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Synthesis and characterization of 2, 9-(disubstituted)-6,13-dimethoxy 5,12-dihydroquinoxalino[2,3-*b*] phenazine derivatives

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Abstract

Phenazine and quinoxaline derivatives represent crucial nitrogen containing heterocyclic architectures with a remarkably broad spectrum of pharmaceutical, agricultural, and technological applications. In this study, we have reported the design, synthesis, and comprehensive spectral characterization of a novel series of 2,9-(disubstituted)-6,13-dimethoxy-5,12-dihydroquinoxalino (2,3-b) phenazine derivatives (6a–d). The synthetic methodology utilizes 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone as a core scaffolding precursor, which undergoes condensation when reacted with one molar equivalents of various substituted ortho-phenylenediamines. This reaction was efficiently executed under reflux conditions in an ethanolic medium containing anhydrous sodium acetate as a mild basic catalyst, delivering the desired ladder type pentacyclic framework in moderate to high yields ranging from 52% to 61%. All synthesized nitrogenous heterocycles were isolated as distinct crystalline solids and rigorously purified via silica gel column chromatography. The molecular structures of the target fluorindine analogues were unambiguously verified through a combination of spectroscopic analytical techniques, including Fourier-transform infrared spectroscopy (FT-IR), proton nuclear magnetic resonance (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR), and electrospray ionization mass spectrometry (ESI-MS), as well as elemental analysis. The spectral data consistently confirmed the complete disappearance of the parent phinazinone carbonyl absorption. The structural versatility, stability, and streamlined synthesis of these novel 5,12-dihydroquinoxalino(2,3-b) phenazine systems position them as highly promising candidates for future investigation as active pharmaceutical agents, agricultural biocides, or building blocks for organic field-effect transistors and optoelectronic semiconductor materials.

Keywords: Phenazine, quinoxaline, 5,12-dihydroquinoxalino(2,3-b) phenazine, 1,4-benzoquinone, heterocyclic synthesis, spectral characterization

Introduction

The design and assembly of complex nitrogen-containing heterocyclic architectures represent a cornerstone of contemporary organic synthesis, pharmaceutical chemistry, and advanced materials engineering. Among these privileged structures, phenazine and quinoxaline scaffolds are heavily investigated due to their unique planar, electron-deficient π-electron systems and strong intramolecular coordination capabilities. Phenazine frameworks are naturally occurring secondary metabolites demonstrating prominent antimicrobial, anti-tumor, and insecticidal profiles, which make them highly valuable in reducing agricultural pesticide reliance. In recent pharmacological developments, the synthesis of novel quinoxaline derivatives with potent cytotoxicity against multiple cancer lines that work by selectively suppressing EGFR and VEGFR-2 pathways to hinder tumor expansion has been reported [1]. Concurrently, it was highlighted that structural modifications targeting the bicyclic benzopyrazine ring optimize binding affinity to various infectious disease receptors while utilizing green synthetic pathways like microwave-assisted and solvent-free protocols [2]. Furthermore, it was demonstrated that tuning the C–N/C=N surface networks of phenazine-derived carbon nanomodulators provides precise, dynamic reactive oxygen species (ROS) regulation, making them excellent candidates for managing complex bacterial infections and chronic diabetic wounds [3].

Beyond biological frameworks, extended polycyclic heteroaromatics show great utility in modern material science, functioning as organic semiconductors, molecular electronics, and light-harvesting systems. For instance, a strategy was developed to design substituted tetraamino-phenazine dyes that facilitate access to near-infrared absorbing benzoquinonediimine-fused quinoxaline matrices for specialized optoelectronic platforms [4]. In the field of dental materials, specialized dibenzo (a, c) phenazines possessing high visible-light sensitivity were synthesized to act as rapid photoinitiators for advanced dental polymerizations [4]. Sustainable energy research has also embraced these networks, an organic cathode containing extended quinoxalino-phenazine π-conjugation was developed that exhibits superior rate capabilities and cycle longevity in aqueous zinc batteries [6]. Additionally, the reversible redox dynamics between phenazine and dihydrophenazine were integrated into conjugated microporous polymers to achieve remarkably efficient, solar-driven hydrogen peroxide production without sacrificial chemical agents [7]. A particularly vital subset of these polycyclic networks is the pentacyclic system known as 5,12-dihydroquinoxalino(2,3-b) phenazine or fluorindine. Traditionally, the installation of this specific core required the high-temperature reflux of complex azophenine networks over strong oxidizers in high-boiling solvents. Alternatively, the condensation of 2,5-dihydroxy-1,4-benzoquinone with one molar equivalents of ortho-phenylenediamine yields the parent 5,12-dihydroquinoxalino(2,3-b) phenazine, which is widely utilized in organic field-effect transistors. Patent literature also describes synthesizing the parent structure alongside

5,12-dihydroquinoxalino(2,3-b) phenazine-2,9-dicarboxylic acid by condensing 2,5-dihydroxy-1,4-benzoquinone with 1,2-phenylenediamine or 3,4-diaminobenzoic acid by refluxing in glacial acetic acid. Moreover, 5,12-dihydroquinoxalino(2,3-b) phenazine was synthesized by reacting 2 moles of 1,2-phenylenediamine with 2,5-dihydroxy-1,4-benzoquinone by refluxing in polyphosphoric acid in N_2 atmosphere [9].

