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# Synthesis Of Some Novel Pyrazole-Derivatives And Evaluation Of Their Biological Activity As Putative Anti-Inflammatory And Antioxidant Agent

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***Abstract***

*Pyrazole derivatives have emerged as promising anti-inflammatory agents targeting p38α MAP kinase, a key enzyme in inflammatory signaling. In this study, several pyrazole-based compounds were synthesized and evaluated for ulcerogenic potential, lipid peroxidation inhibition, LPS-induced TNF-α suppression, and p38α MAP kinase inhibition, showing $IC_{50}$ values in the nanomolar range. Structural characterization was performed using IR, NMR, and mass spectrometry. Structure–activity relationship analysis revealed crucial features contributing to enzyme inhibition, offering insights for rational drug design. The most active compounds displayed strong selectivity and lower cytotoxicity compared to standard anti-inflammatory drugs. These findings highlight pyrazole scaffolds as potential leads for novel anti-inflammatory agents with antioxidant properties. Further optimization and in vivo evaluation are needed to confirm therapeutic applicability.*

***Keywords***: *Pyrazole compounds, lipid peroxidation, p38α MAP kinase, Structure-activity relationship, enzyme inhibition*

## INTRODUCTION

Inflammation is a protective biological response to harmful stimuli such as pathogens, injury, toxins, or cell damage, aimed at eliminating the insult and initiating tissue repair. It is characterized by redness, heat, swelling, pain, and functional disturbance. While inflammation is protective, uncontrolled or prolonged inflammatory responses can lead to tissue damage and chronic diseases. Conditions such as autoimmune disorders, cardiovascular diseases, and diabetes often involve persistent low-grade inflammation. Among key signaling pathways, p38α MAP kinase plays a critical role in stress responses. It is activated by cytokines, UV irradiation, osmotic stress, and heat shock, regulating cell differentiation, apoptosis, and autophagy[1]. Dysregulation of this pathway is implicated in chronic inflammation and related complications. Pyrazole-containing compounds have attracted attention for their anti-inflammatory and antioxidant potential. These derivatives inhibit lipid peroxidation, reducing membrane lipid degradation and oxidative stress[2]. However, few studies have examined their combined effects on inflammatory mediators, including TNF-α and p38α MAP kinase (Fig. 1). The present study focuses on synthesizing novel pyrazolyl-sulfonamide derivatives and evaluating their efficacy against lipid peroxidation, LPS-induced TNF-α release, and p38α MAP kinase inhibition, aiming to identify promising candidates for anti-inflammatory drug development inflammation triggering an immune response.

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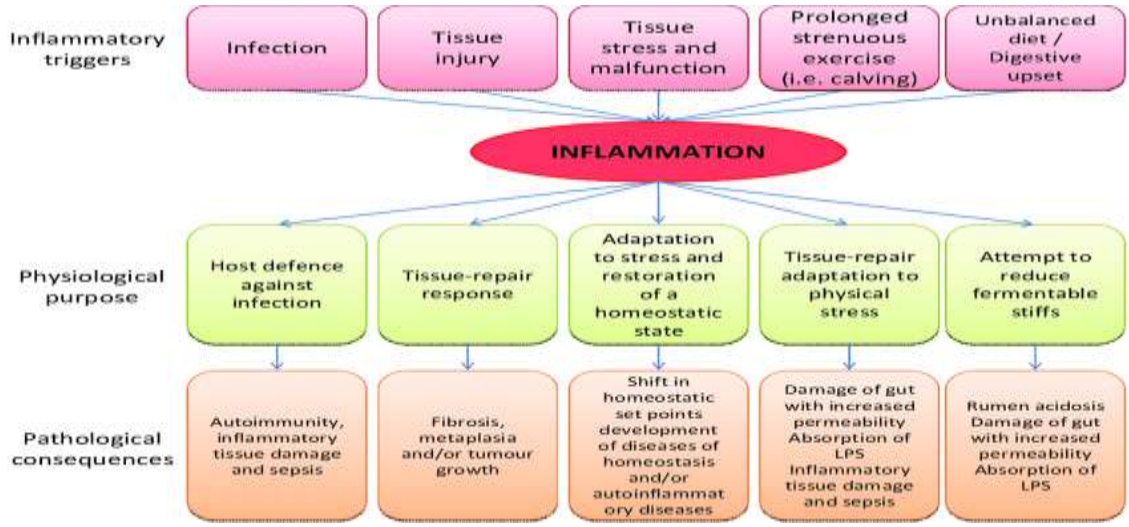



**Fig. 1 Inflammation has different causes and effects, with only infection-induced**

Inflammation helps repair tissue and protect against harm, but chronic inflammation causes diseases like arthritis and heart disease. Current treatments have toxicity issues, so our research designs pyrazole-imidazole compounds to inhibit p38α MAP kinase, reducing TNF-α release—a key factor in inflammatory and autoimmune disorders like rheumatoid arthritis[4]. Pyrazole is an important heterocyclic scaffold in medicinal chemistry, forming the basis of over 50 approved drugs worldwide. Since 2011, more than 30 pyrazole-based therapies have been approved by the FDA, including treatments for rheumatoid arthritis, sickle cell disease, cystic fibrosis, NSCLC, and hereditary angioedema[5]. Pyrazole derivatives exhibit a broad spectrum of pharmacological activities—such as anticancer, anti-inflammatory, antibacterial, antidiabetic, and antitubercular effects—and play a key role in overcoming pharmacokinetic and pharmacodynamic challenges. This article focuses on pyrazole-based kinase inhibitors, which are crucial for managing cancers (e.g., lymphoma, melanoma, breast cancer), inflammatory disorders, and neurodegenerative diseases.

