives. The in-vitro growth inhibitory activity of the chalcone-based phenothiazine derivatives was evaluated against two carcinoma cell lines (human breast cancer cell line MCF-7 cells and human hepatocellular carcinoma HepG-2 cells) and compared with the well-known anticancer standard drugs cisplatin and doxorubicin under the same conditions. Among the tested derivatives, compound 165a and 165b were the most effective compounds [with IC50 values of 7.14 µg/mL and 7.6 µg /mL, respectively] against human hepatocellular carcinoma HepG-2 cells and against the human breast cancer cell line MCF-7 cells [25].

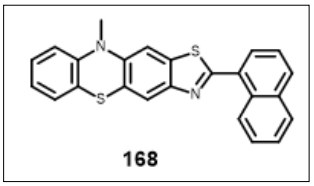


2-acetylphnothiazine was N-alkylated using dodecyl iodide in presence of tetrabutyl ammonium iodide. Further, a base-catalysed Claisen-Schmidt reaction with aromatic aldehydes was carried out to produce desired chalcones 165 (Scheme 23).

Scheme 23:

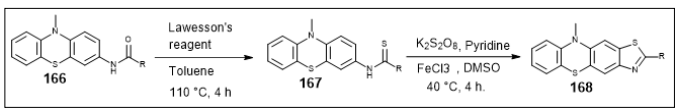


B. Brem et al synthesized novel thiazolo [5,4-b] phenothiazine derivatives. The synthesized compounds were investigated in vitro using cultured HL-60 human promyelocytic and THP-1 human monocytic leukaemia cell lines. Among the tested derivatives compound 168 was identified as the most effective compound [26].

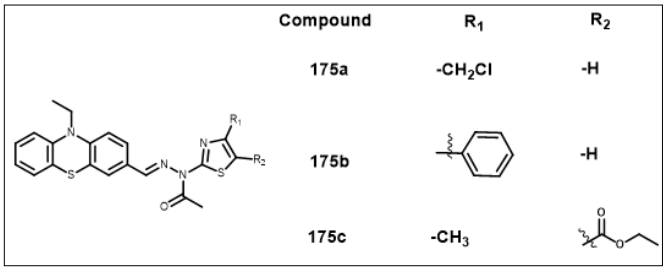


Starting N-(Phenothiazin-3-yl)-amides were prepared from 3-amino-PTZ precursor by coupling with various acyl chlorides. The N-(Phenothiazin-3-yl)-thioamides were prepared by using Lawesson's reagent. In the last step. The thiazole ring was closed by oxidation reaction under Oxone to obtain the target compounds 168 (Scheme 24).

Scheme 24:

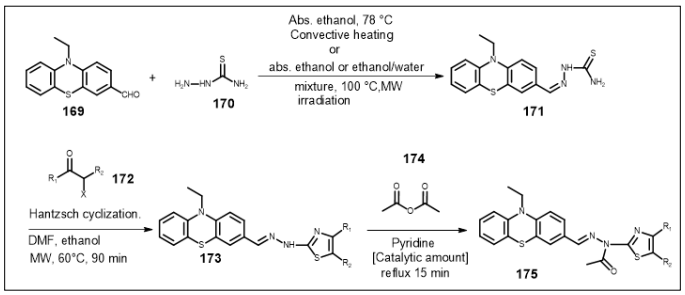


A. Ignat et al synthesized a series of new phenothiazinyl-thiazolyl-hydrazine derivatives by Hantzsch cyclization. The new compounds were tested in vitro for their CC531S cells using spectrometric methods. Among the tested derivatives, compound 175a, 175b and 175c exhibited cytotoxicity against hepatic and colon tumor cells in a dose-dependent mode [27].

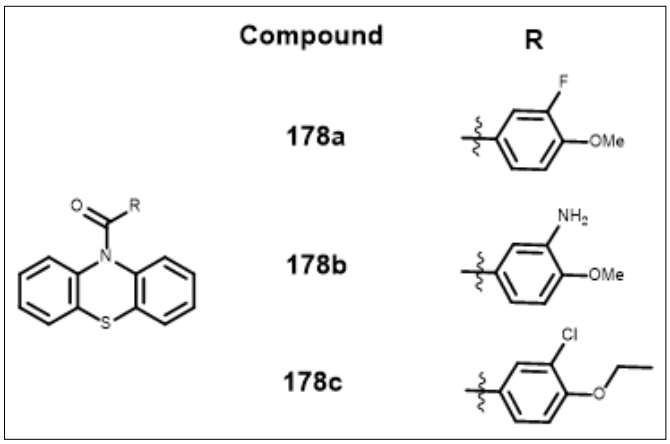


Synthesis was initiated with condensation of 10-ethyl-10H-pheonothiazine-3-carbaldehyde (169) with thiosemicarbazide in absolute ethanol. Hantzsch cyclization of thiosemicarbazole was carried out using α-halocarbonyl derivatives to obtain thiazole intermediates which are then acylated to obtain target compounds 175 (Scheme 25).

Scheme 25:



C. Abuhaie et al synthesized a novel series of phenothiazine derivatives. All the synthesized compounds were evaluated against 60 human tumor cell lines. Among the tested derivatives, compound 178a, 178b and 178c exhibited potent anti-proliferative activity against several types of cancer cells [28].



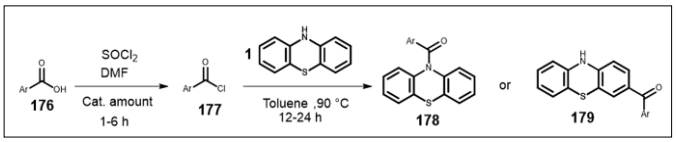
Desired compounds were prepared by treatment of Phenothiazine with aromatic acid chlorides, wherein; acylation occurred at nitrogen atom or FC acylation on the aromatic ring (Scheme 26.1)

To install hetero-aromatic rings on the phenothiazine scaffold; Phenothiazine was coupled with chloroacetyl chloride followed by condensation with substitutes pyridine to obtain an intermediate which was further treated with ethyl propiolate to access 186(Scheme 26.2).

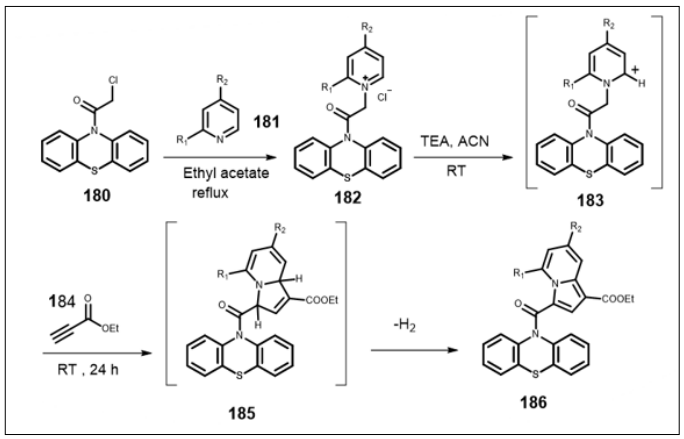
Similarly, a different approach was used to install Imidazo pyridine scaffold on phenothiazine wherein; 2-amino pyridine was treated with DMF/DMA in toluene to obtain 189 which was further treated with 10-(chloroacetyl)-10H-phenothiazine in methanol to which under reflux condition which resulted in coupling followed by cyclization to obtain Imidazo (1,2-a) pyridine formation 190 (Scheme 26.3).

In addition, to complete the SAR studies urea based scaffold were also prepared by treatemtn of 10H-phenothiazine-10-carbonyl chloride with substituted indoles in catalytic DAMP, triethylamine in DCM to obtain urea targets 193 (Scheme 26.4).

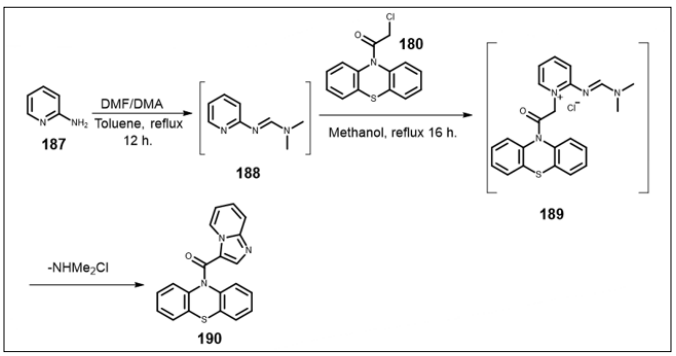
Scheme 26.1:



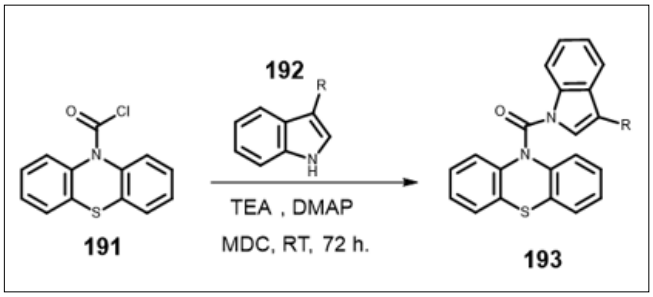
Scheme 26.1:



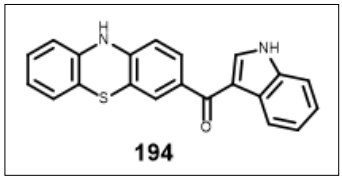
Scheme 26.3:



Scheme 26.4:

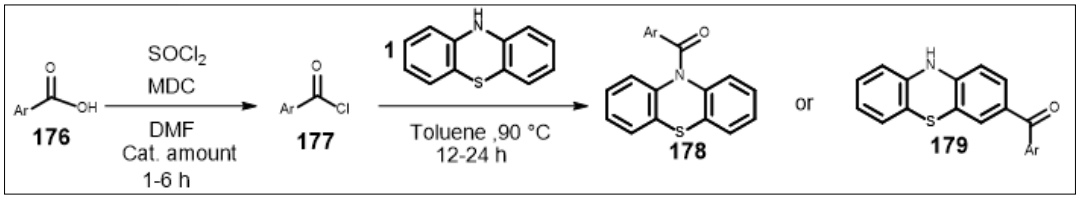


A. Ghinet et al synthesized a series of new phenothiazine derivatives. All synthesized compounds were evaluated against 60 human tumor cell lines. Among the tested derivatives, compound 194 exhibited potent anti-proliferative activity against several types of cancer cells including several multi-drug resistant (MDR) cancer cell-lines [29].

