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Review Article

PIPERIDONE ANALOGS: SYNTHESIS AND THEIR DIVERSE BIOLOGICAL APPLICATIONS

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Abstract: Piperidones are of particular interest due to their unique biochemical properties. They serve as precursors to the piperidine ring, which is a ubiquitous moiety in many alkaloid natural products and drug candidates. In this frame, considerable efforts have been devoted to the synthesis of position isomeric piperidones and their derivatives. The pipiridone analogs that are synthesized have been bio-assayed for their varied activity. The structure-activity relationship of the piperidones has been established. This review article describes up to date methodology for the synthesis of piperidone derivatives and their biological properties.

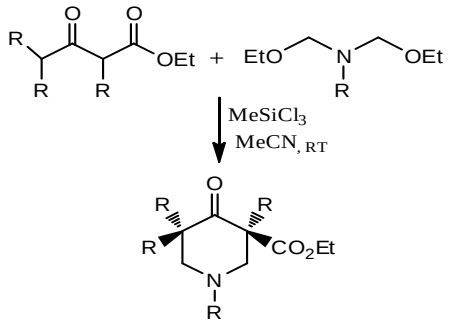
Key words: Piperidones, ultrasonic, citotoxic, antimicrobial, antioxidant, antitumor.

INTRODUCTION

Piperidones are a class of chemical compounds sharing the piperidine skeleton. Advances in organic chemistry are usually measured by the availability of simple, highly functionalized building blocks that can be used in the synthesis of larger molecules with diverse properties and applications. Piperidones are known to exhibit varied biological properties such as antimicrobial, antioxidant, antitumor, citotoxic, analgesic, anticancer, anti-HIV etc. The compounds bearing piperidone skeleton that mimic the naturally occurring alkaloids and steroids have been synthesized in order to study their biological activity and compare with naturally occurring compounds. This review provides up to date information about the methods, catalysts, reaction conditions that are adopted for the synthesis of piperidones and their transformation to a useful derivatives. The stereochemistry of the products and its influence on the biological properties was discussed. The biological activity study of the piperidone analogs; and their structure-activity relationship also described.

SYNTHESIS OF PIPERIDONES

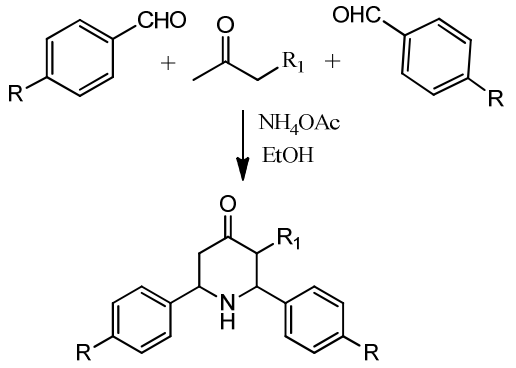
A classical method for the synthesis of piperidones is the Petrenko-Kritschenko piperidone synthesis; which involves combining a alkyl-1,3-acetonedicarboxylate with benzaldehyde and an amine. An efficient two step procedure for the synthesis of *N*-aryl-substituted 4-piperidones involves the use of *L*-proline as the ligand for the Cu(I)-catalyzed Ullmann amination followed by subsequent hydrolysis of resulting ketals.[1] A general route for the construction of 2-substituted-piperidin-4-one derivatives on solid support has been developed using polymer-bound 4-benzylsulfonyl-l-triphenylphosphoranylidene-2-butanone as a convenient precursor for substituted divinyl ketones in the heterocyclization reaction with amines.[2] The double Mannich reaction of acyclic α,γ-substituted β-keto esters and bis(aminol) ethers gives substituted 3,5-substituted-4-piperidones with high levels of diastereoselectivity (Scheme-1).[3]



