

Design, Synthesis, Characterization, and Anti-Breast Cancer Activity of Novel Pyrazole-Based Chalcones: Insights from Molecular Docking and DFT Studies

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Abstract: A novel series of 1-(furan-3-yl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one was designed, synthesized, and characterized with the aim of developing potential anti-breast cancer agents. The synthesis was carried out by a Claisen-Schmidt condensation of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde with 2-acetylfuran in the presence of ethanolic sodium hydroxide under reflux conditionS for 7- 8 hours. The resulting chalcone derivative was purified and confirmed by TLC, Melting point, and Spectroscopic techniques, including IR, ¹H-NMR, ¹³C-NMR, and Mass Spectroscopy. The biological evaluation of the synthesized compounds was performed against the MCF-7 breast cancer cell line, where the compounds exhibited varying degrees of cytotoxic activity, with some derivatives showing promising anti-cancer potential. Furthermore, molecular docking studies were conducted to investigate their binding interactions with breast cancer target proteins. In addition to docking, Density Functional Theory (DFT) studies were carried out to investigate the electronic properties and chemical reactivity of the compounds. DFT calculations provided crucial parameters such as the HOMO-LUMO energy gap, molecular electrostatic potential (MEP) maps, dipole moments, and global reactivity descriptors (e.g., electronegativity, hardness, softness). These theoretical insights help in understanding the structure–activity relationships (SAR) and in predicting the stability and reactivity of the compounds at the molecular level. The results suggest that structural modifications in the pyrazole-furan chalcone framework can significantly influence biological activity.

Keywords: synthesis; 1-(furan-3-yl)-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one; anti-breast cancer; molecular docking.

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1. Introduction

The design of new drugs is a time-consuming, multi-stage process that spans several years and demands substantial financial investment. A critical stage in this process involves medicinal chemistry, particularly the identification and optimization of lead compounds. These lead compounds serve as the starting point for developing molecules with the desired biological activity, while also meeting acceptable ADMET parameters: absorption, distribution, metabolism, excretion, and toxicity. Lead compounds can originate from various sources, including existing drugs, metabolites formed during drug metabolism, and substances currently

undergoing clinical trials. Additionally, they may arise from high-throughput screening efforts or be derived from natural products, which continue to be a rich source of structurally diverse and biologically active compounds [1]. Breast cancer is recognized as one of the most prevalent and impactful cancers affecting women worldwide. It typically originates in the milk ducts (ductal carcinoma) or the lobules that produce milk (lobular carcinoma) and can metastasize to other parts of the body [2]. Although conventional chemotherapy shows initial effectiveness, it frequently fails to eradicate all malignant cells. The persistence of therapy-resistant subpopulations contributes to disease and poses a major obstacle to long-term remission [3]. Breast cancer remains one of the leading causes of cancer-related morbidity and mortality among women worldwide, and the emergence of drug resistance and severe toxicity associated with current chemotherapeutic drugs necessitates the discovery of novel and more selective therapeutic agents. Chalcones, due to the α,β -unsaturated carbonyl framework and structural flexibility, are well recognized precursors for the synthesis of diverse bioactive heterocycles and have demonstrated broad pharmacological profiles, particularly anticancer activity [4]. Similarly, pyrazole scaffolds are known privileged structures in medicinal chemistry and are frequently found in FDA-approved anticancer drugs, owing to their ability to interact with multiple biological targets and modulate key cellular pathways associated with tumor progression [5]. Despite ongoing research and the development of new therapeutic strategies, breast cancer mortality rates have recently begun to rise. In 2020, approximately 2.3 million women were diagnosed with breast cancer, contributing to a global mortality rate of nearly 30% [6]. By the end of 2023, an estimated 7.8 million women who had been previously diagnosed with breast cancer were still alive, underscoring the increasing global burden of this disease. Projections suggest that by 2025, the annual incidence of female breast cancer could reach 3.2 million new cases worldwide [7].

