Review Article

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF PHENOTHIAZINE DERIVATIVES

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ABSTRACT
Phenothiazines are heterocyclic molecules containing two benzene rings linked in a tricyclic system through nitrogen and sulfur atoms.
Phenothiazine derivatives having amino alkyl side chain and these are connected to the nitrogen atom of heterocyclic unit playing crucial role in medicinal chemistry.
From last few decades a considerable amount of attention has been focussed on synthesis of phenothiazines derivatives and screening them for different pharmacological activities. The investigation of substituted 10H-Phenothiazines has steadily strong growth because they exhibit a wide range of applications. These moieties are widely employed as antibacterial, antiviral, anti-inflammatory, anticancer, sedatives, tranquilizers agents etc. Slight change in substitution pattern in phenothiazine nucleus causes distinguishable difference in their biological activities. In this review we are discussing about synthesis and various biological activities of newly synthesized Phenothiazine derivatives.
KEYWORDS Phenothiazine, CNS depressant, Anticancer, Antipsychotic.

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INTRODUCTION

Phenothiazines (Fig 1) was synthesized in 1883 and has been used as an antihelminic for many years[1] The phenothiazine as a class and especially chlorpromazine are most widely used class of neuroleptics.[2] The chemical structure of phenothiazine provides an important molecular template for the development of the agent able to interact with a variety of biological process and synthetic phenothiazine effective in the treatment of a number of medical conditions.[3-4] Phenothiazine and related compound have been reported to possess various biological activities such as Tranquilizer[5], Antiinflammatory[6], Antimalarial[7] Antipsychotropic[8], Antimicrobial[9], Antitubercular[10-11], Antitumor[12-13], Antihistaminic[14] and Analgesic.[1] Due to increased importance of these heterocyclic compound attempts were made during the past few years in the synthesis of new gneration of 10H- phenothiazine that exert their biological activity.

Chlorpromazine (Fig. 1), for example, was one of the first compounds used as a neuroleptic to treat symptoms of psychosis.[15]

It has been observed that some phenothiazines inhibit intracellular replication of viruses including human immunodeficiency viruses (HIV)[16]. On the other hand some of these derivatives have been reported to exhibit significant anticancer activity.[17-18]

Synthesis of substituted phenothiazine derivatives

Scheme 1

Phenothiazine was synthesized exploring diphenylamine as starting material to the preparation of heterocyclic phenothiazine in 89% yield, through the condensation by fusion with powder sulfur and Iodine.[19] (Fig. 2)

Scheme 2

The selected phenothiazine was alkylated with propargyl bromide by means of the potassium tert. butoxide in dimethyl sulphoxide (DMSO) . The final compound was the obtained via the Mannich reaction refluxing the propargyl intermediate with the selected amines (Fig.3) which were not commercially available were prepared by conventional method.[20]

Scheme 3

Suzuki coupling reaction of the 6- chloro – pyrimidine-dione7 by benzylation reduction and deprotection gave the tetrahydropyridine followed by hydrolysis.[21] (Fig.4)

Scheme 4

Synthesis of a series of phenothiazine-N-10- urea derivatives which, tend to be, like the corresponding

amides, selective butyrylcholinesterase inhibitors. However, one sub-class of this series, the substituted aminoureas, is found to be able to produce potent inhibition of both butyrylcholinesterase and acetylcholinesterase.[22] (Fig.5)

Scheme 5

General procedure for the synthesis of N-(2-Choroacetyl) phenothiazine (fig.6). To the solutions of 10 H- Phenothiazine (0.01) mol in dry benzene 50ml , chloracetyl chloride (0.01) ml was added at 0-5^{0}C the reaction mixture was refluxed under the stirring 3-4 hrs at 50-60^{0}C temperature. The resulting mixture was distilled off and poured on ice cold water. The solid thus obtained was recrystallized from ether.[23] (Fig.6)

A mixture of N-(2-Chloroacetyl) phenothiazine 2a-d (0.125m mol) phthalimide (0.125m mol) in 20ml DMSO was stirred at room temperature for 4-5hrs.The reaction mixture was poured on water and crude precipitate was filtered (Fig.7).

