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Review Article

Recent Advances in the Synthesis of Highly Substituted Piperidine Analogs with Biological Activities

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ABSTRACT

The development of novel techniques for the efficient construction of heterocyclic compounds is an major issue in the preparation of organic compounds. The piperidine building block acts as a substantial task in the inhibitory activity of compounds and thus is very important in influencing biological properties such as antioxidant, anti-Alzheimer, and free radical scavenging activities. Highly substituted piperidine analogs play a remarkable role in the synthesis of pharmaceutical compounds as important structural components in active and natural biological compounds. This review summarized advances in the synthesis of highly substituted piperidine analogs and their antioxidant and anti-Alzheimer properties. Antioxidant activities are inversely proportional to IC_{50} value. In addition, new green methods for the preparation of piperidine building blocks, such as: non-toxic catalysis, water-initiated processes, solvent-free reactions, etc. are also presented. This review study is designed to assist scientists looking for suitable substrates for the construction of biologically active piperidine analogs.

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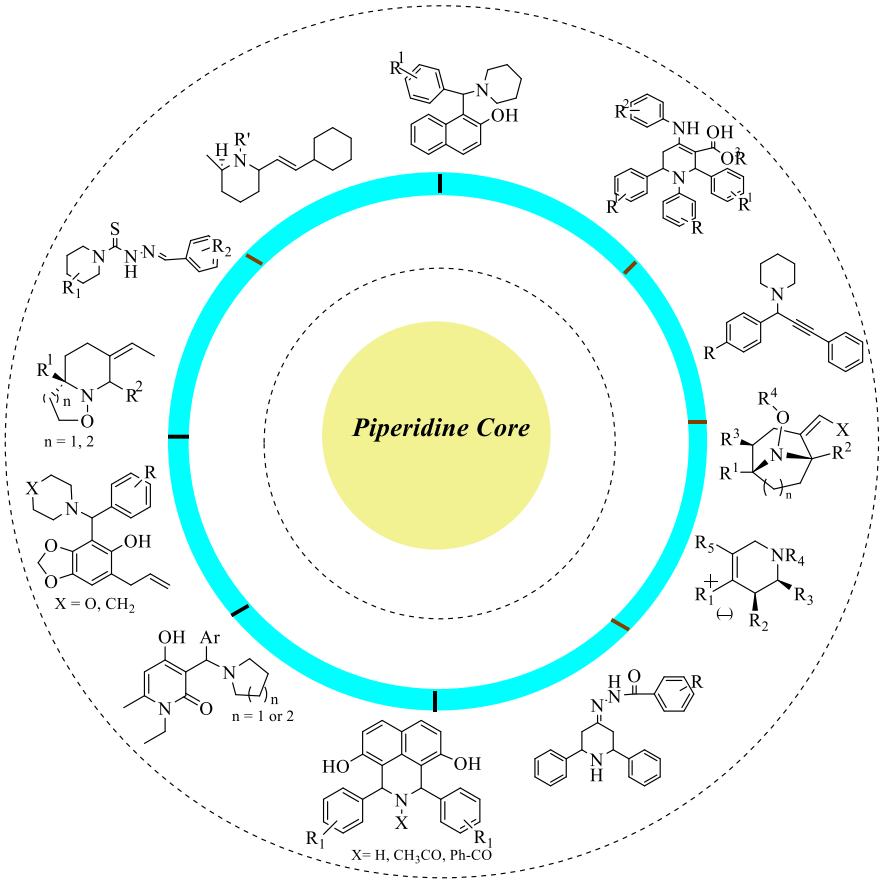
GRAPHICAL ABSTRACT



Introduction

Heterocyclic compounds play an important role in the pharmaceutical industry, and one of the most common structures used in their skeletons is piperidine building blocks. Thus, the development of facile and cost-effective procedures for the production of piperidine analogs is a significant task in organic chemistry. Piperidine building blocks are broadly known in bioactive natural products. Because of their pharmacological properties, they are considered very valuable and prominent synthetic drugs that contain piperidine structure (Figure 1) [1-9,15-20].

A variety of structural features are displayed by synthetic piperidines, including many remarkable biological activities. Several synthesis methods of piperidines have been studied due to their antimicrobial [10], anti-inflammatory [11], anticancer [12], antidepressant [13], and antioxidant [14] properties. Likewise, a series of piperidine derivatives have been isolated from natural compounds and tested for cytotoxicity on human cancer cells (Figure 2) [15-26].

Highly substituted piperidine derivatives synthesis

Various catalysts have been developed for the preparation of piperidine analogs. Generally, these catalysts are used in catalytic amounts to complete the reaction. Simple filtration removes catalysts from the reaction solution, thereby eliminating the need for time-consuming chromatographic work-up. One-step reaction of

anilines **29**, *β*-ketoesters **30**, and various substituted benzaldehydes **31**, in the existence of $TiCl_2 \cdot 2H_2O$ [27], sodium lauryl sulfate (SLS) [28], acetic acid [29], tartaric acid [30], lactic acid [31], $ZrOCl_2.8H_2O$ [32], $InCl_3$ [33], CAN [34], $Bi(NO_3)_3.5H_2O$ [35], $LaCl_3.7H_2O$ [36], $NiCl_2.6H_2O$ [37], trityl chloride [38], $BF_3.SiO_2$ [39], polystyrene sulfonic acid (PSSA) [40], *p*-toluenesulfonic acid monohydrate [41], ethylenediammonium diformate (EDDF) [42], oxalic acid dehydrate [43], and *L*-proline [44] produce highly functionalized tetrahydropiperidines **32** (Scheme 1).

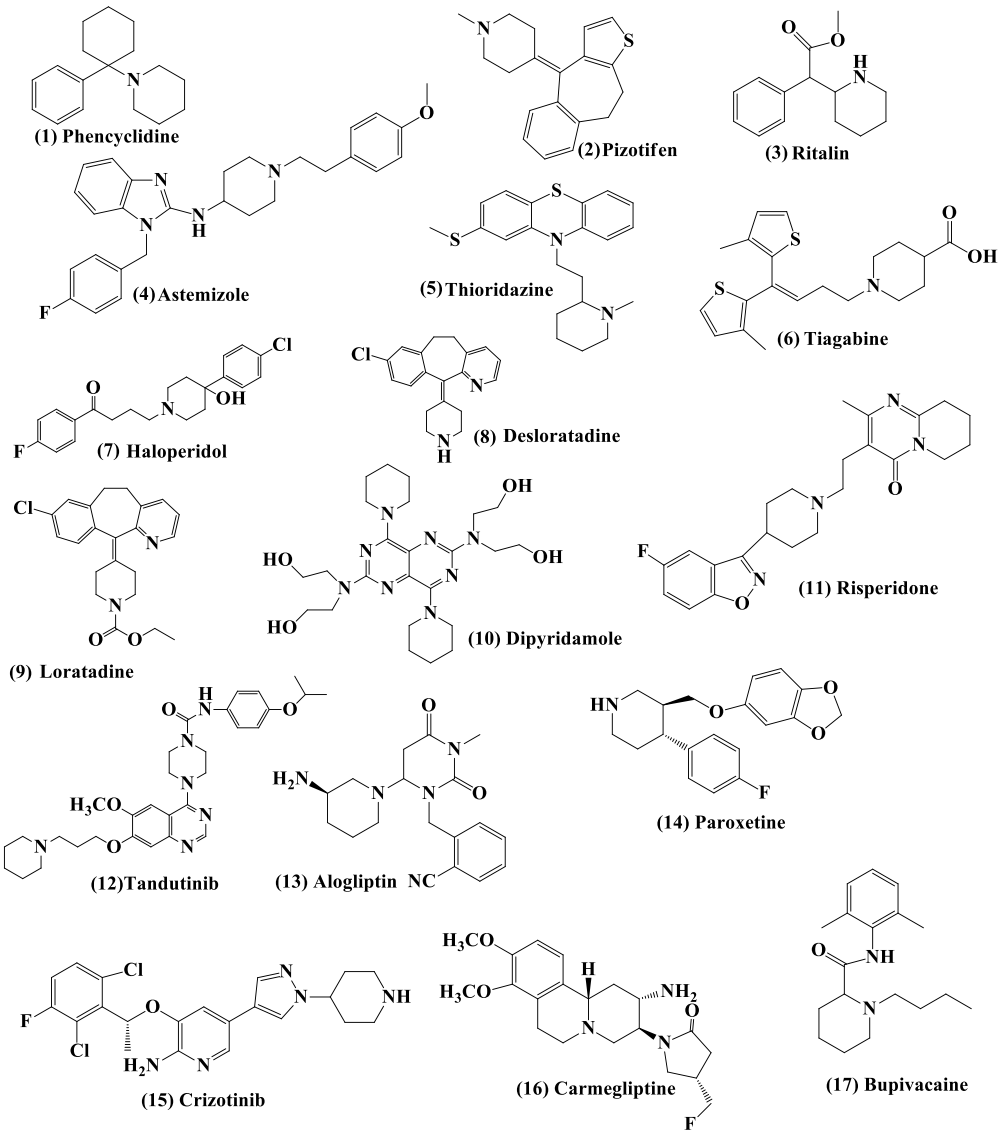
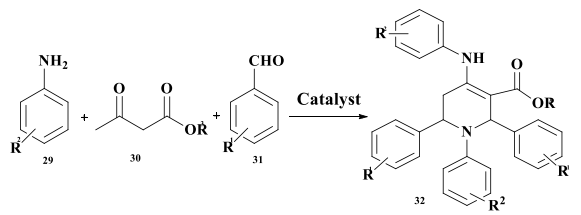


Figure 1. Pharmaceutically available drugs containing piperidine scaffold structure.



Scheme 1. Preparation of highly substituted piperidine.

