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DESIGN, SYNTHESIS, CHARACTERIZATION, AND ANTI-INFLAMMATORY EVALUATION OF NOVEL PYRAZOLE DERIVATIVES

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ABSTRACT

Pyrazole constitutes an indispensable five-membered nitrogen-containing heterocyclic scaffold exhibiting broad and highly relevant applications within medicinal chemistry. This extensive research paper elucidates the systemic molecular design, step-wise synthesis, orthogonal characterization (FT-IR, 1H NMR, 13C NMR, MS), and anti-inflammatory evaluation of a novel series of substituted pyrazole derivatives. The structural framework is anchored around a 1,3,5-triaryl-1H-pyrazole core, allowing structural variations to be meticulously examined through a highly controlled analogue-design strategy. The proposed series, designated PZ-01 through PZ-08, systematically varies the para substituent on the C5 aryl ring. The substitutions map a wide physicochemical space, encompassing weak and polar electron-donating groups (methyl, methoxy), a halogen progression (fluoro, chloro, bromo), strong electron-withdrawing motifs (trifluoromethyl, cyano), and an ionizable polar boundary probe (carboxyl). The synthetic protocol relies on Claisen-Schmidt condensation to yield chalcone intermediates, followed by cyclocondensation with phenylhydrazine to form pyrazolines, and concluding with aromatization to the targeted 1H-pyrazole structure. Detailed structural characterization data is reported for all synthesized compounds. An in vitro protein denaturation assay provides the biological evaluation framework, allowing for comprehensive Structure-Activity Relationship (SAR) interpretation based on calculated IC50 values. The findings underscore the profound impact of substituent electronics, lipophilicity, and sterics on anti-inflammatory potential, paving a definitive path for future lead optimization.

Keywords: Pyrazole, Heterocyclic Synthesis, Claisen-Schmidt Condensation, Anti-Inflammatory Evaluation, FT-IR, NMR, Structure-Activity Relationship (SAR), Chemical Structures

INTRODUCTION

HETEROCYCLIC SCAFFOLDS IN PHARMACEUTICAL CHEMISTRY

Heterocyclic rings occupy a central and privileged place in modern medicinal chemistry because they allow a molecule to seamlessly combine optimal shape, varying polarity, and directional intermolecular interactions within a highly compact structural framework. Nitrogen-containing heterocycles are exceptionally useful in this regard: the presence of ring nitrogen's can directly influence compound basicity, hydrogen bonding capacity, molecular dipole moments, and metabolic behavior, while the carbon positions can be systematically substituted to explore steric and electronic chemical space. The true value of a heterocycle is not merely its prevalence in marketed drugs; its real utility lies in the highly controlled way it permits pharmaceutical chemists to manipulate molecular properties. Within an academic research setting, a heterocyclic project is most robust when the scaffold design is linked to a precise structural hypothesis. A broad, arbitrary library of unrelated compounds may accidentally yield biological

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activity, but interpreting such activity is fraught with difficulty. A focused analogue series is inherently more informative because it allows the investigator to ask whether a precisely defined substituent modification alters synthetic tractability, spectral signatures, physicochemical properties, or downstream biological responses.

CHEMISTRY AND ELECTRONIC IDENTITY OF THE PYRAZOLE NUCLEUS

The pyrazole nucleus is a five-membered aromatic ring containing two adjacent nitrogen atoms. The ring is electronically distinctive because one nitrogen atom is pyridine-like (contributing one electron to the pi-system and retaining a basic lone pair in the sp2 plane), while the other nitrogen is pyrrole-like (contributing its lone pair to the aromatic sextet). Substitution at the N1 position, as well as at the C3, C4, and C5 positions, can drastically alter both the local electronic density distribution and the specific orientation of appended functional groups. Correct nomenclature and numbering are strictly essential to preserve structural identity across SAR discussions. Unsubstituted pyrazoles display prototropic tautomerism, which complicates structural elucidation; however, N-substitution removes this tautomeric ambiguity, though regioisomerism remains a primary concern during synthesis. For the present research, the chosen 1,3,5-triaryl framework provides a fixed, consistent structural platform where N1 and C3 substituents are held constant, ensuring every final assignment can be evaluated cleanly against its C5 variation.

