# The Wide Spectrum Biological Activities of Piperidine -A Short Review

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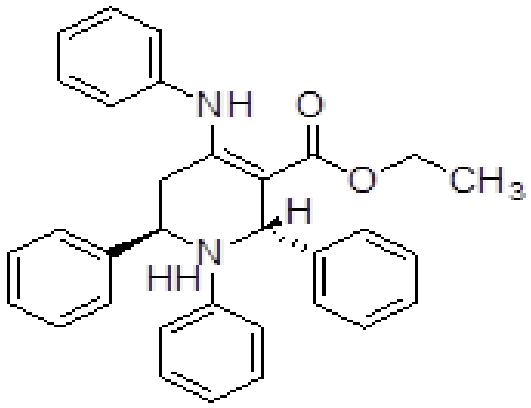
***Abstract*** **- Piperidine is an important heteroatom framework. which demonstrate great function on pharmacological activities, antibacterial, antiviral, antipsychotic, anti-oxidant, anticancer, anti-diabetic anti-HIV ,diuretic activities, neurodegenerative disorders, and so on [1–10]. There are many examples of biologically active piperidine which hold a well-established scientific record as a chemo preventive and therapeutic agent. .Herein the poly functional piperidine endowed with excellent biological and pharmacological activities are reviewed comprehensively. Compounds containing piperidine structural motif exhibiting therapeutic activities are focused.**

***Index Terms*** **- Piperidine, anticancer, anti-diabetic, anti-HIV therapeutic agent.**

## INTRODUCTION

The design and development of highly functionalized Pipyridines moieties[fig.1] have been continuously growing research interest of chemists due to their unique Physiological and photophysical properties [11]. Several natural products and drugs are found to contain piperidine ring as a structural element and demonstrate high biological activity .Compounds containing piperidine structural motif exhibit anti-hypertensive, anti-bacterial anti-convulsant, anti-inflammatory, anti-HIV, histamine H3R ligands, antimalarial, antimicrobial and antifungal activities [2-5]. Piperidine possesing Bodipy moities such as Biodilisant have been reported as the novel fluorescent human histamine H3 receptor ligand. The incorporation of piperidine as bioactive substructure groups into Biodipy platform developes new type of Biodipy dyes illustrating potent phtophysical and biological activities [6]. A novel series of multi-receptor ligands have been developed as polypharmacological antipsychotic agents showing a favorable pharmacokinetic profile with oral bioavailability of 58.8% in rats [7]. During a fairly recent 10-year period, several thousand piperidine compounds have been mentioned in clinical and preclinical studies [11]. Besides the interesting structural features, these compounds are also of pharmaceutical interest as they exhibit a wide range of biological activities [12]. Nevertheless, the variety of functionality and substitution patterns found in piperidine targets and the widely accepted concept that the biological properties of piperidines are highly dependent on the type and location of substituents on the heterocyclic ring [13]. Piperidine derivatives are found to possess pharmacological activity and form an essential part of the molecular structures of important drugs such as raloxifene and minoxidil [14].Selective inhibition of. a number of enzymes involved in the binding andprocessing of glycoproteins has rendered piperidinealkaloids as important tools in the study of biochemical pathways [15].R.Rajalakshmi et al, reported the synthesis of biologically potent , highly functionalized tetrahydropyridines via one-pot multicomponent reaction using a combination of tetrabutylammonium bromide and iodine as a catalyst for C–N, C–C bond formation[16].Herein the wide range of biological applications of poly functional piperidine are discussed




[fig.1]Highly functionalized piperidine derivative

2.1. Piperidine as Anti-cancer agent

The uncontrolled division of cells results in the formation of tumour having the potential to migrate from one part to the other parts of the body (metastasis) that become a major threat to human beings. Since piperidine exhibits great potential in this area it is being further probed to get novel entities for the treatment of cancer. This review aims to throw light on recent pharmacological and biological expansions of piperidine derivatives along with structure activity relationships to deliver association between various synthesized newer/novel derivatives and receptor sites.

