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Recent Developments of Antipsychotic Drugs with Phenothiazine Hybrids: A Review

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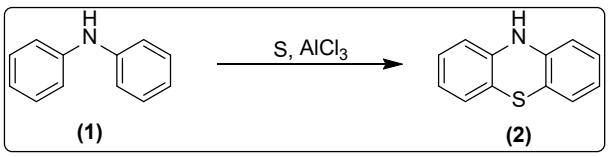
Abstract: Phenothiazine and its derivatives hold an eminent position in biochemistry and medicinal science. The drugs based on phenothiazine moiety are widely used in treatment of psychosis, Parkinson's, schizophrenia, sedation, disturbed/agitated behavior, bipolar conditions, and sleeping disorders. This compound and its derivatives act as neuroleptic agents and mostly affect dopamine receptors. They hinder the transmission of dopamine, muscarinic, and other receptors by binding with their site. In late 1930 the drug was used as an antibiotic and anthelmintic, it was used as an antihistamine in 1940, then in late 1950 the drug was popularly used as sedatives and in psychotic treatment. This review covers the information about phenothiazine based antipsychotic drugs like chlorpromazine, triflupromazine, levomepromazine, mesoridazine, thioridazine, perphenazine, and prochlorperazine and their recent developments in the treatment of other ailments.

Keywords: Phenothiazine, psychosis, sedatives, recent developments, chlorpromazine, triflupromazine

Introduction:

Phenothiazine is associated with thiazine class of heterocyclic compounds which consists of nitrogen and sulphur. The phenothiazine (2) is an organic compound widely used as neuroleptic agent for the treatment of schizophrenia, nausea, bipolar disorder, and several other psychotic disorders including phantasmagoric embodiment. In 1883, Bernthsen prepared the compound (2) by reacting diphenylamine (1) with sulphur (Scheme 1) while he was working on the structures of Lauth's violet and methylene blue [1].



Scheme 1: Synthesis of phenothiazine

In 1934, the compound was espied

to possess insecticidal properties. The derivatives of phenothiazine are bioactive and of speculative scrutiny. The derivatives particularly are beneficial medicines like antihistamines and antihelmintics [2]. Some recent studies delve into its anti-cancer properties in glioblastoma where it induces a seize in the G1 cycle of cancer cells and also reducing production of cyclins responsible for DNA replications. Some other studies show its usefulness in preparation of cells and batteries [3].

The phenothiazine belonging to the class of antipsychotic is employed as sedatives or in certain combinations as medication for patients suffering from anxiety and sleeping disorder. These drugs also show antiemetic effects on patients, and also suppress conditioned behavior by reducing instinctive motor activity. They exercise their effects on various receptors like serotonergic, muscarine, dopaminergic, adrenergic, and muscarinic receptors [4].

The sedatives, in simpler terms are the drugs that reduce central nervous system (CNS) activity and vary in their functions. This can be consumed in the form of pill and sometimes liquid. The CNS depressants increase the activity of gamma-aminobutyricacid (GABA) in brain. This causes a calming effect and drowsiness in consumer, which on addition improves anxiety and sleeping disorders in them. The effect of sedative can generally last for few hours to at least a day. The sedative produces muscular relaxation and physical depression by depressing body functions which require muscle coordination [5].

The phenothiazines are neuroleptic agents, which affect many receptors in brain including dopaminergic sites. They block the post synaptic neurotransmission by binding to dopamine (D_1 and D_2), serotogenic 5-hydroxytryptamine (HT) 2 receptors, muscarinic and histamine H_1 receptors. They also effect adrenergic receptor blockade and cardiac effects which may lower the seizure threshold in patients [6].

The toxicity of phenothiazine drugs includes hypotension, cardiac arrhythmias, and coma. Blurred vision, delirium, agitation, hyperthermia, seizures and decrease in gastrointestinal motility happens due to inhibition of acetylcholine [7]. These drugs have lenitive effect and incite drowsiness in patients, generally prescribed to patients having migraine headaches, motion sickness and vertigo for their fervent vomiting condition. The derivatives of phenothiazine like chlorpromazine, prochlorperazines, perphenazine, thiethylperazine, and promethazine obstructs the D_2 dopaminergic receptors as well as blocks histamine H1 receptors [8].