Scheme-1

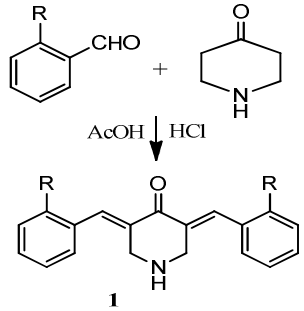
Chiral 2-amino-1,3-butadienes derived from commercially available (*S*)-2-methoxymethylpyrrolidine react with aromatic *N*-trimethylsilylaldimines and *N*-phenylaldimines in the presence of $ZnCl_2$ to give 4-piperidones with moderate to very high yield.[4] Kabilan and co-workers published many articles on the synthesis of alkaloids that contain a piperidine ring; which led them to prepare diversely functionalised piperidones as scaffolds for building more complex structures. For instance, they reported the synthesis of most relevant piperidine synthons: 2-aryl-4-

piperidones, 3-piperidein-2-ones, 3-amino-2-arylpiperidin-4-ones, 3-aminopiperidin-2-ones, oxazolopiperidones, and hydroxylactams by the reaction of aromatic aldehydes and active methylene compounds in ethanol in the presence of ammonium acetate (Scheme-2).[5]



Scheme-2

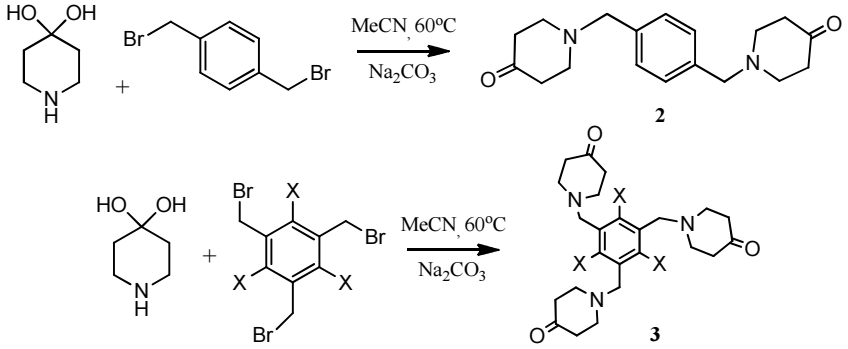
2-Aryl-4-piperidones have been synthesized by condensation of an aromatic aldehyde and a β-aminoketone ethylene ketal, and further cyclization of the resulting iminoketal with dry hydrogen chloride or anhydrous *p*-toluensulfonic acid. Alternatively, reaction of the above iminoketals with methyl fluorosulfonate followed by dry hydrogen chloride treatment and acid hydrolysis gives directly *N*-methyl-4-piperidones.[6] Analogs of 3,5-bis(2-fluorobenzylidene)-4-piperidone (**1**) were synthesized in a simple procedure by the reaction of *o*-substituted benzaldehyde and piperid-4-one in acetic acid medium in good yields (Scheme-3). The synthesized compounds (1) were bio-assayed for their citotoxicity and results of the study revealed that these compounds are potential antitumor agents.[7]



1

Scheme-3

A general and more convenient direct approach to the synthesis of *N*-substituted bipodal piperidin-4-ones (**2**) and tripodal piperidin-4-ones (**3**) by ultrasound method was reported (Scheme-4). The reaction was carried out by the reaction of 4-piperidone hydrochloride monohydrate with different alkylating agents. 4-Piperidone was preferably reduced to respective piperidin-4-ols by ultrasonic irradiation using silica chloride as an effective supporting polymer.[8]

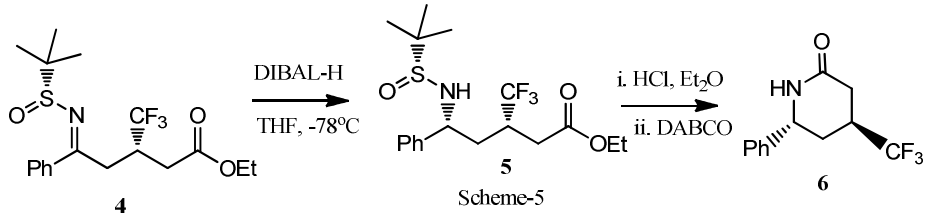


2

3

Scheme-4

1-Benzyl-3,4-unsaturated-4-piperidinyl benzyldimethylsilane prepared readily undergo palladium-catalyzed cross-coupling reactions with a variety of aryl iodides and aryl bromides to generate 3,4-unsaturated 4-arylpiperidines, often at ambient temperature.[9] High yielding diastereoselective asymmetric synthesis of a series of chiral 4-trifluoromethyl-2-piperidones (**6**) involves; the reduction of (**4**) with DIBAL-H at 78˚C to (**5**) followed by subsequent hydrolysis in the presence of hydrochloride ether solution at room temperature to remove tert-butanesulfinyl group and cyclisation with DABCO (1,4-diazabicyclo[2.2.2]octane) (Scheme-5).[10]