A series of 2-amino-4-(1-piperidine) pyridine derivatives that adopted a novel conformation binding to kinase domain of ALK have designed and synthesized by Siming Liu et al[17]., Biological evaluation of most of these new compounds could also potently inhibit ROS1 enzyme, leading to the promising inhibitors against both ROS1 and ALK. These compounds also exhibit moderate to high inhibitory activity in cellular anti-proliferation assay.

Prasad et al[18] synthesised an array of diphenyl(Piperidine-4-yl)methanol derivatives. These were evaluated for their antiproliferative action by MTT assay against HT-29, eLa,MCF-7 and HepG2 cell lines. When all the derivatives were tested against the fore mentioned cell lines, compound displayed superior inhibitory action against all the cell lines .

Vashishtha et al [19] synthesised a vareity of aryloxyaryl Mannich bases containing piperidine ring and screened for their anticancer agents activities against seven colon cancer cell lines the data were compared to standard drug melphalan and 5-FU. The results of their activity against seven cell lines of colon cancer revealed that compounds displayed highest activity against HCT116 (IC50 =3.80 μM) and KM12 (IC50 =2.57 μM) cell lines. When activity was measured against COLO205, HT29 & HCT-15; compound was most potent of all the synthesised mannich bases with IC50 values of 12 μM, 3.31 μM and 3.98 μM,respectively. Similar was the case with compound when tested against SW-620 (IC5012 =6.61 μM) & HCC-2998 (IC50 =12.0 μM) cell lines. Structure activity relationship revealed that Oxygen atom as a linker is essential for cytotoxic action. Replacement of oxygen by Sulphur increases the cytotoxic potential. There is an enhancement in the activity when an electron withdrawing groups (R) is substituted.

A series of 3,5-bis(arylidene)-4-piperidone (DAP) were prepared as curcumin analogue and evaluated [20] for its cytotoxic properties. The anticancer activity of these compounds against H9c2 MCF-7 noncancerous cell lines and A2780 cancer cell line were evaluated. They demonstrated good damages to cell viability in tumour cell line with minimum toxicity to noncancerous cells.

Vinaya et al [21] synthesised 4-[3-(piperidin-4-yl)propyl]piperidin-1-ylmethanone derivatives for further examination of piperidine moiety. Upon evaluation of antiproliferativeaction; compound 57 (IC50 for K562 = 2.0 ± 1.3 μM; for Reh = 2.3 ± 1.5) effectively inhibits the proliferation of human leukemia cell lines- K562 and Reh by induction of apoptosis.Structure activity relation stated that presence of electron withdrawing groups is essential for potential antiproliferative activity.

Paweł. Niedziałkowski et al [22], have lsynthesized a series of novel 9, 10-anthraquinone derivatives containing piperidine. The antiproliferative activities of the studied compounds were evaluated in vitro using drug-sensitive and drug-resistant human cancer cell lines. The conductebut thed test results show that the compound 1 containing a piperidine moiety in their structure is found to be the most active drug among all the molecules subjected to analysis.

Some new hydroxamate derivatives with alkylpiperidine and alkylpiperazine linker moieties have been designed[24], synthesized and biologically evaluated. All these compounds are effective HDAC8 inhibitors comprising more or less similar cytotoxic potential against different cancer cell lines. It is observed that the piperazine scaffold containing compound is more active than the compound with piperidine scaffold for exerting HDAC8 inhibitory activity. Moreover, the 4-quinolyl cap group is better than the biphenyl group which is better than the benzyl group for producing higher HDAC8 inhibition as well as cytotoxicity. These compounds displayed selective HDAC8 inhibition over HDAC3. Moreover, these compounds showed an increased caspase3/7 activity suggesting their anticancer potential through modulation of apoptotic pathways. Molecular docking study with three potent compounds was performed with both HDAC3 and HDAC8 enzymes to understand the selectivity profile of these compounds.