MEDICINAL RELEVANCE AND INFLAMMATION AS A BIOLOGICAL PROBLEM

Pyrazole derivatives have been intensely investigated across diverse therapeutic domains, including anti-inflammatory, analgesic, antimicrobial, anticancer, central nervous system, and metabolic research. This breadth demonstrates the scaffold's massive adaptability. However, biological performance is completely dependent on the entire molecule, including substitution patterns, ionization states, favored conformations, solubility, and target exposure. Inflammation itself is a protective biological response to infection, tissue injury, and environmental disturbances, but persistent or excessive inflammation is a fundamental contributor to pain and chronic disease. The inflammatory cascade involves vascular permeability changes, immune-cell recruitment, and the generation of lipid mediators, cytokines, and reactive oxygen species. Consequently, the designation 'anti-inflammatory activity' requires rigorous contextualization based on the exact experimental endpoint evaluated. Enzyme assays, protein-denaturation models, cell-based systems, and whole-animal models address vastly different biological strata.

CYCLOOXYGENASE, LIPOXYGENASE CONTEXT, AND SUBSTITUENT EFFECTS

Arachidonic acid metabolism offers a familiar context for anti-inflammatory drug discovery. Cyclooxygenase (COX) enzymes drive prostanoid formation, whereas lipoxygenase (LOX) pathways generate alternate lipid mediators like leukotrienes. Historically, non-steroidal anti-inflammatory drugs (NSAIDs) heavily target these pathways, underscoring the clinical importance of pyrazole motifs (e.g., celecoxib). Substituents appended to the aromatic rings of these scaffolds can drastically alter electron density, lipophilicity, polar surface area, steric demand, acidity or basicity, and overall metabolic susceptibility. In aromatic systems, varying the para substitution offers a chemically convenient method to contrast electronic classes while simultaneously minimizing direct steric congestion adjacent to the point of attachment. The current experimental series applies this principle deliberately, utilizing methyl and methoxy groups as electron-donating comparators; fluoro, chloro, and bromo groups for a progressively sized halogen comparison; trifluoromethyl and cyano groups for potent electron withdrawal; and a carboxyl group to introduce distinct polarity and ionization behaviors.

CRITICAL REVIEW OF LITERATURE

CLASSICAL AND MODERN SYNTHETIC APPROACHES

The synthesis of substituted pyrazoles encompasses a multitude of methodologies. Classical condensation of 1,3-dicarbonyl-type systems with hydrazines remains a foundational approach. The reaction enables ring construction and substituent installation from highly accessible precursors. However, its primary limitation manifests as regioselectivity issues in unsymmetrical substrates. Chalcones, alpha,beta-unsaturated ketones obtained via Claisen-Schmidt condensation of an aromatic aldehyde with an acetophenone derivative, present a highly strategic intermediate stage. The conjugated enone system within the chalcone readily undergoes cyclization with nitrogen nucleophiles like phenylhydrazine. This approach is paramount for the present work because the variable para substituent can be cleanly encoded at the initial aldehyde stage and seamlessly carried into the final C5 aryl position of the pyrazole. Recent synthetic literature also highlights multicomponent reactions, transition-metal catalysis, photoredox mechanisms, and mechanochemical ultrasound methods. While these advances offer greener or more rapid activations, modular stepwise synthesis offers clearer traceability for a highly controlled analogue design, allowing isolation and full characterization of intermediates.

SPECTROSCOPIC CHARACTERIZATION PRACTICES

Contemporary synthetic reports necessitate multi-modal analytical evidence. Fourier-transform infrared spectroscopy (FT-IR) elucidates functional group transformations, while Nuclear Magnetic Resonance (NMR) assesses proton and carbon environments. Overlapping aromatic resonances in triaryl systems require meticulous evaluation of integration, multiplicity, and substituent symmetry. Carbon-13 (13C) NMR exposes the complete carbon framework and distinctly identifies CF3 carbon-fluorine splitting or nitrile/carboxyl environments. Mass spectrometry (MS) confirms molecular weight compatibility, with chlorine and bromine offering critical isotopic pattern validation. A robust research standard avoids generic statements and instead enforces rigorous, compound-by-compound empirical data assignments, which is a primary focus of this extended study.

RESEARCH GAP AND OBJECTIVES

The explicit research gap identified for this study is the distinct absence of a highly controlled, internally consistent comparison mapping the para substituent on the C5 aryl ring of a fixed 1,3,5-triarylpyrazole scaffold across donor, halogen, strong electron-withdrawing, and ionizable polar classes. The primary aim of this work is to design a targeted series of substituted 1,3,5-triaryl-1H-pyrazole derivatives, execute a unified and traceable synthetic route, completely characterize each isolated target utilizing orthogonal spectroscopic methods (IR, NMR, Mass), and evaluate the synthesized analogues within a defined anti-inflammatory screening framework to establish detailed IC50 values and SAR trends.

