Design, Synthesis, Spectral Characterization and COX-2 Docking of Isopropenylsulfonyl Quinoxaline Analogues as Potential Anti-inflammatory Leads

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***Abstract*—Quinoxaline is a privileged nitrogen-containing heterocycle with documented potential for modulation of inflammatory targets. In the present study, three isopropenylsulfonyl quinoxaline analogues (Q1–Q3) were synthesized from substituted o-phenylenediamines and methanesulfonyl isopropenyl sulfone in dimethyl sulfoxide in the presence of sulfur. The isolated products were characterized by melting-point determination, Fourier-transform infrared spectroscopy, proton nuclear magnetic resonance spectroscopy and mass spectrometry. The analogues were obtained in comparable yields of 75.83–77.02%, with melting ranges of 178–201 °C. Characteristic FTIR absorptions for the quinoxaline/olefinic system occurred at 1632–1635 cm^{-1}, while the sulfonyl group produced diagnostic bands at 1322–1328 and 1154–1160 cm^{-1}. Proton NMR data showed terminal vinyl signals near δ 6.52 and 5.95–5.96 ppm and an isopropenyl methyl signal at δ 2.19 ppm. Molecular-ion peaks were observed at m/z 234 for Q1, 248 for Q2 and 268/270 for the chloro analogue Q3. Molecular docking against cyclooxygenase-2 (COX-2; PDB ID 3LN1) gave predicted binding scores of −7.1, −7.4 and −7.8 kcal/mol for Q1, Q2 and Q3, respectively. Q3 displayed the most favorable predicted affinity, supported by hydrogen-bonding, hydrophobic and putative halogen interactions in the active pocket. The findings identify the chloro-substituted analogue as the priority lead for experimental COX-2 inhibition, cellular anti-inflammatory testing, selectivity assessment and in-vivo validation. The docking results represent computational predictions and should not be interpreted as confirmed pharmacological activity.**

***Index Terms*—quinoxaline; isopropenylsulfonyl; COX-2; molecular docking; anti-inflammatory lead; spectral characterization**

I. INTRODUCTION

Inflammation is a coordinated protective response to infection, tissue damage and chemical injury. Although the acute response is essential for host defense and repair, persistent activation of cyclooxygenase, cytokine and oxidative pathways contributes to chronic pain, arthritis, cardiovascular disease, metabolic dysfunction and tissue injury. Cyclooxygenase-2 (COX-2) is induced by inflammatory stimuli and catalyzes formation of prostaglandins that promote pain, vasodilation, edema and fever. Conventional non-steroidal anti-inflammatory drugs are effective but may produce gastrointestinal, renal and cardiovascular adverse effects, encouraging the search for structurally new and more selective anti-inflammatory leads [1].

Quinoxaline is a fused benzene–pyrazine ring system whose planarity, electron deficiency and two ring nitrogens enable π-interactions, hydrogen bonding and hydrophobic contacts in enzyme binding sites. Quinoxaline derivatives have been investigated as antimicrobial, antiviral, anticancer, antioxidant and anti-inflammatory agents [2–4]. Substitution at the carbon atoms of the heterocyclic and fused benzene rings can tune lipophilicity, electronic distribution, metabolic stability and target selectivity. In particular, quinoxaline derivatives containing halogens, hydrophobic groups, hydrazones or sulfonyl functionalities have shown promising inhibition of inflammatory mediators and COX-related pathways [5–13].

Sulfonyl groups are valuable medicinal-chemistry motifs because their two oxygen atoms can participate in polar interactions while the sulfur-linked carbon

substituent can occupy hydrophobic regions. Modern one-pot and sulfur-assisted methods also permit efficient construction of substituted quinoxaline systems [14,15]. Computational docking is frequently used to prioritize analogues before biological testing by estimating ligand orientation and relative binding affinity in the COX-2 active site [16].

