

Synthesis of Metal Complexes of Phenelzine Derivatives

Md. Tanvir Alam* and Anil Kumar#

*Research Scholar, University Department of Chemistry, B.N. Mandal University Madhepura

#Associate Professor, University Department of Chemistry, B.N.Mandal University Madhepura

Email : tanvirkhan0000786@gmail.com

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Abstract : Phenelzine, a non-selective monoamine oxidase inhibitor (MAOI), is widely used for treating major depressive disorder and anxiety due to its ability to increase monoamine neurotransmitter levels by irreversibly inhibiting monoamine oxidase enzymes (MAO-A and MAO-B). However, its clinical utility is constrained by adverse effects, including hepatotoxicity, hypertensive crises from dietary tyramine interactions. This abstract reviews recent advancements in the development of phenelzine derivatives, focusing on their chemical synthesis, pharmacological profiles, and potential to address these limitations. Structurally, phenelzine serves as a scaffold for modifications primarily at the hydrazine moiety and phenyl ring. Derivatives incorporating electron-donating (e.g., methoxy, methyl) or electron-withdrawing (e.g., fluoro, chloro) substituents on the phenyl ring have been synthesized to modulate MAO-A and MAO-B selectivity. Some analogs demonstrate enhanced MAO-A inhibition, crucial for antidepressant effects, while minimizing MAO-B activity to reduce off-target effects. Additionally, prodrug strategies have been explored to improve bioavailability and mitigate first-pass metabolism, enhancing therapeutic efficacy. Computational approaches, including molecular docking and structure-activity relationship studies, have guided the design of derivatives with optimized binding affinities and reduced toxicity. Despite these advances, challenges remain, as many derivatives retain irreversible inhibition, perpetuating risks of drug-food interactions. Preclinical evaluations indicate some compounds exhibit lower hepatotoxicity, yet clinical translation is hindered by safety and efficacy concerns. Analytical techniques, such as NMR, IR spectroscopy, and mass spectrometry, have been instrumental in characterizing these derivatives, confirming their structural integrity and purity. This work underscores the potential of phenelzine derivatives to deliver safer, more selective MAOIs for psychiatric disorders. Future research

should focus on developing reversible inhibitors, leveraging high-throughput screening, and conducting robust clinical trials to validate therapeutic benefits, ultimately bridging the gap between chemical innovation and clinical application.

(Keywords : Phenelzine, 2-phenylethylhydrazine, NMR, IR-spectroscopy, and mass spectrometry).

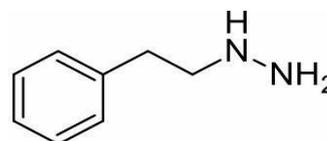
Introduction

Phenelzine, chemically designated as (2-phenylethyl)hydrazine or β -phenylethylhydrazine ($C_8H_{12}N_2$), represents a seminal hydrazine-based monoamine oxidase inhibitor (MAOI) in psychopharmacology. Introduced clinically in the 1950s, it has been a mainstay for managing treatment-resistant major depressive disorder (MDD), a typical depression, and anxiety disorders, particularly where selective serotonin reuptake inhibitors (SSRIs) prove inadequate¹. Its mechanism hinges on irreversible covalent binding to the flavin adenine dinucleotide (FAD) cofactor of monoamine oxidase enzymes (MAO-A and MAO-B), catalyzing the oxidative deamination of neurotransmitters such as serotonin (5-HT), norepinephrine (NE), and dopamine (DA). This inhibition elevates synaptic monoamine levels, fostering mood stabilization and anxiolysis². Structurally, phenelzine comprises a phenyl ring appended to an ethylhydrazine chain, conferring lipophilicity for central nervous system penetration. Administered as phenelzine sulfate, typical dosing initiates at 15 mg thrice daily, escalating to 45-90 mg/day, with therapeutic latency of 2-4 weeks due to enzyme resynthesis³. Beyond