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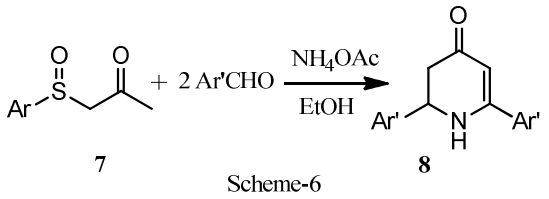
5

6

Scheme-5

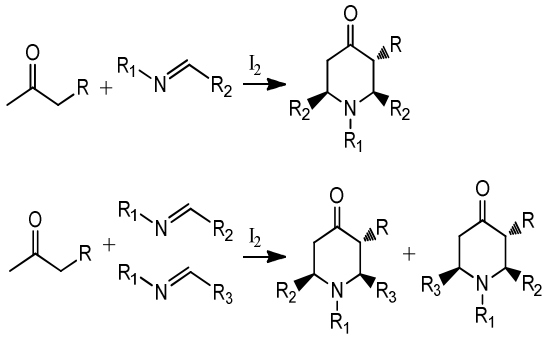
The one-pot, four-component reaction of 1-(phenylsulfinyl) propan-2-one or 1-(4-chlorophenylsulfinyl)propan-2-one (**7**), aromatic aldehydes and ammonium acetate in a 1:2:1 molar ratio in ethanol affords a series of 2,6-diaryl-2,3-dihydro-1*H*-pyridin-4-ones (**8**) in moderate yields (Scheme-6).[11] The reaction proceeds presumably via a double Mannich reaction-elimination tandem sequence.



7 **8**

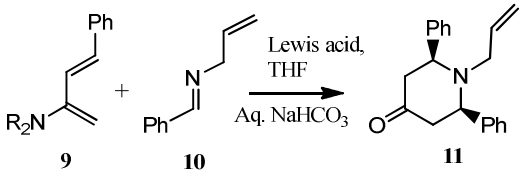
Scheme-6

In recent years, the use of molecular iodine as an inexpensive, nontoxic, readily available, environmentally friendly catalyst for various organic transformations has received considerable attention. A tandem multicomponent double Mannich reaction of amines, aldehydes and ketones was efficiently catalyzed by molecular iodine, producing a series of 4-piperidones in a stereoselectively. Investigation of the reaction between alkyl-imines and ketones showed that imines from amines and ketones were formed *in situ* and isomerized to enamine in the presence of molecular iodine that accelerates the Mannich addition.[12] A convenient approach towards the synthesis of diastereomeric highly substituted 4-piperidones was achieved by cross double Mannich reaction and tandem cyclization catalyzed by iodine (Scheme-7).[13]



Scheme-7

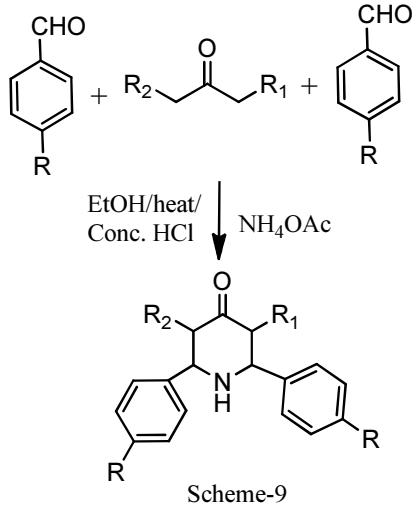
The reaction of *N*-tert-butoxycarbonyl-4-oxopiperidine-3-carboxylic acid ethyl ester with fermenting baker's yeast gave almost racemic *N*-tert-butoxycarbonyl-4-hydroxypiperidine-3-carboxylic acid ethyl ester with complete diastereoselectivity. However, reduction of *N*-tert-butoxycarbonyl-4-oxopiperidine-3-carboxylic acid ethyl ester with non-fermenting yeast produced *N*-tert-butoxycarbonyl-4-hydroxypiperidine-3-carboxylic acid ethyl ester with a 24-41% enantiomeric excess.[14] Imino-Diels–Alder reaction of 4-phenyl-2-amino-1,3-butadienes (**9**) with *N*-allylbenzaldimine (**10**) in the presence of catalytic amount of $Cu(TfO)_2$ lead to stereoselective preparation of meso-2,6-disubstituted-4-piperidones (**11**) (Scheme-8).[15]