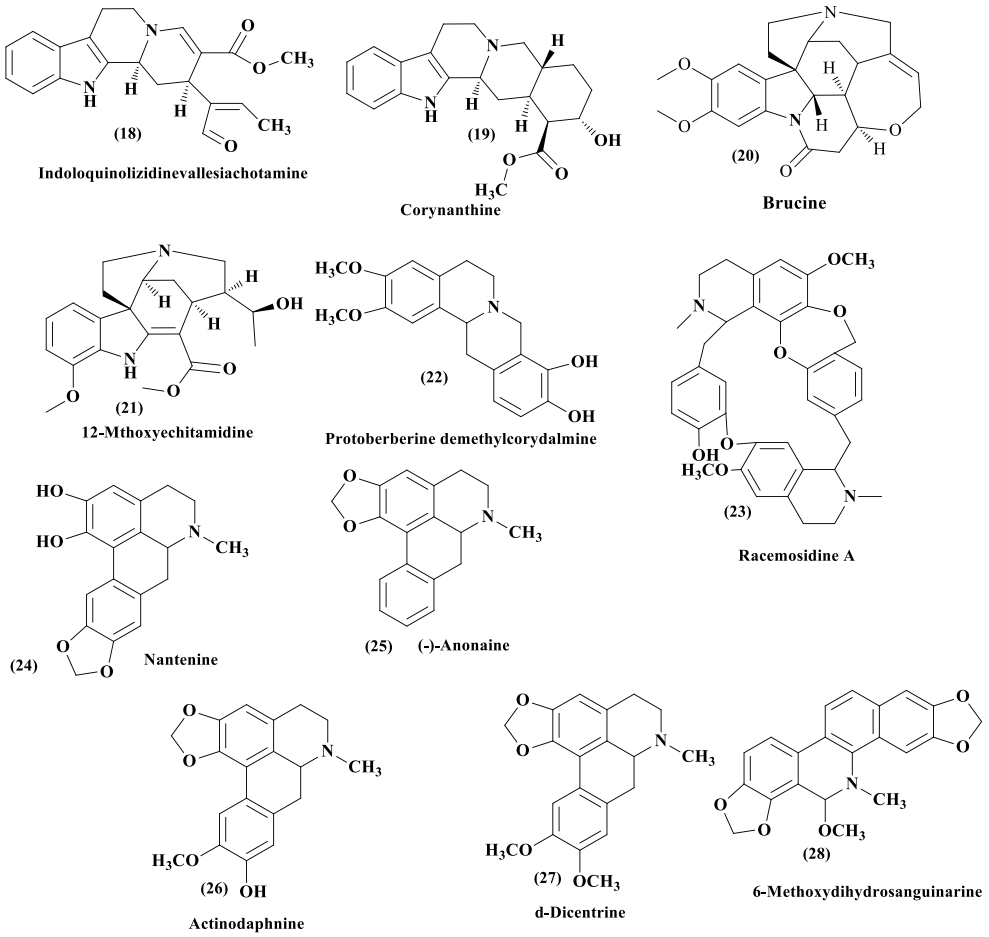
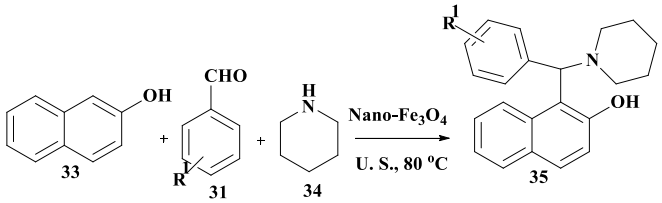


Figure 2. Piperidine derivatives isolated from natural compounds.



Scheme 2. Preparation of substituted naphthalene-2-ol derivatives.

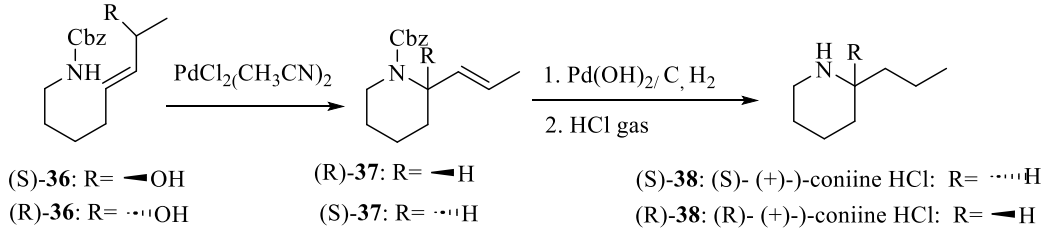
Mokhtary and Torabi [45], used nanomagnetite (Fe_3O_4) as an effective and strong catalyst for the preparation of substituted naphthalene-2-ol analogs **35** by ultrasound irradiation at 80 °C (Scheme 2).

Hande *et al.* [46] developed a general procedure for the preparation of 2- and 2,6-substituted piperidine via Pd^{II}-catalyzed 1,3-chirality transition reaction (Scheme 3). *R*)-(-)- and (*S*)-(+)-coniine were synthesized from the allylic alcohols (*S*)-**36** and (*R*)-**36**, respectively. While the rate of reactions was outstandingly augmented in dichloromethane, tetrahydrofuran had the maximum stereoselectivity. $PdCl_2(CH_3CN)_2$ was established to be a great catalyst for these reactions. A probable reaction direction was suggested, including the Pd π-complex formation directed by the chiral secondary allylic alcohol followed by *syn*-azapalladation, and consequently *syn*-removal of PdCl(OH) was suggested.

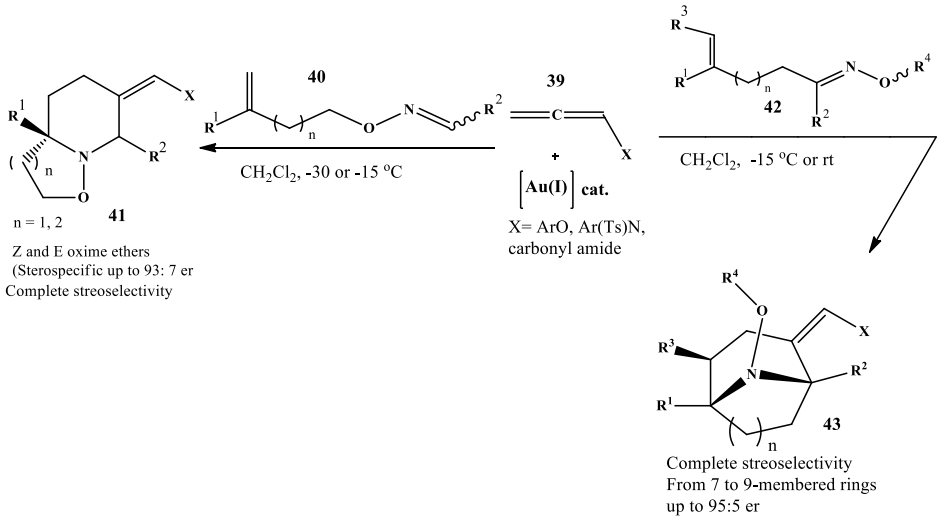
In an approach toward the preparation of highly substituted piperidines, Marcote *et al.* presented a gold-catalyzed annulation procedure, allowing the direct assembly of piperidines **41** as well as piperidine with aza-bridged compounds **43** from *N*-allenamides and alkene-tethered oxime ethers (or esters) (Scheme 4) [47].

Ischay *et al.* reported unstable azomethine ylides **44** for the stereoselective preparation of substituted piperidines **47** (Scheme 5) [48].

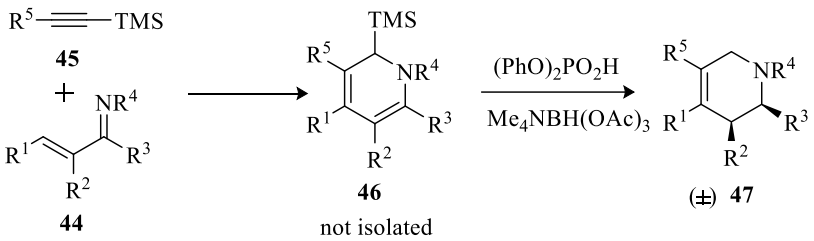
In another study, Zhang *et al.* [49], prepared various benzaldehyde thiosemicarbazide analogs with a piperidine scaffold (Scheme 6). The fungicidal activity of the prepared compounds was determined in laboratory conditions. Compounds with piperidine improve fungicidal properties compared to compounds without piperidine.



Scheme 3. Pd^{II}-catalyzed preparation of (R)-(-)- and (S)-(+)- Coniine.



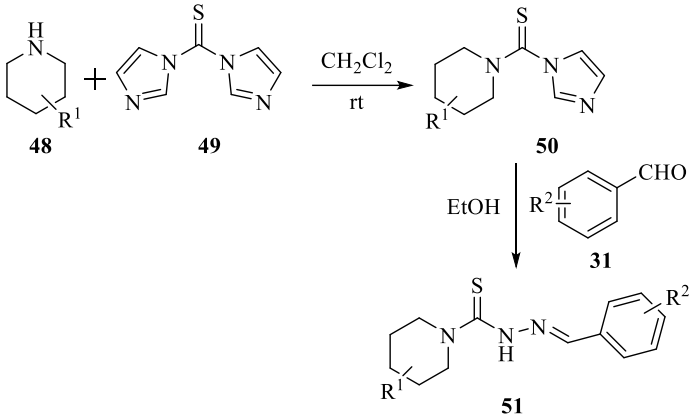
Scheme 4. Synthesis of piperidine-containing aza-bridged products and substituted piperidines.



Scheme 5. Rapid entry into substituted piperidine.

Compound **52** shows great activities against *Gaeu-mannomycesgraminsis, Pythium aphanidermatum*, *Rhizoctoniasolani*, and *Valsamali*with EC50<10 µg/mL (Figure 3).

Diastereoselective preparation of polysubstituted *N*-hydroxypiperidines was performed by intramolecular reductive cyclization of monoxime of the 1,5-diketone **54**, produced from 2-(cyclohexylthio)-1-phenyl-ethanone and arylaldehyde by $NaBH_3CN$ (Scheme 7) [50]. The main product *N*-hydroxypiperidine **55** was found as a racemate of a single diastereomer.



Scheme 6. Synthesis of thiosemicarbazide derivatives containing piperidine fragments.

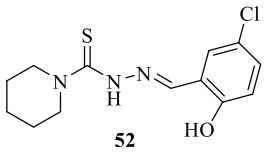
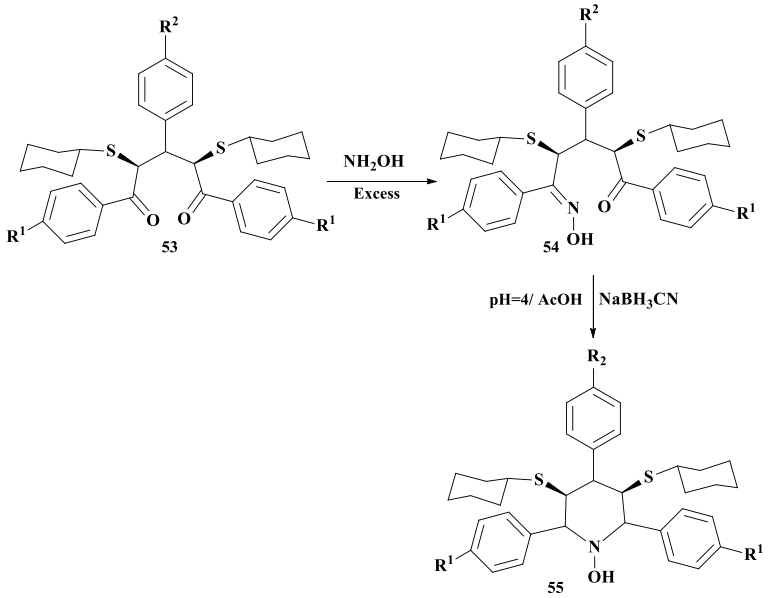


Figure 3. Chemical structure of compound **52.**



Scheme 7. Preparation of polysubstituted *N*-hydroxypiperidine analogs.