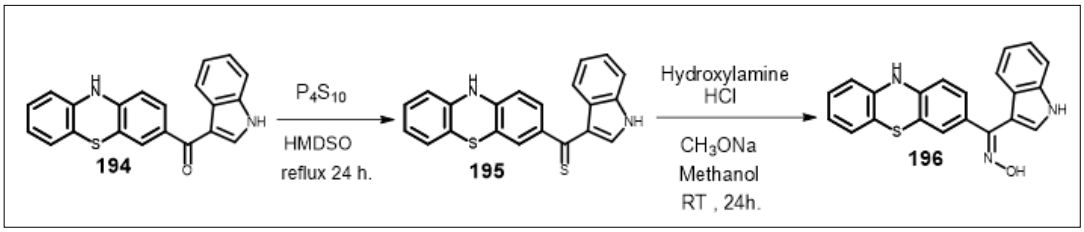


N-substituted phenothiazines were prepared by treatment with suitable benzoyl chlorides by refluxing in toluene. In rare cases, FC acylation reaction product saw precedence over N-acylation (scheme 27.1). To introduce a thiocarbonyl, thioamide or an oxime connector was envisaged. Thus, 194 was treated with P4S10/HDMSO to obtain thioketone which was further treated with hydroxyl amine HCl to furnish desired compund196 (Scheme 27.2). In addition, FC acylation products were prepared using 10-methylphenothiazine when treated with AlCl3 exclusively to 3,7-bis alkylated phenothiazines 200 (Scheme 27.3).

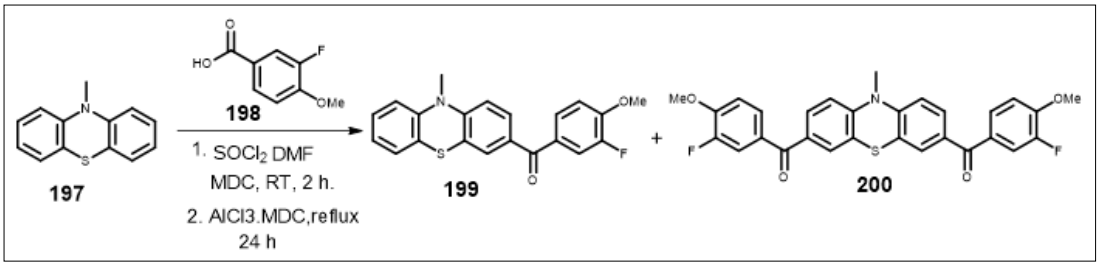
Scheme 27.1:



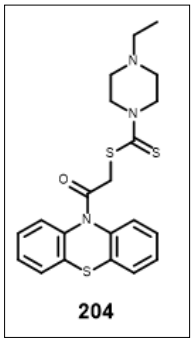
Scheme 27.2:



Scheme 27.3:



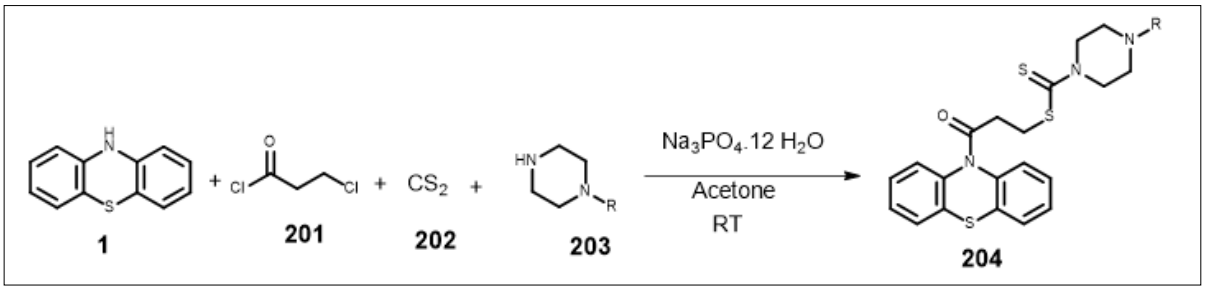
R. Mao et al synthesized Novel phenothiazine-dithiocarbamate analogues. The synthesized derivatives were evaluated for their anticancer activity in vitro against three selected cancer cell lines (EC-109, MGC-803, and PC-3).



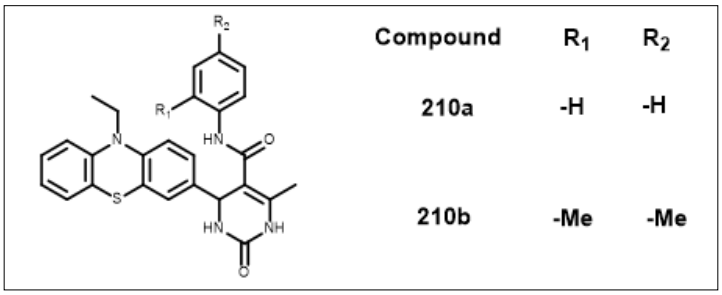
Among the all analogues, compound 204 showed the most potent inhibitory activity with an IC50 value of 11.59μM against PC-3 cells. In addition, compound 204 could arrest the cell cycle at the G1 phase and regulate the expression of G1 checkpoint-related proteins, suggesting that phenothiazine-dithiocarbamate hybrids might be useful as cell cycle blockers [30].

Phenothiazine was treated with 2-chloroacetyl chloride (3-chloropropanoyl chloride or 4-chlorobutanoyl chloride), carbon disulfide and various piperazine analogues to furnish 204 in presence of sodium phosphate decahydrate (Scheme 28).

Scheme 28:

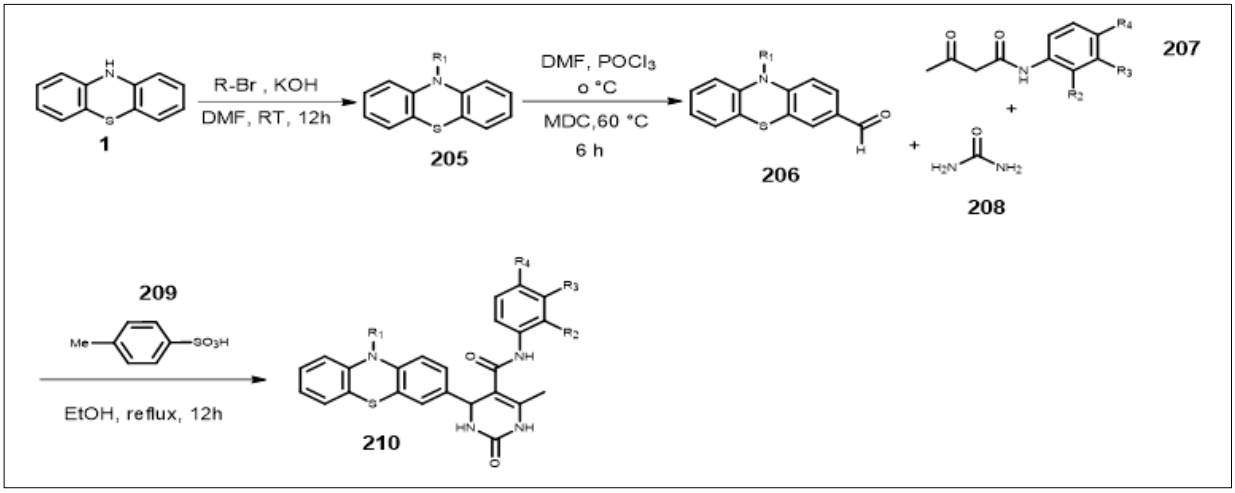


R. Sivaramakarthikeyan et al synthesized phenothiazine and amide ornamented novel nitrogen heterocyclic hybrids. All the synthesized derivatives were evaluated against AsPC1 and SW1990, the pancreatic cancer cell lines by the methodology of Cell-Titre Glo Luminescent Cell Viability Assay. Among the all-tested derivatives, compound 210a and 210b showed potent anticancer activity against both the cancer cell tested [31].