Aside from its sedation properties, phenothiazine is also used in pediatric practices for conditions like nausea and vomiting, in migraine headaches and in treatment of autistic children's movement disorder. Different derivative of phenothiazine shows different affinity towards receptors on which they act. They attach differently to dopamine D_2 receptor, they behave as antagonist on dopamine receptors at chemoreceptor zone making them an antiemetic agent. Adjacently, blocking peripheral α-adrenergic receptor reduces conditions in hypertension. They also act

as Histamine H1 antagonist and show considerable antimuscarinic affinity [9].

The phenothiazine belongs to the main class of antipsychotic drugs and also exhibit properties against antiemetic symptoms.

The phenothiazine drugs are classified into three categories in regards of substitution on nitrogen, these are:

1. Aliphatic the nitrogen is attached to an aliphatic side chain.
2. Piperidine the nitrogen is attached to a piperidine ring.
3. Piperazines the nitrogen is attached to a piperazines ring.

1. Aliphatic phenothiazines

1.1 Chlorpromazine (CPZ):

Chlorpromazine (Figure 1) is first formed derivative of phenothiazine substituted with ring nitrogen at 10th position and attached to C-3 carbon of *N,N*-dimethylpropanamine constituent.

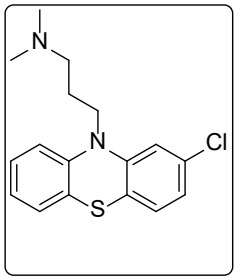
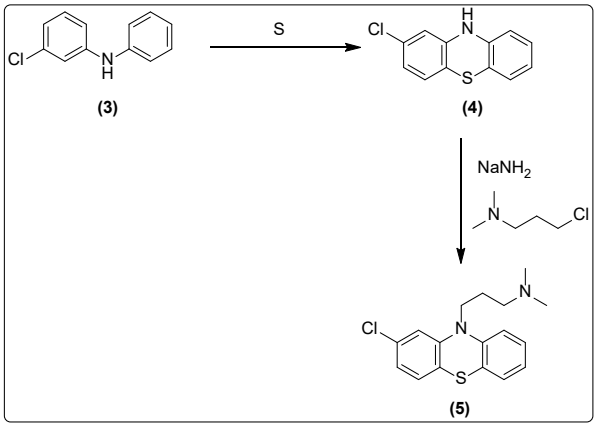


Figure 1: Structure of chlorpromazine

The compound (5) is synthesized by the alkylation of 2-chlorophenothiazine (4) with 3-dimethylaminopropylchloride (Scheme 2). This medication is directed and supervised for the treatment of acute psychosis, bipolar condition, and schizophrenia. The chlorpromazine (5) belongs to first generation antipsychotics, also prescribed for comforting nausea and vomiting [10].



Scheme 2: Synthesis of chlorpromazine

The pharmacodynamics of drugs proves that the drug act as potent antagonist of dopamine receptors D_2, D_3, and D_5. It blocks the receptors of the,forebrain where neural transmission occurs [11].

This derivative of phenothiazine, was synthesized by Paul Charpentier in year 1951 for a French pharmaceutical company. His later investigation on the drug proved its potential for its possible use as anesthesia in year 1952. The derivative is a strong sedative prescribed for patient schizophrenia, the utility of drug for psychiatry was perceived by a French surgeon Henri Laborit. In March 1952, a clinical examination of CPZ was carried out at Saint-Anne hospital where the drug was declared to induce "artificial hibernation". The drug was made available in France in November 1952 by the name of largictil [12].

Recent developments of chlorpromazine:

The chlorpromazine is widely employed in psychiatric treatments, some recent observation about drugs states that it potential varies and can be employed in treatment of human oral cancer. The drug inhibits the cell proliferation and produces a phase arrest in G2/M stage. It also induces apoptosis *via* intrinsic mitochondrial pathways and extrinsic death receptor. It remarkably suppresses tumor growth and can be used as promising alternative for the treatment of oral cancer [13].

Hoertel and his team outlined research regarding the use of chlorpromazine as potent drug exhibiting antiviral and anti-inflammatory activity. After conducting various *in vitro* studies, it was established that chlorpromazine reduces replication of three virus: corona virus-229E, middle east respiratory syndrome (MERS-CoV), and severe acute respiratory syndrome (SARS-CoV-1) through clathrin-mediated endocytosis inhibition [14].