Building upon these diverse biological properties and technological applications, the present work establishes a streamlined route to synthesize a new class of nitrogen-dense heterocycles. Herein, we describe the synthesis and comprehensive spectral characterization of a novel series of 2,9-(disubstituted)-6,13-dimethoxy-5,12-dihydroquinoxalino(2,3-b) phenazine derivatives 6(a–d). By utilizing 7-substituted 3-bromo-1,4-dimethoxyphenazin-2(10H)-one as a core scaffolding precursor instead of conventional dihydroxyquinones, we lock in functional methoxy groups at the 6 and 13 positions of the final pentacyclic platform. The reaction cascades proceed smoothly with one molar equivalent of substituted ortho-phenylenediamines over a mild sodium acetate catalyst in refluxing ethanol, delivering the targeted compounds in favorable yields. This modification offers an efficient synthetic avenue to expand the library of substituted fluorindine frameworks, opening new pathways for electronic and biomedical exploration.

Material and Methods

All chemicals, reagents, and solvents used in this investigation were procured from commercial suppliers and utilized without further purification. Progress of reactions was monitored using silica gel pre-coated thin-layer chromatography (TLC) plates, visualized under ultraviolet light. Melting points were determined using an open capillary tube apparatus and are uncorrected. Infrared (IR) spectra were recorded on a KBr matrix. Nuclear magnetic resonance ^{1}H and ^{13}C NMR spectra were acquired in DMSO-d_6 using a 400 MHz spectrometer with tetramethylsilane as the internal standard. Electrospray ionization mass spectrometry (ESI-MS) data were gathered to confirm molecular weights.

Experimental Section

General procedure for the synthesis and characterization of 5,12-dihydroquinoxalino (2, 3-b) phenazine derivatives

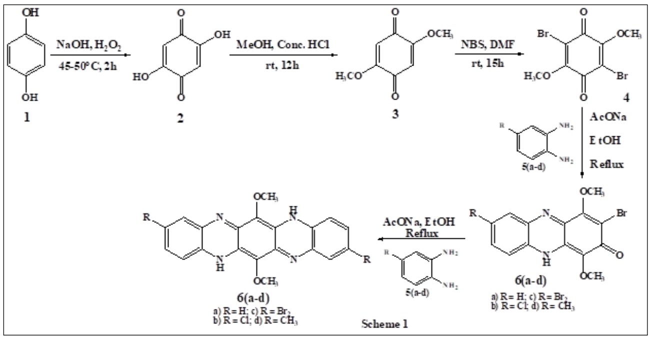
Substituted ortho-phenylenediamine 5(a–d) (1.5 mmol) and anhydrous sodium acetate (1.5 mmol) were dissolved in 15 mL of ethanol in a 50 mL round-bottom flask. The mixture was stirred continuously for 15 minutes at room temperature. Subsequently, 1.5 mmol of 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone [4] was added portion-wise. The resulting reaction mixture was heated under reflux conditions for 5–8 hours, with progress monitored by TLC. Upon completion, the mixture was cooled to room temperature, poured into water, and extracted three times with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude residues were purified by silica gel column chromatography using ethyl acetate–petroleum ether gradients to afford pure products 6(a–d).

6,13-dimethoxy-5,12-dihydroquinoxalino (2, 3-b) phenazine (6a)

Yield: 0.3 g (58%); brown solid; mp 283–285 °C (p. 4). IR (KBr) νmax (cm^{-1}): 3362, 3018, 2924, 2854, 1627, 1599, 1462, 1260, 1070, 752 (p. 4) ^{1}.H NMR (400 MHz, DMSO-d_6): δ 6.72–7.20 (m, 8H, Ar-H), 3.60 (s, 6H, OCH_3, 3.78 (br s, 2H, NH) ^{13}.C NMR (75 MHz, DMSO-d_6): δ 146.6, 136.6, 135.2, 128.1, 127.2, 124.2, 123.6, 120.2, 116.9, 60.7. ESI-MS m/z: 345 $(M+H)^+$. Anal. Calcd for $C_{20}H_{16}N_4O_2$: C, 69.81; H, 4.70; N, 16.20. Found: C, 69.78; H, 4.71; N, 16.25.