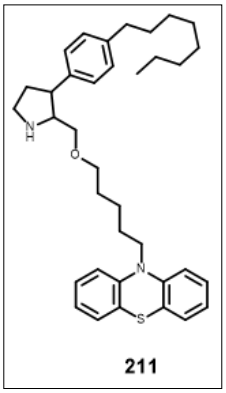


Phenithiazine was treated with Alkyl halide to obtaine 205 and further treated under Vilsmeir-Haack formylation conditions to obtain 206. A multicomponent reaction between 206, 3-oxo-N-substituted-phenybutanamides and urea were treated in the ratio of 1:1.1:1.5 in presence of p-toluenesulfonic acid to furnish desired products in good yields (scheme 29).

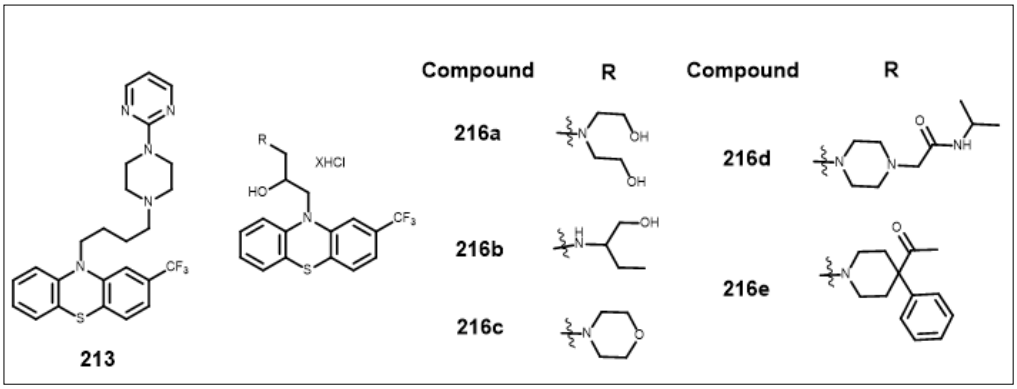
Scheme 29:



J. Garsi et al synthesized a series of novel phenothiazine derivatives. All derivatives were evaluated for their anticancer activity and found that compound 211 has potent anticancer activity among all [32].

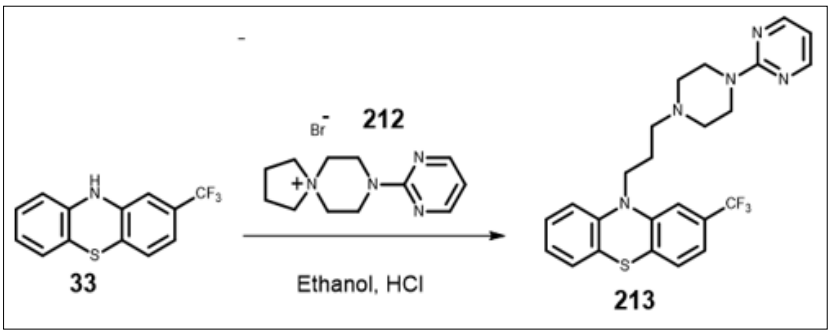


J. Zyta et al synthesized a series of 10 novel analogues of Fluphenazine and evaluated for their apoptotic activity and cytotoxicity in human lymphocyte which were genotoxically damaged in vitro with benzo [a] pyrene. Compounds 216 a-216e exerted a pro-apoptotic effect stronger than that of Fluphenazine and compound 216 a-216e exhibited the weakest cytotoxic effect on normal lymphocytes isolated from venous blood from five health donors, showing selectivity to cancer cell [33].

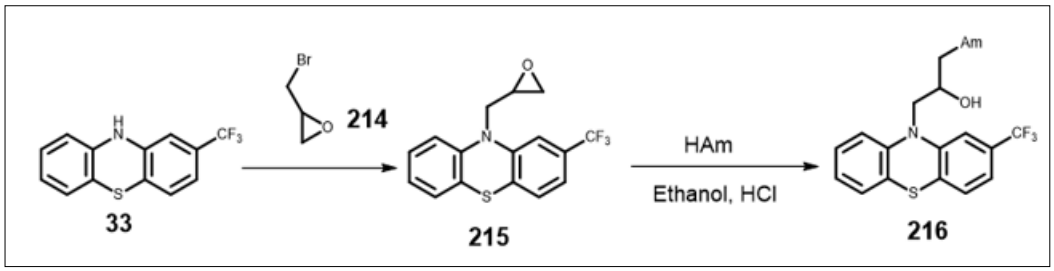


Phenothiazine was treated with 8-(2-pyrimidinyl)-8-aza-5-azaspiro[4,5]-decane bromide (212) in presence of anhydrous potassium carbonate in xylene under reflux to obtain 213 (Scheme 30.1). In addition, Phenothiazine was treated with 1-bromo-2,3-epoxypropane in presenc of sodium hydride and DMF to obtain 215 which was further treated with appropriate amine to furnish desired compound 216 (Scheme 30.2).

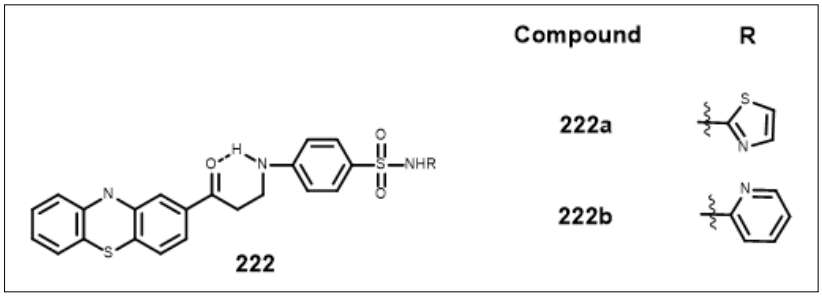
Scheme 30.1:



Scheme 30.2:

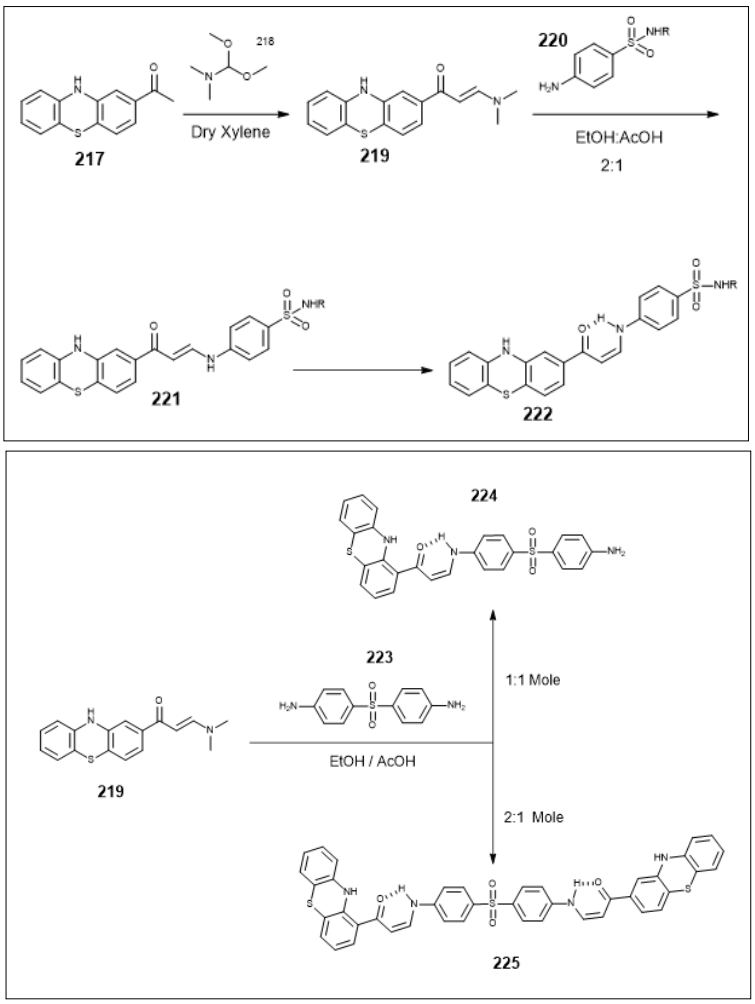


M. Ghorab et al synthesized a series of twenty novel phenothiazine sulfonamide hybrids. All derivatives were screened for their in-vitro cytotoxic activity against T47D human breast cancer cell line utilizing the sulfo-Rhodamine-B Assay. Results indicated that, among all derivatives, compound 222a with unsubstituted thiazolyl ring and compound 222b with unsubstituted pyridine exerted highest activity with IC50 value of 8.1 and 8.8 μM respectively which were more potent than that of the reference drug used, Doxorubicin (IC50 ,9.8 μM) [34].



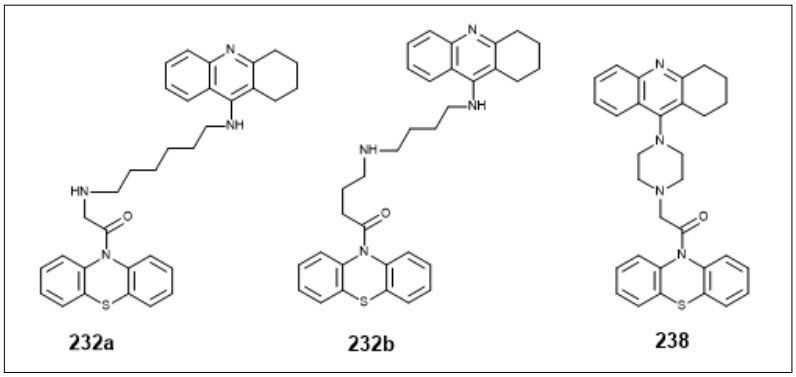
1-(10H-phenothiazine-2-yl)ethenone was treated with DMF-DMA under reflux in dry xylene to produce key starting material (E)-3-(diethylamino)- 1-(10H-phenothiazine-2-yl)-prop-en-1-none. Enaminone 219 was then reacted with sulfa drugs 220 or dapson 223 in ethanol: acetic acid (2:1) to furnish corresponding phenothiazine-sulfonamide derivatives (Scheme 31).