The catecholamine secretion causes a lethal condition known as pheochromocytoma multisystem crisis (PMC), which produces either hypertension or intractable cardiogenic shock. The use of chlorpromazine drug effectively controlled PMC in patients and also managed the vacillating blood pressure. The interaction of this drug with sigma-1 (σ_1) receptor which causes sedation, chlorpromazine decreases systolic blood pressure (BP) in duration of hypertensive state of patient as reported in the studies of Wang and co-workers [15].

1.2 Trifluprom azine:

Trifluprom azine (9) or vesprin (Figure 2) is medication used for the treatment of psychosis. It is used in severe cases of regurgitation and hiccups. The trifluprom azine hydrochloride is 10-[3-(dimethylamino)propyl-7,2-trifluromethylphenothiazine hydrochloride, a white or pale tan crystalline powder with a characteristic odor [16].

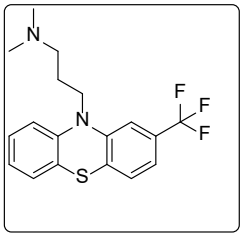
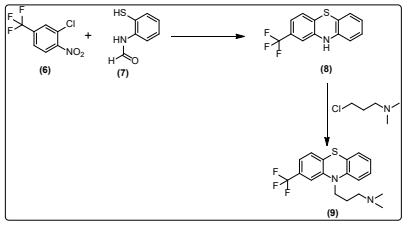


Figure 2: Structure of trifluprom azine

The drug is produced using following two steps, the first step produces a series of intermediate compounds from the reaction of 2-chloro-4-(trifluromethyl)-1-nitrobenzene (6) with *N*-(2-mercaptophenyl)formamide (7). The obtained compound 2-(trifluoromethyl)-1*H*-phenothiazine (8) is alkylated in the second step with 3-chloro-*N,N*-dimethylpropan-1-amine to produce trifluprom azine (9) (Scheme 3) [10].



Scheme 3: Synthesis of trifluprom azine

This drug is not usually used in standard antiemetic therapy because of its side effects, which includes neuroleptic malignant syndrome, tardive, dyskemisia and akathisia.

Recent developments of

trifluprom azine:

In some recent studies, it is found that trifluoperazine dihydrochloride (TFP) has immense potential in suppressing the growth in melanoma metastasis. The experiments conducted by Yong *et al.* on mice showed restricted growth of melanoma. The drug is induced intraperitoneally (40mg/day) and restrained intra-carotid-injections, which establish melanoma brain metastasis [17].

Kornhubber and his team reported that sphingomyelin is cleaved by acid sphingomyelinase (ASM) and turns it into a ceramide which is lipophilic in nature. This ceramide forms a gel like platform in a plasma membrane and act as an entry point for SARS-CoV-2. Several functional inhibitors of acid sphingomyelinase (FIASMAs) are identified which includes fluvoxamine, maprotiline, sertraline etc. The trifluprom azine also act as FIASMAs and has good permeability across the blood brain barrier. The inhibition of ASM lowers the concentrations of ceramides. The screening against MERS-CoV replications, trifluprom azine showed antiviral activity in Huh-7 cells [18].

Apart from antipsychotic effect and management of schizophrenia, trifluoperazine possesses the additional property of reversing drug resistance to cisplatin and doxorubicin. The drug also shows high affinity to calmodulin , which are hydrophobic in nature. In usual pattern calcium binds to this cite but as trifluprom azine attaches to the site, it brings structural changes in it, which inhibits the formation of calcium-calmodulin complex. The inhibition of doxorubicin by the drug also inhibits dox induced myocardial inflammation and fibrosis [19].

1.3 Levomepromazine:

Levomepromazine, an antipsychotic drug is better known as 'dirty drug' for its effects on various receptors including dopamine, histamine, and serotonin for blocking. The compound is also traced by the name of levoprome, neurocil, nozinan, and levotomin.

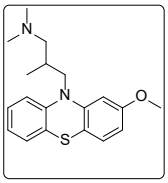


Figure3: Structure oflevomepromazine

The levomepromazine (Figure 3) is a low potency antipsychotic, which acts as strong analgesic, antiemetic, and hypnotic properties and mostly employed in reformatory care. This first-generation antipsychotic drug has been a chief medication for the treatment of schizophrenia.

The metabolism of substrates like steroids and melatonin as well as drugs depends upon enzymatic activity of cytochrome P450. As per studies, reported by Przemyslaw and his co-workers, levomepromazine along with clozapine induce the activity of CYP enzyme in human hepatocytes. The minimum amount of 2.5µM, brought a significant increase in mRNA level and also affected cytochrome P450 3A4 (CYP3A4) cells [20].