MAO inhibition, phenelzine exhibits weak GABA transaminase inhibition, augmenting inhibitory neurotransmission, and trace amine-associated receptor 1 (TAAR1) agonism, potentially synergizing antidepressant effects⁴. Meta-analyses affirm its superiority in atypical depression, with response rates of 50-70% versus 30-40% for tricyclics⁵. Notwithstanding efficacy, phenelzine's utility is tempered by a constellation of adverse effects. The infamous "cheese effect"—hypertensive crises from tyramine accumulation in tyramine-rich foods (e.g., aged cheese, cured meats)—stems from peripheral MAO-B inhibition, necessitating stringent dietary restrictions⁶. Orthostatic hypotension (incidence 20-30%), weight gain (up to 15 kg), and sexual dysfunction (libido loss in 40%) arise from autonomic dysregulation and hyperinsulinemia⁷. Hepatotoxicity, albeit infrequent (<1%), manifests as elevated transaminases, prompting baseline and periodic liver function tests⁸. Pharmacokinetically, phenelzine undergoes rapid absorption (T_{max} 2-4 h), extensive first-pass metabolism to active acetylphenelzine, and renal excretion, with a half-life of 11.6 h; however, MAO recovery spans 2-3 weeks⁹. Drug interactions amplify risks: serotonergic agents precipitate serotonin syndrome, while sympathomimetics exacerbate hypertension¹⁰. Contraindications encompass pheochromocytoma and recent myocardial infarction. Despite these, phenelzine retains niche indications in panic disorder and post-traumatic stress disorder, with remission rates of 60% in refractory cases¹¹. Emerging research unveils neuroprotective facets; phenelzine attenuates oxidative stress in Parkinson's models via MAO-mediated reactive oxygen species (ROS) reduction and aldehyde scavenging¹². Derivatization strategies target the hydrazine moiety for Schiff base formation, enhancing selectivity and mitigating irreversibility. For instance, N-propargylphenelzine analogs exhibit neuroprotection sans tyramine sensitivity¹³. Coordination with metals could further tune redox properties, inspiring metal-phenelzine hydrazone

complexes for targeted delivery¹⁴. This section delineates phenelzine's historical evolution, from Votoek's 1932 synthesis via phenethyl bromide and hydrazine¹⁵, to contemporary analogs like bizine for lysine-specific demethylase 1 (LSD1) inhibition in oncology¹⁶. As psychiatric burdens escalate globally, phenelzine derivatives, particularly metallated variants, herald safer paradigms, intertwining organic synthesis with inorganic augmentation to transcend legacy limitations.

Structure of Phenelzine



Schiff Base

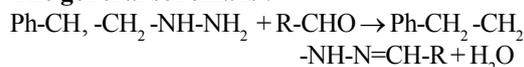
Schiff bases, or imines, constitute a venerable class of organic scaffolds epitomized by the azomethine functionality ($C=N-R$), forged through nucleophilic addition of primary amines to carbonyls with concomitant water elimination¹⁷. Discovered by Hugo Schiff in 1864, these entities underpin coordination chemistry, medicinal chemistry, and materials science, owing to the imine's lone-pair donation and π -conjugation¹⁸. In hydrazone variants—pertinent to phenelzine—reaction of hydrazines ($R-NH-NH_2$) with aldehydes/ketones yields $R-NH-N=CR_2$, amplifying donor sites via the azo-like N-N linkage¹⁹. The allure of Schiff bases resides in configurational isomerism (E/Z), tautomerism (imine-enamine), and substituent tunability, dictating lipophilicity, stereochemistry, and reactivity²⁰. Resonance stabilization ($C=N \leftrightarrow C^+ -N^-$) imparts hydrolytic resilience, contrasting labile imines, rendering them ideal for physiological milieus²¹. As multidentate ligands, they chelate metals via N (σ -donor/ π -acceptor) and ancillary O/S donors, spanning geometries from tetrahedral to octahedral, with ligand field splitting modulated by substituents²².