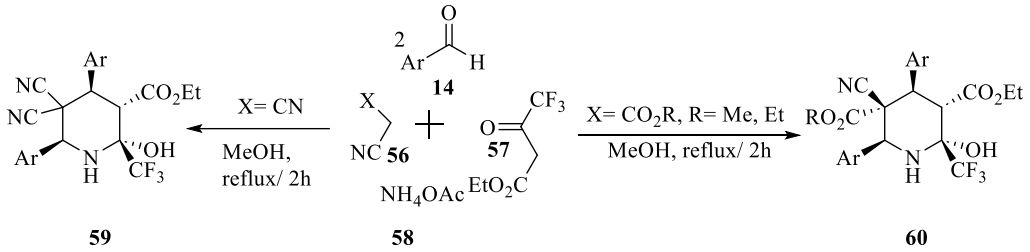
In subsequent investigations, one-step five-component cyclization cascade reaction of aldehydes **14**, cyano-containing C-H acids **56**, ethyl4,4,4-trifluoro-3-oxobutanoate **57**, and NH_4OAc **58** for highly stereoselective construction of 2-hydroxy-2-trifluoromethylpiperidine analogs with four stereogenic centers **59** and five stereogenic centers **60** was reported by Iliyasov *et al.* (Scheme 8) [51].

In 2007, Li and Wang [52], conducted the synthesis of propargylamines **63** by a Mannich ternary reaction of terminal alkyne **61**, amine **62**, and aldehyde, by C–H activation. The reaction was catalyzed bysilica-supported copper (Scheme 9).

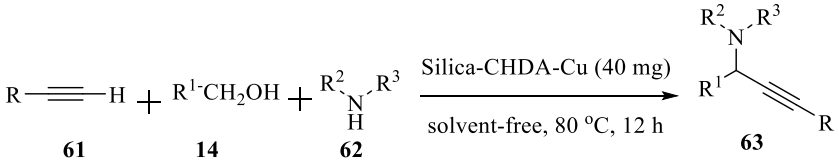
Babaei *et al.* [53], used magnetically recyclable silver nanocatalyst (AgMNPs) for the clean preparation of propargylamines **65** in a one-step condensation of aldehyde and secondary amines (such as piperidine, and terminal alkyne **64**) to produce various propargylamines (Scheme 10).

The nanocatalyst was simply regenerated by an external magnet and utilized in 10 consecutive cycles without a meaningful reduction in its activity.

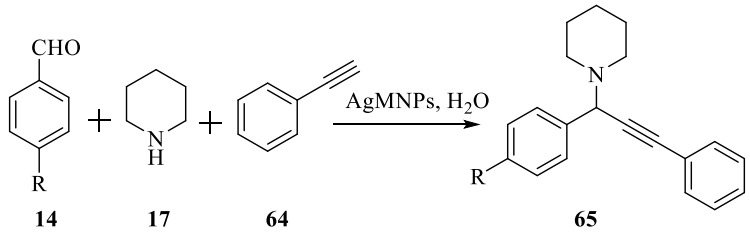
In addition, propargylamine analogs bearing a quaternary carbon center via KA^2 coupling were catalyzed by Cu-doped ZIF-8 [54]. Most favorable reaction conditions were observed under the neat conditions at 120 °C using10 mg catalyst (Scheme 11).



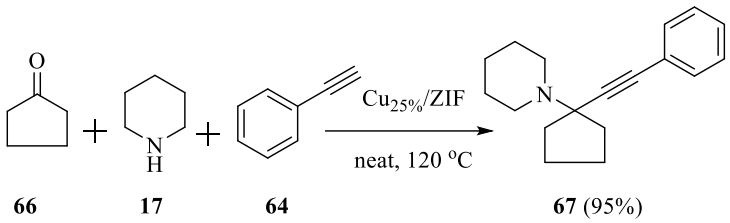
Scheme 8. Construction of polysubstituted 2-hydroxy-2-trifluoromethylpiperidine analogs.



Scheme 9. Preparation of propargylamines via silica-CHDAScheme-Cu.



Scheme 10. Preparation of propargylmine analogs by AgMNPs.



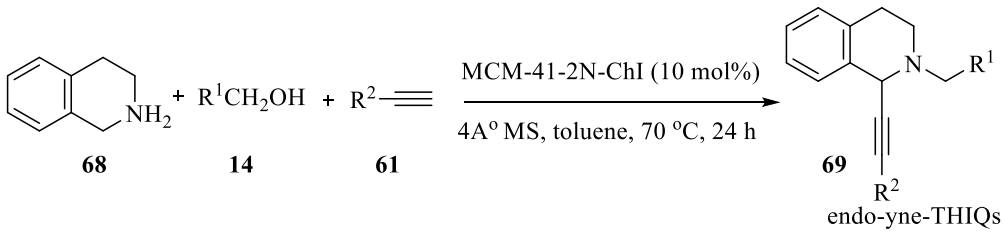
Scheme 11. Construction of propargylamine 48 via KA^2 coupling catalyzed via Cu dopped ZIF-8.

Zhao *et al.* [55], prepared 3-(2-aminoethylamino)propyl-immobilized MCM-41-immobilized copperI) complex [MCM-41-2N–CuI]. It was applied as a heterogeneous copper-catalyzed compound for one-pot coupling of tetrahydroisoquinoline, 1-alkynes, and aldehydes (Scheme 12).

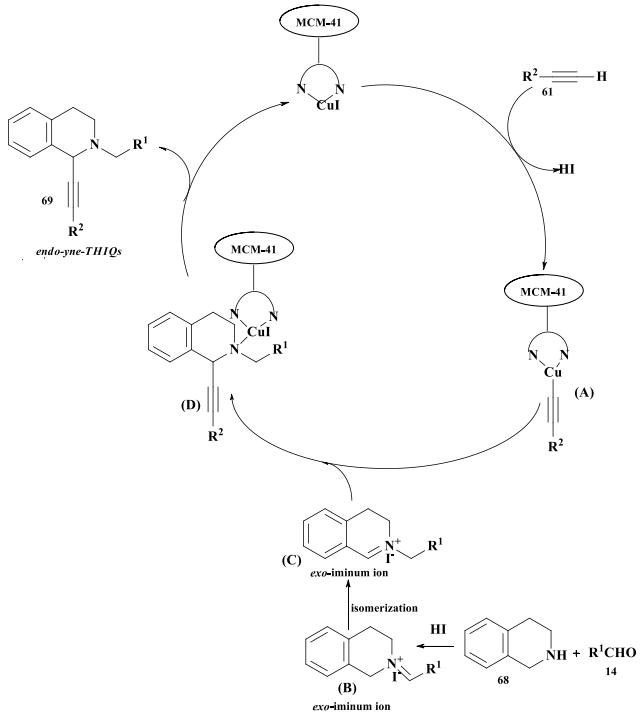
A probable mechanism for the one-pot reaction of tetrahydroisoquinoline **69**, aldehydes **14**, and terminal alkynes **61** catalyzed by heterogeneous copper is shown in Scheme 13. The reaction of MCM-41-2N–CuI with alkyne **61** along with the HI liberation produces an MCM-41-supported copper acetylide intermediate (**A**).

In the existence of HI and 4Å molecular sieves, tetrahydroisoquinoline **69** experiences a condensation reaction with aldehyde **14** and generates an exo-iminium ion (**B**), and then it isomerizes into an endo-iminium ion (**C**) and reacts with the MCM-41-supported copper acetylide intermediate (**A**) to generate a coordinated saturated intermediate (**D**).

Ultimately, the lately produced intermediate (**D**) dissociates a nitrogen ligand to provide the endo-yne-THIQ **50** and reproduce the MCM-41-2N–CuI complex [47]. The reaction affords various C1-alkynylated THIQ analogs with good to excellent yields and is suitable for a broad range of different aldehydes and 1-alkynes. This new method demonstrated the competitiveness of catalyst recycling without activity loss. This catalyst can be regenerated by simple filtration and recycled at least 10 times.



Scheme 12. Preparation of endo-yne-THIQs by copper-catalyzed one-pot coupling reaction.

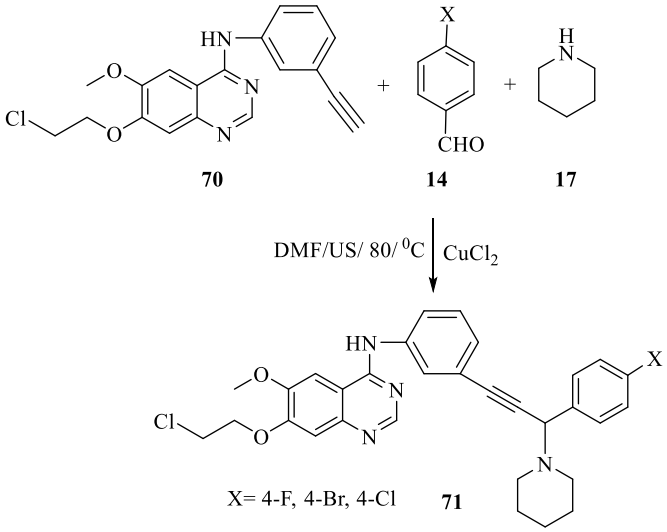


Scheme 13. A mechanism for the copper-catalyzed one-pot coupling reaction.

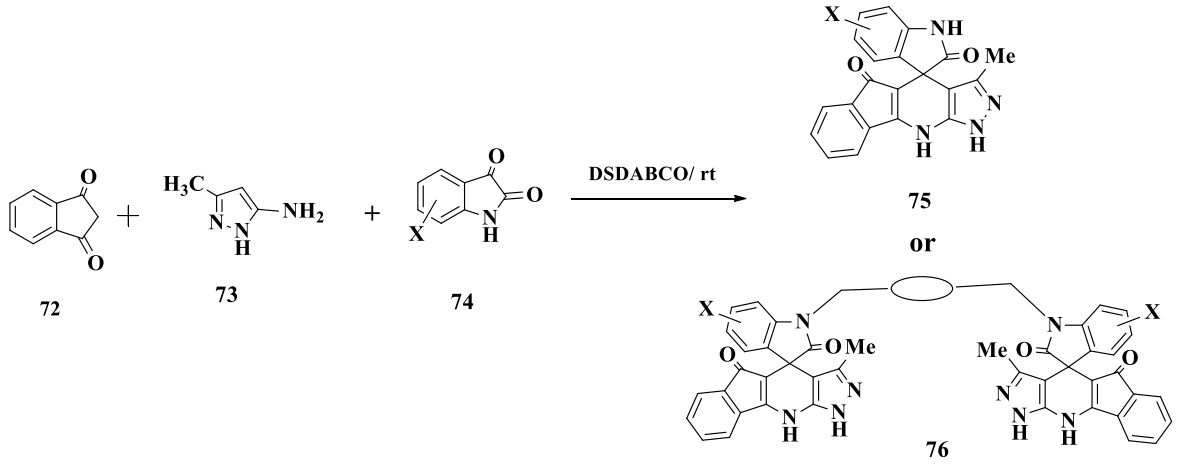
Azmian Moghadam and Mokhtary synthesized new polysubstituted propargylamine analogs **71** having both quinazoline building block and propargylamine scaffolds in good to excellent yields via one-step reaction of 7-(2-chloroethoxy)-*N*-(3-ethynylphenyl)-6-methoxyquinazolin-4-amine **70**, aromatic aldehydes, and pipiridine using $CuCl_2$ in DMF under ultrasound irradiation at 80 °C (Scheme 14) [56].