Biological activity

Antimicrobial activity

Dongre et al has synthesized a novel series of 2-substituted N-acylphenothiazines by using imides. The structures of the newly synthesized compounds, N-carboxymethyl imides, were confirmed by spectral and elemental analyses. All the syntheised compounds were evaluated for antibacterial and antifungal activities. The synthesized compounds were screened for their antibacterial activity against Bacillus subtilis, Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa. Among the entire synthesized derivatives compounds 1(a-d), 2(a-d) and 3(a-d) showed antibacterial activity at a concentration of 10 & 15 µ/ml against the bacterial strains. Ciprofloxacin used as a standard drug in the evaluation of antibacterial activity. Compounds 1(a-d) are active at 10 µ/ml concentration against A. niger, A. flavus, A. fumigatus and C. albicans i.e., almost equivalent to standard drug fluconazole.[23] (Fig.8)

Antitubercular Activity

Madrid et al has synthesized analogs of the psychotropic phenothiazines and examined as antitubercular agents against Mycobacterium tuberculosis H37Rv. The compounds were subsequently counter-screened for binding to the dopaminergic-receptor subtypes D1, D2, D3 and the serotonergic-receptor subtypes' 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}. The most active compounds 4 and 5 showed MICs from 2 to 4 µg/mL and has overall reduced binding to the dopamine and serotonin receptors compared to chlorpromazine and trifluoperazine.[24] (Fig.9)

Some novel 2-heterocycle-substituted phenothiazines having a pyrazolo[3,4-d]pyrimidine nucleus have been synthesized by Viresh SH et al using the Biginelli multi-component cyclocondensation reaction. The antitubercular activity of the compounds was assessed at the Tuberculosis Antimicrobial Acquisition and Co-ordination Facility (TAACF), U.S.A. Primary screening of the compounds was conducted at >6.25 µg/ml against Mycobacterium tuberculosis H37 Rv in BECTEC 12B medium using the BACTEC 460 radiometric system. Compounds 6a, 6b and 6c were found to be particularly active against Mycobacterium tuberculosisH37 Rv strain[24] (Fig.10)

Antitumour Activity

Bisi et al has synthesized a series of easily affordable phenothiazine derivatives having a rigid but-2-ynyl amino side chain and all tested compounds were evaluated for the multidrug resistance (MDR) reverting activity and full antitumor profile. The most active one i.e. compound 7 was shown to increase doxorubicin retention in multidrug resistant cells, suggesting a direct interaction with P-glycoprotein.[25] (Fig.11)

Antivirus Activity

Mucsi et al studied the combined antiviral effects of some benzo[a]phenothiazines and 9-[2 hydroxy(ethoxy) methyl]guanine (acycloguanosine, acyclovir, ACV) on the multiplication of herpes simplex virus type 2 (HSV-2) by using Vero cells. benzo[a]phenothiazine in a yield reduction test. When the two most effective derivatives of 5-oxo-5H-benzo[a]phenothiazine (8) or 6-methyl-5-oxo-5*H*-benzo[a]phenothiazine (9) were simultaneously used with ACV against a wild type HSV-2 strain during consecutive passages, the infective virus titres were decreased, but their effect was moderate. These results suggest that a combination of some benzo[a]phenothiazines with ACV might enhance their antiviral activity probably by reduction of the mutagenic rate in the virus populations.[25] (Fig.12)

Antihistaminic and Anti-Inflammatory Activity

Katsumi et al and evaluated for their affinity toward human histamine H1 receptor and Caco-2 cell permeability. Selected compounds were again evaluated for their oral antihistaminic activity in mice and bioavailability in rats. Finally, promising compounds were examined for their anti-inflammatory potential in mice ovalbumin (OVA)-induced biphasic cutaneous reaction model. Among the compounds tested, phenothiazineacetic acid compound 10 showed both histamine H1-receptor antagonistic activity and anti-inflammatory activity in vivo model.[26] (Fig.13)