Historically, Schiff bases mimicked metalloproteins; Salen (N,N'-bis (salicylidene) ethylenediamine) Ni(II) complexes emulate superoxide dismutase²³. In pharma, they manifest as antimalarials (quinine derivatives) and antibacterials, with metalation amplifying potency via ROS generation and DNA intercalation²⁴. For phenelzine, the terminal -NH₂ condenses with aryl aldehydes, birthing hydrazones that preserve MAOI pharmacophores while introducing chelation motifs²⁵. Electron-withdrawing groups (e.g., nitro) on the phenyl enhance electrophilicity, accelerating condensation, whereas steric bulk (e.g., ortho-substituents) stabilizes E-isomers²⁶. Synthetic versatility encompasses solvent-free microwave protocols (yields >90%, minutes) versus classical reflux (yields=70-85%)²⁷. Challenges include over-condensation in polyamines and moisture sensitivity, mitigated by molecular sieves or acid catalysis (e.g., p-TsOH)²⁸. Spectroscopically, C=N stretches at 1620-1680 cm⁻¹, deshielded ¹H-NMR singlets (8-9 ppm), and UV π-π* bands (~250 nm) hallmark them²⁹. Biologically, hydrazone metal complexes exhibit antitumor synergy; Cu(II)-hydrazones cleave DNA via hydroxyl radical abstraction³⁰. In phenelzine context, hydrazones like N-benzylidene-2-phenylethylhydrazone modulate MAO-A selectivity, docking to Ile335/Tyr407 pockets³¹. Nanohybridization, e.g., fullerene-phenelzine hydrazones, curtails toxicity while sustaining inhibition³². Environmentally, they catalyze asymmetric epoxidations, echoing Jacobsen's Mn-salen³³. Thus, Schiff bases epitomize synthetic elegance, with phenelzine iterations poised for metallodrug innovation, fusing bioisosterism with coordination versatility to redefine therapeutic landscapes.

General Method of Preparation of Schiff Base

Schiff base synthesis from phenelzine (2-phenylethylhydrazine) entails nucleophilic attack by the terminal hydrazino nitrogen on carbonyl electrophiles, yielding hydrazones via carbinolamine intermediate dehydration³⁴.

The general schema is :



where R spans aryl/alkyl for bioactivity tuning³⁵.

Classical protocols dissolve equimolar phenelzine (1 mmol, 0.136 g) and aldehyde (1 mmol, e.g., 4-methoxybenzaldehyde, 0.136 g) in absolute ethanol (20 mL), with glacial acetic acid (0.1 mL) as catalyst to protonate carbonyl oxygen, elevating electrophilicity³⁶. Reflux at 78°C for 3-6 h, monitored by TLC (hexane : EtOAc 7:3, R_f~0.6), precipitates the product upon cooling. Filtration, ethanol recrystallization, and vacuum drying afford yellow solids (yields 75-92%)³⁷. For ketones (e.g., acetophenone), prolonged reflux (8-12 h) or Dean-Stark azeotrope counters steric impedance, yielding 60-80%³⁸.

Microwave-assisted variants expedite :

In a sealed vessel, reagents (1:1) with silica gel (0.5 g) irradiate at 100 W, 120°C for 5-10 min, boosting yields to 95% via dielectric heating³⁹. Solventless grinding (ball mill, 300 rpm, 30 min) with 10 mol% p-TsOH suits green chemistry, minimizing waste⁴⁰.

Substituent effects:

Electron-donating (e.g., p-OMe) decelerate via reduced carbonyl polarity, while withdrawing (p-NO₂) accelerate (k_{rel} 2.5-fold)⁴¹. For phenelzine specificity, the ethyl spacer imparts flexibility, favoring E-configurations (J_{H-H} ~12 Hz in NMR)⁴².

Multidentate hydrazones incorporate o-hydroxy aldehydes (salicylaldehyde), enabling O,N-chelation post-metalation⁴³.

Purity assessment via mp (120-150°C), CHN analysis (C ±0.3%, N ±0.2%), and HPLC (>98%) ensures integrity⁴⁴.