The objective of this work was to synthesize three isopropenylsulfonyl quinoxaline analogues, characterize them using physicochemical and spectroscopic techniques, and compare their predicted binding to COX-2. Because the thesis contained inconsistent positional depictions for the methyl-substituted compound, it is designated Q2 (methyl-substituted analogue) in this manuscript pending definitive regioisomer assignment by two-dimensional NMR or crystallography.

II. MATERIALS AND METHODS

2.1 Materials

Phenylenediamine, substituted phenylenediamines, methanesulfonyl isopropenyl sulfone, elemental sulfur, dimethyl sulfoxide (DMSO), ethanol, methanol and analytical-grade solvents were used as received. Precoated silica-gel plates were used for thin-layer chromatography (TLC). Distilled water was obtained from the institutional laboratory supply.

2.2 General synthesis of quinoxaline analogues

The appropriate o-phenylenediamine derivative (1 mmol) was dissolved in dry DMSO (approximately 10 mL). Methanesulfonyl isopropenyl sulfone (1 mmol) and elemental sulfur were added, and the reaction mixture was heated at 110 °C with stirring for 2–3 h. Reaction progress was monitored by TLC using a hexane–ethyl acetate mobile phase and iodine-vapor visualization. After completion, the mixture was cooled and poured into ice-cold water. The precipitated solid was collected by filtration, washed with water, dried and recrystallized from ethanol or methanol. The routes used for Q1–Q3 are summarized in Figure 1.

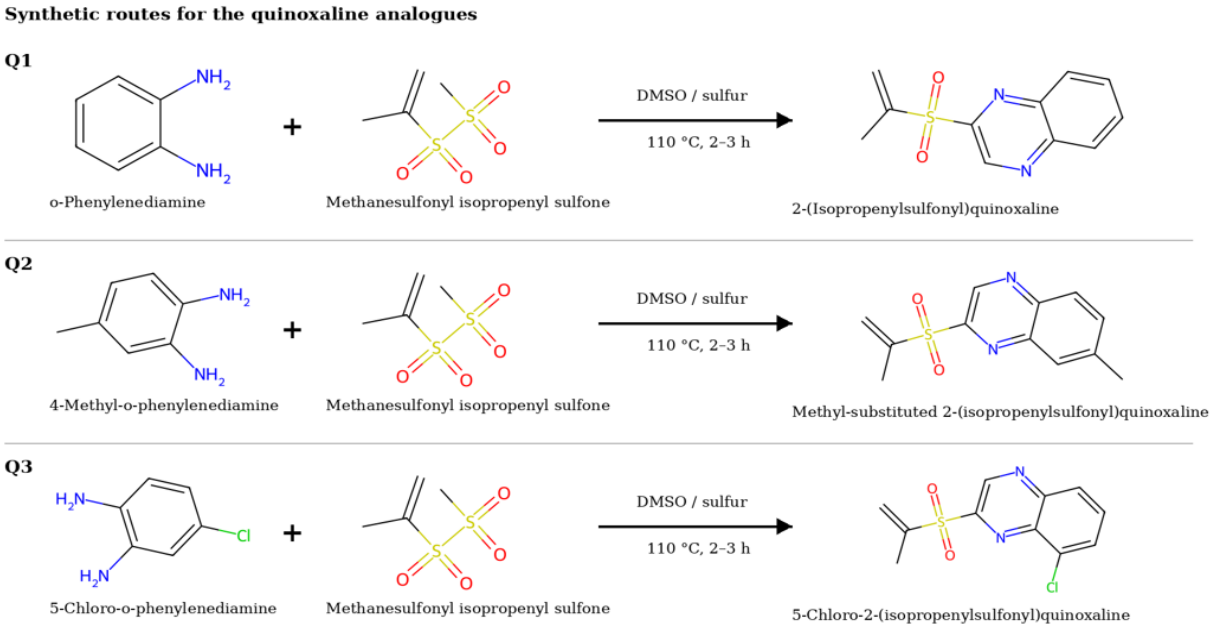

Figure 1. Synthetic routes used to prepare Q1, Q2 and Q3. Q2 is described as the methyl-substituted analogue pending definitive positional assignment.

