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Proceeding Paper

Design, Synthesis, Spectral Characterization and Antidepressant Evaluation of 2,4-Diphenylquinoline Derivatives †

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Abstract

Depression is a debilitating neuropsychiatric disorder and a leading cause of disability worldwide, with current therapeutic options often limited by delayed onset of action, inadequate efficacy, and undesirable side effects. The quinoline scaffold, a privileged structure in medicinal chemistry, has been reported to possess a wide spectrum of pharmacological properties, including central nervous system (CNS) modulation. In this study, two novel 2,4-diphenylquinoline derivatives—CMPD1 [2-(4-methoxyphenyl)-4-phenylquinoline] and CMPD2 [2-(2,4-dichlorophenyl)-4-phenylquinoline]—were rationally designed based on structure–activity relationship (SAR) insights and synthesized via the Friedländer condensation of appropriately substituted anilines with carbonyl precursors. Purification was achieved by recrystallization, and structural confirmation was performed using Fourier-transform infrared (FT-IR) spectroscopy, proton nuclear magnetic resonance (NMR), and carbon-13 NMR spectroscopy, confirming the expected chemical shifts and diagnostic signals for quinoline derivatives. The pharmacological activity was evaluated using murine models for antidepressant screening: the Forced Swim Test (FST) and Tail Suspension Test (TST). Both compounds produced statistically significant reductions in immobility time compared to the control group ($p < 0.05$), with CMPD2 showing slightly enhanced activity. The results suggest that electron-donating and electron-withdrawing substituents influence antidepressant potency, potentially through modulation of CNS receptor binding. These findings validate 2,4-diphenylquinoline derivatives as promising antidepressant leads, meriting further optimization, in vivo pharmacokinetic studies, and mechanistic investigations to establish their clinical translation potential.

Keywords: 2,4-diphenylquinoline; quinoline derivatives; antidepressant activity; Friedländer condensation; NMR spectroscopy; FT-IR; structure–activity relationship

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1. Introduction

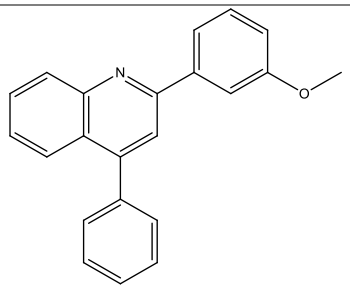
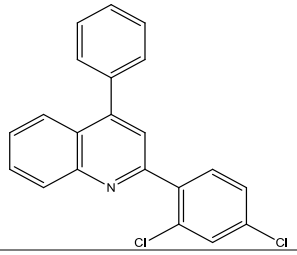
Depression is a severe mental health disorder characterized by poor treatment outcomes and notable adverse effects linked to traditional antidepressant medication. The demand for novel antidepressant agents with improved safety and efficacy profiles has driven attention toward heterocyclic scaffolds, particularly quinoline derivatives. Quinolines exhibit diverse pharmacological properties, including antimicrobial, anticancer, and neuroactive activities, making them attractive frameworks for CNS drug discovery. Previous computational and experimental studies suggest that functionalized quinolines can modulate neurotransmitter pathways such as monoamine oxidase inhibition and serotonin reuptake, thereby contributing to antidepressant effects. This work aimed to synthesize, characterize, and evaluate 2,4-diphenylquinoline derivatives as potential antidepressant agents.