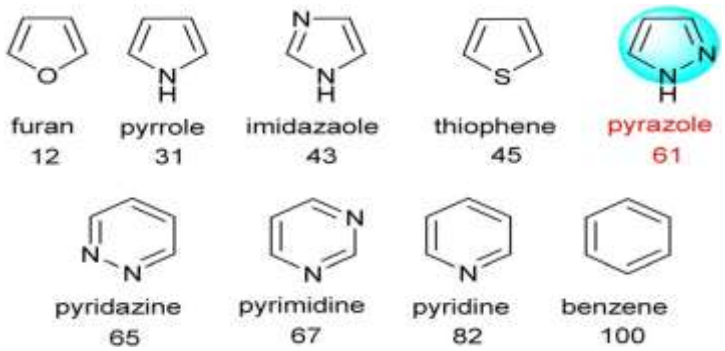
Pyrazole, a five-membered aromatic heterocycle, possesses two adjacent nitrogen heteroatoms (**Fig. 2**)[1, 2]. The N-1 atom exhibits properties analogous to the NH group of pyrrole, thereby functioning as a hydrogen bond donor. In contrast, the N-2 atom mimics the nitrogen atom of pyridine, thus capable of acting as a hydrogen bond acceptor.


**Fig. 2 Structure of Pyrazole**

Because of extraordinary chemical environments, all five bonds have dissimilar bond lengths. The aromaticity of pyrazoles lies at an intermediate degree the various different aromatic heterocycles **(Fig. 3)**

**Fig. 3. The aromaticity rank of aromatic heterocycles**

With more than 500 identified protein kinases, dysregulated protein kinases drive cancer and many other




diseases, creating a strong need for kinase inhibitors, though their clinical safety requires careful

evaluation Currently, numerous kinase inhibitors are approved for clinical use, with some, such as crizotinib, erdafitinib, and ruxolitinib[6] notably incorporating a pyrazole moiety. Pyrazole acts as a bioisostere for arenes, improving efficiency, lipophilicity, and solubility. Compared to benzene, it has lower aromaticity and lipophilicity (Clog P 0.24 vs. 2.14) and can function as an H-bond donor, replacing more lipophilic, metabolically unstable arenes groups like phenol and other heterocycles. For eg.- Losartan(1), the first angiotensin II receptor antagonist, inspired development of more potent imidazole-based metabolites- imidazolic acid (2). Consequently, they identified a series of pyrazole compounds, exemplified by pyrazole (3), which demonstrated potency comparable to the imidazole derivatives (Fig. 6)[7].Later, imidazole was replaced with pyrazole as a bioisostere, yielding compounds with similar potency and enhanced hydrogen bonding potential. Pyrazole's(3) N-atoms enable donor and acceptor interactions within enzyme active sites. The first D1/D5 antagonist with high affinity and selectivity, SCH23390 (4), was reported in the 1980s[8-9]. However, benzazepine (4) exhibited a short duration of action and apparent off-target effects, suggesting potential in vivo metabolic issues. Replacing phenol with pyrazole in D1/D5 antagonists improved pharmacokinetics, while indazole derivatives, though less potent, offered better stability, highlighting hydrogen bonding and metabolic resistance in drug design. The first D1/D5 antagonist with high affinity and selectivity, SCH23390 (4), was reported in the 1980s[8-9]. Benzazepine (4) showed short action and off-target effects, while indazole (5) was 10× less potent but had better PK, and methylation (6) greatly reduced D1 affinity, underscoring the hydrogen bond donor's role **(Fig. 4)**[9].


**Figure 4** Impr

Pyrazole and 2-pyrazoline rings are key heterocyclic scaffolds with broad pharmacological activities, notably anti-proliferative[10-12] and anti-inflammatory effects[13-17]. Several pyrazoline derivatives serve as NSAIDs, including anti-pyrine and others like felcobuzone, mefobutazone and ramifenazone[18]. Beyond anti-inflammatory[18, 19-23] action, they exhibit antidepressant, antibacterial[24-25], anticancer, anti-tubercular, analgesic[26-27], antidiabetic[28], and CB1 antagonist properties(for obesity)[29]. Regan *et* al. (2002)[30] optimized N-pyrazole, N′-aryl ureas for p38α MAP kinase inhibition, leading to BIRB 796 as a clinical candidate. Additionally, Alsaedi *et* al.[31] synthesized pyrazolo\[1, 5-a] pyrimidine derivatives with phenylsulfonyl groups, demonstrating antimicrobial activity.

## MATERIAL & METHODS:

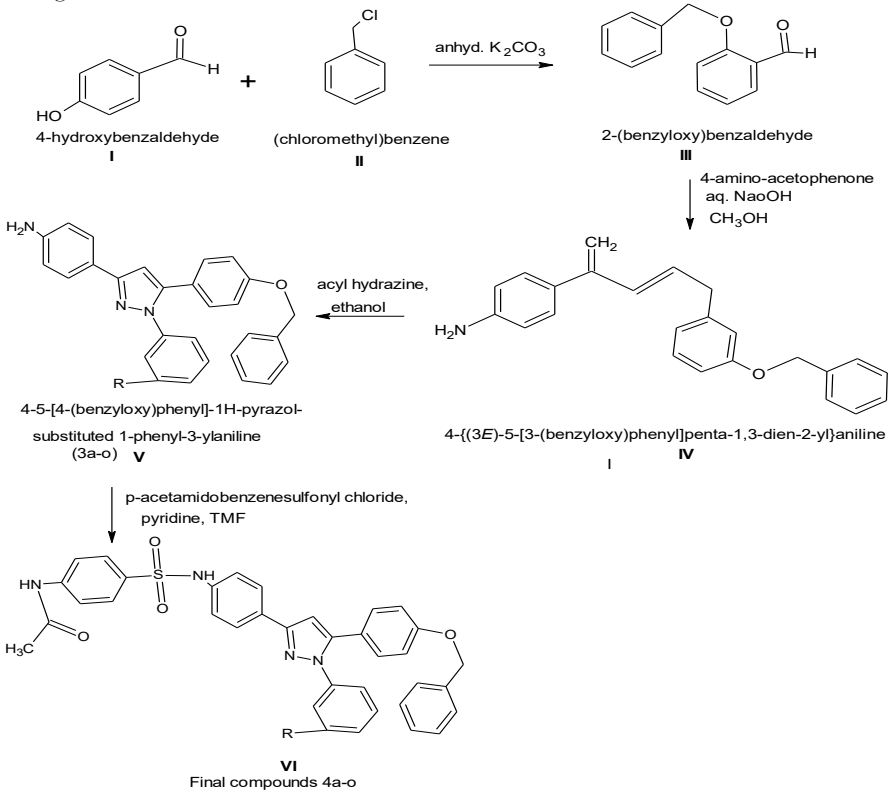
For synthesis, all chemical compounds and reagents, including starting materials, catalysts, ligands, and solvents, were purchased from Sigma Aldrich and used without further purification. Melting points were determined using a Griffin apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu 435 spectrometer using KBr discs. $^1$H NMR and $^{13}$C NMR spectra were measured on a Bruker 400 MHz spectrometer in $D_2O$ and DMSO-$d_6$ with TMS as the internal standard; *J* (coupling constant) values were estimated in Hertz (Hz). Mass spectra were obtained using a Hewlett Packard 5988 spectrometer.