Scheme 31:



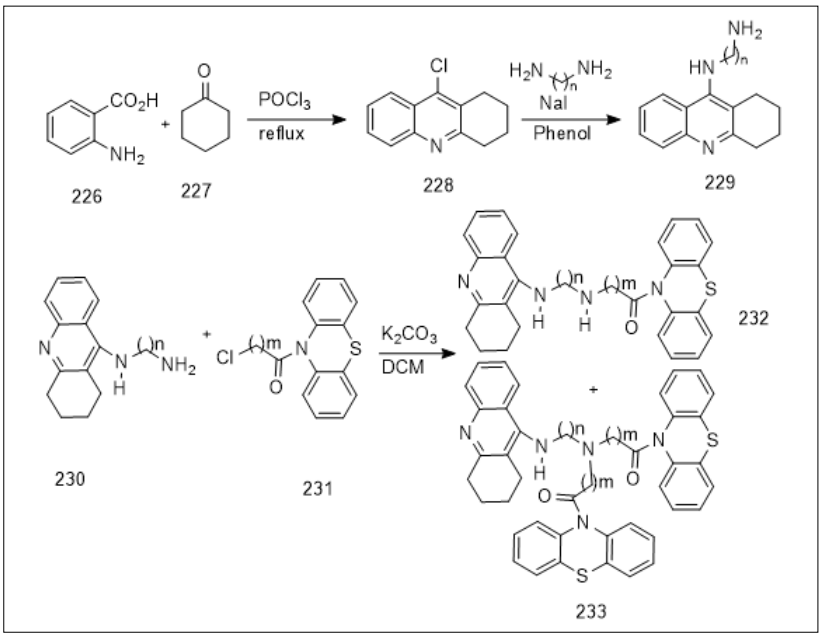
Anti-Alzheimer Activity

Y. Chen et al synthesized a series of novel tacrine phenothiazine hybrids as multi-target drugs for Alzheimer's disease, these synthesized hybrids were evaluated for their anti-acetylcholinesterase activity, according to AChE enzyme-linked immunosorbent assay kit using tacrine and donepezil as reference compound. Among tested derivatives it was found that compound 232a was most potent compound with IC50 89 nm, lower than donepezil with IC50 30 nm other two compound 232a and 238 has showed moderate activity for Alzheimer's disease [35].



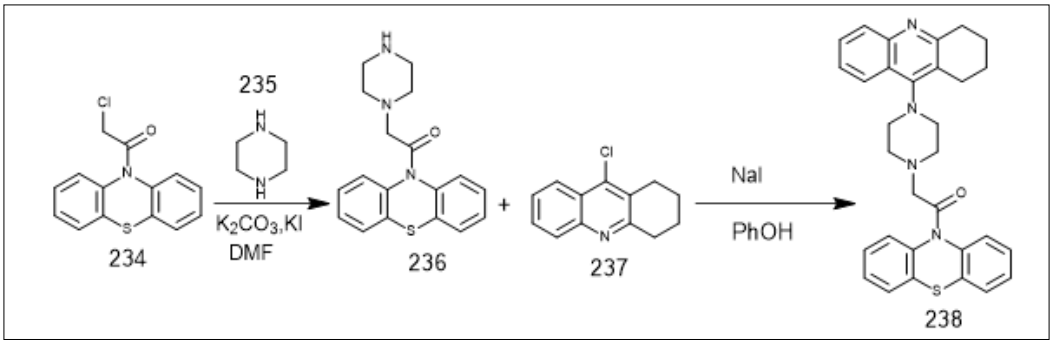
Condensation of anthranilic acid with cyclohexanone provided the chlorotetrahydroacridine. Diplacement of chloride with diamine provided the precursor for 229. Then the terminal amine group displaced the chloride from phenothiazine derivative to provide mixture of products which were isolated by column chromatography (Scheme 32.1).

Scheme 32.1

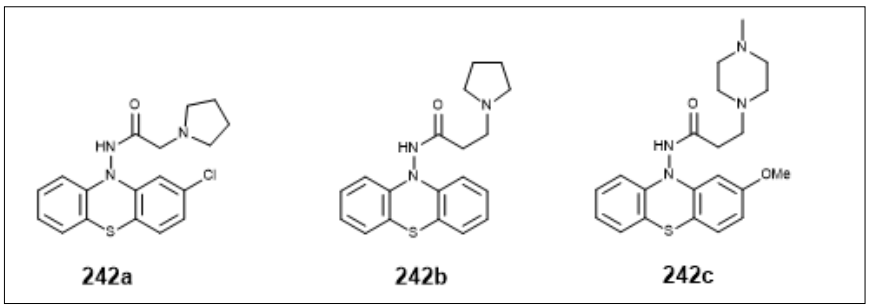


Following similar reaction pathway, the chloride from phenothiazine was displaced by piperazine and subsequent displacement of chloride on terahydroacaridine provided the compound 238 (Scheme 33).

Scheme 33:

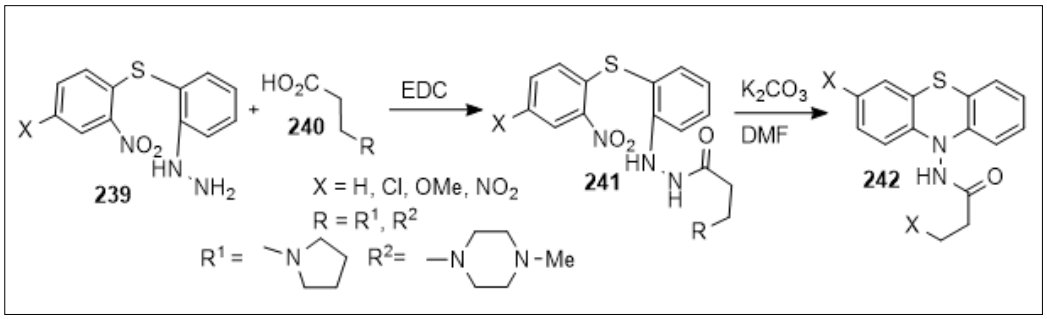


G. Gonzalez-Munoz et al synthesized a series of N-Acylamino phenothiazines for a potential treatment of Alzheimer's disease. These synthesized derivatives were evaluated for their anti-oxidant activity by sequestration of exogenous and mitochondrial free radicals and among the tested derivatives compound 242a-c showed potent anti-oxidant activity and Butyrylcholinesterase (BuChE) inhibitory activity. Therefore, these compounds may important in the development of new drugs for the treatment of Alzheimer disease [36].

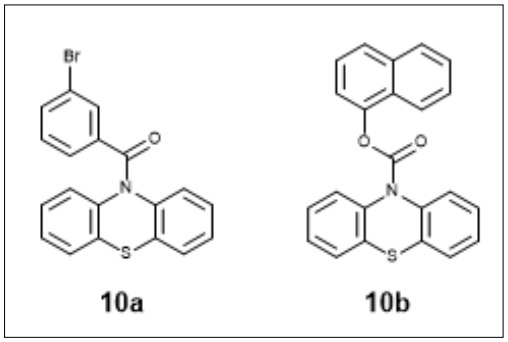


Terminal nitrogen from hydrazine 239 was acylated using EDC with corresponding acids furnishing precursors for phenothiazines. Following Smiles rearrangement these acylated hydrazine provided the desired compounds (Scheme 34).

Scheme 34:

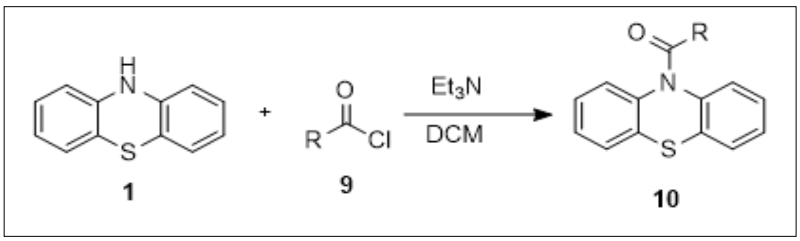


S. Darvesh et al synthesized N-(10)-aryl and N-(10)- alkyl aryl amides of phenothiazines. All these synthesized derivatives were evaluated for their biological activity. Among all the tested new phenothiazine hybrids compound 10a and 10b showed potent and reversible Butyrylcholinesterase (BuChE) inhibitors and are interact poorly with dopamine transporter proteins and have limited interaction with different CNS receptors. The relatively non-polar nature of the aryl and alkyl aryl phenothiazine amides suggest that these compounds could readily cross the blood-brain barrier for the effective treatment of Alzheimer's disease [37,38].