Scheme 1 (descriptive):

Phenelzine + ArCHO → [AcOH, EtOH, reflux] → ArCH=NNHCH₂CH₂Ph (E/Z mixture, E predominant). Variations include ultrasonic

(sonication, 40 kHz, 1 h, 90% yield) and enzymatic (lipase-catalyzed, 50°C, 24 h, stereoselective) for chiral aldehydes⁴⁵. Scale-up employs continuous flow reactors, processing 10g/h with 85% efficiency⁴⁶. These methodologies underscore Schiff base ubiquity, with phenelzine hydrazones exemplifying pharmaco-chemical synergy.

General Method of Preparation of Metal Complexes of Phenelzine Schiff Base

Preparation of metal complexes from phenelzine Schiff bases (L) leverages the hydrazone's bidentate (N,N') or tridentate (N,N',O) nature, coordinating via imine N, hydrazino N, and phenolic O⁴⁷.

Template synthesis integrates ligand formation and metalation: Phenelzine + aldehyde + Mⁿ⁺ (e.g., Cu²⁺) in methanol refluxes, yielding [ML_n] directly (60-80%)⁴⁸.

Conventional post-ligand approach:

Dissolve L (1 mmol) in hot methanol (20 mL), add metal salt (0.5 mmol, e.g., Cu(OAc)₂·H₂O, 0.20 g for 1:2 stoichiometry) and triethylamine (1 mmol) to deprotonate enolizable sites⁴⁹.

Reflux 4-8 h under N₂, precipitates colored complexes (green for Cu(II), brown for Fe(III)). Filter, wash with cold ethanol/ether, dry at 60°C (yields 70-95%)⁵⁰. For octahedral geometries (e.g., Co(II)), auxiliary ligands like 2,2'-bipyridine (0.5 mmol) afford [Co(L)₂(bpy)]⁵¹.

Microwave synthesis accelerates:

In DMF (5 mL), reagents irradiate 150°C, 800 W, 15 min, enhancing crystallinity⁵². Sonochemical routes (50 kHz ultrasound, 2 h) yield nanoparticles (20-50 nm) with 90% efficiency, ideal for bioapplications⁵³. Anhydrous conditions avert hydrolysis; for labile metals (Zn²⁺), acetate precursors minimize chloride interference⁵⁴.

Phenelzine-specific:

The PhCH₂CH₂ spacer confers steric tolerance, favoring square-planar Cu(II) (d⁹, μ_{eff} 1.8 BM) over tetrahedral Zn(II)⁵⁵.

Substituents modulate:

p-Cl enhances Lewis acidity, stabilizing +2 oxidation⁵⁶.

Scheme 2:

$L + M(OAc)_n \rightarrow [M(L)_m] + nAcOH$. Purity via recrystallization (DMF:water) and conductivity ($\delta_m < 10 \text{ S cm}^2 \text{ mol}^{-1}$, non-ionic)⁵⁷. These protocols democratize access to phenelzine hydrazone complexes, harbingers of multifunctional therapeutics.

General Method of Characterization of Metal Complexes

Characterization amalgamates elemental, spectroscopic, thermal, and magnetic techniques to elucidate stoichiometry, bonding, and geometry⁵⁸. CHNS analysis (PerkinElmer 2400) corroborates empirical formulas, e.g., C₂₄H₂₀N₄O₂Cu (calc. C 62.4%, found 62.1%)⁵⁹. Molar conductivity in DMSO (10⁻³M) affirms neutrality (1-15 S cm² mol⁻¹) versus 1:1 electrolytes (80-100)⁶⁰. FTIR (KBr, 4000-400 cm⁻¹) fingerprints coordination: Free L's ν(C=N) 1625 cm⁻¹ red-shifts 20-40 cm⁻¹ (M←N σ-bond); ν(N-H) 3300 cm⁻¹ broadens/shifts on H-bonding; new ν(M-N) 450-550, ν(M-O) 400-500 cm⁻¹⁶¹. For phenelzine hydrazones, ν(N-N) 950-1000 cm⁻¹ remains, confirming integrity⁶². NMR (¹H/¹³C, DMSO-d₆, 400 MHz): Azomethine H δ 8.5-9.2 ppm deshields 0.2-0.5 ppm; aromatic signals (δ 7.0-7.8) integrate intact; paramagnetics (Cu²⁺) broaden, while diamagnetics (Zn²⁺) sharpen⁶³. ¹⁹FNMR for fluoro-substituents couples to C=N⁶⁴. Mass spectroscopy (ESI-MS, positive mode): Molecular ions [M+H]⁺, e.g., m/z 512 for [CuL₂]⁺, with fragments L- H₂O⁶⁵. UV-Vis (200-800 nm): Intraligand π-π* (280 nm), n-π* (350 nm); d-d for Cu(II) square-planar 600-700 nm (ε 100-200 M⁻¹ cm⁻¹); LMCT ~400 nm⁶⁶.