**Synthesis of compound 4a**

**General method for the synthesis of *N*-(4-(*N*-(4-(5-(4-(benzyloxy) phenyl)-1-(substituted phenyl)-1*H*-pyrazol-3-yl) phenyl) sulfaomoyl) phenyl) acetamide(4a-o)**

Equal amounts of 4-[5-[4-(Benzyloxy) phenyl]-1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl] aniline and p-acetamidobenzenesulfonyl chloride (0.005 mol each) were mixed together and agitated at ambient temperature for 6-9 hours in the presence of pyridine (0.005 mol) in 30 mL of THF. Subsequently, the concoction was introduced into crushed ice, resulting in the formation of a solid substance. This solid

was then separated from the liquid by filtration, and subsequently dried and purified by crystallization using ethanol as the solvent.




**Scheme**

**R=a:2-Cl; b:3-Cl; c:4-Cl; d:3,4-dichloro; e:4-F; f: 4F-3-Cl; g:4-Br; h: 4-Nitro; i:2,4-dinitro, j:2-Methyl; k: 3-Me; l:4 –Me; m:2,6-Dimethyl; n:2-Methoxy; o:4-Methoxy**

**General analytical profile of Synthesized compounds**

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide (Compound 4a)**

**Yield**- 78%; M.P.- 193-194 °C; **Molecular Formula**-$C_{35}H_{28}ClN_5O_4S$ ; **%Nitrogen found**:10.71,Calcd: 10.77%

**IR(cm$^{-1}$,KBr):** 3332, 3321 (NH), 1640 (C=O), 1610(C=N), 1184($SO_2$), 743(C-Cl).

**$^1$H NMR** (DMSO-*d*6):δ 2.76 (s, 3H, $COCH_3$), 5.15(s, 2H, $OCH_2$),7.05 (s,1H, pyrazole-H-4), 7.07-8.38(m, 21H, ArH), 8.40 (s,1H, CONH, $D_2O$ exchangeable), 10.26 (s, 1H, $SO_2NH$, $D_2O$ exchangeable);

**$^{13}$C NMR** (DMSO-*d*6):- δ 29.81 (-$CH_3$), 71.49 (-$OCH_2$), 105.38 (pyrazole $C_4$). 113.79, 114.05, 114.80, 115.38, 118.79, 119.83, 121.27, 122.38, 123.58, 125.13, 128.42, 128.67, 128.73, 128.90, 130.18, 130.45, 134.72, 136.48, 136.93, 138.27, 144.65, 151.52, 159.07 (pyrazole $C_5$), 160.83 (pyrazole $C_3$), 171.83 (-CONH);

**ESI-MS** (m/z): 650$[M+2]^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(3-chlorophenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl)acetamide(Compound 4b)**

**Yield**- 71%; M.P.- 185-186 °C; **Molecular Formula**-$C_{35}H_{28}ClN_5O_4S$ ; **%Nitrogen found**:10.79,Calcd: 10.77%

**IR(cm$^{-1}$,KBr)**: 3338, 3217(NH), 1630(C=O), 1612(C=N), 1191($SO_2$), 792(C-Cl).

**$^1$H NMR** (DMSO-*d*6):δ 2.89 (s, 3H, $COCH_3$), 5.18(s, 2H, $OCH_2$),7.13(s,1H, pyrazole-H-4), 7.29-8.14(m, 21H, ArH), 8.42 (s,1H,CONH, $D_2O$ exchangeable), 10.18 (s, 1H, $SO_2NH$, $D_2O$ exchangeable);

**$^{13}$C NMR** (DMSO-*d*6):- δ 29.33(-$CH_3$), 71.62(-$OCH_2$), 105.28(pyrazole $C_4$), 113.61, 114.24, 114.63, 115.13, 118.62, 118.91, 120.87, 122.51, 123.78, 126.73, 127.32, 128.24, 128.50, 128.81, 130.15, 130.42, 133.49, 136.75, 137.58, 138.75, 142.35, 152.16, 158.87 (pyrazole $C_5$), 159.61 (pyrazole $C_3$), 170.24 (-CONH);

**ESI-MS** (m/z): 650$[M+H]^+$; 651$[M+2]^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(4-chlorophenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4c)**

**Yield**- 70%; M.P.- 183-184 °C; **Molecular Formula**-$C_{35}H_{28}ClN_5O_4S$ ; **%Nitrogen found**:10.71,Calcd: 10.77%

**IR(cm$^{-1}$,KBr):** 3337, 3220(NH), 1645(C=O), 1614(C=N), 1190($SO_2$), 790(C-Cl).

**$^1$H NMR** (DMSO-*d*6):δ 2.78(s, 3H, $COCH_3$), 5.19(s, 2H, $OCH_2$),7.05(s,1H, pyrazole-H-4), 7.11-7.83(m, 21H, ArH), 8.90 (s,1H,CONH, $D_2O$ exchangeable), 10.22 (s, 1H, $SO_2NH$, $D_2O$ exchangeable);

**$^{13}$C NMR** (DMSO-*d*6):- δ 32.17(-$CH_3$), 71.92(-$OCH_2$), 105.17(pyrazole $C_4$), 113.44, 114.16, 114.83, 115.57, 116.78, 119.52, 120.57, 122.38, 123.58, 125.74, 127.74, 128.71, 128.93, 129.61, 130.31, 130.85, 133.80, 136.18, 137.46, 139.03, 142.58(pyrazole $C_5$), 160.71(pyrazole $C_3$), 171.80(-CONH);