9 **10** **11**

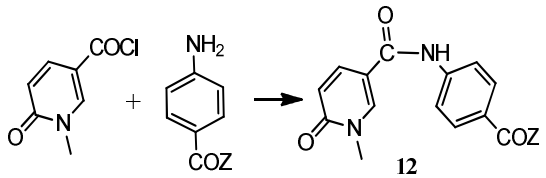
Scheme-8

A series of 2,6-diarylpiperidin-4-ones were synthesized in a multi-component tandem process using substituted aromatic aldehydes, active methylene compounds, ammonium acetate/ammonia in ethyl alcohol in the presence of conc. Hydrochloric acid (Scheme-9). Then these 2,6-diarylpiperidin-4-ones were transformed in to new 1,3,4-thiadiazolines derivates. All the synthesized compounds were virtually screened against bacterial and fungal strains. QSAR study indicated that the increase in weakly polar component of solvent accessible surface area will favor antibacterial activity while increase in polarizability and decrease in ionisation potential and hydrogen bond donor will favor antifungal activity.[16]



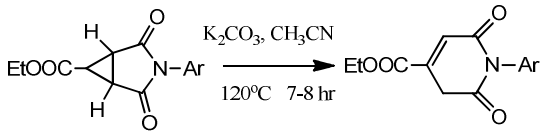
Scheme-9

In search for nonsteroidal inhibitors of So-reductase for the treatment of benign prostatic hyperplasia (BPH) and possibly prostate cancer, substrate mimicks (**12**) were synthesized comprising of a 1-methyl-2-pyridone or 1-methyl-2-piperidone moiety (mimicking steroidal ring A) and a diisopropyl or a tert-butyl benzamide (mimicking steroidal ring D). The bridge connecting the rings consisted of amide (Scheme-10). The compounds (**12**) have been tested for Sa-reductase inhibitory properties using rat ventral prostate, as well as human BPH and prostate cancer. The study revealed that there was a significant differences observed between rat and human enzyme.[17]



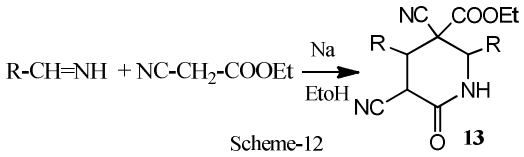
Scheme-10

Recently, Ajay Kumar and co-workers[18,19] reported the synthesis of a series of ethyl *N*-aryl-2,6-dioxo-piperid-3-ene-4-carboxylates by thermal ring expansion reaction of ethyl *N*-aryl-2,4-dioxo-3-azabicyclo[3.1.0]hexane-6-carboxylates in acetonitrile medium in the presence of K_2CO_3 and they obtained in good yield. The products have been evaluated *in vitro* for their antimicrobial and antioxidant activity. The results of their study revealed that these compounds exhibit remarkable antimicrobial activity and relatively less antioxidant activity (Scheme-11).



Scheme-11

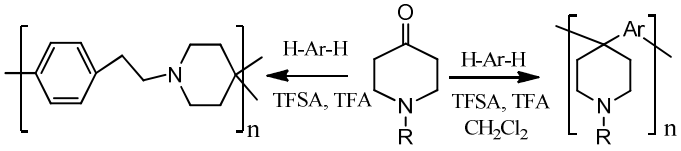
A facile and one pot synthesis of series of ethyl 3,5-dicyano-4,6-diaryl-piperid-2-one-5-carboxylates (**13**) by the intermolecular condensation of imines with ethyl cyanoacetate in absolute alcohol in the presence of sodium metal under sealed tube conditions was reported by Lokanatha Rai and co-workers.[20] They carried out a reaction of an equimolar mixture of imines and ethyl cyanoacetate in dry ethyl alcohol in the presence of sodium metal under reflux conditions on an oil bath and obtained the products in 55-78% yield (Scheme-12). The synthesized compounds have been evaluated for their antimicrobial activity.[21] They were prepared the required precursor imines by the reaction of aromatic aldehydes with amines/ammonia in the presence of base sodium hydroxide under mild conditions.[22]