Nikpassand and Zare Fekri produced mono **75** and bis pyrazolopyridines **76** using of disulfo-1,4-diazoniabicyclo[2.2.2]octane chloride (DSDABCO) from isatin analogs **72**, indanedione **73** and 3-methyl-5-aminopyrazole **74** ionic liquid (Scheme 15) [57].

Esan *et al.* studied the corrosion inhibitive potentials of some amino acid analogs of 1,4-naphthoquinone by density functional theory through calculating their electronic activities and reactivity descriptors. The energy band gaps suggested that molecules **77** and **78** would react better compared with that of the other molecules. Therefore, their ability to shield metals' surface from rusting is better than others [58].



Scheme 14. Synthesis of highly functionalized quinazolines.



Scheme 15. Construction of spiro-pyrazolopyridine analogs by ionic liquid DSDABCO.

A catalyst-free, and environmentally benign, has been developed for the efficient preparation of 3,3-(piperidin-1-ylmethylene)bis(4-hydroxy-2*H*-chromen-2-one) **81** using one-step three-component condensation of 4-hydroxycoumarin **79**, piperidineine **34** and glyoxalic acid **80** in water under reflux condition. In this green synthetic procedure, the water catalyzed the reaction through hydrogen bonding (Scheme 16) [59].

Design and synthesis of substituted piperidine derivatives with anti-Alzheimer and anti-cancer activities

Meena *et al.* [60], synthesized piperidine derivatives **86** as multi-targeted agents to treatAlzheimer's (Scheme 17). The *in vitro* investigations demonstrated that most of the prepared analogs mainly inhibit butyrylcholinesterase (BuChE) and acetylcholinesterase (AChE) with IC_{50} values in the range of low-nanomolar, and are more effective than Donepezil as a reference compound. Among them, inhibitor **86a** strongly inhibited AChE with IC_{50} value of 2.13 nM, and compound **86a** was highly selective for AChE (~38-fold).

Furthermore, both the docking study and the kinetic analysis of AChE inhibition showed that **86a** simultaneously binds to the peripheral anionic site and catalytic active site of AChE. Aiming to optimize the interaction of the prepared compounds with peripheral and catalytic binding sites of AChE, benzyl substituted piperidine and the position of the electron-rich substituents on the benzyl group was varied. Most of the target compounds inhibited both ChEs showing IC_{50} values in the nanomolar range. **86a** (Figure 5) was introduced as a promising lead compound for Alzheimer's disease drugs.

Also, Hu *et al.* [61], prepared 2-styryl-5-hydroxy-4-pyrone analogs **92** as multiple functional agents with the treatment potential of Alzheimer's (Scheme 18).

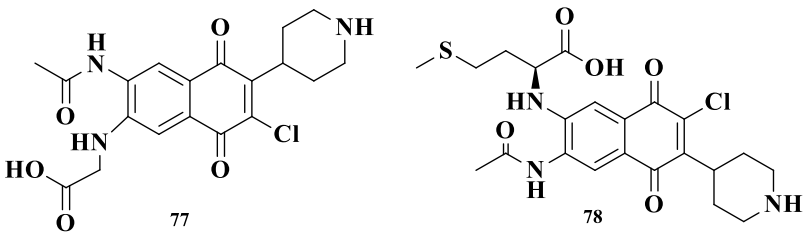
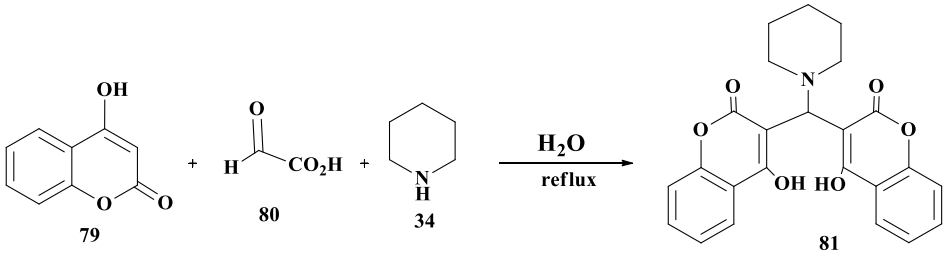
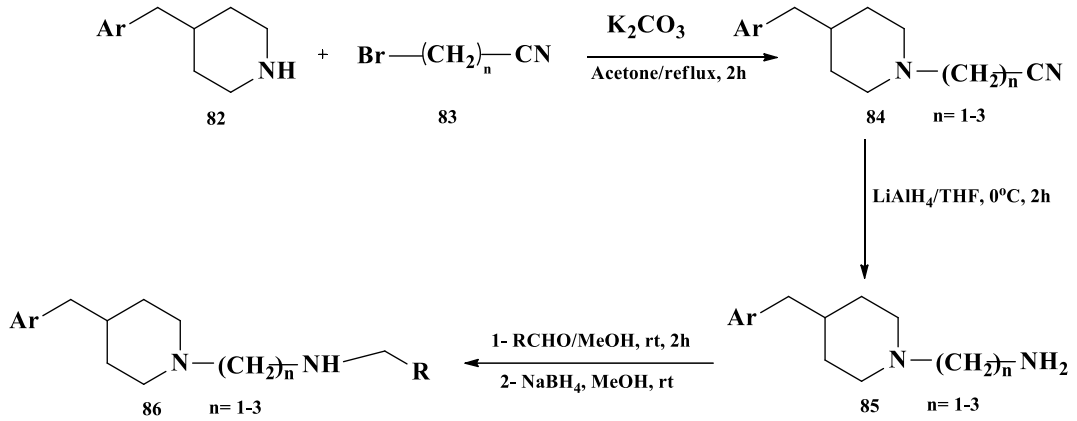


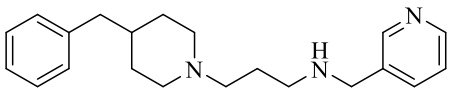
Figure 4. Chemical structure of compounds **77** and **78.**



Scheme 16. Preparation of 3,3-(piperidin-1-ylmethylene)bis(4-hydroxy-2*H*-chromen-2-one).

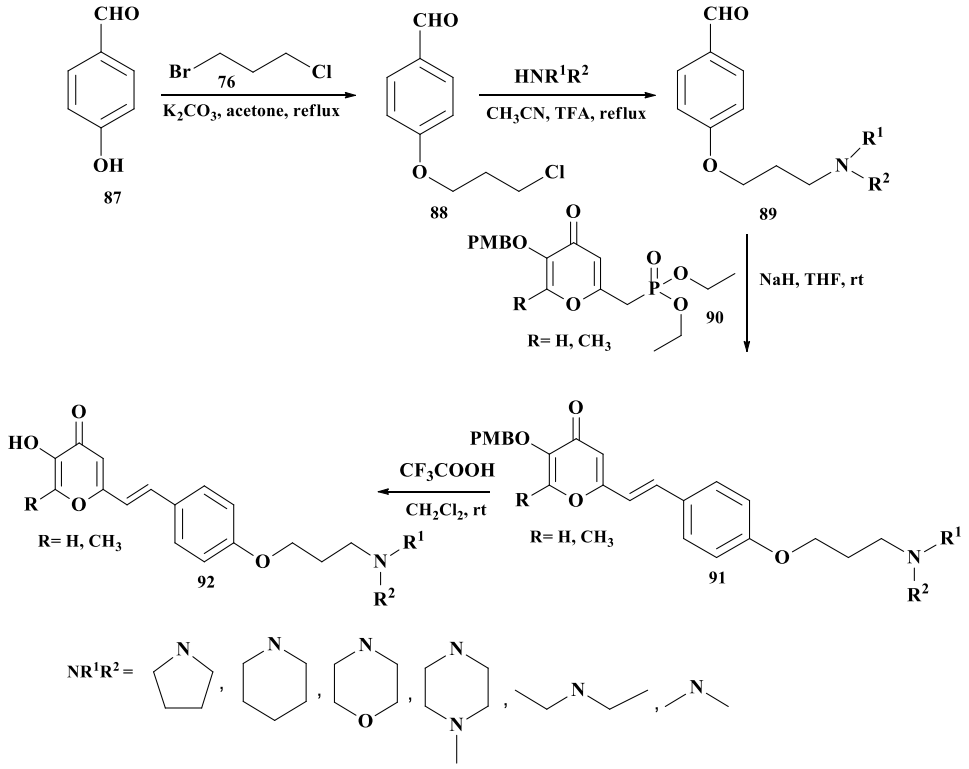


Scheme 17. Synthesis of substituted piperidine derivatives with anti Alzheimer's disease activity.



86a

Figure 5. Chemical structure of compound **86a.**



Scheme 18. Synthetic pathway to 2-styryl-5-hydroxy-4-pyrone analogs.

Compounds **92a** and **92b** (Figure 6) had nanomolar IC_{50} values on H_3 receptor antagonism, more potent $ABTS^{\bullet+}$ scavenging property than Trolox, very good metal ion chelating capability, Cu^{2+}-induced aggregation inhibitory properties, and efficient Aβ self-

aggregation. They also had disaggregation properties against Aβ self/Cu^{2+}-induced aggregation.

In addition, Youssef *et al.* [62], introduced *N*-substituted-piperidine analogs **98** as anti-Alzheimer agents (Scheme 19). According to their research, the ability of derivatives including nipecotic acid building blocks was served in the design of *N*-benzyl-piperidine linked multipotent molecules to treat Alzheimer's disease. Compound **98a** demonstrated high free radical scavenger property with 99.51% inhibition value. The Carbamoylpiperidine derivatives were proposed as multi-targeted drugs to combine AChE inhibition and with antioxidant activity, more active analogs were obtained as a new anti-Alzheimer compound. Furthermore, compound **98b** had high free radical scavenger property with 95.58% inhibition value.

Seth *et al.* [63], synthesized some piperidine-3-carboxylic acid analogs **103** with the potential of anticonvulsants (Scheme 20).