Compound containing 4-quinolyl cap group with alkyl piperazinyl urea linker moiety has been emerged out as the lead molecule that may be further modified to design more effective and selective HDAC8 inhibitors in future.

2.2. Piperidine as Anti-diabetic agent

Siva Prasad Kasturi et al [24]., have synthesized novel 3, 4-dihydroxypiperidine compounds and evaluated their α-glucosidase inhibitory activity. All the compounds have shown excellent activity. Polar substituents on phenyl ring improve the potency of the compounds.

Diabetes is a life long disorder and needs long-term medical treatment extensive studies to explore more effective and safe drugs are essential. In this therapeutic field, chemists have reported recently the first biological evaluation of aza-flavanones[25] and natural product inspired scaffolds of piperidine as potent nhibitors of α-glucosidase i[26].

It is known that compounds containing the piperidine heterocycle have crucial

biological and pharmacological properties such as anaplastic, tyrosinase, proteasome, lymphoma kinase(ALK), Poly (ADP-ribose) polymerase (PARP), aromatase, telomerase, topoisomerase, carbonic anhydrase inhibitors[27-35]. So, synthetic organic chemist aimed to bind the piperidine groups to their targeted organic compounds to increase the biological and pharmacological properties of the planned organic compounds

2.3As Potential Multireceptor Antipsychotics

The atypical antipsychotics (AAP; also known as second generation antipsychotics (SGAs)) are a group of antipsychotic drugs (antipsychotic drugs in general are also known as major tranquilizers and neuroleptics, although the latter is usually reserved for the typical antipsychotics) largely introduced after the 1970s and used to treat psychiatric conditions. Some atypical antipsychotics have received regulatory approval Atypical antipsychotics are typically used to treat schizophrenia or bipolar disorder[36-40].]They are also frequently used to treat agitation associated with dementia, anxiety disorder, autism spectrum disorder, and obsessive-compulsive disorder (an off-label use)[41].]"Therefore this review focused on the recent developments in drugs incorporated with piperidine nucleus possessing antipsychotic activity.

The discovery and optimization of novel acetylcholine-binding protein ligands through screening, structure-activity relationships and structure-based design was reported by Jian shen et al[42].. They manually screened in-house CNS-biased compound library in vitro and identified compound 1, a piperidine derivative, as an initial hit with moderate binding affinity against AChBP (17.2% inhibition at 100 nmol/L). The results suggested that a different piperidinyl substitution might confer a better fit for epibatidine as the reference compound. Thus, compound 15 was designed and identified as a highly affinitive acetylcholine-binding protein ligand. In this study, through two rounds of optimization, compound 15 (Ki=2.8 nmol/L) has been identified as a novel, piperidine-based acetylcholine-binding protein ligand with a high affinity.

A novel series of multireceptor ligands incorporated with piperidine nucleus was developed [43]as polypharmacological antipsychotic agents using the designed multiple ligand approach between dopamine receptors and serotonin receptors[42]. They possess unique pharmacological features, exhibiting high affinities for D2, D3, 5-HT1A, 5-HT2A, and 5-HT6 receptors and low efficacy at the off-target receptors (5-HT2C, histamine H1, and adrenergic α1 receptor). Showing dose-dependent inhibition of apomorphine- and MK-801-induced motor behavior, and the conditioned avoidance response with low cataleptic effect. Moreover, Additionally, these compounds exhibits a favorable pharmacokinetic profile with oral bioavailability of 58.8% in rats. Furthermore, these compounds display procognition properties in a novel object recognition task in rats. Taken together,

A series of novel benzoxazole-piperidine (piperazine) derivatives combining high dopamine D2 and serotonin 5-HT1A, 5-HT2A receptor affinities were developed[44]. Of these derivatives, the pharmacological features of these compound exhibited high affinities for the DA D2, 5-HT1A and 5-HT2A receptors, but low affinities for the 5-HT2C and histamine H1 receptors and human ether-a-go-go-related gene (hERG) channels. Furthermore, benzoxazole-piperidine reduced apomorphine-induced climbing and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced head twitching without observable catalepsy, even at the highest dose tested. Thus, benzoxazole-piperidine is a

promising candidate as a multi-target antipsychotic treatment.