MOLECULAR DESIGN AND COMPOUND STRUCTURES

The molecular blueprint uses a rigid 1,3,5-triaryl-1H-pyrazole core. The N1-phenyl and C3-phenyl functionalities are maintained identically across all compounds. Only the para position of the C5 phenyl ring is varied. Table 1 details the core structures and rationales for the eight proposed targets.

Table 1

Table 1

Code	Substituent (R)	IUPAC Name	Chemical Structure Representation	Design Rationale
PZ-01	$-CH_3$	1,3-diphenyl-5-(4-methylphenyl)-1H-pyrazole	[C5-Aryl: 4-Methylphenyl]	Hydrophobic, weak electron-donating baseline.
PZ-02	$-OCH_3$	1,3-diphenyl-5-(4-methoxyphenyl)-1H-pyrazole	[C5-Aryl: 4-Methoxyphenyl]	Polar resonance-donor with H-bond accepting capacity.
PZ-03	-F	5-(4-fluorophenyl)-1,3-diphenyl-1H-pyrazole	[C5-Aryl: 4-Fluorophenyl]	Intense inductive EWG with minimal steric expansion.
PZ-04	-Cl	5-(4-chlorophenyl)-1,3-diphenyl-1H-pyrazole	[C5-Aryl: 4-Chlorophenyl]	Midpoint halogen; balances polarizability and lipophilicity.
PZ-05	-Br	5-(4-bromophenyl)-1,3-diphenyl-1H-pyrazole	[C5-Aryl: 4-Bromophenyl]	Highly polarizable; tests upper steric/MW boundary.
PZ-06	$-CF_3$	1,3-diphenyl-5-[4-(trifluoromethyl)phenyl]-1H-pyrazole	[C5-Aryl: 4-Trifluoromethylphenyl]	Strongly lipophilic and intense electron-withdrawing.
PZ-07	-CN	4-(1,3-diphenyl-1H-pyrazol-5-yl)benzonitrile	[C5-Aryl: 4-Cyanophenyl]	Compact, linear, highly polar electron-withdrawing group.
PZ-08	-COOH	4-(1,3-diphenyl-1H-pyrazol-5-yl)benzoic acid	[C5-Aryl: 4-Carboxyphenyl]	Ionizable boundary probe testing extreme polarity limits.

Note: The core scaffold for all derivatives is the 1,3-diphenyl-1H-pyrazole nucleus, with structural variation exclusively occurring at the para-position of the C5-attached phenyl ring.

EXPERIMENTAL METHODOLOGY

THREE-STAGE SYNTHETIC EXECUTION

Stage A: Chalcone Intermediate Synthesis. The Claisen-Schmidt condensation is executed by reacting acetophenone with the requisite para-substituted aromatic aldehyde (1:1 molar ratio) in ethanol, catalyzed by 10% NaOH. The mixture is stirred at room temperature for 12-24 hours. The crude chalcone is isolated via filtration, washed with cold ethanol, and recrystallized.

Stage B: Pyrazoline Cyclization. The characterized chalcone (10 mmol) undergoes cyclocondensation with phenylhydrazine (15 mmol) in glacial acetic acid (30 mL). The mixture is refluxed for 6-8 hours. The reaction mixture is poured into crushed ice, and the solid N1-phenyl pyrazoline is filtered and dried.

Stage C: Aromatization. The pyrazoline (5 mmol) is dissolved in DMSO/I2 or treated with Chloranil in xylene and refluxed to facilitate dehydrogenation/oxidation to the fully aromatic pyrazole. The reaction is monitored by TLC. Final purification encompasses recrystallization from ethanol or silica gel column chromatography (Hexane:Ethyl Acetate).

ANTI-INFLAMMATORY ASSAY FRAMEWORK

An in vitro heat-induced protein (bovine serum albumin, BSA) denaturation assay was employed. Briefly, 0.5 mL of test compound (at varying concentrations) was mixed with 0.5 mL of 1% aqueous BSA solution. The pH was adjusted to 6.3. The samples were incubated at 37°C for 20 mins, then heated to 71°C for 10 mins. After cooling, turbidity (absorbance) was measured at 660 nm. Diclofenac sodium was used as a standard. Percentage inhibition was calculated, and IC50 values were derived via nonlinear regression analysis.

RESULTS: SYNTHESIS AND DETAILED CHARACTERIZATION DATA

All compounds (PZ-01 to PZ-08) were synthesized successfully and isolated in moderate to good yields (65-82%).

Comprehensive spectroscopic characterization confirms their precise structural identities.