Though vomiting and nausea are not

frequent and related while treating cancer but it happens to almost every next patient suffering from it. The use of levomepromazine at low doses relieves nausea in patient as reported by Eisenchlas *et al*. The drug is usually employed as a second line medication on patient when the earlier drug fails initially. This was established after a trial run in Australia, the controlled amount of drugs was provided orally twice a day to cancer patients for 3 days. The experiments provided evidence that levomepromazine act as antiemetic in the low level of doses and induce drowsiness on high level. It also reduced nausea and vomiting in palliative care [21].

2. Piperidine phenothiazines

2.1 Mesoridazine:

Mesoridazine (Figure 4) is a piperidine neuroleptic drug employed in treatment of schizophrenia. This metabolite of thioridazine drug's name is acquired because of functional group like methyl sulphoxy and piperidine present in its chemical structure.

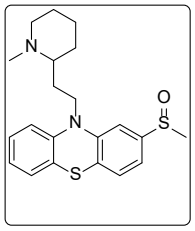
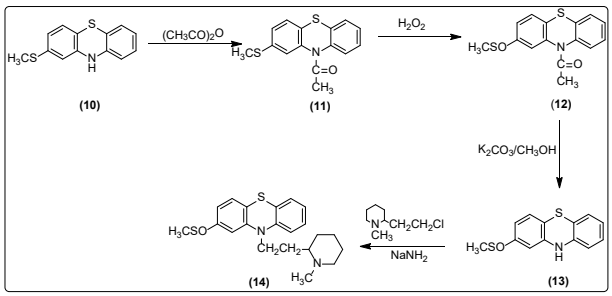


Figure 4: Structure of mesoridazine

The synthesis of drug involves the alkylation of the acidic form of 2-methylthiphenothiazine (11) with 2-(2-chlorethyl)-1-methylpiperidine. The compound 2-methylthiophenothiazine (12) is acylated at nitrogen atom by acetic anhydride producing 10-acetyl-2-methylthiophenothiazine (13), which is oxidized with hydrogen peroxide. The oxidized derivative (14) is deacylated using potassium carbonate in methanol solution, which gives 2-methylsulfonylphenothiaizne (15), which is further alkylated by 2-(2-chlorethyl)-1-methylpiperidine in the presence of sodium amide producing desired mesoridazine (16) (Scheme 4) [22].



Scheme 4: Synthesis of mesoridazine

The drug has a short life and acts as a sleep inducer and a potent hypnotic, which shows central antidopaminergic, anticholinergic, and weak muscarinic effects on its patients, but it was withdrawn in 2004 from the market of United States as it exhibited serious side effects like irregular heart beat and prolongation of QT of the electrocardiogram along with primary effects of akarhasia and fatal neuroleptic malignant syndrome [23].

Recent developments of mesoridazine:

The pore-forming units of rapid delayed rectifier K+ channel are encoded by human ether a-go-go-related gene (HERG). The usual action potential repolarization of cardiac muscles depends upon K+ current (IKr). It acts as important membrane current and is affected by rapid delayed

rectifier K+ channel. Hence inhibiting IKr impedes repolarization of muscle and leads to prolongation of QT intervals as documented through electrocardiogram (ECG). The mesoridazine is a potential drug utilized in a dose-dependent manner to prolong QT interval of ECG as reported by Zhi and his colleagues. The drug affects the activity of HERG K+ channels [24].

2.2 Thioridazine:

Thioridazine (Figure 5) belongs to the first-generation anti-psychotic and is well known as Mellaril. The drug is widely employed for the treatment of schizophrenia. This drug affects psychosis by blocking dopamine receptors and acts against symptoms like delusions and hallucinations. This is low potency drug and also shows activity at muscarinic receptors which is source of anticholinergic effects [25].

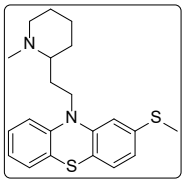
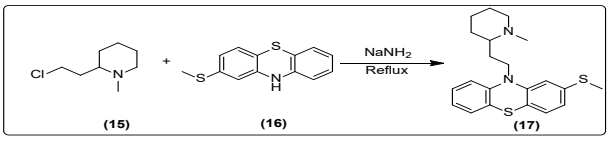


Figure 5: Structure of thioridazine

The synthesis of thioridazine (17) was achieved by reacting 2-(2-chloroethyl)-*N*-methylpiperidine (15) with 2-(methylthio)-10*H*-phenothiazine (16) incorporating sodium amide and refluxed in xylene (Scheme 5) [26].