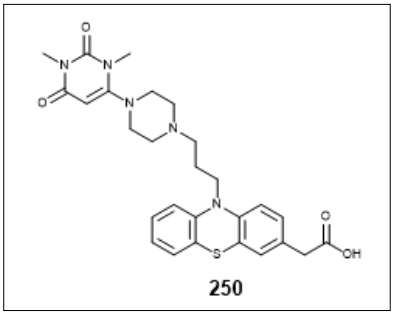
Phenothiazines on exposure to acid chlorides under basic conditions provided the corresponding amides 10. (Scheme 35).

Scheme 35:



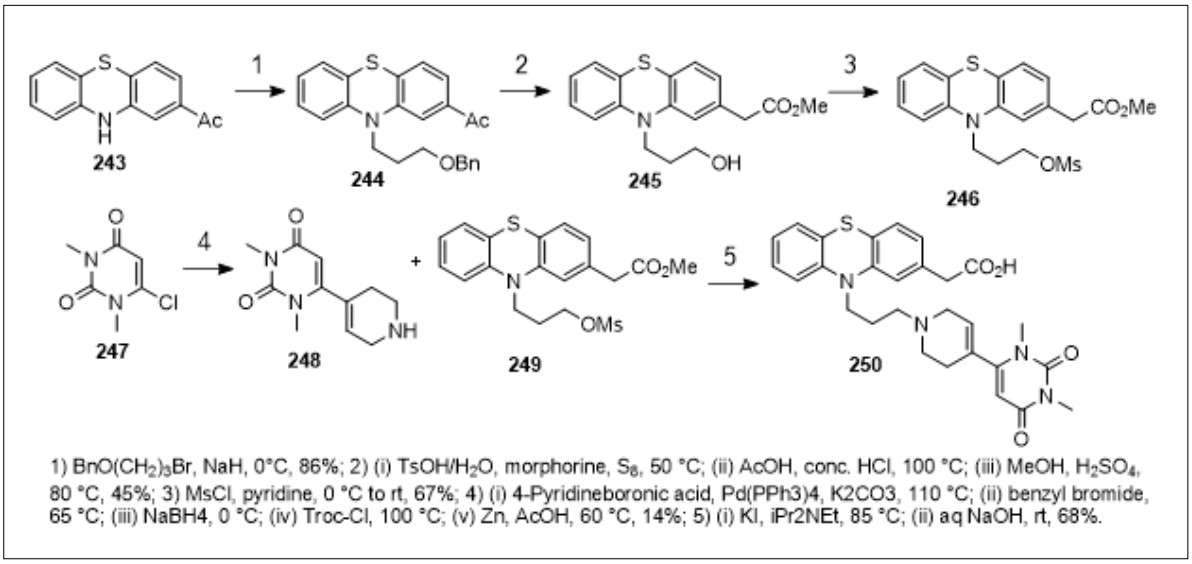
Antihistaminic Activity

K. Kubota et al synthesized a series of phenothiazine carboxylic acid derivatives having 6-amino pyrimidine -2,4(1H,3H)-dione moiety via appropriate linker. These synthesized derivatives evaluated for their affinity toward human histamine H1 receptor and Caco-2 cell permeability and were further evaluated for their oral anti-histaminic activity in mice and bioavailability in rats, Among the tested derivatives compound 250 showed histamine H1-receptor antagonistic activity in vivo model [39].



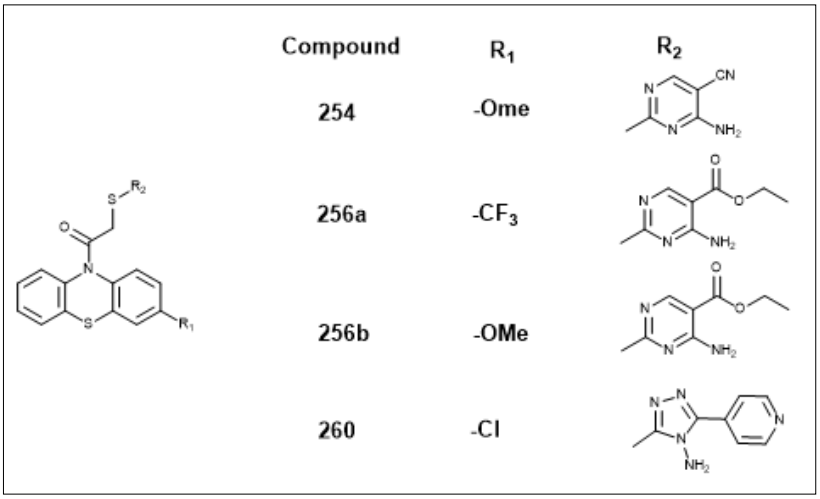
Acyl phenothiazine was treated with protected 3-brompropanol to provide the N-substituted phenothiazine. Oxidative rearrangement of the ketone provided the methyl ester and removal of benzyl group as well. Terminal hydroxyl group was converted to Mesyl. Suzuki coupling of pyridine and N,N-dimethyl-1,3-pyrimidine dione followed by tertiary salt formation with benzyl bromide provided the precursor for compound 250. Reduction of 249 with sodium borohydride provided the Piperidine which was then coupled with 248 to provide 250.(Scheme 36).

Scheme 36:



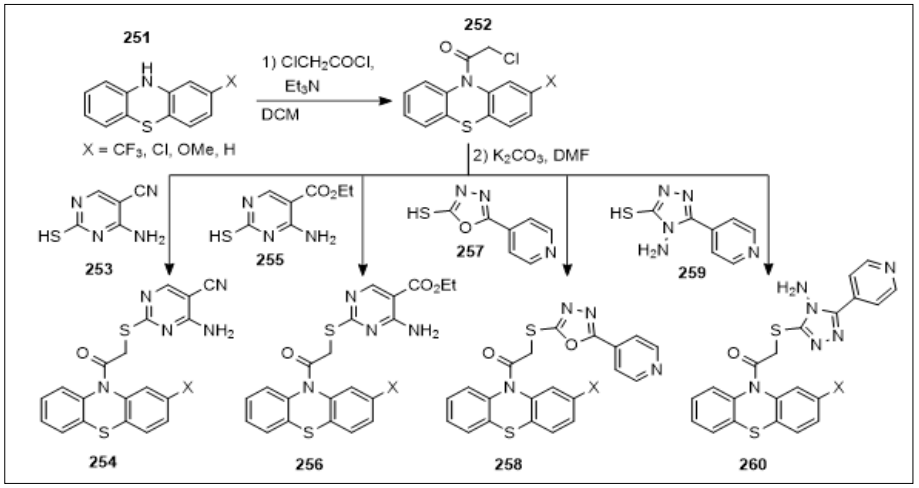
Anti-Obesity Activity

M. Yadav et al synthesized a series of novel phenothiazine derivatives, The synthesized compounds evaluated for their cannabinoid 1(CB1) receptor antagonistic activity, Among the synthesized derivatives, compound 254, 256a, 256b and 260 showed decrease in food intake, suggesting their potential application in the management of obesity through CB1 receptor antagonist activity [40].



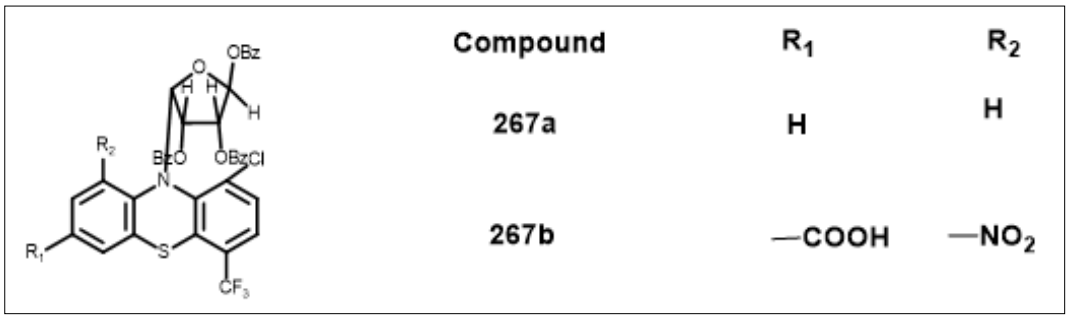
Acylation phenothiazine with chloroacetyl chloride followed by displacement of terminal chloride using various substituted thiols provided compounds 254, 256, 258 and 260 (Scheme 37).