**ESI-MS** (m/z): 650$[M+H]^+$; 651$[M+2]^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(3,4-chloro phenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl) phenyl) acetamide (Compound 4d)**

**Yield**- 77%; M.P.- 220-222 °C; **Molecular Formula**-$C_{35}H_{27}Cl_2N_5O_4S$ ; **%Nitrogen found**:10.31,Calcd: 10.23%

**IR(cm$^{-1}$,KBr):** 3342, 3219(NH), 1665(C=O), 1609(C=N), 1187($SO_2$), 788(C-Cl).

**$^1$H NMR** (DMSO-*d*6):δ 2.73(s, 3H, $COCH_3$), 5.21(s, 2H, $OCH_2$),7.08(s,1H, pyrazole-H-4), 7.23-8.10(m, 20H, ArH), 8.45 (s,1H,CONH, $D_2O$ exchangeable), 10.30 (s, 1H, $SO_2NH$, $D_2O$ exchangeable);

**$^{13}$C NMR** (DMSO-*d*6):- δ 31.52(-$CH_3$), 71.33(-$OCH_2$), 107.39(pyrazole $C_4$), 113.21, 114.19, 114.62, 115.30, 115.73, 118.76, 119.68, 120.13, 123.83, 125.93, 127.58, 128.04, 128.52 129.43, 130.81, 131.97, 133.65, 134.18, 136.25, 137.31 139.77, 142.46, 152.38(pyrazole $C_5$), 160.05(pyrazole $C_3$), 171.80(-CONH);

**ESI-MS** (m/z): 684$[M+H]^+$; 685$[M+2]^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(4-Fluorophenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4e)**

**Yield**- 77%; M.P.- 226-227 °C; **Molecular Formula**-$C_{35}H_{27}FN_5O_4S$ ; **%Nitrogen found**:11.12,Calcd: 11.05%

**IR(cm$^{-1}$,KBr)**: 3340, 3221(NH), 1669(C=O), 1613(C=N), 1192($SO_2$), 1184(C-F).

**$^1$H NMR** (DMSO-*d*6):δ 2.92(s, 3H, $COCH_3$), 5.21(s, 2H, $OCH_2$),7.06(s,1H, pyrazole-H-4), 7.11-7.86(m, 21H, ArH), 8.51 (s,1H,CONH, $D_2O$ exchangeable), 10.24 (s, 1H, $SO_2NH$, $D_2O$ exchangeable)

**$^{13}$C NMR** (DMSO-*d*6):- δ 31.59(-$CH_3$), 72.18(-$OCH_2$), 105.13(pyrazole $C_4$), 113.97, 114.33, 114.91, 115.58, 119.82, 120.46, 123.21, 125.53, 127.75, 128.13, 128.90, 129.13, 130.28, 131.65, 133.44, 134.25, 135.56, 137.83, 139.21, 140.13 152.67(pyrazole $C_5$), 160.72(pyrazole $C_3$), 171.40(-CONH);

**ESI-MS** (m/z): 633$[M+H]^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(3-Chloro-4-Fluorophenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4f)**

**Yield**- 74%; M.P.- 224-225 °C; **Molecular Formula**-$C_{35}H_{27}ClFN_5O_4S$ ; **%Nitrogen found**:10.42,Calcd: 10.48%

**IR(cm$^{-1}$,KBr)**: 3345, 3235(NH), 1675(C=O), 1630(C=N), 1172($SO_2$), 784(C-Cl), 1175(C-F).

**$^1$H NMR** (DMSO-*d*6):δ 2.91(s, 3H, $COCH_3$), 5.23(s, 2H, $OCH_2$),7.09(s,1H, pyrazole-H-4), 7.15-7.96(m, 21H, ArH), 8.31 (s,1H,CONH, $D_2O$ exchangeable), 10.54 (s, 1H, $SO_2NH$, $D_2O$ exchangeable)

**$^{13}$C NMR(DMSO-*d6*)**:δ28.59(-CH3),71.68(-OCH2),105.42(pyrazole C4),113.13, 113.40, 113.55,114.03,114.35, 115.86, 119.01, 120.68,121.21,125.72,127.25,128.97,129.58,129.80, 130.65,131.13,133.37,134.58,135.81,137.23, 139.21, 140.56, 152.67 (pyrazoleC5), 160.28(pyrazole C3),172.47(-CONH);

**ESI**-MS(*m/z*):668$[M+H]^+$,669$[M+2]^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(1-bromophenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4g)**

**Yield**- 75%; M.P.- 284-286 °C; **Molecular Formula**-$C_{35}H_{27}BrN_5O_4S$ ; **%Nitrogen found**:10.06,Calcd: 10.68%

**IR (cm$^{-1}$,KBr):**3345,3320(NH),1645(C=O), 1608(C=N),1183(SO2); 671(C-Br)

**$^1$H NMR** (DMSO-*d6*):δ 2.76(s, 3H, $COCH_3$), 5.21(s, 2H, $OCH_2$),7.06(s,1H, pyrazole-H-4), 7.11-7.89(m, 21H, ArH), 8.72 (s,1H,CONH, $D_2O$ exchangeable), 10.19(s, 1H, $SO_2NH$, $D_2O$ exchangeable)

**$^{13}$C NMR(DMSO-*d6*)**:δ 32.68(-CH3),72.19(-OCH2),105.32(pyrazole C4),113.74, 114.31, 114.87,115.56,119.68, 120.28, 121.23, 121.21, 125.72,127.10, 128.58, 129.02,129.45, 130.35,131.21, 133.98,134.39, 135.56, 137.33, 138.67, 142.51, 152.59 (pyrazole C5), 160.83 (pyrazole C3),172.60(-CONH);

**ESI**-MS(*m/z*):694[M+H] $^+$,669[M+1]$^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(4-nitrophenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4h)**