Scheme-12

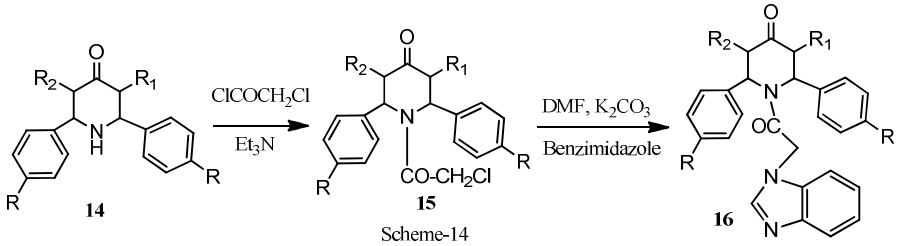
REACTIONS OF PIPERIDONES

The piperidine ring system is a frequently encountered heterocyclic unit in natural compounds and drug candidates. Piperidine alkaloids exhibit a range of biological activities and as such represent important synthetic targets. Piperidones serve an important role as intermediates *en route* to substituted piperidines and can be found as a part of more complex biologically active compounds. For instance, 4-Piperidone and 4-alkyl piperidones react selectively with aromatic hydrocarbons in a mixture of trifluoromethanesulfonic acid (TFSA) and CH_2Cl_2 to give linear polymers, while *N*-(2-phenethyl)piperidone undergoes self-polymerization to yield virtually 100%-hyperbranched polymer (Scheme-13).[23]



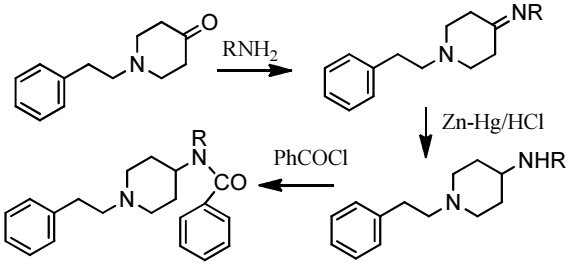
Scheme-13

Chloroacetylation of 2,6-diarylpiperidin-4-ones (**14**) with chloroacetyl chloride using triethylamine as base produces chloroacetyl derivatives (**15**). Then, condensation of compounds (**15**) with benzimidazole in the presence of calcinated K_2CO_3 in DMF furnished the novel compounds (**16**) (Scheme-14). The synthesized compounds (**15**) and (**16**) have been evaluated for their antibacterial activities against a wide number of bacterial pathogens and antitubercular activity. The results of the study revealed that some derivatives have exhibited promising antibacterial and antitubercular activity.[24]



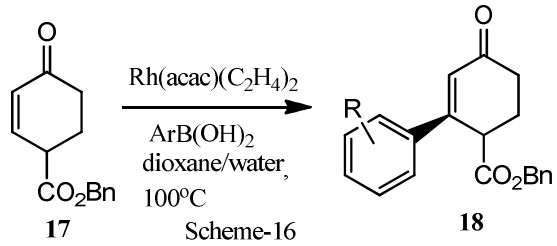
Scheme-14

Phenyl ethyl 4-piperidone reacts with different amines in toluene as a solvent to form corresponding Schiff bases. The Schiff bases on reduction with Zn-Hg /HCl to give reduced products (Scheme-15). The Schiff bases prepared have reported to exhibit remarkable microbial growth inhibiting properties.[25]



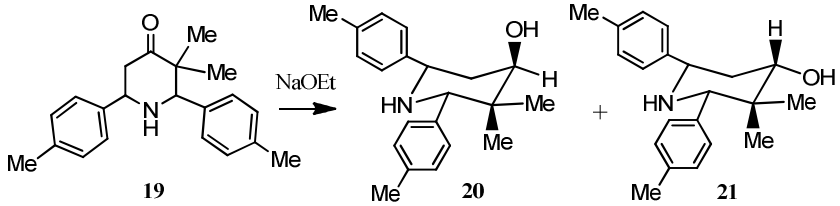
Scheme-15

The highly enantioselective synthesis of 2-aryl-4-piperidones by rhodium/phosphoramidite-catalyzed conjugate addition of arylboroxines to 2,3-dihydro-4-pyridones was reported. Both enantiomers of a variety of products with sterically and electronically different R substituents were obtained in high isolated yield and with excellent enantioselectivity up to 99%. The introduction of aryl groups to (**17**) using the rhodium/phosphoramidite-catalyzed conjugate addition of arylboronic acids, could provide a pathway to 2-substituted 4-piperidones (**18**) (Scheme-16).[26]