Scheme 5: Synthesis of thioridazine

The drug may show some not so specific side effects amongst patients such as sedation, weight gain, erectile dysfunction, constipation, and dry mouth and eyes. Due to its evident cardiac complications, the drug was restricted in 2000 and withdrawn completely in 2005.

Recent developments of thioridazine:

The extensive use of thioridazine for its antipsychotic properties has been one of the reasons for its rapid research and development of drug for its potential. The idea of utilizing thioridazine as antibacterial drug was cultivated due to it activity against intracellular methicillin-susceptible *S. aureus* (MSSA) as reported by Thanacoody, he demonstrated activity against MRSA and inhibitions of replication of phagocytosed MRSA, also in changed cell envelope structure, the drug in addition also shows inhibition activity against *E. faecalis* and *E. faecium* strains at concentration of 16-32 mg. The *in vitro* activities against *M. tuberculosis*, reported utilizing 6-32 mg and acted synergistically with antituberculosis drug [27].

In recent research, which was reported by Zhang *et al.*, showed effect of thioridazine on colorectal stem cells (CSCs). The effect on the growth of human colon cancer cell line HCT116 and its proliferation ability as studied where incubation with different concentration of thioridazine affected its invasion ability as well as cell apoptosis [28].

Yuanyuan and co-workers reported that thioridazine was used to sensitize cisplatin against cisplatin-resistant human lung cancer cells. This linked cisplatin escalated the percentage of dead

and apoptotic cells and indicated the potential of thioridazine as it decreased the capacities of DNA repair, as result improving cisplatin-induced DNA damage in resistant cells [29].

The structural similarity of agents from all the categories of phenothiazines drug, were tested for their inhibition of corona virus spike pseudo type virus, which affects the ACE2 cells. When the drug was incorporated for the treatment in ratio of ±0.11 then inhibited virus entry into ACE2 cells. The drug inhabited the binding sites of SARS-CoV-2, showed inhibition of viral entry as reported by Jiayu and his team. It was also divulged that thioridazine also inhibit EBOV entry by combining to the glycoprotein of EBOV [30].

3. Piperazine phenothiazine

3.1 Perphenazine:

Perphenazine (Figure 6) is a piperazinyl phenothiazine drug marketed as trilafon and has been prescribed in clinical use for decades. It is a medium potency antipsychotic formulated in 1950s with concept of preparing similar drug like haloperidol. It is widely used in North European countries and Japan. The main treatment of this drug is to deal with the state of schizophrenic patients who often hallucinate and has several delusions and often hear voices. But this drug is no more or less different from other drugs due to its side effects that includes uncontrollable shaking, regular tremors, and restlessness [31].

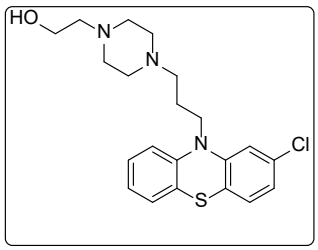


Figure 6: Structure of perphenazine

Recent developments of perphenazine:

The use of perphenazine doesn't cease up to psychosis treatment but also incorporated in treatment of malignant brain tumor as reported by Otreba *et al.* The study explored the effects of perphenazine on ABCB1, ABCG2 (multidrug resistant protein), E-cadherin and integrins (α3, α5, and β1), and annexation of glioblastoma cells. The drug impaired the proteins and inhibited migration of cell line. Therefore, the drug can be used in therapy of glioblastoma [32].

The research outlined by Yousefi and co-workers explains that perphenazine not only just act as antipsychotic drug but can also be used against viral activity of COVID-19. The drug binds with amino acid pocket site and interferes in attachment as well as function of virus making it a suitable candidate for COVID-19 infection [33].

The use of ligand-affinity chromatography integrated with mass spectrometry; it was found that perphenazine targets the protein phosphatase 2A site. The T-cell acute leukemia (T-ALL) is a cancer form, which activates mutations in Notch receptor 1: protein coding gene (NOTCH1) and dysregulation

master regulator of cell cycle entry (MYC). When T-ALL cells are treated with perphenazine, dephosphorylation of many PP_2A units occurred along with rapid apoptosis. It also exhibited suppression in cell growth both *in vivo* and *in vitro*. This indicates that perphenazine shows antileukemic activity [34].