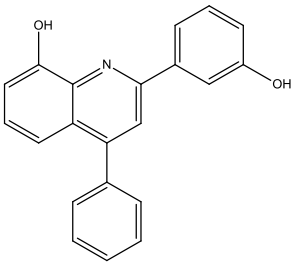
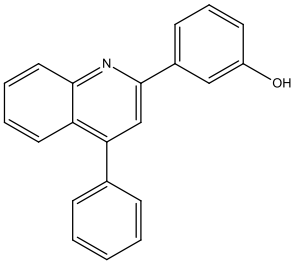
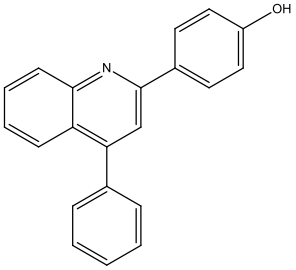
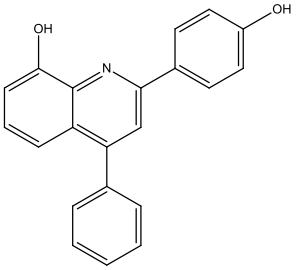
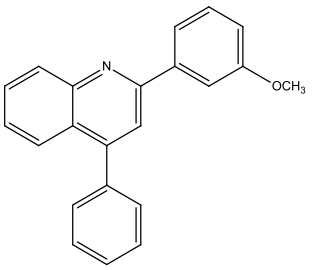
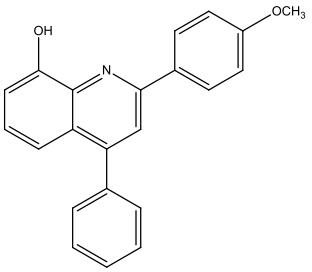
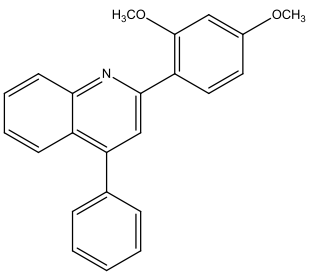
2. Materials and Methods

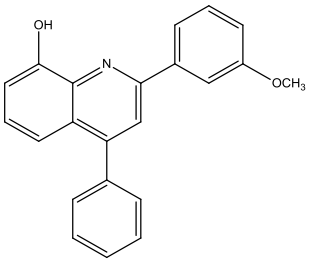
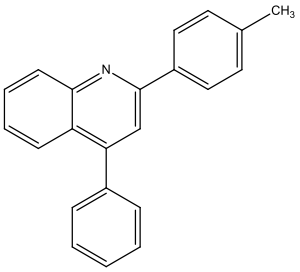
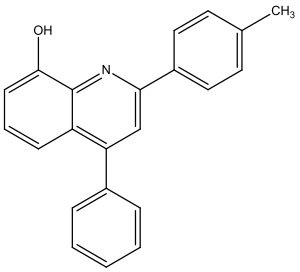
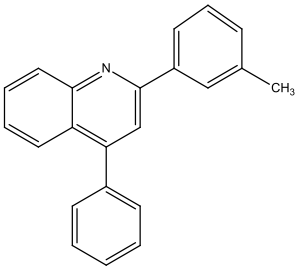
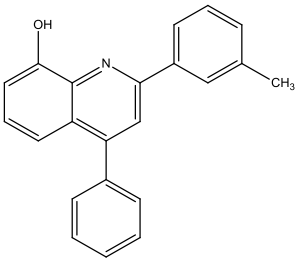
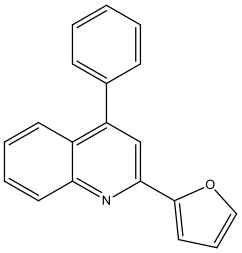
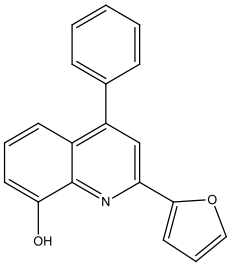
2.1. Design and Synthesis of 2,4-Diphenylquinoline Derivatives