Scheme-16

The reduction of piperidones (**19**) by sodium ethoxide, efficiently transformed in to a mixture of isomeric alcohols (**20,21**) (Scheme-17). The isomeric alcohols were separated and were evaluated *in vitro* for their antioxidant activity. It has been found that piperidone (**19**) demonstrated much better radical scavenging activity than its isomeric alcohols.[27]

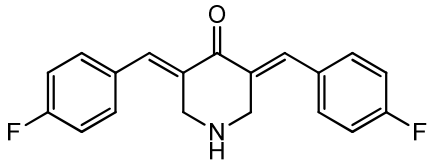


Scheme-17

BIOLOGICAL APPLICACTIONS OF PIPERIDONES:

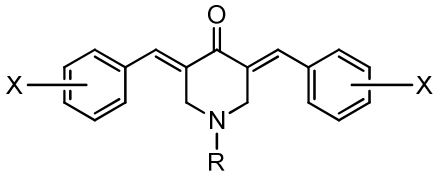
Piperidones often serve a role as advanced intermediates prior to their conversion to piperidines. Hydroxylated piperidine alkaloids are frequently found in living systems and display a wide range of biological activities due to their ability to imitate carbohydrates in a variety of enzymatic processes. A novel difluorodiarylidenyl piperidone (**22**) (H-4073) synthesized was evaluated for its anticancer potency in human ovarian cancer. Studies were done using

established human ovarian cancer cell lines (A2870, A2780-DDP, OV-4, SKOV3, PA-1, and OVCAR3) as well as in a murine xenograft tumor (A2780) model. The compound was comparably and significantly cytotoxic to A2780 cells. The study revealed that (**22**) may be useful as a safe and effective anticancer agent for ovarian cancer therapy.[28]



22 H-4073

A series of 3,5-bis(arylidene)-4-piperidones (**23**) (DAP) compounds are considered as synthetic analogues of curcumin for anticancer properties. The studies were performed on the structure-activity relationship of number of DAPs as potent antioxidant moieties. The anticancer efficacy of (**23**) was tested by measuring their cytotoxicity to cancer cell lines A2780 and MCF-7 cell line. The results showed that all DAP compounds induced a significant loss of cell viability in the human cancer cell lines tested.[29]



X = F, CF_3, OCH^3;
R = nitroxides and their precursors

23

N-Substituted-2-piperidones bearing 1,4-benzodioxan ring were prepared by aldol condensation of the lithium enolate of *N*-substituted-2-piperidones with 1,4-benzodioxan-6-carbaldehyde were evaluated for their activity to induce lateral roots in lettuce seedlings. Among the series; *N*-cinnamyl-3-[1-(1,4-benzodioxan-6-yl)-1-hydroxymethyl]-2-piperidone had the highest activity.[30] 3,5-Diarylidene-4-piperidones were prepared principally as candidate cytotoxic agents. The testing was done on 54 human tumor cell lines from eight neoplastic diseases. Selective toxicity was demonstrated by some of the compounds, especially toward leukemia.[31] A series of twenty 2,6-diarylpiperidin-4-one *O*-methyloximes synthesized were evaluated for their *in vitro* antiproliferative activity against human cervical carcinoma (HeLa) cell line. Preliminary SAR suggests some lead molecules are with a scope of further structural optimization of the piperidone pharmacophore toward the development of anticancer drug synthesis.[32]

3,5-Bis(benzylidene)-4-piperidones prepared were shown 100-9700 times greater the activity of N,N'-bis(2-chloroethyl)-*N*-nitrosourea towards P388 leukemia cells. Molecular modification of the compounds by forming two mono-benzylidene compounds, a related acyclic derivative and an N-acyl compound resulted in diminished but retained high cytotoxicity.[33] The increasing resistance of the malaria parasites has enforced new strategies of finding new drug targets. Experiments with the antifungal drug ciclopiroxolamine, an α-hydroxypyridone, and the plant amino acid L: -mimosine, a 4-pyridone, resulted in an antiplasmodial effect *in vitro*. Using mimosine as a lead structure, alkyl 4-oxo-piperidine 3-carboxylates were found to have the most efficient antiplasmodial effects *in vitro* and *in vivo.*[34]