2.3 Physicochemical and spectral characterization

Melting points were determined by the capillary method. FTIR spectra were recorded by the KBr-pellet method and interpreted using characteristic functional-group frequencies. Proton NMR spectra were recorded at 400 MHz using DMSO-d_6 as solvent. Mass spectra were examined for molecular-ion and diagnostic fragment peaks. Reported NMR assignments were condensed to structure-consistent diagnostic resonances; complete positional confirmation requires ^{13}C NMR and two-dimensional experiments.

2.4 Molecular docking

The crystal structure of COX-2 (PDB ID 3LN1) was prepared by removing crystallographic water molecules and the co-crystallized ligand, followed by addition of polar hydrogens and Kollman charges. Ligands were drawn, energy-minimized and converted to PDBQT format. A grid box was defined around the native-ligand binding pocket, and docking was performed with AutoDock Vina. Binding affinities were reported in kcal/mol. Predicted hydrogen bonds, hydrophobic contacts and π-type interactions were inspected using Discovery Studio Visualizer and PyMOL. Celecoxib was used as the reference ligand in the thesis docking workflow.

III. RESULTS AND DISCUSSION

3.1 Synthesis and physicochemical properties

All three analogues were isolated as crystalline solids in closely comparable yields. Q2 gave the highest practical yield (77.02%), followed by Q1 (76.07%) and Q3 (75.83%). The small range in yields indicates that methyl and chloro substitution did not substantially impair the sulfur-assisted cyclization under the reported conditions. The sharp melting ranges support satisfactory isolation and recrystallization, although chromatographic purity or elemental analysis would be required for quantitative purity confirmation.

Table 1. Physicochemical characteristics of synthesized quinoxaline analogues.

Code	Compound designation	Molecular formula	Molecular weight (g/mol)	Yield (%)	Melting point (°C)
Q1	2-(Isopropenylsulfonyl)quinoxaline	$C_{11}H_{10}N_2O_2S$	234.27	76.07	186–189
Q2	Methyl-substituted 2-(isopropenylsulfonyl)quinoxaline	$C_{12}H_{12}N_2O_2S$	248.30	77.02	178–181
Q3	5-Chloro-2-(isopropenylsulfonyl)quinoxaline	$C_{11}H_9ClN_2O_2S$	268.72	75.83	198–201

Note: Q2 is reported as "4-methyl" in the thesis; the exact ring locant should be confirmed by 2D NMR or single-crystal analysis before publication.

The chloro analogue Q3 showed the highest melting range, consistent with stronger crystal packing and the greater polarizability of chlorine. The lower melting range of Q2 may reflect altered packing caused by the methyl substituent. These observations are qualitative and should be supported by thermal analysis if solid-state behavior is a major focus.

3.2 FTIR characterization

The FTIR data supported formation of the quinoxaline–isopropenylsulfonyl framework. Aromatic C–H stretching occurred near 3075–3082 cm^{-1} and aliphatic C–H stretching near 2962–2986 cm^{-1}. Bands at 1632–1635 cm^{-1} were assigned to overlapping olefinic C=C and quinoxaline C=N vibrations. The two most diagnostic sulfone absorptions were observed at 1322–1328 cm^{-1} (asymmetric SO_2 stretching) and 1154–1160 cm^{-1} (symmetric SO_2 stretching). Terminal $=CH_2$ out-of-plane bending was found near 972–974 cm^{-1}. Q3 additionally showed a band at 760 cm^{-1} assigned to aromatic C–Cl stretching. Representative spectra are shown in Figure 2.

Table 2. Diagnostic FTIR absorption bands of Q1–Q3.