A new diaryl-methylene piperidine derivative, [45], displayed an atypical antipsychotic profile both in vitro and in vivo. The main pharmacological characteristics of this compound appears to reside in a more potent antagonism of the 5-HT2 serotonergic receptor than of the D2 dopaminergic receptor. This confirms that molecules displaying a D2/5-HT2 binding ratio < 1 possess clozapine-like antipsychotic activity.

A series of 2-substituted-5-thiopropylpiperazine (piperidine) -1,3,4-oxadiazoles derivatives have been synthesized[46] and the target compounds were evaluated for binding affinities to D(2), 5-HT(1A) and 5-HT(2A) receptors. Preliminary results indicated that compounds 14, 16 and 22 exhibited high affinities to D(2), 5-HT(1A) and 5-HT(2A) receptors among these compounds. Further binding tests showed that compound 22 had high affinity for D(3) receptor, and low affinity for serotonin 5-HT(2C) and H(1) receptors. In addition, compound 22 inhibited apomorphine-induced climbing behavior and MK-801-induced hyperactivity with no extrapyramidal symptoms liability in mice. They have showen an atypical antipsychotic activity without liability for extrapyramidal symptoms.

2.4. As HIV-1 Inhibitors

A novel series of piperidine-substituted triazine derivatives[47] have been synthesized and evaluated for anti HIVactivities in MT-4 cells. Most compounds displayed extremely promising activity against wild-type HIV-1 with EC50 values in low nanomolar concentration, better than that of Nevirapine,Delaviridine and Dideoxycitidine, and higher potency towards the resistant mutant strain K103N/Y181C than that of Nevirapine and Delavirdine. Selected compounds were also assayed against reverse transcriptase with lower IC50 values than that of Nevirapine.

A series of novel N-arylmethyl substituted piperidine-linked aniline derivatives were designed, synthesized and evaluated for their anti-HIV activity in MT-4 cell [48]s. All the new compounds showed moderate to potent activities against wild-type (wt) HIV-1 with an EC50 range from 0.022 to 2.1μM. All the compounds (EC50=0.022±0.0091μM, SI >10,770) were confirmed to be the most potent and selective inhibitor, which proved more potent than DDI and DLV in a cell-based assay against wt HIV-1, and more efficient than NVP in an RT (reverse transcriptase) assay.

A novel series of 1-acetylpiperidin-4-yl group led were synthesized and reported as potent CCR5 antagonists [49]. Introduction of small hydrophobic substituents on the central phenyl ring increased the binding affinity, providing low to sub-nanomolar CCR5 antagonists. The selected compound 11f showed excellent antiviral activity against CCR5-using HIV-1 replication in human peripheral blood mononuclear cells (EC50=0.59 nM) and an acceptable pharmacokinetic profile in dogs

A series of N2-(1-(substituted-aryl)piperidin-4-yl)-N6-mesityl-9H-purine-2,6-diamine derivatives were synthesized and proved as potent antiviral agents. Preliminary biological evaluation indicated that nearly half of them possessed remarkable HIV inhibitory potencies in cellular assays[50]. In particular, FZJ13 appeared to be the most notable one, which displayed anti-HIV-1 activity compared to 3TC. Moreover, an unexpected finding was that FZJ05 displayed significant potency against influenza A/H1N1 (strain A/PR/8/34) in MDCK cells with EC50 values much lower than those of ribavirin, amantadine and rimantadine. The results suggest that these novel purine derivatives incorporated with piperidine nucleus have the potential to be further developed as new therapeutic agents against HIV-1 or influenza virus.