A series of 3,5-bis(arylidene)-4-piperidone (DAP) compounds are the synthetic analogues of curcumin for anticancer properties. We performed structure-activity relationship studies by synthesizing a number of DAPs N-alkylated or acylated with nitroxides or their amine precursors as potent antioxidant moieties. Both subtituents on arylidene rings and on piperidone nitrogen (five- or six-membered, 2- or 3-substituted or 3,4-disubstituted isoindoline nitroxides) were varied. The anticancer efficacy of the new DAP compounds was tested by measuring their cytotoxicity to cancer cell lines A2780 and MCF-7 and to the H9c2 cell line. The results showed that all DAP compounds induced a significant loss of cell viability in the human cancer cell lines tested; however, only pyrroline appended nitroxides showed limited toxicity toward noncancerous cell lines. Computer docking simulations support the biological activity tested. These results suggest that antioxidant-conjugated DAPs will be useful as a safe and effective anticancer agent for cancer therapy.[35]

Dysregulated Notch signaling plays an important role in the progression of cancer. Notch signaling affects tumor growth and angiogenesis through the actions of its ligand Jagged-1. 3,5-bis(2,4-difluorobenzylidene)-4-piperidone (DiFiD) showed that it inhibits cancer cell growth and its effects on Notch signaling. Intraperitoneal administration of DiFiD significantly suppressed growth of pancreatic cancer tumor xenografts. In vitro, DiFiD inhibited the proliferation of various human and mouse pancreatic cancer cells.[36] Series of 2,6-diaryl-3-methyl-4-piperidones synthesized by Mannich reaction of ethyl-methyl ketone, substituted aromatic aldehydes and ammonium acetate were converted to oximes and thiosemicarbazone derivatives. The compounds

were screened for acute toxicity, analgesic, local anaesthetic and antifungal activity. The study revealed that 2-(4-methylphenyl)-3-methyl-6-(4-chlorophenyl)-piperidin-4-one exhibited the highest analgesic and local anaesthetic activity. The oximes and thiosemicarbazones derivatives were completely devoid of analgesic and local anaesthetic activity.[37]

The N-acyl-3,5-bis(arylidene)-4-piperidones and related analogues stimulate a protein tyrosine kinase enzyme. Molecular modelling suggested that the compounds interact transiently with the ATP binding site of fyn kinase thereby enhancing the catalytic phosphorylation of proteins.[38] A series of bis[3,5-bis(benzylidene)-4-oxo-1-piperidinyl]amides display potent cytotoxic properties towards a wide range of tumours. These compounds have the following important properties. First, greater toxicity was demonstrated towards certain tumours than various non-malignant cells. Second, various compounds in series are toxic to a number of human colon cancer and leukaemic cells. Third, these compounds reverse P-gp mediated multidrug resistance.[39]

A number of 3,5-diarylidene-4-piperidones prepared principally as candidate cytotoxic agents in two screens. The first test system used an average of 54 human tumor cell lines from eight neoplastic diseases, namely leukemia, melanoma, colon, non-small-cell lung, small-cell lung, central nervous system, ovarian, and renal cancers. Selective toxicity was demonstrated by some of the compounds, especially toward leukemia. The second screen used L1210 lymphoid leukemia cells. In general, the compounds were less cytotoxic than the reference drug melphalan in both screens. Evaluation against the human tumor cell lines revealed that 3,5-bis-[[4'-(methylthio)phenyl]methylene]-1-methyl-4-piperidone methiodide had significant cytotoxicity, and 3,5-bis(4-pyridylmethylene)-1-methyl-4-piperidone methiodide was virtually inactive in both screens.[40]