**Yield**- 71%; M.P.- 230-232 °C; **Molecular Formula**-$C_{35}H_{28}N_6O_6S$ ; %**Nitrogen found**:12.78,Calcd: 12.72%

**IR (cm$^{-1}$,KBr):**3338, 3221(NH),1642(C=O), 1610(C=N),1190(SO2); 1596(N=O)

**$^1$H NMR** (DMSO-*d6*):δ 2.94(s, 3H, $COCH_3$), 5.22(s, 2H, $OCH_2$),7.04(s,1H, pyrazole-H-4), 7.16-7.83(m, 21H, ArH), 8.87 (s,1H,CONH, $D_2O$ exchangeable), 10.29(s, 1H, $SO_2NH$, $D_2O$ exchangeable)

**$^{13}$C NMR(DMSO-*d6*)**:δ 32.38(-CH3),72.82(-OCH2),109.23(pyrazole C4),113.61, 114.26, 114.81,115.14,119.42, 120.81, 124.76, 125.13, 127.89, 128.35, 129.97,130.16, 133.28,133.65, 134.21,135.73, 137.88, 138.97, 142.25, 155.08 (pyrazole C5), 160.46 (pyrazole C3), 171.82(-CONH);

**ESI**-MS(*m/z*):660[M+H] $^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(2,4-dinitrophenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4i)**

**Yield**- 71%; M.P.- 256-257 °C; **Molecular Formula**-$C_{35}H_{27}N_7O_8S$ ; %**Nitrogen found**:13.80,Calcd: 13.89%

**IR (cm$^{-1}$,KBr):** 3342, 3220(NH),1642(C=O), 1607(C=N),1188(SO2); 1595(N=O)

**$^1$H NMR** (DMSO-*d6*):δ 2.89(s, 3H, $COCH_3$), 5.21(s, 2H, $OCH_2$), 7.06(s,1H, pyrazole-H-4), 7.06-7.63(m, 21H, ArH), 8.47 (s,1H,CONH, $D_2O$ exchangeable), 10.35(s, 1H, $SO_2NH$, $D_2O$ exchangeable)

**$^{13}$C NMR(DMSO-*d6*)**: δ 31.38(-CH3),72.82(-OCH2),105.73(pyrazoleC4),112.18,113.89, 114.25,114.70,115.42, 118.73, 119.61, 120.21, 124.38,125.76,127.29,128.14,129.38,129.79, 130.51,133.68,134.19,135.25,135.63, 137.17,138.25,141.18, 155.82 (pyrazole C5), 160.74(pyrazole C3),171.20(-CONH).

**ESI**-MS(*m/z*):705[M+H] $^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(o-tolylphenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4j)**

**Yield**- 72%; M.P.- 150-152 °C; **Molecular Formula**-$C_{36}H_{31}N_5O_4S$ ; %**Nitrogen found**:11.08, Calcd: 11.12%

**IR (cm$^{-1}$,KBr):** 3343, 3323(NH),1642(C=O), 1616(C=N),1191($SO_2$);

**$^1$H NMR** (DMSO-*d6*):δ 2.82(s, 3H, $COCH_3$), 5.24(s, 2H, $OCH_2$), 7.14(s,1H, pyrazole-H-4), 7.09-7.73(m, 21H, ArH), 8.68 (s,1H,CONH, $D_2O$ exchangeable), 10.48(s, 1H, $SO_2NH$, $D_2O$ exchangeable)

**$^{13}$C NMR**(DMSO-*d6*): δ 18.23 (-$C_6$H5-CH3),32.38 (-CO-CH3),71.82(-OCH2),105.76(pyrazole C4), 112.48, 113.22, 113.68, 114.19, 114.54, 115.63, 119.28, 120.47, 124.83, 126.91, 127.89, 128.45, 129.36, 129.89, 130.17, 134.68, 134.92, 135.15, 135.82, 138.37, 138.52, 141.63, 155.25 (pyrazoleC5),160.34(pyrazole C3),169.92(-CONH);

**ESI-MS**(*m/z*):629[M+H]$^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(m-tolylphenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4k)**

**Yield**:73%; M.P.:155-156$^o$C;MolecularFormula:C36H31N5O4S; %**Nitrogen:Found**:11.17,

Calcd:11.12%.

**IR (cm$^{-1}$,KBr):** 3344, 3326(NH),1648(C=O), 1625(C=N),1179($SO_2$);
$^1$**H NMR** (DMSO-*d*6):δ 2.88(s, 3H, $COCH_3$), 5.34(s, 2H, $OCH_2$), 7.08(s,1H, pyrazole-H-4), 7.17-7.82(m, 21H, ArH), 8.42 (s,1H,CONH, $D_2O$ exchangeable), 10.61(s, 1H, $SO_2NH$, $D_2O$ exchangeable)
$^{13}$**C NMR**(DMSO-*d*6): δ 17.13 (-$C_6H_5$-$CH_3$),32.92 (-CO-$CH_3$),71.53(-$OCH_2$),109.35(pyrazole C4),112.37, 114.05, 114.19, 114.41, 115.36, 115.82, 119.12, 122.08, 124.48, 126.78, 127.69, 128.25, 129.14, 129.68, 130.47, 133.54, 134.63, 135.29,135.82, 138.23, 138.91, 140.63, 155.72(pyrazoleC5),160.71(pyrazole C3),171.34(-CONH);

**ESI-MS**(*m/z*):629$[M+H]^+$.

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(p-tolylphenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4l)**
**Yield**:73%; **M.P**.:159-160°C; **Molecular Formula**: $C_{36}H_{31}N_5O_4S$; %**Nitrogen Found**:11.19,**Calcd**:11.12%.