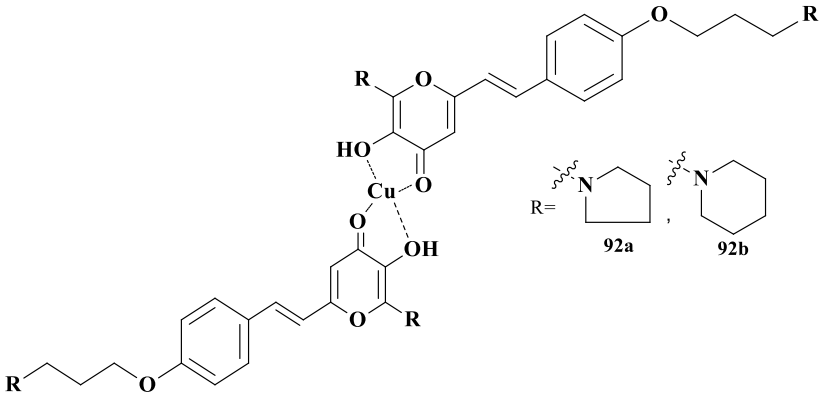
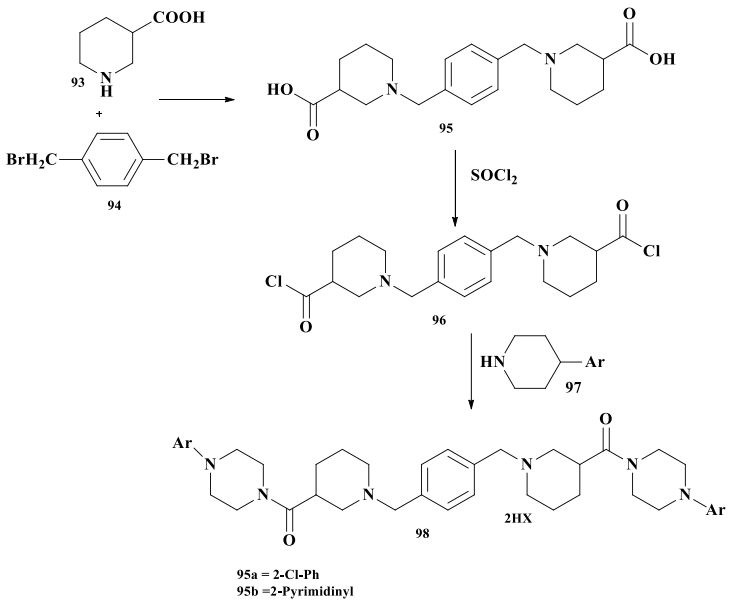
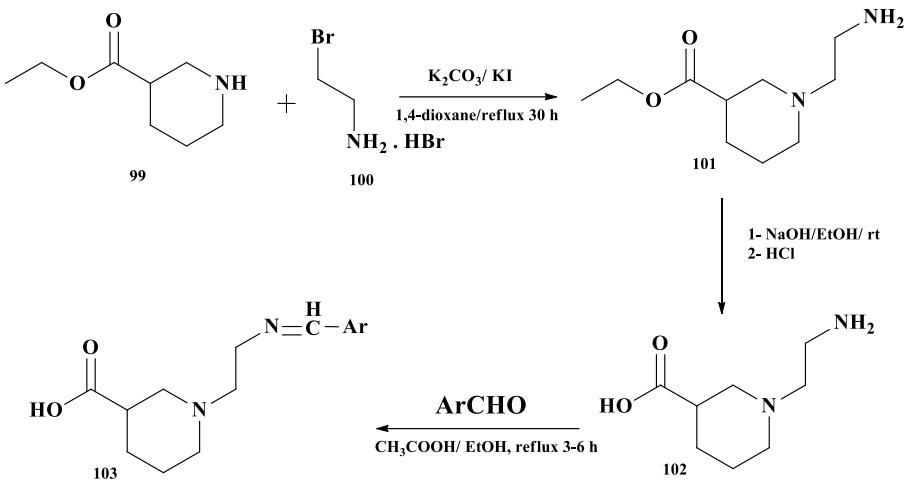


Figure 6. Probable chelation modes of compounds **92a** and **92b** with Cu^{2+}.



Scheme 19. Synthesis of *N*-substituted-piperidine analogs as anti-Alzheimer agents.



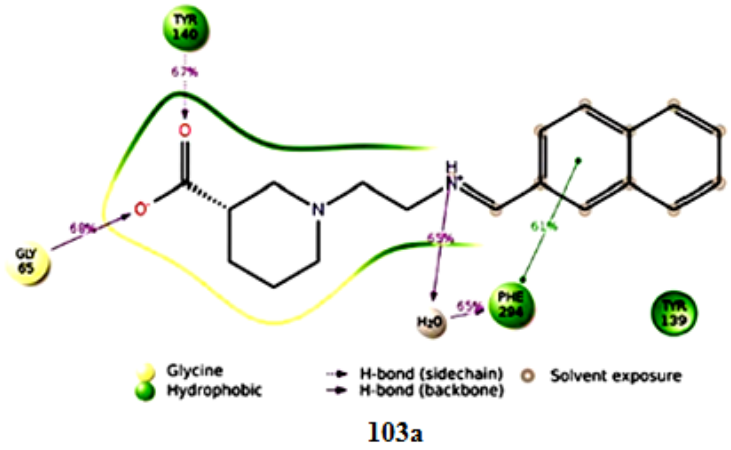
Scheme 20. Synthesis of piperidine-3-carboxylic acid analogs.

The prepared analogs were considered for *in vitro* blood-brain barrier (BBB) permeability by parallel artificial membrane permeability BBB method. Dynamics simulations and *in silico* molecular docking were performed on the homologous protein of human GABA transporter 1 (GAT-1), showing perfect interactions of compound **103a** in the active binding site (Figure 7).

Various tetrahydroisoquinoline analogs **109** (Scheme 21) were prepared. They had proper activity versus three ABC transporters of P-gp, BCRP, and MRP1 [64].

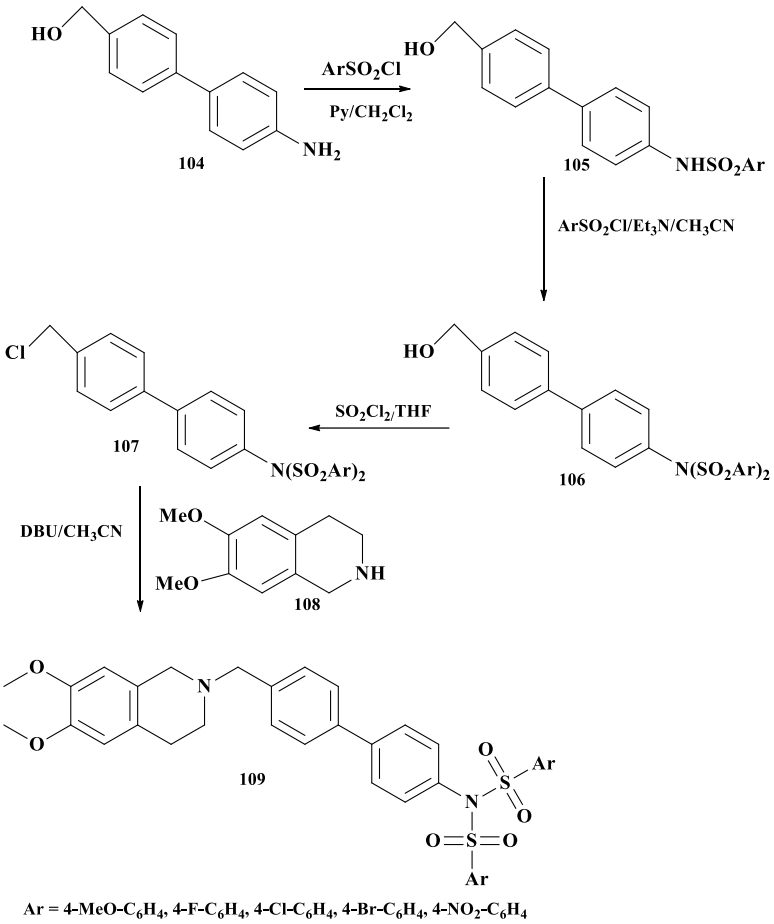
The synthesized compounds had selectivity against *P*-gp. One of the compounds, **109a** (Figure 8), showed property in the nanomolar range (EC50 ¼ 94 nM). Therefore, *N*-{4'-[(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)methyl]-[1,1′-biphenyl]-4-yl}-4-methoxy-*N*-(4-methoxy benzenesulfonyl)benzene-1-sulfonamide **109a** was experienced to examine its ability to restore the cytotoxic activity of a recognized anti-cancer agent, *P*-gp substrate, and doxorubicin, as a first proof of concept. In addition, compound **109a** was verified in an in vitro model of competent gastro-intestinal barrier (Caco-2 cells) to determine its ability to inhibit *P*-gp, present on the luminal side, and augmentthe apical-to-basolateral transport of some structurally uncorrelated drugs, belonging to various therapeutic areas but actively was excreted by *P*-gp. Significantly, the transport of the drugs across the gastro-intestinal barrier was augmented by a concentration of **109a** devoid of toxicity as well as without detrimental influences on barrier function. Due to its molecular mechanism of action, it was effective in restoring the cytotoxic activity of Doxorubicin. Furtehrmore, it was reported that it increased the efficacy of chemotherapeutic drugs in *P*-gp-expressing tumors.

Xu *et al.* [65], synthesized magnolol-based Mannich base derivatives **112** (Scheme 22) and evaluated their anticancer properties against the panel of human tumor cell lines (A549, T47D, Hela, and MCF-7) by the MTT method. The mechanism study showed that the analog**112a** (Figure 9) well-inhibited cancer cells by inducing autophagy. Among all derivatives, compound **112a** showed the strongest antiproliferative property against MCF-7,T47D, and Hela cell lines with IC_{50} values of 3.32,0.91, and 1.71 mM, respectively. The study of the mechanism showed that the derivative **112a** well inhibited cancer cells by inducing autophagy.



103a

Figure 7. Interactions of compound **103a** with the main active amino acid residues containing GABA GAT-1 (PDB code:4XP4).



Scheme 21. Synthesis of tetrahydroisoquinoline derivatives.