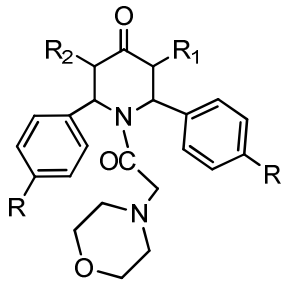
1-Piperideine, 5-aminopentanoic acid, and its lactam, 2-piperidone, were identified as metabolites of cadaverine in 10,000 g mouse liver supernatants to which diamine oxidase had been added. Both metabolites were also found when the cadaverine metabolite 1-piperideine was incubated with the preparation which suggested that 1-piperideine is an intermediate in the formation of 5-aminopentanoic acid and 2-piperidone. Identification of the metabolites was based on gas chromatography-mass spectrometric analysis in comparison to authentic standards. Mouse brain homogenates converted 1-piperideine to 5-aminopentanoic acid. The results suggest that the metabolic fate of cadaverine may provide precursors of pharmacologically active analogues of GABA.[41]

Difluorodiarylidenyl piperidone (H-4073) and its N-hydroxypyrroline modification (HO-3867) were evaluated for their anticancer potency in human ovarian cancer cell lines (A2870, A2780cDDP, OV-4, SKOV3, PA-1, and OVCAR3) as well as in a murine xenograft tumor (A2780) model. Results revealed that both compounds were comparably and significantly cytotoxic to A2780 cells. However, HO-3867 showed a preferential toxicity toward ovarian cancer cells while sparing healthy cells. In addition, HO-3867 significantly inhibited the growth of the ovarian xenografted tumors in a dosage-dependent manner without any apparent toxicity. The study suggested that HO-3867 may be useful as a safe and effective anticancer agent for ovarian cancer therapy.[42]

The compound 3,3,5,5-tetramethyl-4-piperidone (TMP), extracted from Marasmius androsaceus was evaluated for antihypertensive effect. Besides, the hemodynamic profiles and pertinent mechanism of the compound were explored. Acute and chronic antihypertensive effects of TMP were examined in spontaneous hypertensive rats (SHRs) and reno-hypertensive rats. Anesthetized dogs were used to evaluate the hemodynamic effects of TMP. Moreover, the cat nictitating membrane response was used to test the ganglionic blocking property of TMP. TMP notably reduced the blood pressure of SHR in 30 min. The results of hemodynamic study in anesthetized dogs showed that, except for the reduction in blood pressure and left ventricular work, no other changes were detected. The results of heart rate variability analysis indicated an intact sympathetic-vagal balance after TMP treatment.[43] A series of 3,5-bis(phenylmethylene)-1-(N-arylmaleamoyl)-4-piperidones synthesized were displayed potent cytotoxicity towards human Molt 4/C8 and CEM T-lymphocytes as well as murine P388 and L1210 leukemic cells. Molecular modeling revealed certain interplanar and bond angles and interatomic distances which were perceived to contribute to the observed bioactivity as well as providing suggestions for future structural modifications of the piperidones.[44]

N-Morpholinoacetyl-2,6-diarylpiperidin-4-ones (**24**) were prepared in search of new leads towards potent antimicrobial agents. The compounds have been evaluated *in vitro* for their antibacterial activity against *S. aureus, E. coli, P. aeruginosa* and *S. typhi*; and antifungal activity against *C. albicans, A. niger* and *A. flavus*. Structure-activity relationship results for these compounds have shown that these exerted excellent

antibacterial activity against all the bacterial strains, and good antifungal activities.[45]



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The compounds 2,6-diphenylpiperidin-4-one (2,6-DPP); 3-methyl-2,6-diphenylpiperidin-4-one (3-Me-2,6-DPP); 2,2-dimethyl-6-phenylpiperidin-4-one (2,2-DMe-6-PP); and *N*-chloro-2-6-diphenylpiperidin-4-one(*N*-Cl-2,6-DPP) on the corrosion of copper in sulphuric acid has been investigated by means of spectrophotometric measurements of the metal ions in solution and potentiostatic polarization method. The inhibitors retard the corrosion process by blocking anodic reaction sites. The negative free energy of adsorption, the positive heat of adsorption and the decrease in apparent free energy of activation in the presence of inhibitors are suggestive of chemisorption of inhibitors on the surface.[46]

SUMMARY

This report highlights methodologies that have been used to synthesize piperidones and their transformation in to biologically potent derivatives. Much focus was given on their biological activity studies, stereochemistry of the products and their influence on the activity. The review may become useful tool for the researchers to devise new molecules and study their biological studies.

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