Scheme 37:



Antioxidant Activity

V. Gautam et al synthesized a series of novel substituted 10-H phenothiazines via Smiles rearrangement and formed heterocyclic base were then treated with appropriate sugar to yield ribofuranoside. The synthesized derivatives were evaluated for their anti-oxidative

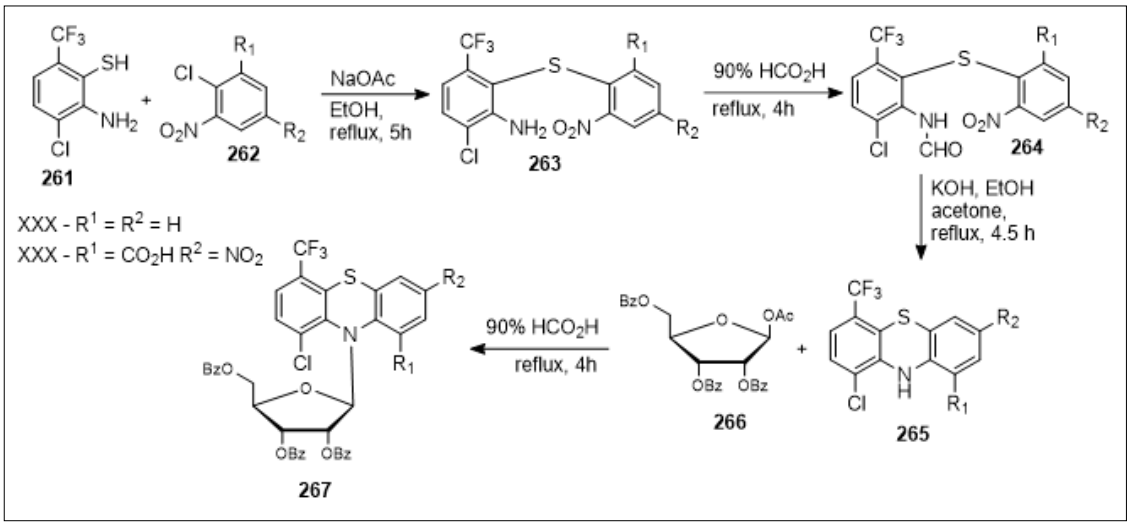


Compound	R_1	R_2
267a	H	H
267b	—COOH	—NO_2

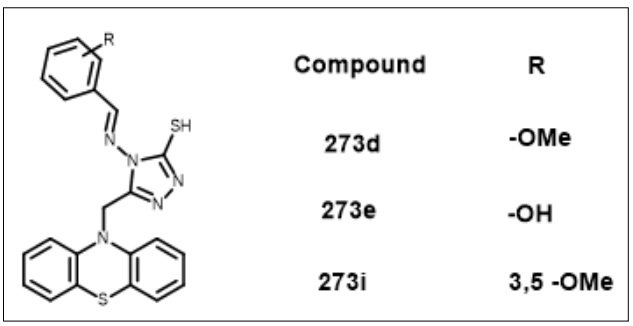
properties through in vitro and in vivo studies in Swiss albino mice, showed that compound 267a and 267b have potent anti-oxidant activity [41].

Aryl thioethers were formed from o-chloronitro aryls and tetra substituted alpha-aminothiophenols. Formylation of amine followed by a Smiles rearrangement provided the precursor substituted phenothiazines which was then coupled with beta-D-ribofuranosyl-1-acetate-1,3,5-tribenzoate 267 (Scheme 38).

Scheme 38:



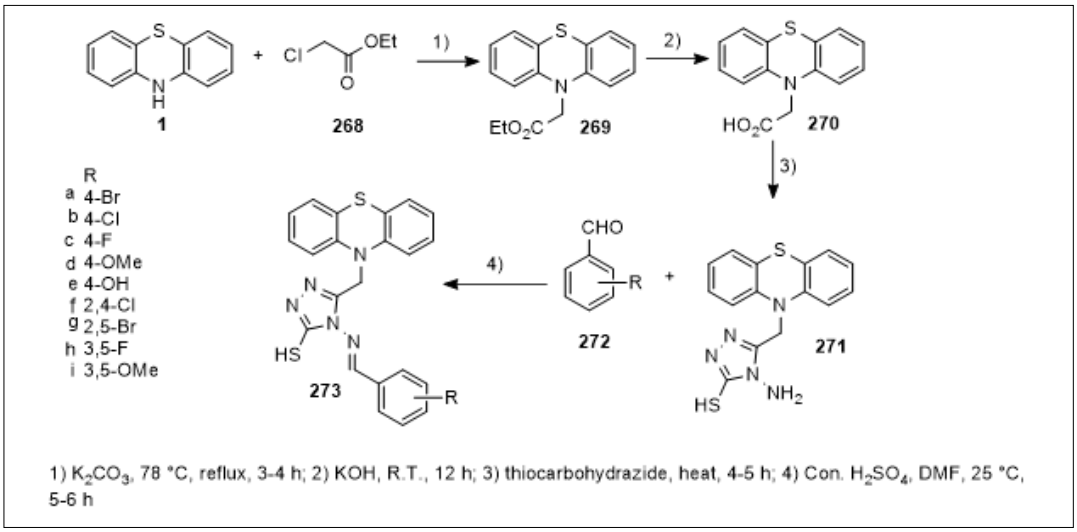
S. Maddila et al synthesized a series of novel 1,2,4 triazole derivatives of phenothiazine. All these synthesized derivatives are screened for their in vitro anti-oxidant activity by employing nitric oxide, hydrogen peroxide and DPPH radical scavenging assay the compound 273d, 273e and 273i showed potent anti-oxidant activity as these compounds contains the electron-releasing groups [42].



Compound	R
273d	-OMe
273e	-OH
273i	3,5 -OMe

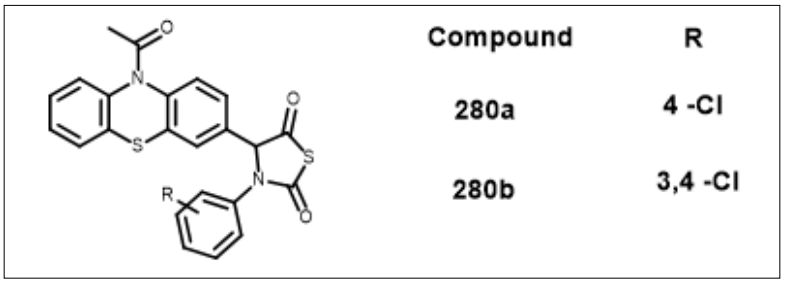
Phenothiazine was treated with Ethyl-2-chloroacetate followed by ester hydrolysis furnished the acid precursor. Treatment of 270 with thiocarbohydrazide furnished the 1,2,4 triazole which on treatment with various aldehydes provided the imine compounds (Scheme 39).

Scheme 39:



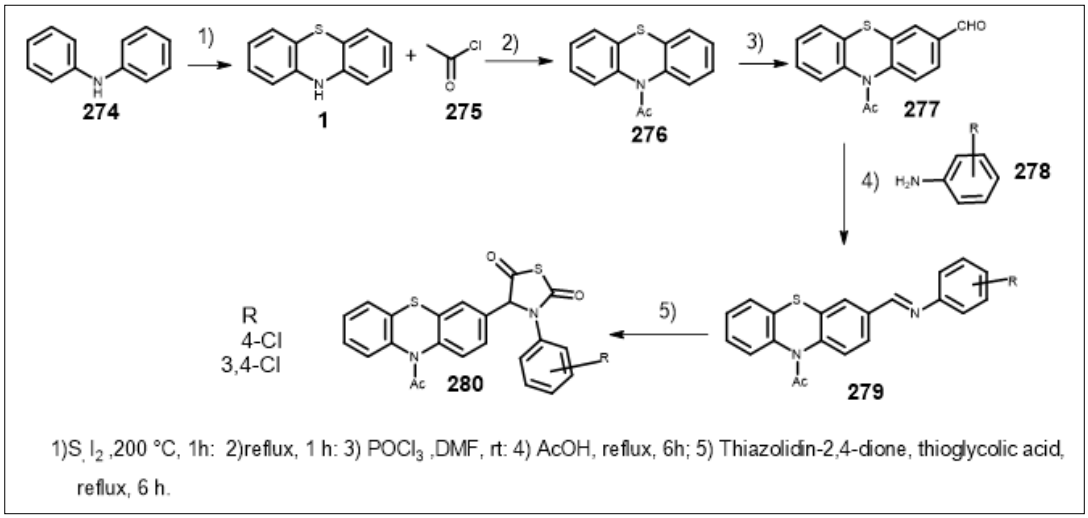
Antidiabetic Activity

P. Saini et al synthesized a new series of phenothiazine based thiazolidine-2,4 dione derivatives. All these synthesized derivatives were evaluated for their anti-diabetic activity by using Streptozotocin induced method. Among the tested derivatives, compound 280a and 280b were found to possess potent anti-diabetic activity [43].



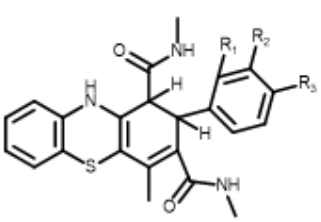
Diphenylamine was converted to phenothiazine using sulfur and catalytic iodine. Protecting nitrogen as amide using acetyl chloride provided the precursor 276 for formylation reaction. Formyl group was introduced at 3-position followed by imine formation with various anilines furnishing the imine precursor 277. Exposing these imine derivatives to thioglycolic acid and thiazolidin-2,4-dione provided the target compounds (Scheme 40).

Scheme 40:

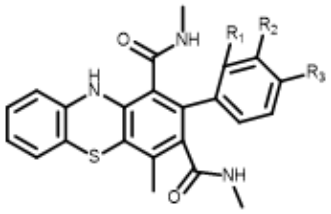


Enzyme Inhibitory Activity

Y. Sadanandam et al synthesized number of substituted phenothiazines and screened for their biological activity against regulatory enzymes involved in inflammatory diseases. Among the tested derivatives compound 286a, 286b, 286c, 287a, 287b and 287c Exhibited promising target specific inhibition against phosphodiesterase, Prostaglandin dehydrogenase and superoxide dismutase activity depending on steric factors of molecules [44].