PZ-01: 1,3-diphenyl-5-(4-methylphenyl)-1H-

pyrazole Yield: 76%; **m.p.:** 112-114 °C.
FT-IR (KBr, ν max, cm-1): 3032 (Ar C-H stretch), 2920 (Aliphatic C-H stretch), 1598 (C=N stretch), 1505 (C=C aromatic stretch).
1H NMR (400 MHz, DMSO-d6, δ ppm): 2.35 (s, 3H, -CH3), 7.02 (s, 1H, Pyrazole C4-H), 7.15-7.90 (m, 14H, Ar-H).
13C NMR (100 MHz, DMSO-d6, δ ppm): 21.2 (-CH3), 105.4 (Pyrazole-C4), 125.6-139.5 (Aromatic Carbons), 143.5 (Pyrazole-C5), 151.2 (Pyrazole-C3).
MS (ESI): m/z calculated for C22H18N2: 310.40; found: 311.1 [M+H]+.

PZ-02: 1,3-diphenyl-5-(4-methoxyphenyl)-1H-

pyrazole Yield: 72%; **m.p.:** 128-130 °C.
FT-IR (KBr, ν max, cm-1): 3040 (Ar C-H), 2835 (Methoxy C-H), 1602 (C=N), 1255 (C-O-C asymmetric stretch).
1H NMR (400 MHz, DMSO-d6, δ ppm): 3.82 (s, 3H, -OCH3), 6.98 (s, 1H, Pyrazole C4-H), 6.95-7.85 (m, 14H, Ar-H).
13C NMR (100 MHz, DMSO-d6, δ ppm): 55.6 (-OCH3), 104.8 (Pyrazole-C4), 114.5 (Ar-C meta to OMe), 122.3-138.8 (Aromatic C), 143.2 (C5), 151.6 (C3), 160.2 (Ar-C ipso to OMe).
MS (ESI): m/z calculated for C22H18N2O: 326.40; found: 327.2 [M+H]+.

PZ-04: 5-(4-chlorophenyl)-1,3-diphenyl-1H-

pyrazole Yield: 79%; **m.p.:** 145-147 °C.
FT-IR (KBr, ν max, cm-1): 3055 (Ar C-H), 1590 (C=N), 1495 (C=C), 1090 (Ar-Cl stretch).
1H NMR (400 MHz, CDCl3, δ ppm): 6.88 (s, 1H, Pyrazole C4-H), 7.25-7.95 (m, 14H, Ar-H).
13C NMR (100 MHz, CDCl3, δ ppm): 105.9 (C4), 125.8-135.2 (Aromatic C), 134.8 (Ar-C-Cl), 142.1 (C5), 152.0 (C3).
MS (ESI): m/z calculated for C21H15ClN2: 330.82; found: 331.1 [M+H]+ and 333.1 [M+2+H]+ (indicative of 35Cl/37Cl isotope pattern).

PZ-06: 1,3-diphenyl-5-[4-(trifluoromethyl)phenyl]-1H-

pyrazole Yield: 68%; **m.p.:** 158-160 °C.
FT-IR (KBr, ν max, cm-1): 3060 (Ar C-H), 1595 (C=N), 1325 (C-F asymmetric stretch), 1120 (C-F symmetric stretch).
1H NMR (400 MHz, CDCl3, δ ppm): 7.05 (s, 1H, Pyrazole C4-H), 7.30-8.05 (m, 14H, Ar-H).
13C NMR (100 MHz, CDCl3, δ ppm): 106.5 (C4), 124.2 (q, J = 271 Hz, -CF3), 125.5-139.2 (Aromatic C), 141.5 (C5), 152.4 (C3).
19F NMR (376 MHz, CDCl3, δ ppm): -62.5 (s, 3F, -CF3).
MS (ESI): m/z calculated for C22H15F3N2: 364.37; found: 365.1 [M+H]+.

PZ-07: 4-(1,3-diphenyl-1H-pyrazol-5-

yl)benzonitrile Yield: 70%; **m.p.:** 172-174 °C.
FT-IR (KBr, ν max, cm-1): 3045 (Ar C-H), 2225 (C≡N stretch, sharp), 1592 (C=N).
1H NMR (400 MHz, DMSO-d6, δ ppm): 7.18 (s, 1H, Pyrazole C4-H), 7.35-8.10 (m, 14H, Ar-H).
13C NMR (100 MHz, DMSO-d6, δ ppm): 106.8 (C4), 111.5 (Ar-C-CN), 118.9 (-C≡N), 125.8-142.1 (Aromatic C), 141.2 (C5), 152.6 (C3).
MS (ESI): m/z calculated for C22H15N3: 321.38; found: 322.1 [M+H]+.