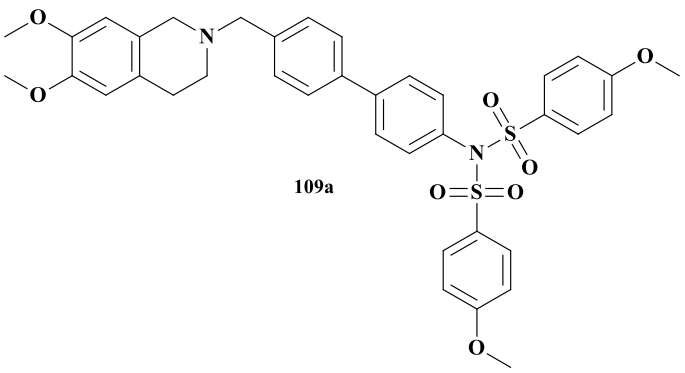
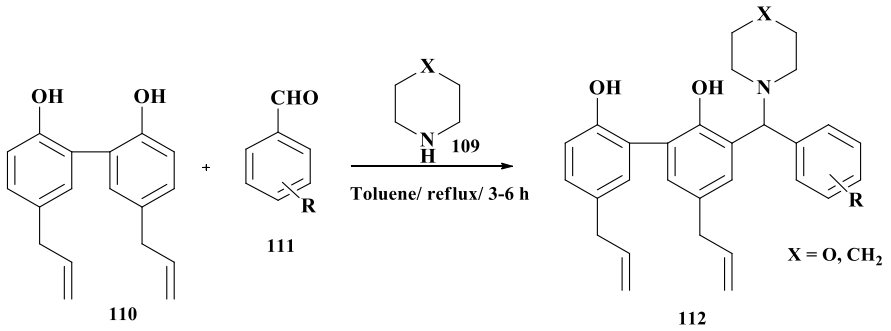


Figure 8. Chemical structure of compound **109a.**



Scheme 22. Synthetic pathway of magnolol-based Mannich base analogs.

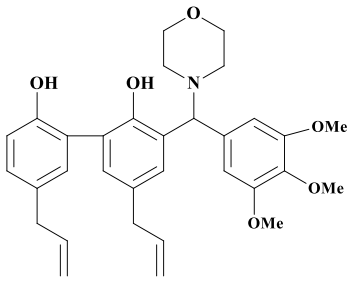
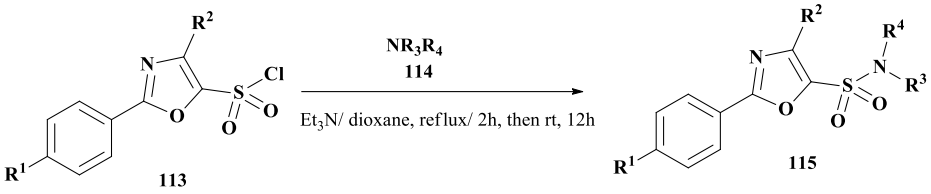
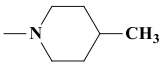
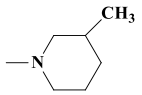
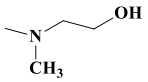
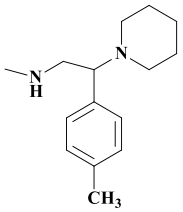


Figure 9. Chemical structure of compound **112a**

Kachaeva *et al.* [66], prepared some piperidine-substituted sulfonamides **115** as potent anticancer agents (Table 1). The highest anticancer property of compounds **115d** and **115e** was due to the existence of the piperidine ring including the methyl group on positions 3 or 4 in their structure. The lower antitumor property of compound **115** compared to compounds **115d** and **115e** was also noteworthy. The compound **115g** contained a piperidine ring analogs to compounds **115d** and **115e**, but it was located at a larger distance from the sulfonamide group and did not have any methyl group.

Table 1. Synthesis of sulfonamides as inhibitors of tubulin-analogs E7010

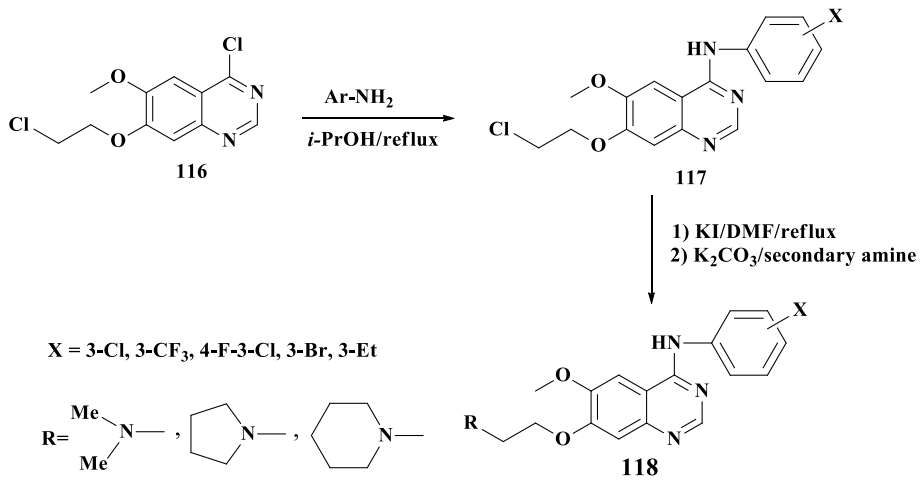


Compound	R_1	R_2	NR_3R_4
113a	H	CN	-
113b	CH_3	CN	-
113c	H	$COOCH_3$	-
113d	H	CN	
113e	H	CN	
113f	CH_3	CN	
113g	H	CN	

Naziri *et al.* reported novel substituted quinazoline analogs **118** by the reaction of *N*-arylquinazoline-4-amine **117** and secondary amines such as piperidine, pyrrolidine, and dimethylamine. MTT technique was utillized to study the cytotoxicity of all prepared quinazoline analogs on A431 (human carcinoma cell) and HU02 (foreskin fibroblast) cell lines. The results showed that compared to Erlotinib as positive control, the highest cytotoxic activity with IC_{50} equal to 1.21 μM belonged to compound **118a** (Figure 10) contaning piperidine with 3-chloroaniline. The authors suggested that the reasons for the highest cytotoxic property of compound **118a** can be attributed to the greater flexibility and lipophilicity of the piperidine (Scheme 23) [67].

Synthesis of piperidine derivatives with antioxidant properties

Piperidine derivatives have also been evaluated for their antioxidant activities by a number of researchers. Harini *et al.* [68] reported the antioxidant property of piperidin-4-one oxime esters derived from vanillin **125**. Superior role of the phenyl ester substituents on the piperidin-4-one oxime core, by four-step reaction including Mannich condensation of vanillin, acetone, and ammonium acetate to obtain compound **122** followed by *N*-methylation and oximation was observed (Scheme 24). Compounds **125a** and **125b** are better antioxidants compared to standard butylated hydroxy anisole (BHA) (Figure 11).



Scheme 23. Synthesis of substituted quinazoline analogs

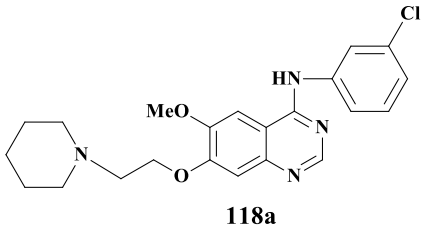
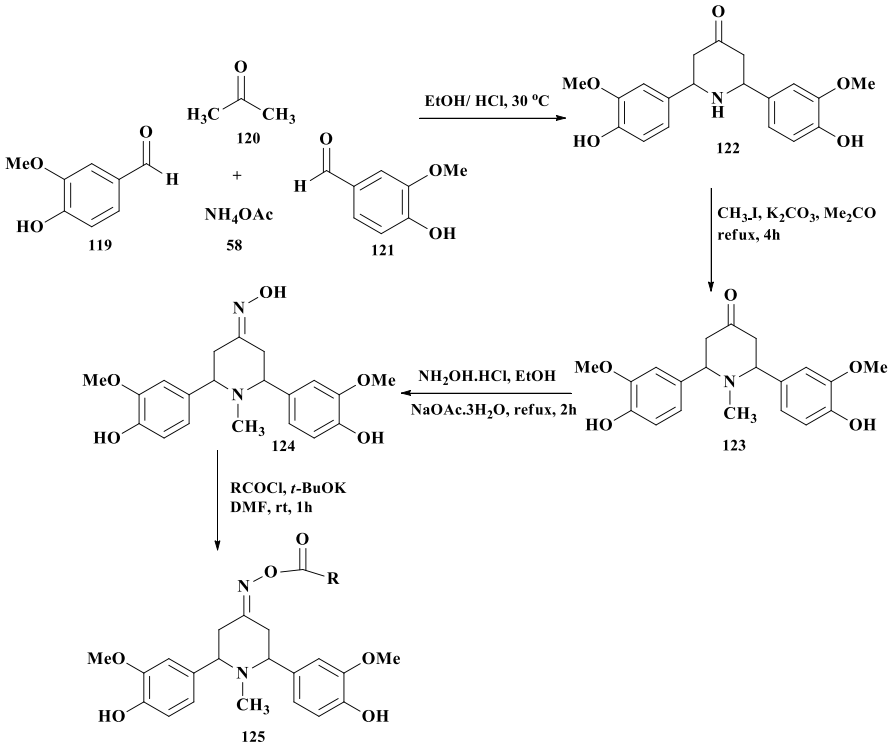


Figure 10. Chemical structure of compound **118a.**



Scheme 24. Synthetic pathway of vanillin-derived piperidin-4-one oxime esters.

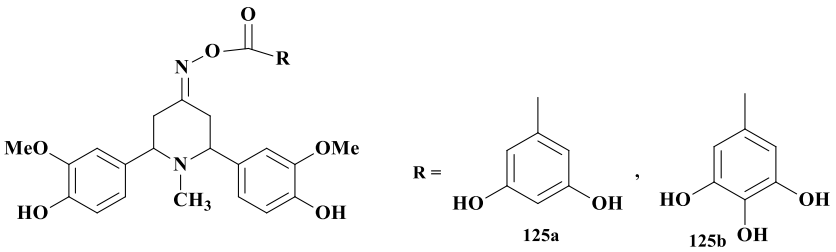
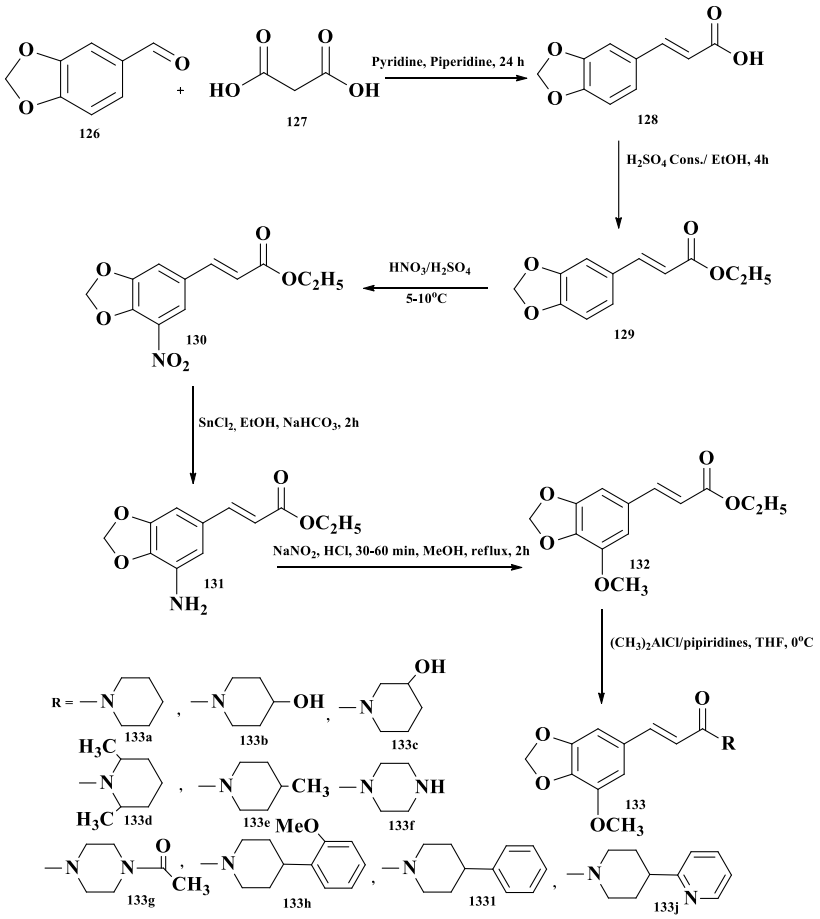