**IR (cm $^1$,KBr)**:3341,3220(NH),1637(C=O), 1614(C=N), 1190($SO_2$);
$^1$**H NMR** (DMSO-*d*6):δ 2.79(s, 3H, $COCH_3$), 5.41(s, 2H, $OCH_2$), 7.02(s,1H, pyrazole-H-4), 7.06-7.72(m, 21H, ArH), 8.30 (s,1H,CONH, $D_2O$ exchangeable), 10.47(s, 1H, $SO_2NH$, $D_2O$ exchangeable)
$^{13}$**C NMR (DMSO-*d6*):** δ 17.48 (-$C_6H_5$-$CH_3$),32.92 (-CO-$CH_3$),71.12(-$OCH_2$),110.35 (pyrazole C4), 112.95, 113.84, 114.72, 115.23, 119.69, 122.83, 124.10, 126.37, 127.54, 128.25, 129.07, 129.81, 130.24, 133.97, 134.51, 134.72, 135.25, 138.98 , 140.12, 155.34(pyrazole C5), 160.17(pyrazole C3), 172.39(-CONH);

**ESI-MS**(*m/z*):629$[M+H]^+$.
**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(2,6-dimethylphenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4m)**
**Yield**: 70%; **M.P**.:262-264°C; **MolecularFormula**: $C_{37}H_{33}N_5O_4S$; %**Nitrogen Found**:10.81,**Calcd**:10.88%;

**IR (cm $^1$,KBr)**:3346,3210(NH),1626(C=O), 1618(C=N), 1187($SO_2$);
$^1$**H NMR** (DMSO-*d*6):δ 2.81(s, 3H, $COCH_3$), 5.57(s, 2H, $OCH_2$), 7.12(s,1H, pyrazole-H-4), 7.16-7.92(m, 21H, ArH), 8.46 (s,1H,CONH, $D_2O$ exchangeable), 10.51(s, 1H, $SO_2NH$, $D_2O$ exchangeable)
$^{13}$**C NMR(DMSO-*d6*):** δ 17.73 (-2 $C_6H_5$-$CH_3$),32.65 (-CO-$CH_3$),71.35 (-$OCH_2$),110.31(pyrazole C4), 113.22, 114.45, 114.91, 115.49, 119.75, 122.79, 124.38, 127.32, 127.60, 128.82, 129.15, 129.57,130.92,133.97, 134.72,134.94,135.07, 138.86, 138.92, 140.35, 155.56 (pyrazole C5), 160.73(pyrazole C3), 171.38(-CONH);

**ESI-MS(*m/z*)**: 643$[M+H]^+$

**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(2 methoxyphenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl) acetamide(Compound 4n)**
**Yield**: 74%; **M.P**.:285-286°C; **Molecular Formula**:$C_{36}H_{31}N_5O_5S$; % **Nitrogen Found**:10.82,**Calcd**:10.85%;

**IR (cm $^1$,KBr)**:3316, 3218(NH),1621(C=O), 1610(C=N), 1192($SO_2$);
$^1$**H NMR** (DMSO-*d*6):δ 2.83(s, 3H, $COCH_3$), 5.61(s, 2H, $OCH_2$), 7.21(s,1H, pyrazole-H-4), 7.12-7.81(m, 21H, ArH), 8.36 (s,1H,CONH, $D_2O$ exchangeable), 10.31(s, 1H, $SO_2NH$, $D_2O$ exchangeable).
$^{13}$**C NMR(DMSO-*d6*)**: δ 32.03(-CO-$CH_3$),56.17(-$C_6H_5$-$OCH_3$),71.37 (-$OCH_2$),110.15 (pyrazole C4), 113.46, 113.73, 114.25, 114.96, 115.41, 119.72, 122.53, 124.09, 127.47, 127.68, 128.13, 129.58, 129.81, 130.45, 133.18, 133.39, 134.62, 134.97, 135.84, 138.30, 138.57, 140.27, 155.09(pyrazole C5), 160.16(pyrazole C3),171.65(-CONH);

**ESI-MS(*m/z*)**:647$[M+H]^+$.
**N-(4-(N-(4-(5-(4-(benzyloxy) phenyl)-1-(4- methoxyphenyl)-1*H*-pyrazol-3-yl) phenyl) sulfamoyl)phenyl)**

**acetamide(Compound 4o)**

**Yield**:74%; **M.P**.:286-287°C; **Molecular Formula**: $C_{36}H_{31}N_5O_5S$; % **Nitrogen Found**:10.88, **Calcd**:10.85%;

**IR (cm$^{-1}$, KBr)**:3337,3215(NH), 1653(C=O), 1615(C=N),1186($SO_2$);

**$^1$H NMR (DMSO-*d6*)**:δ2.72(s,3H,$COCH_3$),3.76(s,3H,$OCH_3$),5.21(s,2H,$OCH_2$),7.08(s, 1H,pyrazole-H-4), 7.14 -7.92(m,21H,ArH), 8.34 (s,1H, CONH, $D_2O$ exchangeable), 10.20(s,1H,$SO_2NH$, $D_2O$ exchangeable);

**$^{13}$C NMR (DMSO-*d6*)**: δ 32.63(-CO-$CH_3$), 57.20(-$C_6H_5$-$OCH_3$),71.68 (-$OCH_2$),110.78 (pyrazole $C_4$), 113.23, 113.27, 114.65, 115.19, 119.72, 120.74, 122.60, 124.51, 127.38, 127.43, 128.92, 129.04, 129.65, 130.15, 134.58, 134.62, 135.89, 138.39, 138.57, 140.81, 153.75 (pyrazole $C_5$), 160.61 (pyrazole $C_3$), 172.45 (-CONH);

**ESI-MS(*m/z*)**:647$[M+H]^+$.

### 2.1 p38α MAP kinase assay

With an $IC_{50}$ of 0.031 ± 1.27 µM, compound 4c, which contains a 4-chlorophenyl group rather than a 2-chlorophenyl group, showed somewhat less activity. With a percentage inhibition of 48.39 as opposed to SB 203580's 51.79%, compound 4b, which contains a 3-chlorophenyl group, demonstrated greater activity. With percentage inhibition values of 44.58 and 41.32, respectively, compounds 4e and 4g showed p38α MAPK inhibition that was similar to SB 203580 (Table 1).