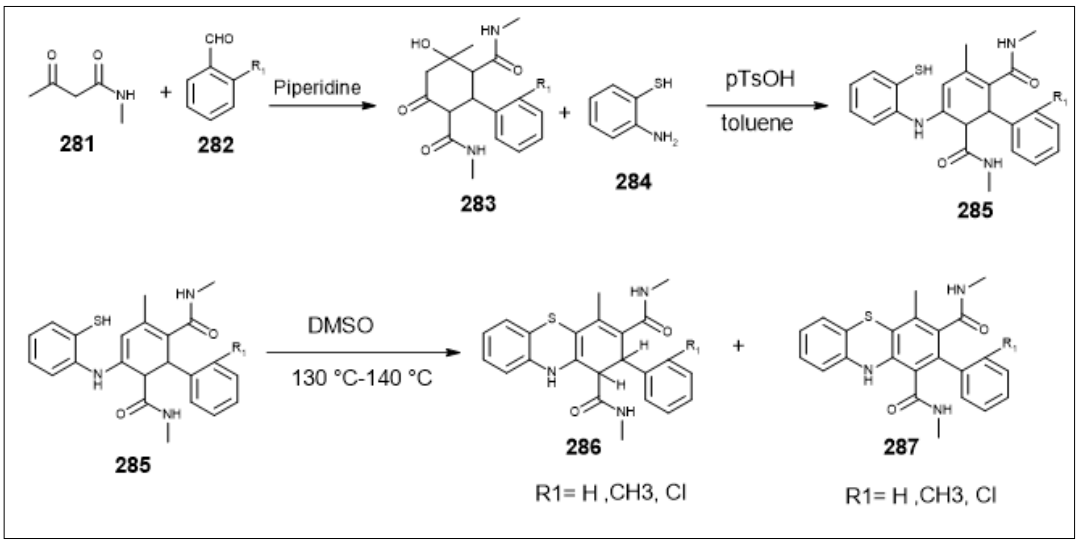
Compound	R_1	R_2	R_3
286a	-H	-H	-H
286b	$-CH_3$	-H	-H
286c	-Cl	-H	-H



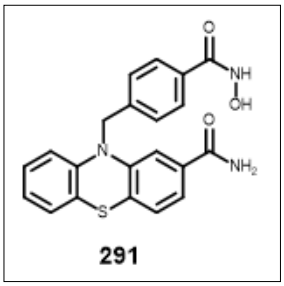
Compound	R_1	R_2	R_3
287a	-H	-H	-H
287b	$-CH_3$	-H	-H
287c	-Cl	-H	-H

Condensing N-methylacetoacetamide with ortho-substituted aldehydes provided the polysubstituted cyclohexanone (283). Compound 283 on treatment with 2-aminobenznethiol provided the precursor for phenothiazine (285). Exposing this thiol to high temperatures in DMSO provided a mixture of tetra-substituted phenothiazines and dihydrphenothiazines (Scheme 41).

Scheme 41:

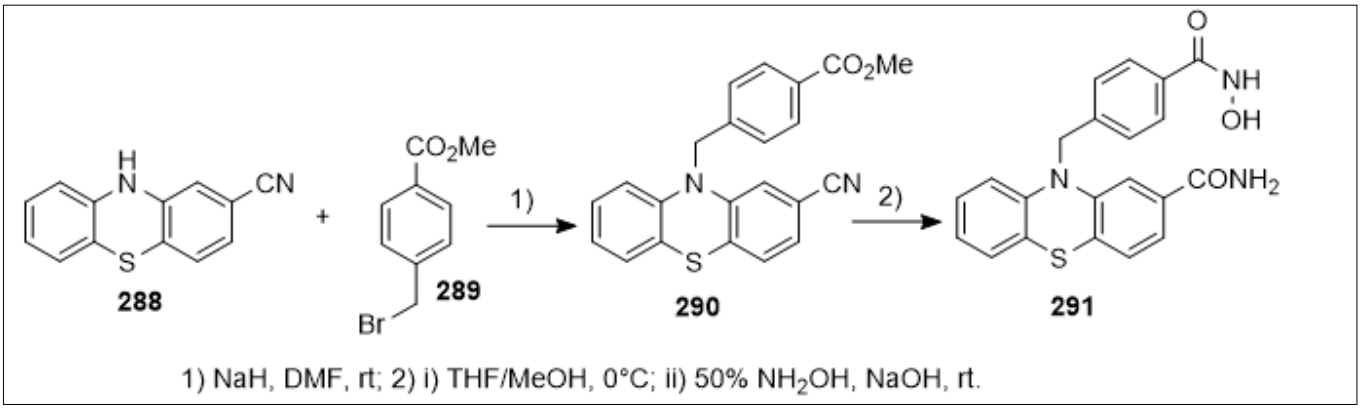


J. Tseng et al synthesized a new series of phenothiazine derivatives containing hydroxamic acid. The enzyme inhibitory activity of synthesized derivatives was evaluated against a panel of HDAC isoforms using Suberanilohydroxamic acid (SAHA) as reference. These isoform enzymes include Hela nuclear HDACs, class IIa HDAC and class IIb HDAC. Among the tested derivatives, compound (291) showed most potent enzyme inhibition activity [45].



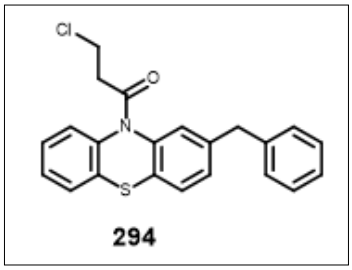
N-alkylation of 2-cyanophenothiazine with aryl bromide followed by conversion of nitrile to amide and ester to N-hydroxybenzamide furnished the target compound 291 (scheme 42).

Scheme 42:



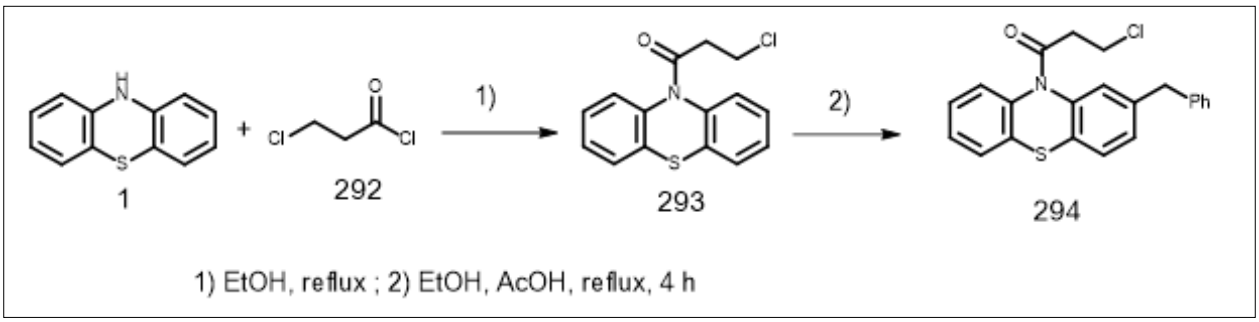
Anti-Inflammatory Activity

Logesh et al synthesized a phenothiazine derivative. Synthesized derivative was subjected to in vitro anti-inflammatory activity using diclofenac sodium as a standard by HRBC membrane stabilization method. It was found that compound 294 has significant anti-inflammatory activity when compared with that of standard drug [46].

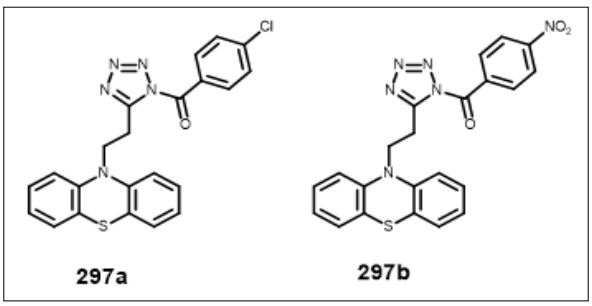


Acylation of phenothiazine with 3-chloropropyl chloride followed reaction with benzaldehyde provided the desired compound 294 (Scheme 43).

Scheme 43:

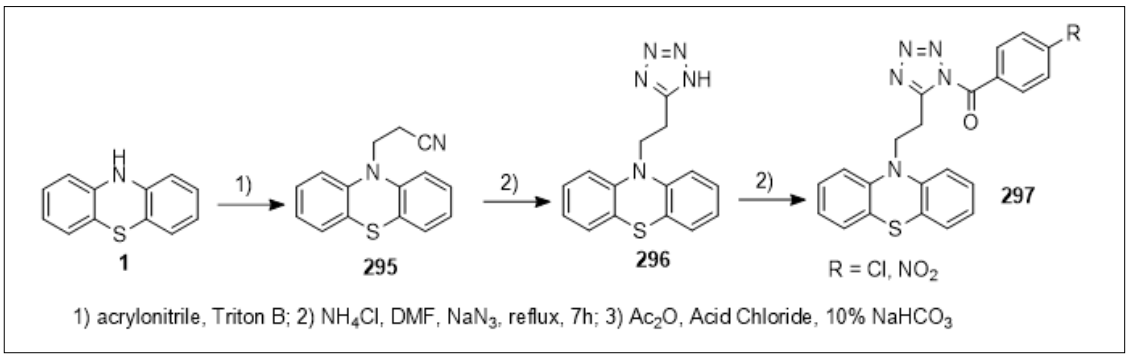


A. Rajasekaran et al synthesized a series of novel phenothiazine derivative containing -1,2,3,4-tetrazoles. All these synthesized derivatives evaluated by carrageenan induced rat paw edema method using diclofenac sodium as standard. Among the tested derivatives, compound 297a and 297b has showed significant anti-inflammatory activity when compared with that of standard [47].