A series of substituted phenothiazines were synthesized by Bhaskar Rao et al and screened for their biological

activity against the regulatory enzymes involved in inflammatory diseases such as asthma, autoimmune diseases including allergic rheumatoid and encephalomyelitis. Among all the newly synthesized compounds, compounds 11a-c and 12a-c exhibited promising target specific enzyme inhibition against phosphodiesterase, prostaglandin dehydrogenase and superoxide dismutase activity depending on steric factors of the molecules. methylphenyl)-N,N',4-trimethyl-2,10-dihydro-1Hphenothiazine-1,3-dicarboxamide (11b) and 2-(The compounds, 2-phenyl-N,N', 4-trimethyl-2,10-dihydro-1H-phenothiazine-1,3-dicarboxamide (11a), 2-(2-2-chlorophenyl)-N, N',4-trimethyl-2,10-dihydro-1H-phenothiazine-1,3-dicarbo-xamide (11c), exhibited promising phosphodiesterase, prostaglandin synthetase and superoxide dismutase inhibition activity, when compared to standard drug aspirin. Within the 10H-phenothiazine derivatives, the compounds 2-phenyl (12a), 2-(2-methyl-phenyl) (12b) and 2-(2-chlorophenyl) (12c) have shown better enzyme inhibitory activity due to hydrophilic nature of the compounds.[27](Fig.14)

Antioxidant Activity

Vibha Gautam et al had synthesised a series of novel substituted 10H-Phenothiazines via Smiles rearrangement using specific precursors. Synthesized Phenothiazines in form of heterocyclic base were treated with appropriate sugar to yield ribofuranosides. All the synthesized compounds and their ribofuranosides were screened for their antiradical activity by 1,1-diphenyl-2-picryl hydrazyl (DPPH) radial scavenging assay and 2,2-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical cation decolorization assay.

The study reveals that ribofuranosides (13a and 13d) showed better antiradical effect than their respective bases in DPPH assay. Ribofuranosides (13a, 13c, 13d) showed better antiradical effect than their respective base in ABTS assay.

The above value shows there was significant increase in Glutathione content of liver in animals treated with compounds 12a, 13a, 13d, also in these animals the value of Lipoprotein oxidase was significantly decreased showing potent antioxidant activities in Swiss albino mice. However, other compounds show increase in GSH content and decrease in LPO level but not statistically significant.[28] (Fig.15)

Cytotoxic Activity

Phenothiazine dose-dependently reduced the viable cell number in human promyelocytic leukemic HL-60 cells, and the 50% cytotoxic concentration (CC_{50}) was 0.81 mM (Table 1). Among ten N-acylphenothiazines, 10-(3-aminopropyl)-2-chloro-10Hphenothiazine mal-eate compound 14 and chlorpromazine hydrochloride compound 15 showed the greatest cytotoxic activity (CC50B0.031 mM), than parent compound, phenothiazine[29] (Fig.16)

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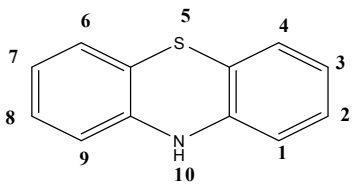