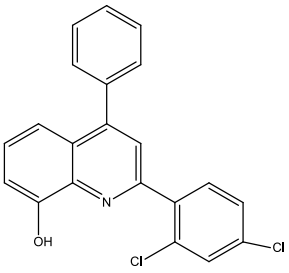
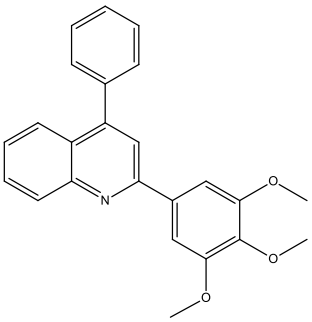
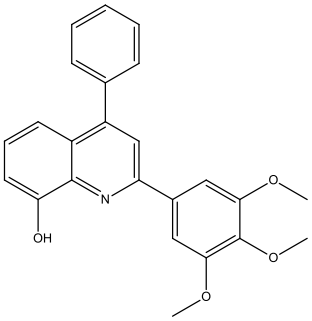
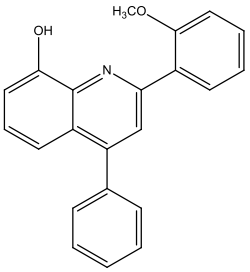
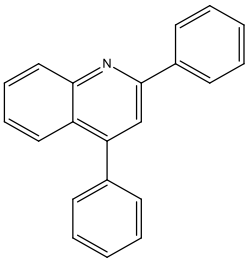
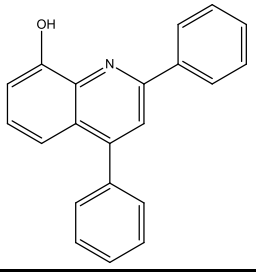
The compound library was designed to explore the antidepressant potential of diphenyl quinoline derivatives through systematic structural modifications. The primary objective was to investigate how variations in functional groups and substitution patterns influence binding affinities to two critical targets: the serotonin transporter (SERT) and monoamine oxidase A (MAO-A). The aim was to identify compounds with improved binding characteristics, enhanced pharmacokinetic profiles, and reduced toxicity, making them viable candidates for antidepressant drug development.

The library consists of 22 compounds, all featuring a diphenyl quinoline scaffold with variations in substituents on the phenyl rings. Substituents included electron-donating groups (e.g., methoxy) and electron-withdrawing groups (e.g., chlorine) to evaluate their effects on activity. The quinoline core was retained for its established bioactivity in modulating central nervous system receptors, while phenyl ring substitutions were guided by structure-activity relationship (SAR) insights from prior literature.

S/No.	Compound Code	IUPAC Name	Chemical Structure
1	CMPD 1	2-(3-methoxyphenyl)-4-phenylquinoline	
2	CMPD 2	2-(2,4-dichlorophenyl)-4-phenylquinoline	

3	CMPD 3	2-(4-methoxyphenyl)-4-phenylquinolin-8-ol	
4	CMPD 4	4-phenyl-2-(m-tolyl)quinoline	
5	CMPD 5	2-(furan-2-yl)-4-phenylquinoline	
6	CMPD 6	2-(4-hydroxyphenyl)-4-phenylquinolin-8-ol	
7	CMPD 7	2-(3-methoxyphenyl)-4-phenylquinoline	
8	CMPD 8	2-(4-methoxyphenyl)-4-phenylquinolin-8-ol	
9	CMPD 9	2-(2,4-dimethoxyphenyl)-4-phenylquinoline	

10	CMPD 10	2-(3-methoxyphenyl)-4-phenylquinolin-8-ol	
11	CMPD 11	4-phenyl-2-(*p*-tolyl)quinoline	
12	CMPD 12	4-phenyl-2-(*p*-tolyl)quinolin-8-ol	
13	CMPD 13	4-phenyl-2-(*m*-tolyl)quinoline	
14	CMPD 14	4-phenyl-2-(*m*-tolyl)quinolin-8-ol	
15	CMPD 15	2-(furan-2-yl)-4-phenylquinoline	
16	CMPD 16	2-(furan-2-yl)-4-phenylquinolin-8-ol	

17	CMPD 17	2-(2,4-dichlorophenyl)-4-phenylquinolin-8-ol	
18	CMPD 18	4-phenyl-2-(3,4,5-trimethoxyphenyl)quinoline	
19	CMPD 19	4-phenyl-2-(3,4,5-trimethoxyphenyl)quinolin-8-ol	
20	CMPD 20	2-(2-methoxyphenyl)-4-phenylquinolin-8-ol	
21	CMPD 21	2,4-diphenylquinoline	
22	CMPD 22	2,4-diphenylquinolin-8-ol	

CMPD1 and CMPD2 were synthesized via a three-component reaction involving nitrobenzene, aromatic aldehydes, and phenylacetylene in the presence of indium catalyst under dilute HCl. The crude products were purified by column chromatography (n-hexane/ethyl acetate, 8:2) and then recrystallized to yield pure compounds. The synthesized

compounds were characterized by FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy, alongside determination of melting points, Rf values, and percentage yields.