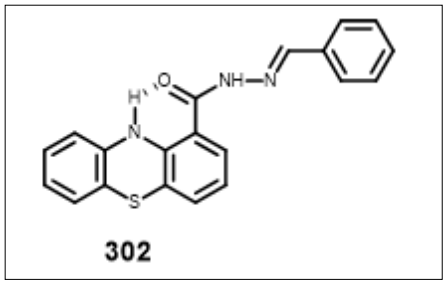
Phenothiazine was N-alkylate with acrylonitrile in presence of triton B. The click reaction with sodium azide furnished the tetrazole. Acylation with p-substituted benzylchloride provided the target compounds (Scheme 43).

Scheme 43:



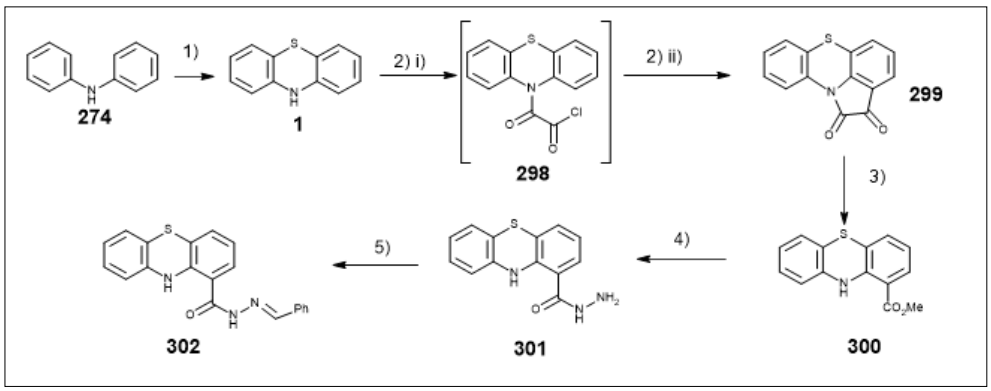
Antiplatelet Activity

G. Silva et al synthesized a series of novel phenothiazine derivatives containing acyl hydrazine. The synthesized derivatives were screened in order to evaluate their effects on in vitro rabbit platelet aggregation induced by arachidonic acid (AA). Among the tested derivatives, it is found that compound 302 is the new potent prototype of antiplatelet derivative, which acts in AA pathway probably by inhibition of platelet COX-1 enzyme [48].



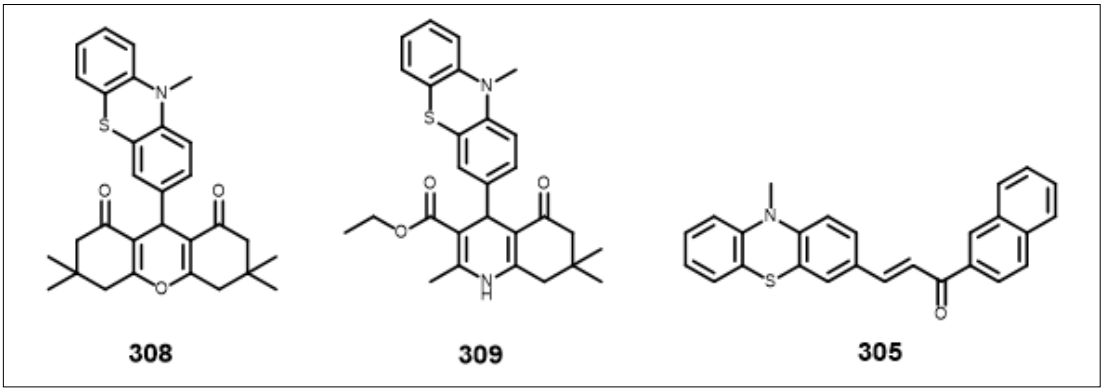
Diphenylamine furnished the phenothiazine in presence of sulfur and iodine at 200 °C. Phenothiazine was then acylated with oxalyl chloride and N-acyl phenothiazine was further treated with aluminum chloride to obtain the tetracyclic pyrrolo dione 299. The dione was cleaved under basic conditions followed by oxidation to furnish the acid which was converted to methyl ester using the diazomethane. Ester 300 was further treated with hydrazine to furnish the hydrazide precursor which formed the Schiff's base with benzaldehyde (Scheme 44).

Scheme 44:



Antitumor Activity

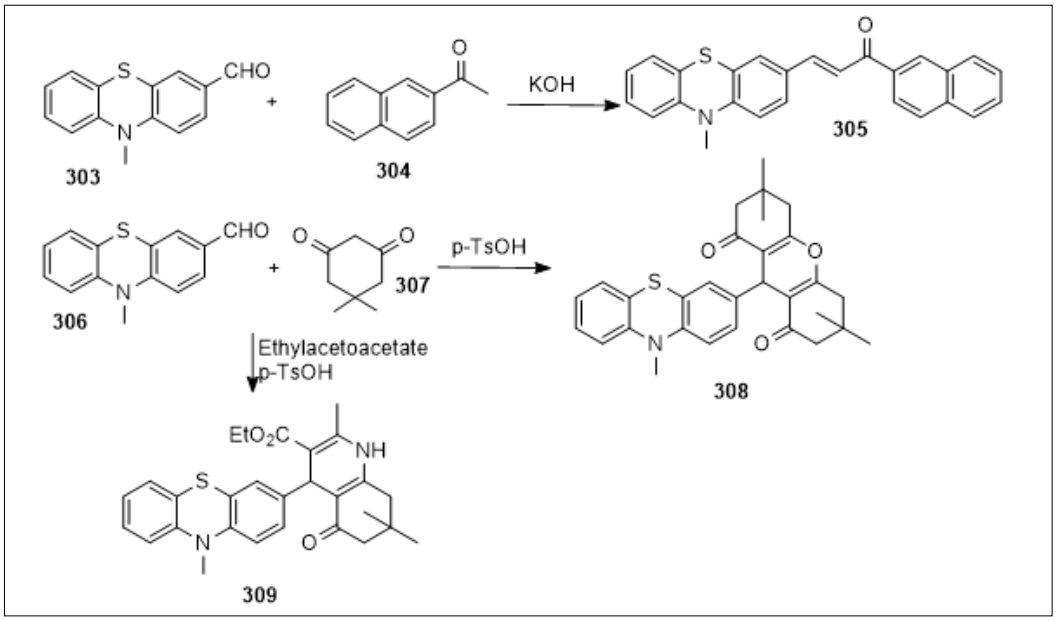
K. Venkatesan et al synthesized a series of novel phenothiazine derivatives. The synthesized derivatives evaluated for their antitumor activity using MTT and LDH assay against HeLa cell lines. The result showed that among the test derivatives compound 305, 308 and 309 have maximum LDH release (57.69 ± 4.69, 57.7 ± 4.6 and 67.8 ± 4.9) respectively at 1000 mg concentration [49].



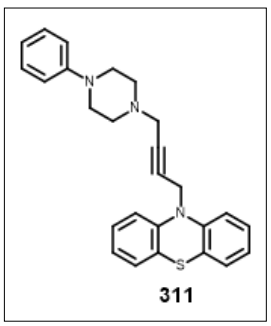
N-methyl-3-formylphenothiazine was subjected to aldol condensation with naphthylmethyl ketone to provide the target compound 305. Exposing to the N-methyl-3-formylphenothiazine to excess of dimedone under acidic conditions provided the target compound. The interesting feature is dimedone forms a tricyclic aldol product with phenothiazine by double aldol reaction to provide the target molecule.

Similarly, when dimedone, ethylacetoacetate and phenothiazine are reacted under acidic conditions product 309 is formed (Scheme 45).

Scheme 45:

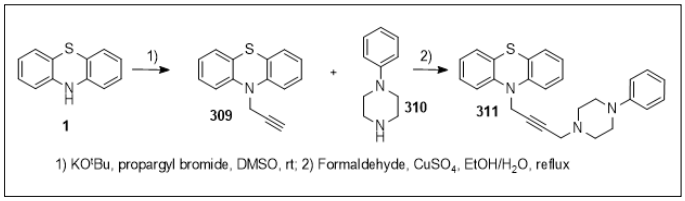


A. Bisi et al synthesized a series of phenothiazine derivatives bearing a rigid side chain and different amines. All the synthesized derivatives are evaluated for the multi drug resistance (MDR) reverting activity and full antitumor profile. Among the tested compound, it was found that compound 311 is most active and shows to increase doxorubicin retention in multidrug resistant cells. Suggesting a direct interaction with p-glycoprotein [50].



N-alkylation of phenothiazine with propargyl bromide followed by reaction with formaldehyde and N-phenylpiprazine provided the target molecule (scheme 46).

Scheme 46:



Conclusion

In this article, we reviewed recently synthesized phenothiazine derivatives and associated with exciting in vivo and in vitro biological activities. The phenothiazine is not only synthetically important scaffold but also possesses a wide range of versatile and promising biological activities. Phenothiazine drugs or derivatives have been the subject of great curiosity due to their interesting aggregation properties and ability to interact with surfactants, model lipid bilayers, and bio membranes. Since these derivatives shows enormous pharmacological actions and deposits on the bio membranes, their pharmacological activities seem to be related to the drug-membrane interactions or to the absorbability on the membrane. Phenothiazine has many biological activities which are important in future. Some phenothiazine derivatives have better activity than standard drugs and have potential to become a new candidate of drug for the market in near future.

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