Compound	Key absorption bands (cm^{-1})	Principal assignments
Q1	3078, 2986, 1632, 1574, 1322, 1154, 972, 822	Aromatic/aliphatic C–H; C=C/C=N; aromatic C=C; SO_2 asymmetric/symmetric; terminal $=CH_2$; aromatic C–H bending
Q2	3082, 2962, 1635, 1582, 1452, 1326, 1158, 974, 824	Aromatic/aliphatic C–H; C=C/C=N; aromatic C=C; CH_3 bending; SO_2 asymmetric/symmetric; terminal $=CH_2$; aromatic C–H bending
Q3	3075, 2984, 1634, 1580, 1328, 1160, 972, 824, 760	Aromatic/aliphatic C–H; C=C/C=N; aromatic C=C; SO_2 asymmetric/symmetric; terminal $=CH_2$; aromatic C–H bending; C–Cl

Figure 2. FTIR spectra of Q1–Q3 showing the characteristic aromatic C–H, conjugated C=N/C=C and sulfonyl (SO_2) stretching bands.

In all three spectra, bands near 3075–3080 cm^{-1} indicate aromatic C–H stretching, while signals near 2984–2986 cm^{-1} correspond to aliphatic C–H stretching of the isopropenyl methyl group. The strong absorptions around 1632–1635 cm^{-1} and 1574–1582 cm^{-1} support the conjugated quinoxaline C=N/C=C system. Most importantly, the pair of diagnostic sulfone bands at approximately 1322–1328 cm^{-1} and 1158–1176 cm^{-1} confirms successful introduction of the isopropenylsulfonyl group. Additional bands around 972–974 cm^{-1} are consistent with terminal $=CH_2$ bending, and the chloro-substituted analogue Q3 shows the expected aromatic out-of-plane bending features in the lower fingerprint region.

The reproducibility of the SO_2 and vinyl-region bands across the three analogues indicates retention of the common isopropenylsulfonyl pharmacophore. The C–Cl absorption in Q3 provided an additional substitution-specific marker. Sulfone-containing quinoxalines are of interest because the polar sulfonyl oxygen atoms can serve as hydrogen-bond acceptors in COX-2 and related inflammatory targets [5,18–20].

3.3 Proton NMR characterization

Q1 and Q3 showed a strongly deshielded quinoxaline H-3 signal at δ 8.70 ppm. The terminal methylene protons of the isopropenyl unit appeared as two nonequivalent signals near δ 6.52 and 5.95–5.96 ppm, and the methyl group attached to the olefinic carbon appeared at δ 2.19 ppm. Q2 displayed additional methyl substitution, with a reported ring-methyl signal at δ 2.34 ppm. The diagnostic assignments are summarized in Table 3. The spectral profiles are illustrated in Figure 3.

Table 3. Selected diagnostic ^1H NMR signals reported for the synthesized analogues.