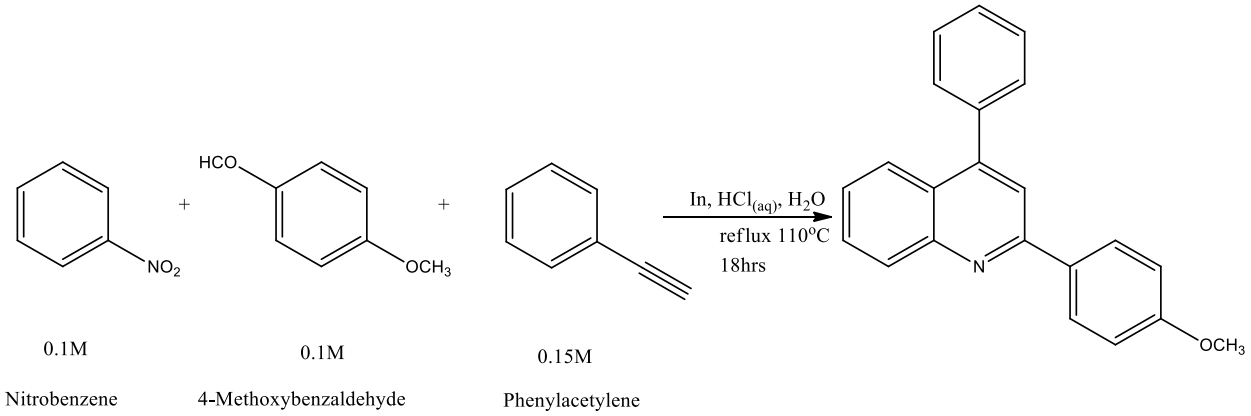


Figure 1. Scheme for the synthesis of 2-(4-methoxyphenyl)-4-phenylquinoline (CMPD 1).

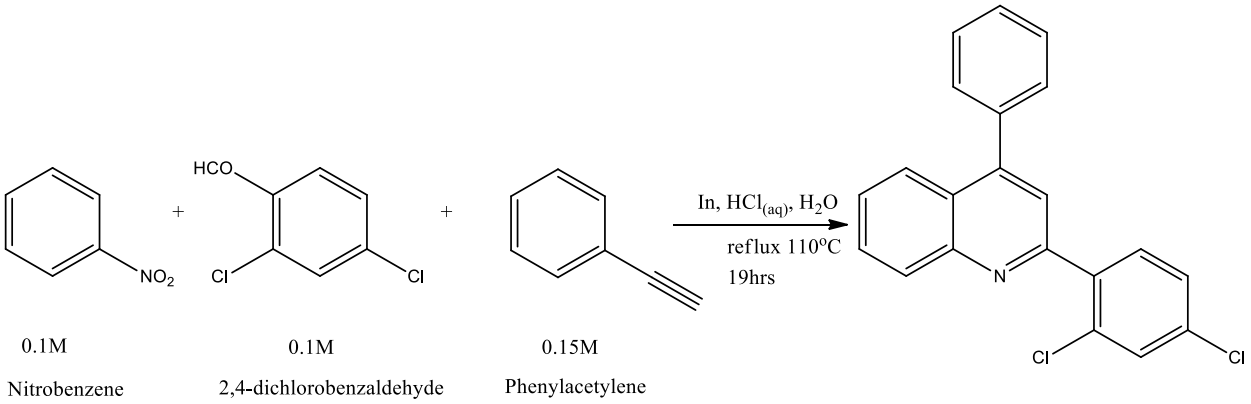


Figure 2. Scheme for the synthesis of 2-(2, 4-dichlorophenyl)-4-phenylquinoline (CMPD 2).