Figure 11. Chemical structure of compounds **125a** and **125b.**

A series of piperamide derivativs **133** were prepared and their potential for antimicrobial, antioxidant, and antidepressant properties was tested (Scheme 25) [69]. Results showed that out of ten prepared piperamide analogs, six compounds had antidepressant properties with forced swimming and tail suspension tests. Meantime compounds **133a**, **133b**, and **133c** inhibited mouse brain MAO-A and MAO-B properties. The antioxidant property of these compounds was due to their hydrogen radical or electron releasing ability to DPPH and producing stable diamagnetic molecules. This might be the reason for the better antioxidant property of the above compounds. Compounds containing MeO and OH groups were comparatively more active. For example, compounds **133b** and **133c** (OH derivative) were more active than **133h** (MeO derivative). **133b** and **133c** displayed a significant difference in radical scavenging property owing to having a OH group at various positions.



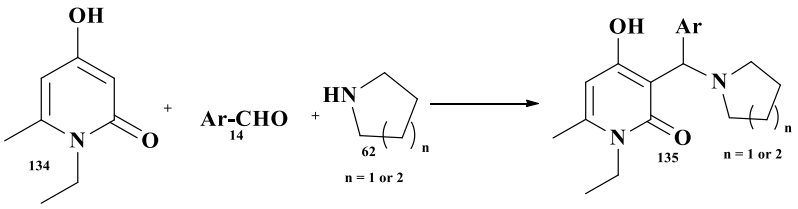
Scheme 25. The reaction pathway for the preparation of new piperamide analogs.

Kamali *et al.* [70] developed a class of 4-hydroxy-2-pyridones **135** by reaction of 1-ethyl-4-hydroxy-6-methylpyridin-2-one **134**, an aromatic aldehyde and a secondary amine under solvent-free conditions in the absence of catalyst at room temperature (Scheme 26), and then the antioxidant property of the prepared compounds was studied by DPPH radical scavenging procedure. Overall, all products showed significant radical scavenging potential and compound **135a** showed the highest scavenging activity on DPPH (Figure 12).

Karaman *et al.* [71] derived benzoyl hydrazones from compound **141** and compound **144** (Scheme 27). The antioxidant property of this compound was studied. The results indicated that compounds **142g** and **145h** had higher lipid peroxidation inhibitory capacity than other compounds. In the DPPH˙ scavenging method, compounds **142e**, **142f**, **145a**, **145e**, and **145h** showed better activity than standard BHT, though, in $ABTS^{+\cdot}$ scavenging assay, compounds**142f** and **145h** exhibited better activity.

Kim *et al.* [72] synthesized substituted piperidines enantioselectively to study their antioxidant capacity (Scheme 28). The substituted piperidines containing TEMPO **150** and a especially proximal hydroxy group **154** and **155** indicated suitable antioxidant properties. The authors suggested that TEMPO produced from the homolysis of the C-ON bond of substituted piperidines functions acts as a radical-scavenging entity. The OH group of piperidine analogs showed a synergistic influence on antioxidant properties.

Siddiqui *et al.* [73] synthesized 2,6-diphenylpiperidine-4-one compounds (**157a** and **157b**) and their imine analogs (**158a**, **158b**, **159a**, and **159b**) (Scheme 29). Compounds **159a** and **159b** were synthesized using Mannich condensation reaction. Compound **157b** showed better antioxidant properties (IC_{50} 1.84±0.15µg/mL) in comparison with standard ascorbic acid (IC_{50}1.65± 0.16µg/mL).



Scheme 26. Synthesis of 4-hydroxy-2-pyridone derivatives.

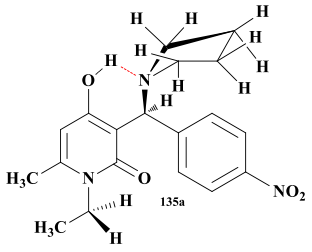
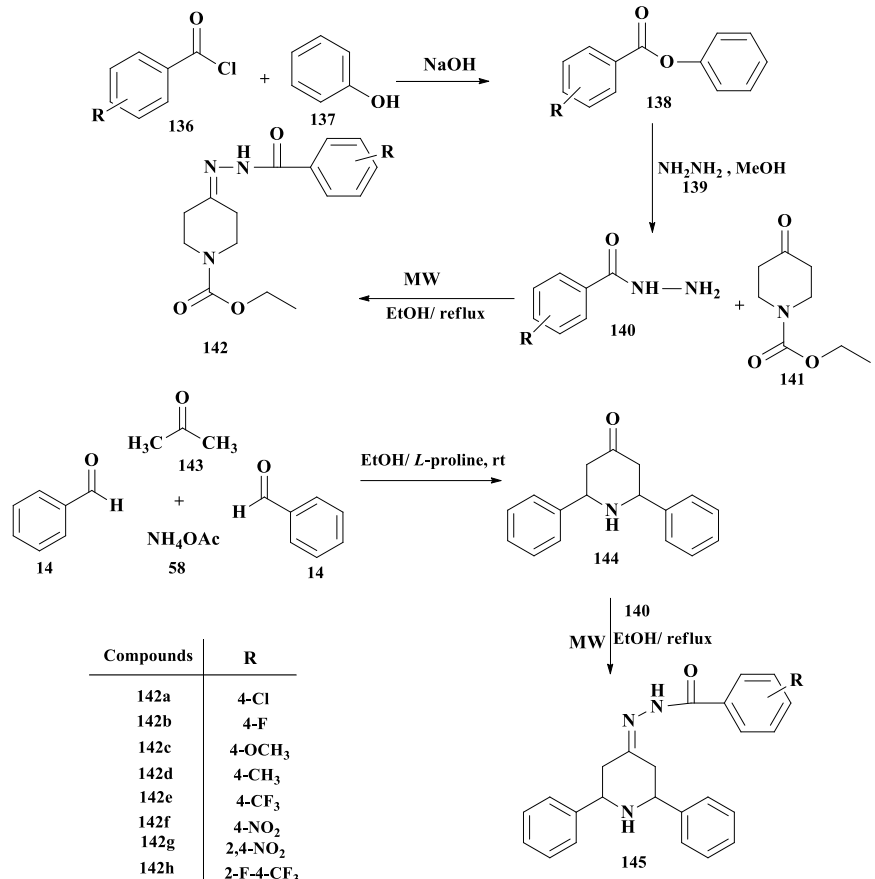


Figure 12. Chemical structure of **135a.**

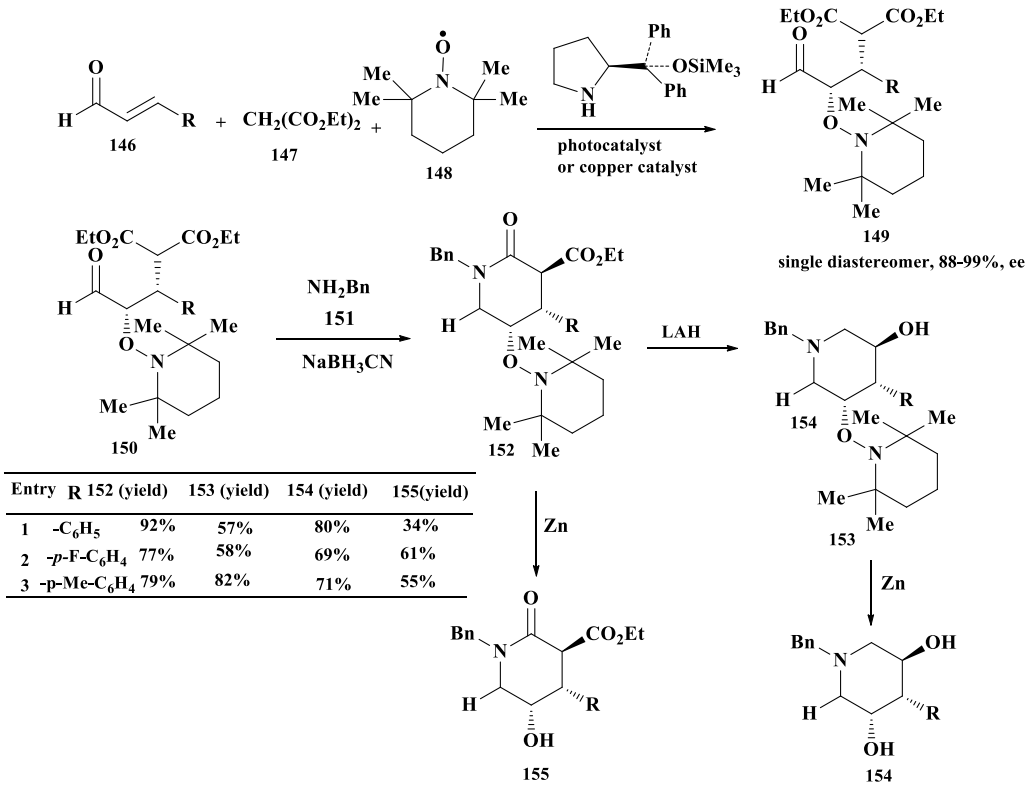


Compounds	R
142a	4-Cl
142b	4-F
142c	4-OCH_3
142d	4-CH_3
142e	4-CF_3
142f	4-NO_2
142g	2,4-NO_2
142h	2-F-4-CF_3
142i	4-F-2-CF_3
145a	H
145b	4-Cl
145c	4-F
145d	4-OCH_3
145e	4-CH_3
145f	4-CF_3
145g	4-NO_2
145h	2,4-NO_2
145i	2-F-4-CF_3
145j	4-F-2-CF_3

Scheme 27. Synthetic pathway of 4-substituted phenylbenzoyl hydrazones.