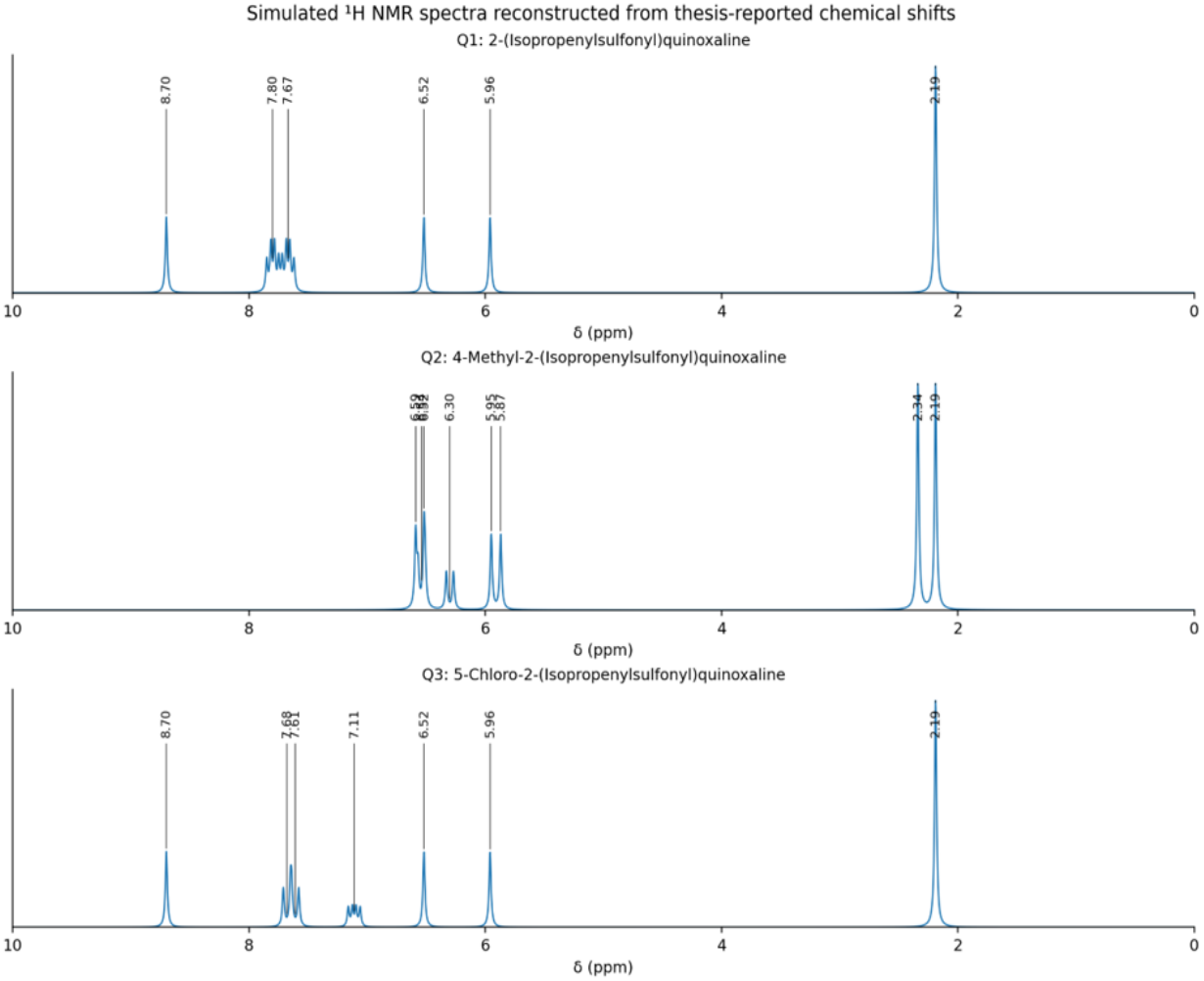

Figure 3. Simulated ^1H NMR spectra of Q1–Q3 reconstructed from the chemical shifts reported in the thesis.

The reconstructed ^{1}H NMR profiles visualize the reported proton environments for the three synthesized analogues. Q1 and Q3 each show a markedly downfield singlet at δ 8.70 ppm assigned to H-3 of the quinoxaline ring, reflecting deshielding by the adjacent ring nitrogens and the sulfonyl substituent. In every analogue, two separate vinyl signals at approximately δ 6.52 and 5.95–5.96 ppm confirm the non-equivalent terminal methylene protons of the isopropenyl fragment, while the singlet at δ 2.19 ppm supports the olefinic methyl group. Q2 additionally shows a methyl singlet at δ 2.34 ppm attributable to ring methyl substitution. The aromatic region differentiates the analogues: Q1 contains four benzene-ring protons, Q2 shows the modified pattern expected for methyl substitution, and Q3 exhibits the three-proton pattern expected for chloro substitution. These features collectively support the proposed substitution pattern of the quinoxaline derivatives. Because the original thesis contained reported chemical-shift assignments rather than exported spectral image files, this panel is a reconstructed representation for manuscript illustration.