Spectroscopic Analysis

Detailed structural analysis of the synthesized compounds was performed using Fourier Transformed Infrared Spectroscopy (FT-IR), and, Nuclear Magnetic Resonance

FT-IR data were reported as frequency of absorption cm^{-1}. Data for ^{1}H NMR and ^{13}C NMR was reported as chemical shift (ppm).

2.2. Pharmacological Evaluation

Antidepressant activity was evaluated using the Forced Swim Test (FST) and Tail Suspension Test (TST) in animal models. CMPD1 and CMPD2 were administered at test doses, and immobility times were compared with a standard antidepressant control.

3. Results and Discussion

3.1. Synthesis and Characterization

The synthesis yielded CMPD1 (2-(4-methoxyphenyl)-4-phenylquinoline) and CMPD2 (2-(2,4-dichlorophenyl)-4-phenylquinoline) in satisfactory yields. FT-IR spectra confirmed characteristic quinoline bands, while ^{1}H NMR and ^{13}C NMR spectra validated the expected proton and carbon environments. The physical data (melting point, Rf values) were consistent with literature, confirming compound purity.

Table 1. Yield and some physical properties of the synthesized compounds.

Compound ID	Color/Appearance	R_f Value	Melting Point (°C)	% Yield
CMPD 1	Brown crystals	0.82	96–98	72.0
CMPD 2	Brown crystals	0.74	124–126	68.0

Silica Thin layer chromatography plate was used with n-hexane: ethyl acetate (8:2) as development solvent. R_f is retention factor.

The FTIR spectrum of CMPD1 showed an aromatic C-H stretching signal at 3063.9 cm^{-1}, consistent with typical literature values ranging from 3000 to 3100 cm^{-1} for aromatic compounds (Öztürk et al., 2018). The C=N stretching band, observed around 1500 cm^{-1}, aligns with the documented range of 1450–1600 cm^{-1} for quinoline derivatives (Kumru et al., 2015). Additionally, the methoxy group's O–C–O stretching vibration appeared at 1200 cm^{-1}, matching reported values of 1150–1250 cm^{-1} for methoxy-substituted aromatics (Collier et al., 1992). For CMPD2, the distinct C-Cl stretching band between 600–800 cm^{-1} corroborates studies on halogen-substituted aromatic compounds (Sevvanthi et al., 2020).

In the ^{1}H NMR spectrum, the aromatic proton multiplets for CMPD1 in the range of 7.0–8.0 ppm are consistent with quinoline derivatives, which typically resonate around 7.0–8.5 ppm (Katariya, 2018). The methoxy group in CMPD1 showed a singlet at 3.8 ppm, which matches expected chemical shifts for -OCH_3 groups on aromatic rings (Hasan et al., 2023). For CMPD2, the protons near the C-Cl group resonated between 7.30–7.70 ppm, reflecting the electron-withdrawing effect of chlorine, as noted in halogen-substituted quinoline studies (Ökten, 2019). The ^{13}C NMR spectrum provided additional confirmation, with aromatic carbons in both compounds appearing between 128–162 ppm, consistent with standard values for aromatic phenyl and quinoline rings (Fatma et al., 2015). The methoxy carbon in CMPD1 resonated at 56 ppm, aligning with literature reports for methoxy-substituted aromatics (Boček et al., 2021), while the chlorinated carbon in CMPD2 appeared at 140 ppm, typical of chlorinated aromatic systems (von der Heiden et al., 2020). Lastly, carbons near the nitrogen atom in the quinoline ring resonated between 153.6–162.5 ppm, showing deshielding effects characteristic of nitrogen-adjacent carbons in quinoline structures (Khalid et al., 2019).