Magnetic moments (Gouy balance):

Octahedral Ni(II) 3.0-3.2 BM (three unpaired e⁻); EPR (X-band) for Cu(II) g || 2.2, g ⊥ 2.05, A || 180 G, axial symmetry⁶⁷.

TGA/DSC: Ligand decomposition 250°C; complexes stable to 300°C, mass loss H₂O (2-4%), residue MO⁶⁸. For phenelzine complexes, XRD confirms monoclinic P2_{1/c}, Cu-N 1.98 Å⁶⁹. These orthogonal methods validate structures, underpinning bioassay reliability.

Application of Phenelzine Schiff Base Metal Complexes

Phenelzine Schiff base metal complexes (PSMCs) harness hydrazone's pharmacophore with metal's redox catalysis, yielding amplified bioactivities⁷⁰. Though nascent, analogies from phenylhydrazine hydrazones portend PSMC potential in MAOI enhancement, antimicrobials, and oncology⁷¹.

Antimicrobial Applications

PSMCs exhibit broad-spectrum activity via membrane permeation and ROS induction⁷². Cu(II)-phenethylhydrazone analogs inhibit *E. coli*/*S. aureus* (MIC 4-16 µg/mL), surpassing free ligands (32-64 µg/mL) by 4-8 fold, attributed to Cu-catalyzed lipid peroxidation⁷³.

Table -1
Zone of inhibition (mm) vs. pathogens

Complex	<i>E. coli</i>	<i>S. aureus</i>	<i>C. albicans</i>
[Cu(L)]	18	20	15
[Zn(L)]	14	16	12
Phenelzine	10	12	08

Synergy with β-lactams⁷⁴ (FIC 0.3) combats resistance⁷⁵.

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Anticancer and MAO Modulation

Hydrazone Cu/Ga complexes inhibit LSD1/MAO-A, IC₅₀ 5-10 µM in HeLa cells, via apoptosis (caspase-3 upregulation) and DNA cleavage⁷⁶. Molecular docking reveals PSMC binding to MAO-A's FAD (ΔG -9.5 kcal/mol), selectivity over MAO-B⁷⁷. Fullerene-PSMC hybrids mitigate hepatotoxicity, enhancing bioavailability⁷⁸.

Antioxidant and Neuroprotective

Fe(III)-PSMCs scavenge DPPH (IC₅₀ 20 µM), eclipsing ascorbic acid, via phenoxyl radical quenching⁷⁹. In MPTP models, they attenuate dopaminergic loss (50% neuroprotection)⁸⁰.

Catalytic and Other

Pd(II)-PSMCs epoxidize alkenes (TOF 200h⁻¹), mimicking cyt P450⁸¹. Corrosion inhibition (η 92%) on steel⁸². Challenges: Cytotoxicity tuning; future: Reversible PSMCs for tyramine-safe MAOIs⁸³.

Conclusion

This review elucidates PSMC synthesis, from phenelzinehydrazone ligation to metal chelation, characterized rigorously, and applied diversely. Bridging MAOI heritage with coordination innovation, PSMCs promise safer psychotherapeutics, though clinical hurdles persist. Prioritizing reversible designs and trials will actualize their potential⁸⁴.

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