Compound	Reported δ (ppm)	Assignment
Q1	8.70 (1H); 7.80 (2H); 7.67 (2H); 6.52 and 5.96 (2H); 2.19 (3H)	H-3; fused-ring aromatic protons; terminal $=CH_2$; isopropenyl CH_3
Q2	6.59, 6.54, 6.30 and 5.87; 6.52 and 5.95; 2.34; 2.19	Reported quinoxaline-region signals; terminal $=CH_2$; ring CH_3; isopropenyl CH_3
Q3	8.70; 7.68, 7.61 and 7.11; 6.52 and 5.96; 2.19	H-3; chloro-substituted fused-ring protons; terminal $=CH_2$; isopropenyl CH_3

Only diagnostic, formula-consistent signals are summarized. The Q2 regioisomer and full assignments should be confirmed using ^{13}C, COSY, HSQC and HMBC data.

For a publication-quality structural claim, the reported proton data should be supplemented by carbon NMR and two-dimensional correlation spectra. This is particularly important for Q2 because positional substitution cannot be assigned confidently from the available one-dimensional data alone.

3.4 Mass-spectrometric characterization

The mass spectra supported the molecular weights of all three analogues. Q1 and Q2 showed molecular-ion peaks at m/z 234 and 248, respectively. Q3 produced peaks at m/z 268 and 270, consistent with the characteristic approximately 3:1 isotope pattern of a monochlorinated compound. Common fragmentation included loss of a methyl radical and cleavage of the SO_2 group, producing stabilized quinoxaline-derived ions. Representative spectra are shown in Figure 4.

Table 4. Molecular-ion and selected fragment peaks.

Compound	Molecular-ion peak(s), m/z	Selected fragment peaks, m/z	Interpretation
Q1	234	219, 170, 156, 130	M^+; loss of CH_3; loss of SO_2; quinoxaline-derived fragments
Q2	248	233, 184, 169, 144	M^+; loss of CH_3; loss of SO_2; methylquinoxaline fragment
Q3	268 and 270	253, 204, 189, 169	M/M+2 chlorine isotope pair; loss of CH_3 and SO_2; chloroquinoxaline fragment

The molecular-ion values were consistent with the reported molecular formulae. The 268/270 isotope pair is particularly useful evidence for incorporation of chlorine in Q3. High-resolution mass spectrometry would further strengthen elemental-composition confirmation.