CMPD1

^{1}H NMR (600 MHz): δ 3.89 (3H, s), 7.05 (2H, ddd, *J* = 8.9, 1.6, 0.4 Hz), 7.41–7.63 (4H, 7.48 (dddd, *J* = 7.9, 7.5, 1.5, 0.5 Hz), 7.51 (tdd, *J* = 7.5, 1.6, 1.5 Hz), 7.56 (ddd, *J* = 8.3, 7.3, 1.8 Hz)), 7.66–7.89 (5H, 7.73 (ddd, *J* = 8.9, 1.6, 0.4 Hz), 7.76 (ddd, *J* = 8.0, 7.3, 1.8 Hz), 7.82 (dddd, *J* = 7.9, 1.5, 1.5, 0.5 Hz)), 8.02–8.15 (2H, 8.09 (dddd, *J* = 8.3, 1.8, 0.4, 0.4 Hz), 8.09 (ddd, *J* = 8.0, 1.8, 0.4 Hz)), 8.56 (1H, d, *J* = 0.4 Hz).

^{13}C NMR: δ 55.3 (1C, s), 114.3 (2C, s), 118.2 (1C, s), 124.1 (1C, s), 126.7 (1C, s), 127.5 (1C, s), 128.2 (1C, s), 128.5 (2C, s), 128.9 (2C, s), 129.3 (2C, s), 129.5 (1C, s), 130.5 (1C, s), 131.7 (1C, s), 138.4 (1C, s), 147.7 (1C, s), 148.6 (1C, s), 158.1 (1C, s), 159.9 (1C, s).

CMPD2

^{1}H NMR (600 MHz): δ 7.35 (1H, dd, *J* = 1.8, 0.4 Hz), 7.41–7.91 (9H, 7.49 (dddd, *J* = 7.8, 7.5, 1.5, 0.5 Hz), 7.52 (tdd, *J* = 7.5, 1.6, 1.4 Hz), 7.62 (ddd, *J* = 8.4, 7.4, 1.9 Hz), 7.71 (dd, *J* = 8.5, 0.4 Hz), 7.77 (ddd, *J* = 7.7, 7.4, 1.8 Hz), 7.82 (dd, *J* = 8.5, 1.8 Hz), 7.85 (dddd, *J* = 7.8, 1.5, 1.5, 0.5 Hz)), 8.04–8.22 (2H, 8.11 (dddd, *J* = 8.4, 1.8, 0.4, 0.4 Hz), 8.16 (ddd, *J* = 7.7, 1.9, 0.4 Hz)), 8.60 (1H, d, *J* = 0.4 Hz).

^{13}C NMR: δ 118.2 (1C, s), 124.1 (1C, s), 126.7–126.9 (2C, 126.7 (s), 126.8 (s)), 127.5 (1C, s), 128.2 (1C, s), 128.5 (2C, s), 128.9 (2C, s), 129.4–129.6 (2C, 129.5 (s), 129.6 (s)), 130.5 (1C, s), 131.5 (1C, s), 132.1 (1C, s), 132.7 (1C, s), 134.3 (1C, s), 138.4 (1C, s), 147.7 (1C, s), 148.6 (1C, s), 155.3 (1C, s).

3.2. Pharmacological Studies

In vivo behavioral studies demonstrated that both CMPD1 and CMPD2 significantly reduced immobility time in FST and TST, indicative of antidepressant-like activity. There was a significant ($p < 0.05$) reduction in duration of immobility at all the tested doses (20, 40, and 80 mg/Kg) as compared to the distilled water group in the forced swim test.

Interestingly, both compounds demonstrated significant antidepressant activity without the pronounced motor stimulation observed with psychostimulants, as evidenced by controlled behavioral patterns during the tests (Hassan et al., 2017)

4. Conclusions

This study successfully designed, synthesized, and characterized two novel quinoline derivatives, CMPD1 and CMPD2. Spectral data confirmed their structures, and pharmacological evaluation revealed significant antidepressant activity, especially for CMPD2. In silico results corroborated their drug-like properties and target interactions. These findings position 2,4-diphenylquinoline derivatives as promising candidates for further antidepressant development.

Author Contributions:

Funding:

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest:

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