**Table 1: p38α MAPK inhibition of pyrazolyl sulfonamide derivatives**

| Compound | %inhibition | IC50value(µM) |
|---|---|---|
| Solvent control | - | |
| 4a | 59.31 | 0.028 ± 0.04 |
| 4b | 48.39 | - |
| 4c | 56.83 | 0.031 ± 1.27 |
| 4e | 44.58 | - |
| 4g | 41.32 | - |
| SB 203580 | 51.79 | 0.043 ± 3.62 |

### 2.2 In vivo studies:

**Ulcerogenicity**

In addition to their significant anti-inflammatory properties compounds 4a–c, 4e, and 4g showed ulcer-causing potential with lower ulcer severity (0.42–0.92) than diclofenac (1.83), indicating better GI safety and reduced risk of stomach ulcers.Diclofenac sodium showed a higher severity index (1.83±0.25), while compounds 4a (0.42±0.38) and 4c (0.67±0.52) respectively exhibited greater potency and lower ulcer risk, suggesting improved gastric safety less harm to the stomach's lining cells.

**Table 2: Ulcerogenic potential of pyrazolyl sulfonamide derivatives**

| Compound | Severity index± SEM |
|---|---|
| 4a | 0.417 ± 0.154 |
| 4b | 0.833 ± 0.105 |
| 4c | 0.667 ± 0.211 |
| 4e | 0.833 ± 0.167 |
| 4g | 0.917 ± 0.271 |
| Diclofenac sodium | 1.833 ± 0.105 |

### 2.3 Lipid peroxidation

Compounds 4a–c, 4e, and 4g significantly reduced lipid peroxidation (≈4.69±0.355) compared to the standard drug (6.53±0.22), with 4a and 4c being most effective, though still above control (3.23±0.044) (Table 3).

**Table 3: Lipid peroxidation results of pyrazolyl sulfonamide derivatives**

| Compound | Nmol MDA/100mg tissue ± SEM |
|---|---|
| Control | 3.23 ± 0.044 |
| 4a | 4.69 ± 0.355 |
| 4b | 5.89 ± 0.178 |
| 4c | 5.26 ± 0.613 |
| 4e | 5.69 ± 0.274 |
| 4g | 6.12 ± 0.207 |
| Diclofenac sodium | 6.53 ± 0.091 |

### 2.4 Suppression of TNF-α generation produced by LPS.

On assessing the inhibitory effects compounds 4a–c, 4e, and 4g inhibited LPS-induced TNF-α production, with 4a being most potent ($ID_{50}$ = 6.23 mg/kg) versus SB 203580 ($ID_{50}$ =28.40 mg/kg), while 4b and 4c showed strong activity ($ID_{50}$ =10.96 mg/kg) & ($ID_{50}$ =10.83 mg/kg) respectively and 4e/4g and achieved ˜52.8% TNF-α suppression, similar to the standard52.1% suppression observed with the conventional inhibitors SB 203580 (Table 4).

**Table 4 :LPS induced TNF-α inhibition results of pyrazolyl sulfonamide derivatives**

| Compound | %inhibition ±SEM | $ID_{50}$value (mg/kg) |
|---|---|---|
| 4a | 64.06 ± 1.243 | 6.23 |
| 4b | 56.41 ± 1.804 | 10.83 |
| 4c | 57.32 ± 0.661 | 10.96 |
| 4e | 52.79 ± 1.002 | - |
| 4g | 52.84 ± 0.851 | - |
| SB 203580 | 52.11 ± 1.963 | 28.40 |

**CONFLICT OF INTEREST:** The authors have no conflicts of interest regarding this investigation.

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REFERENCES

1. Nathan, C. 2002, "Points of control in inflammation" Nature, 420, pp. 846–852.
2. Medzhitov, R. 2008, "Origin and physiological roles of inflammation", Nature, 454, pp. 428–435.
3. Kolls, J.K., and Lindén, A., 2004, "Interleukin-17 family members and inflammation", Immunity, 21(4), pp. 467–476.
4. Li, G., Cheng, Y., Han, C., Song, C., Huang, N., and Du, Y., 2022, " Pyrazole-containing pharmaceuticals: target, pharmacological activity, and their SAR studies", RSC Medicinal Chemistry, 13, pp. 1300–1321.
5. El-Gamal, M.I., Zaraei, S.-O., Madkour, M.M., and Anbar, H.S., 2022, "Evaluation of substituted pyrazole-based kinase inhibitors in one decade (2011–2020): Current status and future prospects", Molecules, 27(1), pp. 330.
6. Ashton, W.T., Hutchins, S.M., Greenlee, W.J., Doss, G.A., Chang, R.S., Lotti, V.J., Faust, K.A., Chen, T.B., Zingaro, G.J., and Kivlighn, S.D., 1993, "Nonpeptide angiotensin II antagonists derived from 1H-pyrazole-5-carboxylates and 4-aryl-1H-imidazole-5-carboxylates", J. Med. Chem., 36, pp. 3595–3605.
7. Neisewander, J.L., Fuchs, R.A., O'Dell, L.E., and Khroyan, T.V.,1998, Effects of SCH-23390 on dopamine D1 receptor occupancy and locomotion produced by intraaccumbens cocaine infusion", Synapse, 30, pp. 194–204.
8. Hyttel, J., 1983, "SCH 23390—The first selective dopamine D-1 antagonist", European Journal of Pharmacology, 91(1), 153–154.
9. Bouabdallah, L.A., M'Barek, A., Zyad, A., Ramdani, I., Zidane, I., and Melhaoui, A., 2006, "Anticancer effect of three pyrazole derivatives", Natural Product Research, 20, pp.1024–1030.
10. Nitulescu, G.M., Draghici, C., and Missir, A.V., 2010, "Synthesis of new pyrazole derivatives and their anticancer evaluation", European Journal of Medicinal Chemistry, 45, pp. 4914–4919.
11. Kumar, H., Saini, D., Jain, S., and Jain, N., 2013, Pyrazole scaffold: a remarkable tool in the development of anticancer agents", European Journal of Medicinal Chemistry, 70, pp. 248–258.
12. Ando, K., and Kawamura, K., 2003, "Sulfamoyl heteroaryl pyrazole compounds as anti-inflammatory/analgesic agents". Google Patents- US6951876B2
13. Amir, M., and Kumar, S., 2005, "Synthesis and anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities of 3,5-dimethyl pyrazoles- 3-methyl pyrazol-5-ones and 3,5-disubstituted pyrazolines", Indian Journal of Chemistry, 44B, pp. 2532–2537.
14. Farghaly, A.A., Bekhit, A.A., and Park, J.Y., 2000, "Design and synthesis of some oxadiazolyl, thiadiazolyl, thiazolidinyl, and thiazolyl derivatives of 1H-pyrazole as anti-inflammatory antimicrobial agents", Archiv der Pharmazie, 333, pp. 53–57.
15. Bakr, R.B., Azouz, A.A., and Abdellatif, K.R., 2016, "Synthesis, cyclooxygenase inhibition, anti-inflammatory evaluation and ulcerogenic liability of new 1-phenylpyrazolo[3,4-d]pyrimidine derivatives", Journal of Enzyme Inhibition and Medicinal Chemistry, 31, pp. 6–12.
16. Abdellatif, K., Abdelall, E., and Bakr, R., 2017, " Nitric oxide–NSAIDs donor prodrugs as hybrid safe anti-inflammatory agents",