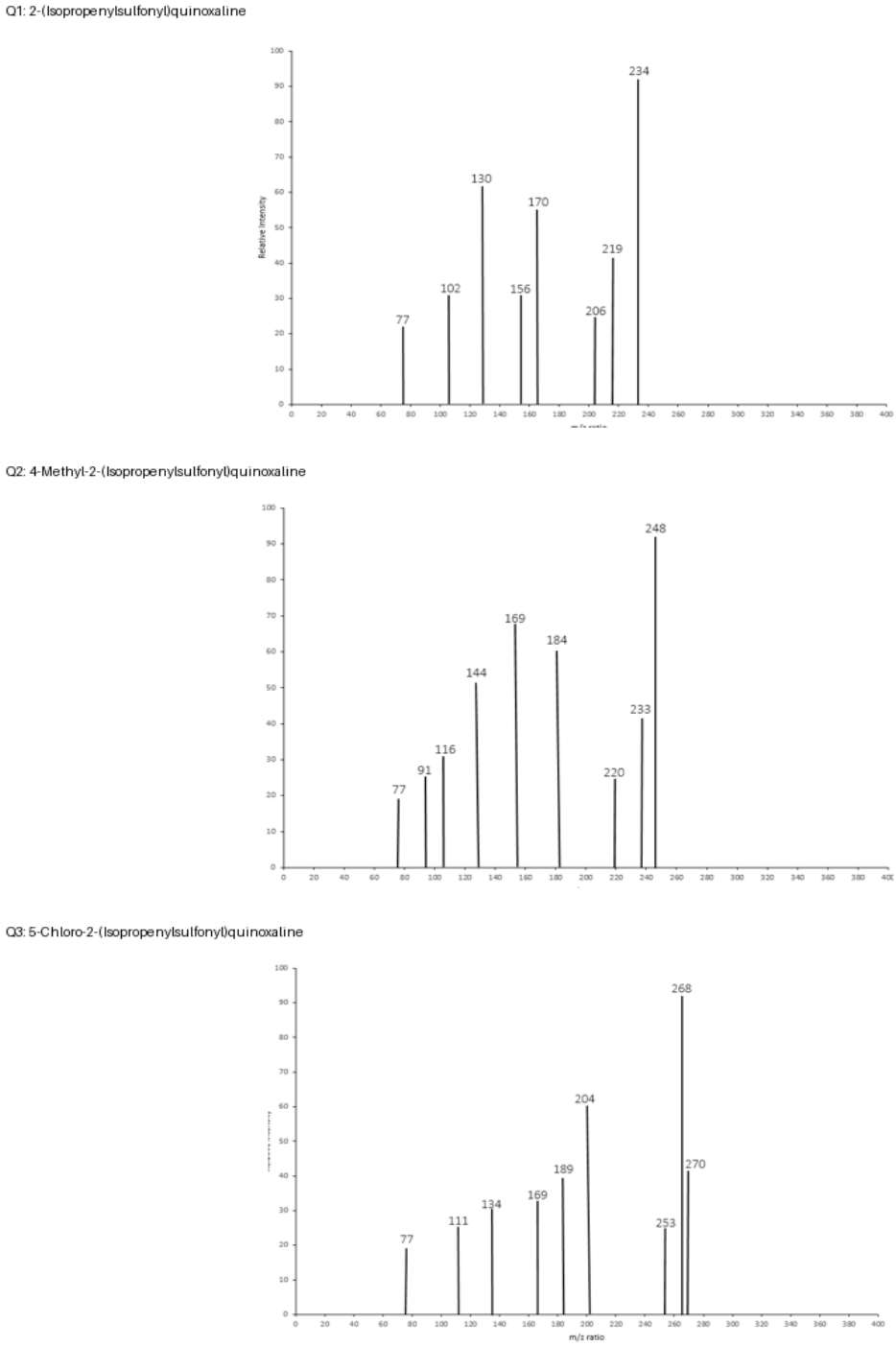

Figure 4. Mass spectra of Q1–Q3 showing the molecular-ion peaks and characteristic fragment ions of the synthesized quinoxaline analogues.

The three mass spectra support the expected molecular weights of the synthesized derivatives. Q1 shows a molecular-ion peak at m/z 234, consistent with the parent isopropenylsulfonyl quinoxaline nucleus, together with fragment ions at m/z 219, 206, 170, 156, 130, 102 and 77 arising from loss of methyl and cleavage within the sulfone-linked side chain and aromatic heterocycle. Q2 exhibits a molecular-ion peak at m/z 248, in agreement with the additional methyl substituent, and fragment ions at m/z 233, 220,

184, 169, 144, 116, 91 and 77. The prominent fragment at m/z 184 is particularly consistent with loss of the SO_2-containing portion and formation of a stabilized quinoxaline-derived cation. Q3 displays the characteristic chlorine isotope pattern with peaks at m/z 268 and 270 (approximately 3:1 intensity), providing strong evidence for incorporation of a single chlorine atom. Additional fragments at m/z 253, 204, 189, 169, 134, 111 and 77 further support the proposed structure. Overall, the mass-spectrometric results corroborate the assigned molecular formulae of Q1–Q3 and complement the FTIR and ^{1}H NMR characterization.

3.5 Molecular docking and preliminary structure–affinity relationship

All analogues were predicted to occupy the COX-2 binding pocket with negative docking scores. Q1 gave a score of −7.1 kcal/mol and was reported to interact with Arg120 and Tyr355 through hydrogen bonding, together with hydrophobic contacts involving Leu352 and Val523. Addition of a methyl substituent in Q2 improved the score to −7.4 kcal/mol, consistent with greater hydrophobic contact. Q3 showed the most favorable score (−7.8 kcal/mol), with reported interactions involving His90, Ser530, Arg513, Val523 and Leu352. The thesis reported an approximate celecoxib score of −8.5 kcal/mol under the same workflow.