Figure 1

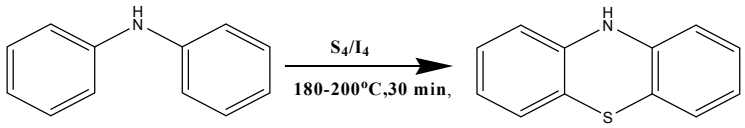


Figure 2 % yield = 89%

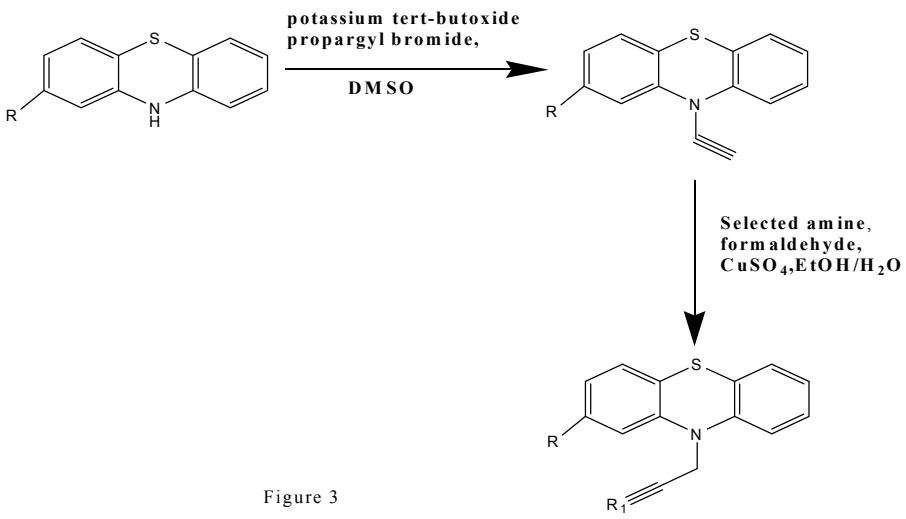
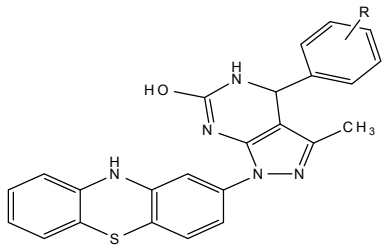