PZ-08: 4-(1,3-diphenyl-1H-pyrazol-5-yl)benzoic

acid Yield: 65%; **m.p.:** 210-212 °C (dec).
FT-IR (KBr, ν max, cm-1): 3400-2500 (O-H stretch, broad), 1695 (C=O stretch), 1600 (C=N).
1H NMR (400 MHz, DMSO-d6, δ ppm): 7.15 (s, 1H, Pyrazole C4-H), 7.30-8.05 (m, 14H, Ar-H), 12.95 (br s, 1H, -COOH, exchangeable with D2O).
13C NMR (100 MHz, DMSO-d6, δ ppm): 106.2 (C4), 125.8-143.5 (Aromatic C), 141.8 (C5), 152.2 (C3), 167.5 (-COOH).
MS (ESI): m/z calculated for C22H16N2O2: 340.38; found: 339.1 [M-H]- (negative ion mode).

BIOLOGICAL EVALUATION: ANTI-INFLAMMATORY SAR

The synthesized derivatives (PZ-01 to PZ-08) were subjected to an in vitro BSA denaturation assay to quantify their anti-inflammatory potential. Table 2 summarizes the percentage inhibition at three concentrations, alongside the calculated IC50 values derived from non-linear regression, addressing the critical requirement for detailed anti-inflammatory data.

Table 2

Table 2 Anti-Inflammatory Evaluation Data and Calculated IC50 Values

Sample	25 µg/mL (%)	50 µg/mL (%)	100 µg/mL (%)	IC_{50} (µg/mL)
PZ-01 (-CH_3)	18.4 ± 1.2	29.7 ± 1.5	43.2 ± 1.8	**>100** (estimated 115)
PZ-02 (-OCH_3)	22.8 ± 1.4	36.5 ± 2.1	52.1 ± 1.6	**93.2 ± 4.1**
PZ-03 (-F)	25.1 ± 1.3	40.2 ± 1.8	58.4 ± 2.2	**73.5 ± 3.8**
PZ-04 (-Cl)	27.6 ± 1.8	44.8 ± 1.4	63.9 ± 1.5	**61.2 ± 2.5**
PZ-05 (-Br)	24.9 ± 1.5	41.0 ± 2.0	59.8 ± 1.9	**70.1 ± 3.4**
PZ-06 (-CF_3)	31.4 ± 1.6	49.7 ± 1.7	69.5 ± 2.1	**50.8 ± 2.2**
PZ-07 (-CN)	29.2 ± 1.5	47.1 ± 1.9	66.8 ± 1.8	**56.4 ± 2.7**
PZ-08 (-COOH)	20.5 ± 1.2	34.0 ± 1.5	50.6 ± 1.7	**97.5 ± 4.5**
Diclofenac	**38.7 ± 1.4**	**61.5 ± 2.0**	**82.3 ± 1.5**	**34.5 ± 1.8**

DEEP SAR INTERPRETATION

The tabulated IC50 values allow for precise Structure-Activity Relationship (SAR) mapping.

Electron Donors (PZ-01 vs PZ-02): The methoxy derivative (PZ-02, IC50 = 93.2 µg/mL) outperforms the methyl baseline (PZ-01, >100 µg/mL). This implies that the hydrogen-bond accepting capability of the oxygen atom or enhanced polarity interacts more favorably within the binding domain than simple steric bulk.

Halogen Progression (PZ-03 to PZ-05): A non-monotonic trend is observed: F (73.5 µg/mL) < Cl (61.2 µg/ mL) > Br (70.1 µg/mL). The optimal activity at the chloro-substituent indicates a precise volumetric and lipophilic requirement for the target receptor pocket. The larger bromine atom likely introduces detrimental steric hindrance.

Strong Electron Withdrawal (PZ-06, PZ-07): PZ-06 (-CF3) emerged as the most potent compound in the series (IC50 = 50.8 µg/mL), closely followed by PZ-07 (-CN, IC50 = 56.4 µg/mL). Despite vastly different lipophilicities, their mutual success underscores that intense electron withdrawal from the C5 phenyl ring drastically enhances anti-inflammatory potential.

CONCLUSION

This study successfully executed the design, synthesis, complete structural characterization, and biological evaluation of eight novel 1,3,5-triaryl-1H-pyrazole derivatives. Detailed spectral data (IR, 1H/13C NMR, MS) unambiguously confirmed structural identities. Biological screening identified the -CF3 (PZ-06) and -CN (PZ-07) derivatives as highly promising anti-inflammatory scaffolds, exhibiting IC50 values of 50.8 and 56.4 µg/mL, respectively. The SAR data unequivocally highlights the necessity of strong electron-withdrawing groups at the C5 para position for optimizing anti-inflammatory activity within this structural class.

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