3.2 Prochlorperazine:

Prochlorperazines (Figure 7) is a piperazine phenothiazine belonging to the first class of antipsychotics which consists 10*H*-phenothiazine and a chloro substituent at second position. The N-10 position is substituted with 3-(4-methylpiperazin-1-yl)propyl group.

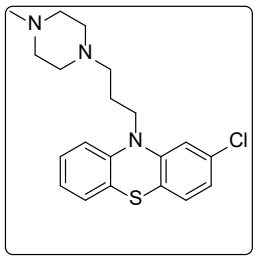
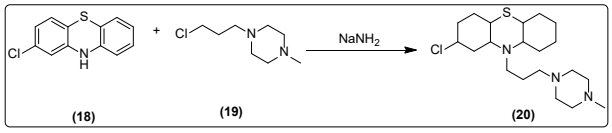


Figure 7: Structure of prochlorperazine

The brand name under which this drug was sold is Comprazine and was advised to the patient of migraine and anxiety. The compound acts as an anti-sickness medicine and is usually employed in prevention of vomits caused due to chemotherapy, dizziness, and post operative conditions. The prochlorperazine (20) is synthesized in the presence of sodium amide by the reaction of 2-chloro-10*H*-phenothiaizne (18) and 1-(3cholropropyl)-4-methylpiperazine (19) [35] (Scheme 6).



Scheme 6: Synthesis of prochlorperazines

Analogous to chlorpromazine, prochlorperazine also blocks D_2 receptors along with other pathways of CNS. It exhibits less sedative activity than other phenothiazines such as chlorpromazine [36].

Recent developments prochlorperazines:

In recent years, the drug has been used not only as an antipsychotic medication but also in various disease treatment as of found in a study, produced by Simanjuntak and his team, they found that prochlorperazines not only act as dopamine D_2 inhibitor but can also target viral binding. The drug shows *in vitro* and *in vivo* activity against dengue virus. It inhibits the entry of virus through D_2R and clathrin associated mechanism, the researchers proved its effect by observation on the administration of drug on mouse model immediately and 6 hours after Dengue virus (DENV) infection. The results obtained stated two beneficial effects: the first is the blocking of DENV infection and secondly, in prevention of development of dengue hemorrhagic fever [37].

In other studies, it was found that prochlorperazine other than antiemetic and sedative activities, also shows biological activities by acting as a good barrier in blood-brain permeability. Otreba and coworkers analyzed potency

of the drug towards U87-MG cells (cell line with epithelial morphology). The drugs possess cytotoxic properties and on inducing it produces concentration-dependent loss in cell growth. This drug carries potential for their development as a new and effective anticancer treatment.

The cutaneous melanoma (type of skin cancer) is rare and amongst one of the deadliest malignant tumors [38]. The recent studies proved phenothiazine derivatives to possess anticancer properties along with sedative and antiemetic properties. Otreba *et al.* determined the effect of prochlorperazine on viability and motility of cells as well as tyrosinase content in melanotic (COLO829) and amelanotic (C32) melanoma cells. The prochlorperazine impairs motility and decrease tyrosinase and also inhibits cell viability. It also reduces microphthalmia-associated transcription factor (MITF) amounts. It consists of ability to restrain the proliferation amelanotic melanoma and can be helpful in therapies [39].

Conclusions:

The phenothiazine compounds are distinguished for their core ring structure, different side chains and their wide-ranging antipsychotic effects. The phenothiazine drugs not only induced desired sedative properties but are recently employed as an alternative in developing drugs and treatment for severe brain blastoma, particular cancer types and specifically it was widely researched for its potential in its effects in SARS-CoV treatment. The use of the compounds doesn't restrict here but can be utilized for development of drugs for other maladies related to brain and CNS because of its better affinity and permeability to the receptor. This review summarizes the information about seven anti psychotic drugs: chlorpromazine, trifluprom azine, levomepromazine, mesoridazine, thioridazine, perphenazine, and prochlorperazine, which contain phenothiazine nucleus and their progress in recent development. We aspire that the present review stimulates further research on phenothiazine-based drugs.

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Conflict of Interest: The authors have no conflict of interest

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