A series of novel piperidine-substituted thiophene[3,2-d]pyrimidine derivatives[51] were designed to explore the hydrophobic channel of the non-nucleoside reverse transcriptase inhibitors binding pocket (NNIBP) by incorporating an aromatic moiety to the left wing of the lead K-5a2. The newly synthesized compounds were evaluated for anti-HIV potency in MT-4 cells and inhibitory activity to HIV-1 reverse transcriptase (RT). Most of the synthesized compounds exhibited broad-spectrum activity toward wild-type and a wide range of HIV-1 strains carrying single non-nucleoside reverse transcriptase inhibitors (NNRTI)-resistant mutations.

2.5.As Anti-inflammatory agent

4,5-disubstituted-thizolyl amides, derivatives of 4-hydroxy-piperidine and of 4-N-methyl piperazine, were synthesized and tested as anti-inflammatory

agents[52]. Log P values were theoretically calculated and experimentally determined. These compounds were tested for antioxidant activity, as hydroxyl radical scavengers and for their ability to interact with stable 1,1-diphenyl-2-picryl hydrazyl free radical (DPPH). The effect of the synthesized compounds on inflammation, using the carrageenin induced mice paw edema model was studied. Both anti-inflammatory and antioxidant activities depended on some structural characteristics of the synthesized compounds.

The synthesis and pharmacological evaluation of novel carboxamide and thioamide derivatives from the benzophenone and piperidine nucleus was reported by K.vinaya et al.,[53] Variation in the functional group at the N-terminal of piperidine led to two sets of compounds, bearing the carboxamide and thioamide, respectively. The characterization of this new class of compounds was performed with (1)H-NMR, LC-MS, IR, and elemental analysis. The newly synthesized compounds were screened for their anti-inflammatory activity by carrageenan-induced foot pad oedema assay and were compared with a standard drug. All the compounds exhibited anti-inflammatory activity at the dose of 30 mg/kg p.o. with varying degree from 52 to 67% inhibition of oedema. The compounds and with dichloro and fluoro substitution showed more potent activity at 30 mg/kg p.o. than the standard drug.

A new series of 5-(1-adamantyl)-4-arylideneamino-3-mercapto-1,2,4-triazoles, theN-Mannich bases 5-(1-adamantyl)-4-arylideneamino-2-(4-substituted-1-piperazinylmethyl)-1,2,4-triazoline-3-thiones and 5-(1-adamantyl)-4-arylideneamino-2-(4-ethoxycarbonyl-1-piperidyl-methyl)-1,2,4-triazoline-3-thiones were synthesized and their antimicrobial and anti-inflammatory activity was determined[54]. Several of the newly synthesized derivatives displayed promising antimicrobial and anti-inflammatory activities compared to known antibacterial, antifungal and anti-inflammatory drugs.

Antioxidant and anti-inflammatory activity of 1,3-dimethyl 2,6-diphenyl piperidine 4-one oxime were investigated. Results of the study indicates that higher dose of 3, 3-dimethyl 2,6-dimethyl piperidine 4-one oxime has potent anti-inflammatory activity close to standard drug[55]. The antioxidant activity of 3,3-dimethyl 2,6-dimethyl piperidine 4-one oxime was concentration dependent and approximately comparable to commercial synthetic antioxidants as ascorbic acid. Anti-inflammatory activity was evaluated using the carrageenan induced rat paw oedema. On the basis of the results, it is clearly indicated that 3,3- dimethyl 2,6-dimethyl piperidine 4-one oxime had powerful anti-inflammatory and in vitro antioxidant activity.

A series of some novel 2,4-dimethoxy-6-(piperazin-1-yl)-1,3,5-triazine aryl ureido/aryl amido derivatives of biological interest were prepared and screened for their pro-inflammatory cytokines (TNF-α and IL-6) and antimicrobial activity. All the compounds were found to have promising anti-inflammatory activity[56]

## CONCLUSION

This review brought out piperidine containing heterocyclic compounds as a privileged molecule in the field of pharmaceutical sciences with its broad spectrum biological profile including various targets to explore huge scientific knowledge for designing and development of newer/novel piperidine analogs. The thorough knowledge of structure activity relationship will definitely help the scientific community to produce potent drugs with enhanced pharmacological activity.

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