Current Topics in Medicinal Chemistry, 17, pp. 941–955.
17. Abdellatif, K.R.A., Abdelgawad, M.A., Elshemy, H.A.H., Alsayed, S.S.R., and Kamel, G., 2015, "Synthesis and anti-inflammatory evaluation of new 1,3,5-triaryl-4,5-dihydro-1H-pyrazole derivatives possessing an aminosulphonyl pharmacophore", Archives of Pharmacal Research, 38, pp. 1932–1942.
18. Rathish, I.G., Javed, K., Ahmad, S., Bano, S., Alam, M.S., Pillai, K.K., Singh, S., and Bagchi, V., 2009, "Synthesis and anti-inflammatory activity of some new 1,3,5-trisubstituted pyrazolines bearing benzene sulfonamide", Bioorganic & Medicinal Chemistry Letters, 19, pp. 255–258.
19. Bano, S.K., Javed, K., Ahmad, S., Rathish, I.G., Singh, S., and Alam, M.S., 2011, "Synthesis and biological evaluation of some new 2-pyrazolines bearing benzene sulfonamide moiety as potential anti-inflammatory and anti-cancer agents", European Journal of Medicinal Chemistry, 46, pp. 5763–5768.
20. Bashir, R., Ovais, S., Yaseen, S., Hamid, H., Alam, M.S., Samim, M., Singh, S., and Javed, K., 2011, " Synthesis of some new 1,3,5-trisubstituted pyrazolines bearing benzene sulfonamide as anticancer and anti-inflammatory agents", Bioorganic & Medicinal Chemistry Letters, 21, pp. 4301–4305.
21. Ovais, S., Bashir, R., Yaseen, S., Rathore, P., Samim, M., and Javed, K., 2012, "Synthesis and pharmacological evaluation of some novel 2-pyrazolines bearing benzene sulfonamide as anti-inflammatory and blood glucose lowering agents", Medicinal Chemistry Research, 22, pp. 1378–1385.
22. Ovais, S., Yaseen, S., Bashir, R., Rathore, P., Samim, M., Singh, S., Nair, V., and Javed, K., 2013, "Synthesis and anti-inflammatory activity of celecoxib-like compounds", Journal of Enzyme Inhibition and Medicinal Chemistry", 28, pp. 1105–1112.
23. Johnson, M.B., Younglove, L., Lee, R., LeBlanc, H.H. Jr., Hills, P., Mackay, H., Brown, T., Mooberry, S.L., and Lee, M., 2007, "Design, synthesis, and biological testing of pyrazoline derivatives of combretastatin-A4", Bioorganic & Medicinal Chemistry Letters, 17, pp. 5897–5901.
24. Rostom, S.A.F., 2006, "Synthesis and in vitro antitumor evaluation of some indeno[1,2-c]pyrazol(in)es substituted with sulfonamide, sulfonylurea(-thiourea) pharmacophores, and some derived thiazole ring systems, Bioorganic & Medicinal Chemistry, 14,pp. 6475–6485.
25. Sahu, S.K., Banerjee, M., Samantray, A., Behera, C., and Azam, M.A., 2008, "Synthesis, analgesic, anti-inflammatory and antimicrobial activities of some novel pyrazoline derivatives", Tropical Journal of Pharmaceutical Research, 7, pp. 961–968.
26. Chandra, T.N., Garg, S., Lata, K.K., Saxena, K., and Kumar, A., 2010, "Synthesis of substituted acridinyl pyrazoline derivatives and their evaluation for anti-inflammatory activity", European Journal of Medicinal Chemistry, 45, pp. 1772–1776.
27. Ahn, J.H., Kim, H.M., Jung, S.H., Kang, S.K., Kim, K.R., Rhee, S.D., Yang, S.D., Cheon, H.G., and Kim, S.S., 2005, "Synthesis and DPIV inhibition of cyano-pyrazoline derivatives as potent antidiabetic agents", Bioorganic & Medicinal Chemistry Letters, 14, pp. 4461–4465.
28. Lange, J.H.M., Stuivenberg, H.H.V., Veerman, W., Wals, H.C., Stork, B., Coolen, H.K.A.C., McCreary, A.C., Adolfs, T.J.P., and Kruse, C.G., 2005, "Novel 3,4-diarylpyrazolines as potent cannabinoid CB1 receptor antagonists with lower lipophilicity", Bioorganic & Medicinal Chemistry Letters, 15, pp. 4794–4798.
29. Liu, X.-R., Wu, H., He, Z.-Y., Ma, Z.-Q., Feng, J.-T., and Zhang, X., 2014, "Design, synthesis and fungicidal activities of some novel pyrazole derivatives", Molecules, 19, pp. 14036–14051.
30. Bettencourt, A.P., Castro, M., Silva, J.P., Fernandes, F., Coutinho, O.P., Sousa, M.J., Proença, M.F., and Areias, F.M., 2019, "Phenolic imidazole derivatives with dual antioxidant/antifungal activity: Synthesis and structure–activity relationship", Medicinal Chemistry, 15(4), pp. 341–351.
31. Desai, N.C., Patel, B.Y., and Dave, B.P., 2017, "Synthesis and antimicrobial activity of novel quinoline derivatives bearing pyrazoline and pyridine analogues", Medicinal Chemistry Research, 26, pp. 109–119.