Table 5. Predicted COX-2 docking results for Q1–Q3.

Compound	Docking score (kcal/mol)	Major reported interactions	Interpretation
Q1	−7.1	H-bonds: Arg120, Tyr355; hydrophobic: Leu352, Val523	Favorable predicted binding
Q2	−7.4	Sulfonyl oxygen H-bonding; hydrophobic contacts with Leu352 and Val523	Improved predicted affinity
Q3	−7.8	Reported contacts with His90, Ser530, Arg513, Val523 and Leu352; possible halogen contribution	Best predicted affinity
Celecoxib (reference)	≈ −8.5	Reference value reported in thesis	Stronger reference binding

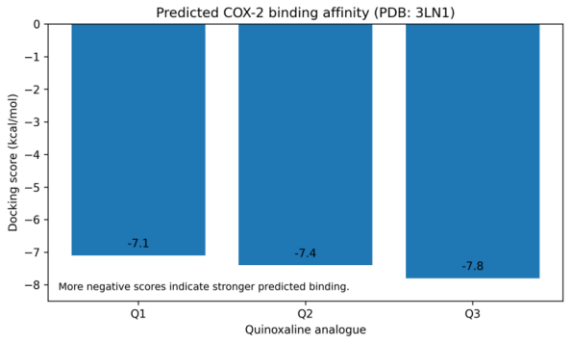

Figure 5. Comparison of reported COX-2 docking scores for the synthesized analogues. More negative values indicate stronger predicted binding.

The ranking Q3 > Q2 > Q1 suggests that hydrophobic and electron-withdrawing substitution can improve predicted COX-2 affinity. Chlorine may enhance van der Waals contacts and can support directional halogen interactions, while the sulfonyl oxygen atoms provide polar anchoring. Similar trends have been described for substituted quinoxaline anti-inflammatory scaffolds, in which halogenation and optimized lipophilicity improve target complementarity [5–13,16,21,22].

Docking scores alone do not demonstrate enzyme inhibition or anti-inflammatory efficacy. The numerical differences are modest and may be sensitive to protonation state, ligand structure, grid definition and scoring-function limitations. In addition, the Q2 structural depiction should be finalized and re-docked before submission. Enzyme assays, cellular readouts and orthogonal computational validation are required before drawing pharmacological conclusions.

IV. CONCLUSION

Three isopropenylsulfonyl quinoxaline analogues were prepared in yields of approximately 76–77% and characterized by physicochemical, FTIR, proton NMR and mass-spectrometric data. The common sulfone and terminal alkene functionalities were supported by consistent spectroscopic features, and the chloro analogue showed the expected chlorine isotope pattern. COX-2 docking ranked Q3 as the most

favorable analogue (−7.8 kcal/mol), followed by Q2 (−7.4 kcal/mol) and Q1 (−7.1 kcal/mol). The results support Q3 as the priority compound for experimental evaluation; however, the present evidence establishes only predicted binding, not confirmed anti-inflammatory activity.

V. LIMITATIONS AND FUTURE WORK

The study did not include direct COX-2 enzyme inhibition, cellular anti-inflammatory assays, cytotoxicity, in-vivo pharmacology, stability or pharmacokinetic studies. Structural confirmation should be strengthened using ^{13}C NMR, COSY, HSQC, HMBC, high-resolution mass spectrometry and, where possible, single-crystal X-ray diffraction. The Q2 positional assignment requires particular attention. Future studies should include COX-1/COX-2 selectivity testing, inhibition of nitric oxide or cytokine production in stimulated macrophages, dose–response and IC_{50} determination, mammalian-cell safety assessment, molecular-dynamics simulation, binding-free-energy calculations and ADMET profiling.

DECLARATIONS

Ethics approval: Not applicable; no human or animal experiments were reported.
Consent for publication: Not applicable.
Availability of data: All data used in this manuscript were derived from the submitted thesis and are summarized in the article.
Competing interests: The author declares no competing interests.
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