Figure 3



Compound	R
3c	4-OH
3d	2-Cl
3e	4-Cl

Figure 10

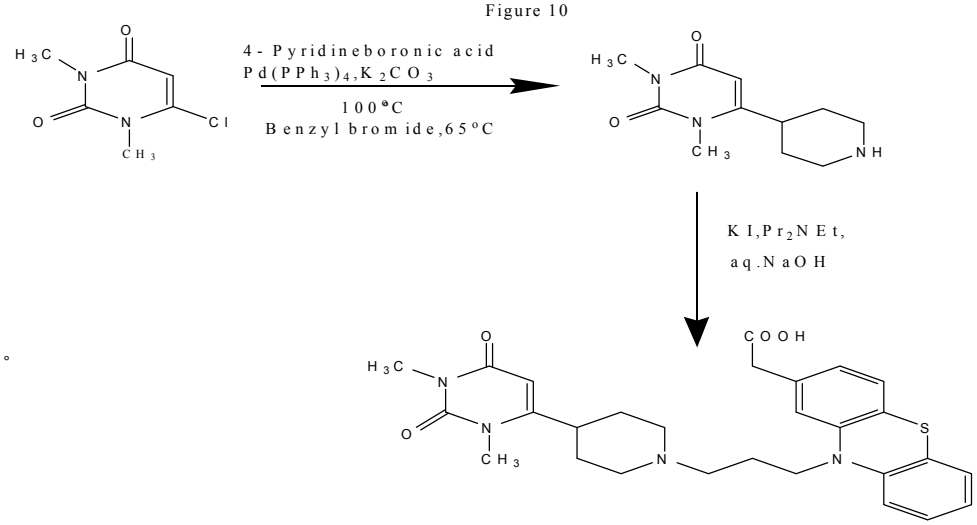


Figure 4

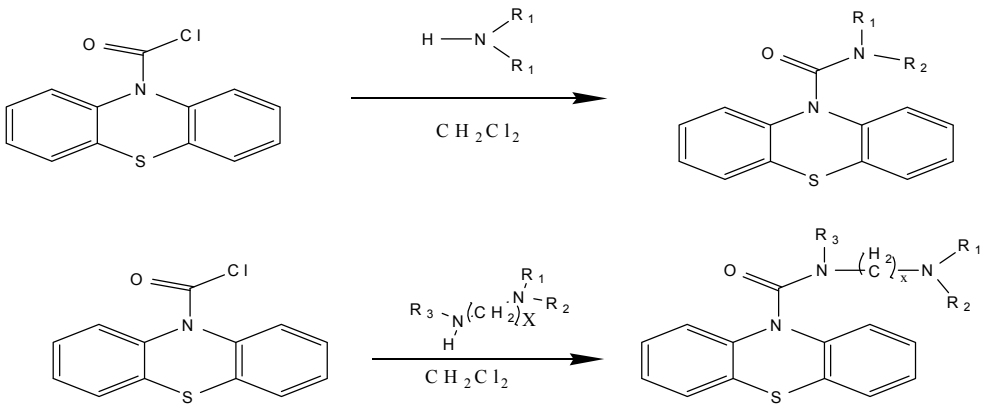


Figure 5

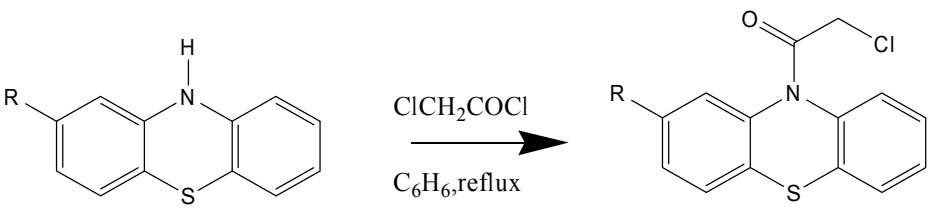


Figure 6

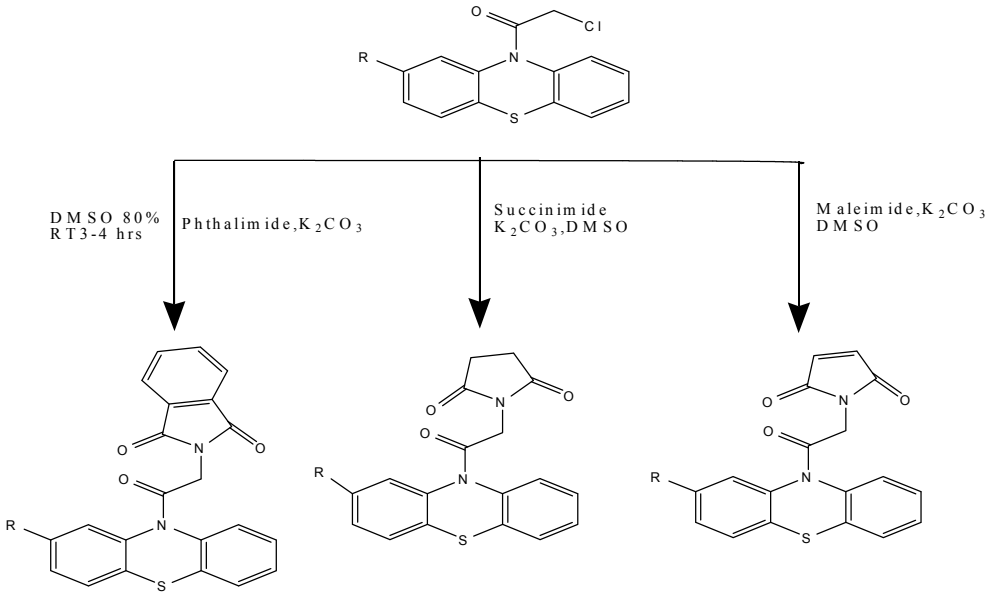
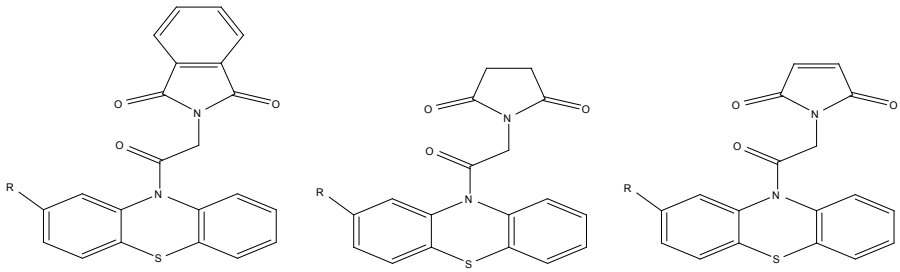


Figure 7

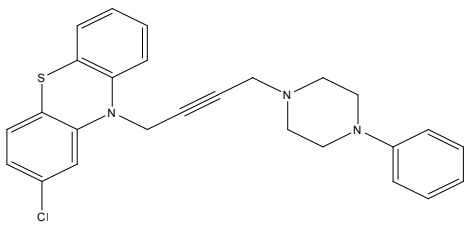


1a) R= H
1b) R= Cl
1c) R= CF3
1d) R= Ac
Compound 1

2a) R= H
2b) R= Cl
2c) R= CF3
2d) R= Ac
Compound 2

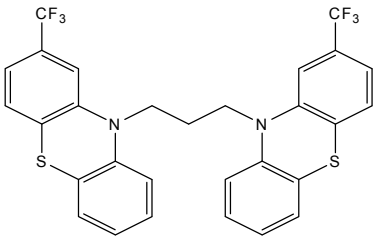
3a) R= H
3b) R=Cl
3c) R= CF3
3d) R= Ac
Compound 3