2,9-dichloro-6,13-dimethoxy-5,12-dihydroquinoxalino (2, 3-b) phenazine (6b)

Yield: 0.34 g (55%); dark brown solid; mp > 300 °C. IR (KBr) νmax (cm^{-1}): 3366, 3029, 2948, 1628, 1468, 1267, 1075, 765 ^{1}.H NMR (400 MHz, DMSO-d_6): δ 7.15–7.32 (m, 6H, Ar-H), 3.85 (s, 6H, OCH_3, 3.81 (br s, 2H, NH) ^{13}.C NMR (75 MHz, DMSO-(d_6): δ 146.4, 135.6, 135.3, 128.3, 124.4, 123.5, 121.3, 120.4, 120.0, 118.0, 60.8. ESI-MS m/z: 413 $(M+H)^+$. Anal. Calcd for $C_{20}H_{14}Cl_2N_4O_2$: C, 58.17; H, 3.35; N, 13.48. Found: C, 58.10; H, 3.43; N, 13.53.



Scheme 1

2,9-dibromo-6,13-dimethoxy-5,12-dihydroquinoxalino (2, 3-b) phenazine (6c)

Yield: 0.39 g (52%); dark brown solid; mp > 300 °C. IR (KBr) νmax (cm^{-1}): 3364, 3027, 2940, 1628, 1452, 1263, 1072, 759 [1].H NMR (400 MHz, DMSO-d_6): δ 7.06–7.50 (m, 6H, Ar-H), 3.83 (s, 6H, OCH_3), 3.80 (br s, 2H, NH) ^{13}.C NMR (75 MHz, DMSO-d_6): δ 146.4, 135.4, 133.6, 128.1, 125.7, 125.4, 125.1, 124.4, 118.6, 115.1, 60.6. ESI-MS m/z: 503 $(M+H)^+$. Anal. Calcd for $C_{20}H_{14}Br_2N_4O_2$: C, 47.80; H, 2.74; N, 12.02. Found: C, 47.86; H, 2.83; N, 11.09.

6,13-dimethoxy-2,9-dimethyl-5,12-dihydroquinoxalino (2, 3-b) phenazine (6d)

Yield: 0.34 g (61%); thick brown solid; mp > 300 °C (p. 5). IR (KBr) νmax (cm^{-1}): 3359, 3017, 2920, 1624, 1460, 1257, 1060, 742 (p. 5) ^{1}.H NMR (400 MHz, DMSO-d_6): δ 7.09–7.32 (m, 6H, Ar-H), 3.84 (s, 6H, OCH_3), 3.75 (br s, 2H, NH), 2.30.(6H, s, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 146.7, 135.5, 134.7, 128.2, 126.1, 124.5, 124.0, 123.4, 122.8, 116.9, 60.9, 21.2 (p. 5). ESI-MS m/z: 373 $(M+H)^+$. Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 71.01; H, 5.38; N, 15.09. Found: C, 70.98; H, 5.40; N, 15.12.

Result and Discussions

The structural elucidation of the synthesized 2,9-substituted-6,13-dimethoxy-5,12-dihydroquinoxalino(2,3-b) phenazines (6a–d) was systematically accomplished via general spectral interpretations. In the FT-IR profiles, all derivatives exhibited prominent stretching vibrations around 3359–3366

cm^{-1} confirming secondary amine (N–H) groups, and 1624–1628 cm^{-1} indicating imine (C=N) linkages. Crucially, the total absence of any phenazin-2-one or quinone carbonyl (C=O) band around 1650 cm^{-1} validated successful double condensation. The ^{1}H NMR spectra displayed a characteristic broad singlet at δ 3.75–3.81 ppm corresponding to the two symmetrically equivalent N–H protons, alongside a sharp singlet integrating for six protons at δ 3.60–3.85 ppm confirming the core methoxy ($–OCH_3$) functions. Complex aromatic proton multiplets resolved cleanly between δ 6.72 and 7.50 ppm. In ^{13}C NMR, diagnostic peaks emerged near δ 146.4–146.7 ppm for $C–OCH_3$ environments and δ 135.4–136.6 ppm for imine carbons, while ESI-MS cleanly exhibited prominent $(M+H)^+$ peaks matching the expected pentacyclic core structures.

Conclusion

In summary, a series of novel 2,9-disubstituted-6,13-dimethoxy-5,12-dihydroquinoxalino(2,3-b) phenazines was successfully synthesized through the controlled condensation of 2,5-dibromo-3,6-dimethoxy-1,4-benzoquinone with various ortho-phenylenediamines. This straightforward protocol yields stable ladder-type heterocyclic derivatives in moderate to high capacities without needing harsh reagents. Comprehensive spectral analysis confirmed high structural integrity and exceptional regioselectivity across all derivatives. Given the foundational importance of extended, nitrogen-rich polycyclic frameworks, these newly generated dimethoxy fluorindine analogues hold valuable potential as functional semiconductor building blocks for organic transistors and show high promise as specialized multi-target agricultural or biomedical agents in future exploratory applications.

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