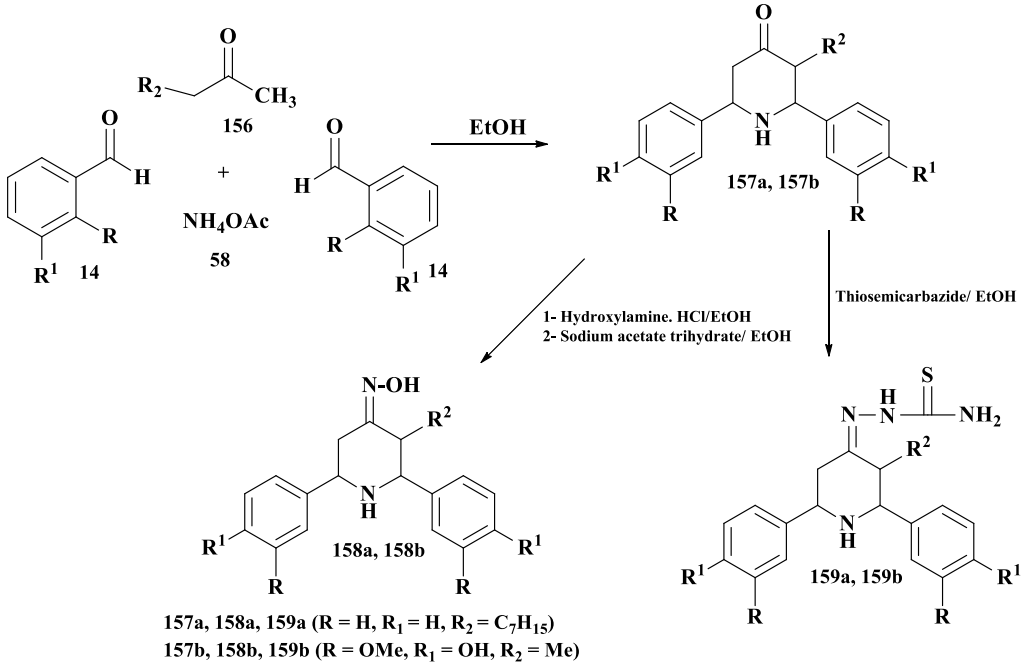
Guo *et al.* [74] synthesized a series of Mannich bases, 4-(aminoalkyl)-6-allyl-sesamols **161** from sesamol **160**, benzaldehydes **14**, and piperidine/morpholine **62** by a single-pot reaction (Scheme 30). Antioxidant procedures proved that the sesamolanalog **159a** exhibited very good antioxidant properties (Figure 13).

Mahooti *et al.* [75] described the single-step preparation and antioxidant activities of highly substituted piperidine analogs in the existence of choline chloride/urea at 80 °C (Scheme 31). In this study, a simple pseudo-four-component reaction of aldehydes, 2,7-naphthalenediol, and ammonium carboxylates was carried out to generate a series of non-acylated and *N*-acylated piperidine analogs. The prepared highly substituted piperidine analogs were screened for their antioxidant capacities. It was concluded that the substituted piperidine compound **164a** (Figure 14) has higher antioxidant activity.

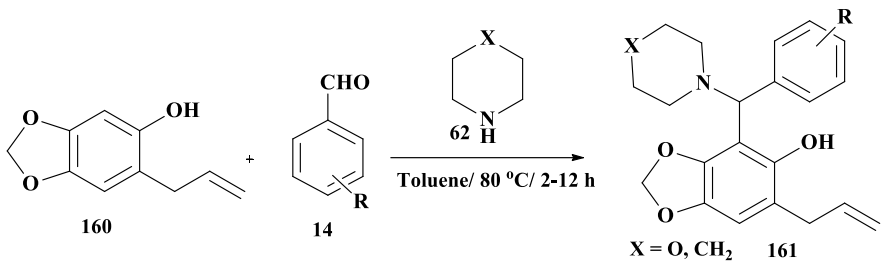


Entry	R	152 (yield)	153 (yield)	154 (yield)	155(yield)
1	-C_6H_5	92%	57%	80%	34%
2	-*p*-F-C_6H_4	77%	58%	69%	61%
3	-p-Me-C_6H_4	79%	82%	71%	55%

Scheme 28. Preparation of 3,4,5-trisubstituted piperidine analogs.



Scheme 29. Synthetic scheme of 2,6-diphenylpiperidine-4-ones and their imine analogs.



Scheme 30. Synthetic sequences of Mannich bases, 4-(aminoalkyl)-6-allyl-sesamols.

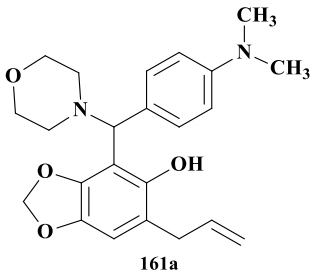
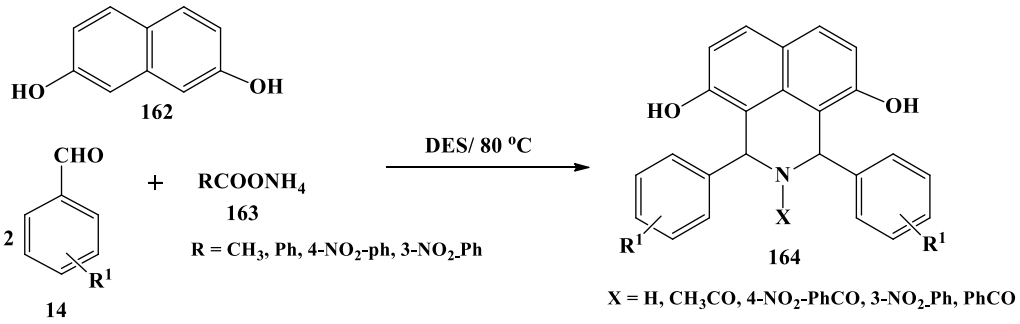


Figure 13. Structure of compound **161a.**



Scheme 31. Synthesis of highly substituted piperidine analogs.

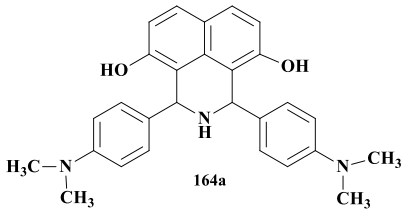
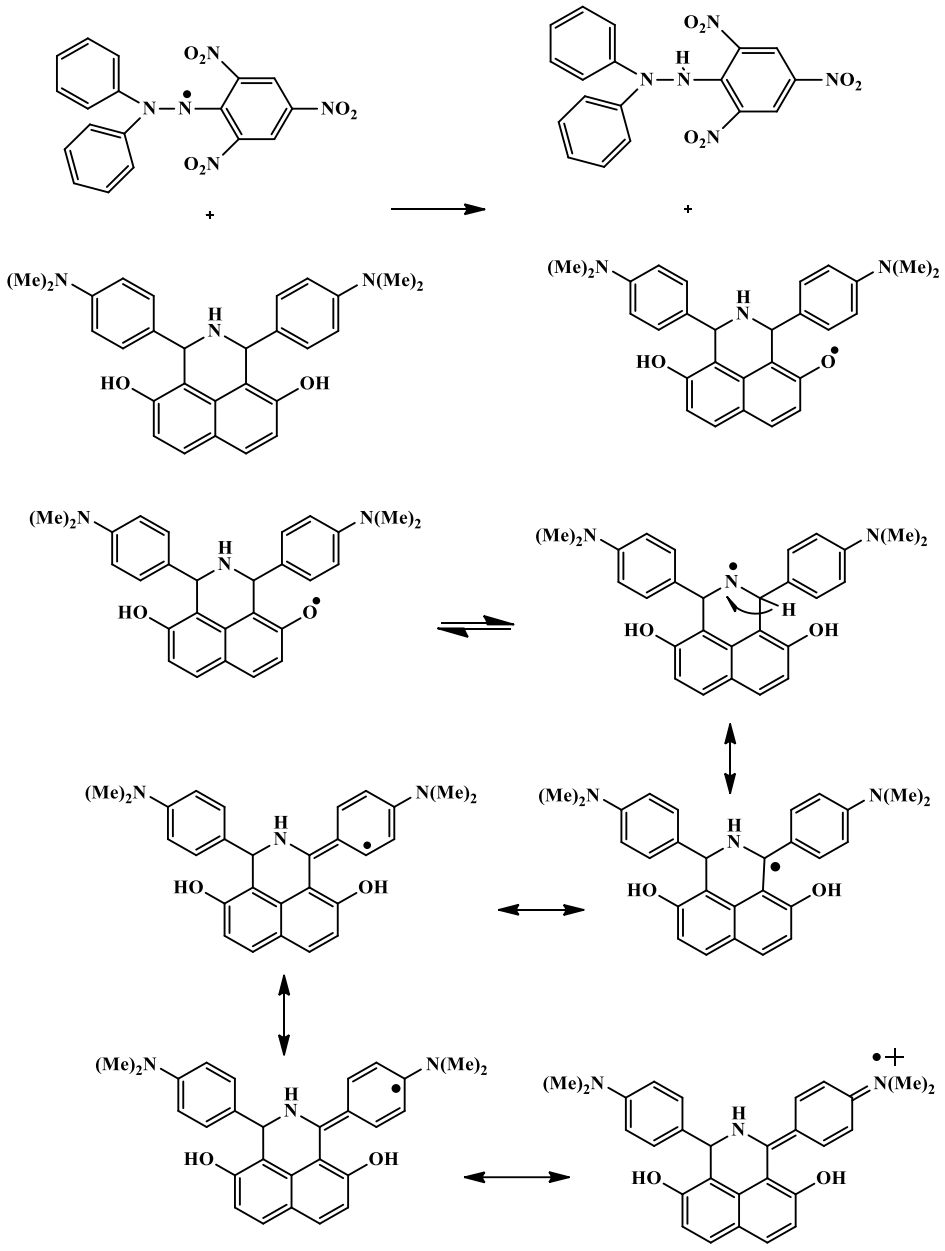


Figure 14. Structure of compound **164a.**

The high antioxidant capacity of **164a** was due to the existence of the electron donating group $N(CH_3)_2$ in the aromatic ring. The benzylic hydrogen of the pyridine ring easily donated hydrogen radicals to DPPH and formed a more stable radical (Scheme 32).



Scheme 32. Proposed antioxidant mechanism of compound **164a.**

Conclusion

The present review summarizes recent advances in the preparation of highly substituted piperidine compounds that have varying degrees of antioxidant and anti-Alzheimer properties and free radical scavenging activity. The antioxidant activities are directly proportional to the percentage of scavenging activity while inversely proportional to the IC_{50} value. The piperidine scaffold acts as a substantial function in the inhibitory activity of compounds, and thus is very important in influencing biological properties. This review clarifies broad information on piperidine as a versatile building block with potential properties. Furthermore, it may increase the interest of researchers who wish to prepare various piperidine analogs for the development of lead molecules as an effective drug.

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Disclosure statement

The authors declare that they have no conflict of interest

Orcid

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