Figure 8



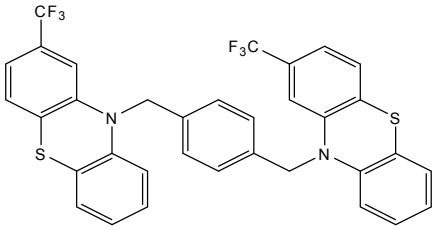
2-Chloro-10-[4-(4-phenylpiperazin-1-yl)but-2-ynyl]-10H-phenothiazine
Compound 7

Figure. 11



2-(trifluoromethyl)-10-(3-(2-(trifluoromethyl)-10H-phenothiazin-10-yl)propyl)-10H-phenothiazine

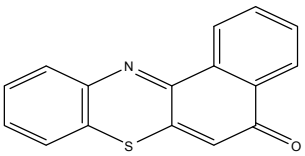
Compound 4



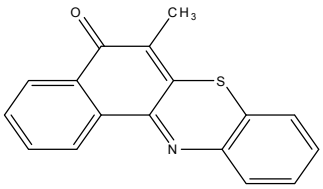
2-(trifluoromethyl)-10-((4-((2-(trifluoromethyl)-10H-phenothiazin-10-yl)methyl)phenyl)methyl)-10H-phenothiazine

Compound 5

Figure 9

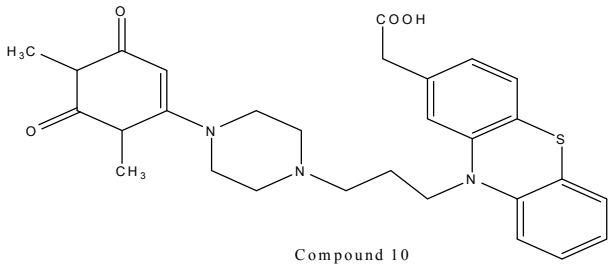


5-oxo-5H-benzo[a]phenothiazine
Compound 8



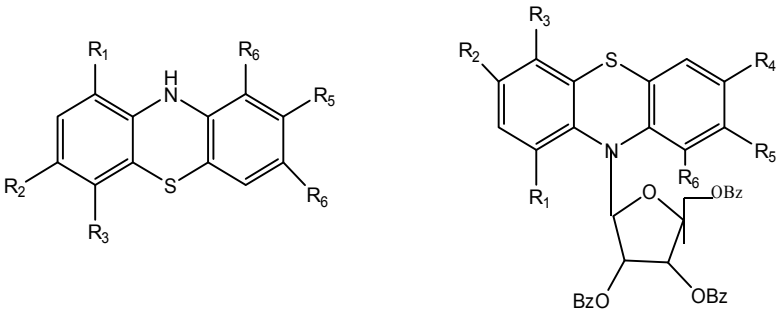
6-methyl-5-oxo-5H-benzo[a]phenothiazine
Compound 9

Figure. 12



Compound 10

Figure. 13



Compounds	R_1	R_2	R_3	R_4	R_5	R_6
Va	Cl	H	CF_3	NO_2	H	NO_2
VIIa	Cl	H	CF_3	H	H	H
VIId	Cl	H	CF_3	COOH	H	NO_3

Figure. 15

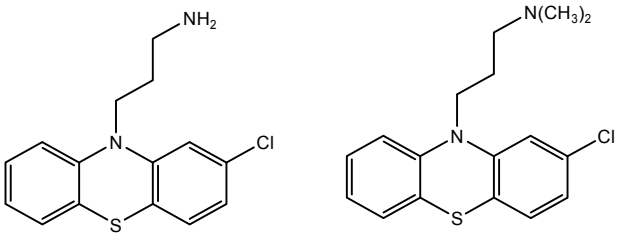


Figure. 16