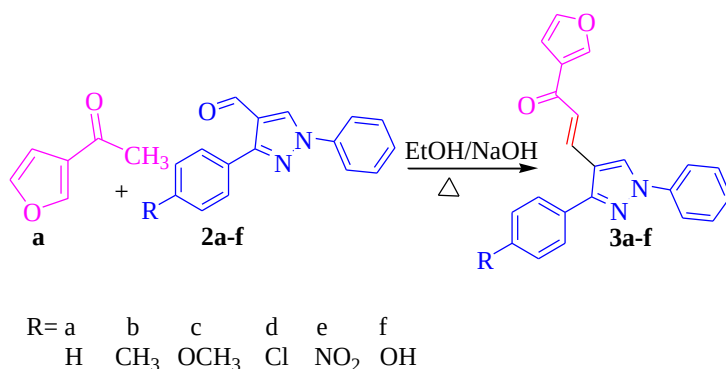
Pyrazole is a heterocyclic compound with a five-membered ring, only one endocyclic bond, and three carbon and two nitrogen atoms [8]. Heterocyclic moieties are fundamental to synthetic organic chemistry because of their broad application across pharmaceutical, veterinary, and agrochemical sectors. Among them, pyrazole derivatives have gained considerable attention in the history of nitrogen heterocyclic chemistry due to their wide range of biological activities [9]. The presence of the pyrazole nucleus in different structures leads to diversified applications in different areas, such as medicine and agriculture [10]. They are widely reported to have significant applications in many fields such as agrochemical, biological, pharmaceutical, and industrial [11]. Developing lead molecules and potent drugs against the known targets has been challenging work in medicinal chemistry. Among the heterocyclic compounds, the pyrazole and pyrazoline nuclei stand out due to their potency to inhibit many chronic diseases [12]. Moreover, a number of biologically active compounds have been synthesized from pyrazole-4-carbaldehydes. These compounds showed antimicrobial [13], antitumor and antiangiogenic [14], antiviral [15], antitubercular [16], and antiparasitic [17,18]. In view of the pharmacological importance of both chalcones and pyrazole moieties, the present research aims to design and synthesize hybrid pyrazole-based chalcones, with the expectation that combining these bioactive structural motifs may result in molecules with enhanced anticancer properties through synergistic interactions [19]. Furthermore, incorporation of the furan ring is expected to improve lipophilicity and target affinity, potentially increasing biological performance [20].

The development of medicinal chemistry depends on the conception, synthesis, and evaluation of novel chemical entities with potential therapeutic uses [21]. Chalcones are an

interesting target class of compounds showing broad-spectrum pharmacological activities and the presence of reactive groups [22]. Chemically, they are open-chain flavonoids in which the two aromatic rings are joined by a three-carbon α,β -unsaturated carbonyl system. Chalcones are among the leading bioactive flavonoids with a therapeutic potential implicated in a range of bioactivities investigated by a series of preclinical and clinical studies. Various scientific databases were systematically searched to identify studies reporting on the biological activities of chalcones and their derivatives [23]. Chalcone compounds were used in many heterocyclic reactions to produce a variety of biologically active target molecules. The produced molecules showed analgesic [24], anti-arthritic [25], anti-inflammatory [26], antibacterial [27], antiviral, and anticancer [28,29] effects. Numerous studies have demonstrated that chalcones exhibit significant anti-proliferative and cytotoxic effects [30,31]. Certain chalcone derivatives, in particular, have shown high cytotoxicity and strong inhibitory activity against various cancer cell lines [32,33]. Despite extensive research on chalcones and pyrazole-containing derivatives individually, reports on pyrazole–furan conjugated chalcone hybrids remain limited. Therefore, this study introduces a novel series of chalcone derivatives integrating the pyrazole and furan pharmacophores to improve biological potency and selectivity toward breast cancer cells. To strengthen the drug-design approach, the synthesized molecules were evaluated not only through *in vitro* cytotoxic assays against the MCF-7 breast cancer cell line, but also through molecular docking studies against human 17- β -hydroxysteroid dehydrogenase type 1 (a key enzyme implicated in estrogen-mediated breast cancer progression) [34], providing molecular-level insights into target binding interactions. Additionally, the present study integrates synthetic chemistry, computational modeling, and biological evaluation to identify potent lead molecules with breast-cancer-inhibitory potential, contributing to the development of next-generation anticancer agents with improved efficacy and reduced toxicity [35]. In this study, all newly synthesized compounds were evaluated using physicochemical techniques such as thin-layer chromatography (TLC) and melting point analysis, along with spectro-analytical methods including IR, ^1H -NMR, ^{13}C -NMR, and mass spectrometry. The synthesized compounds were further assessed for their anti-breast cancer activity. In addition, density functional theory (DFT) calculations and molecular docking studies were performed to support the experimental findings.

2. Materials and Methods

1,3-Diphenyl-1*H*-pyrazole-4-carbaldehyde was purchased from Sigma-Aldrich, Bangalore, Karnataka, India. 2-Acetylfuran and sodium hydroxide were procured from Hi-Media, Bangalore, Karnataka, India, and ethanol was obtained from Spectrochem Pvt. Ltd., Mumbai, India, and used without further purification. Infrared (IR) spectra were recorded using a Shimadzu FTIR spectrometer (Model: IR Spirit, Serial No: A224159, Made in Japan) at Sahyadri Science College, Shivamogga, Karnataka, India. The samples were prepared using KBr pellets formed with a hydraulic press, and spectra were recorded in the range of 500-4000 cm^{-1} . Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker Avance spectrometer operating at 400MHz for ^1H -NMR and 100 MHz for ^{13}C -NMR in DMSO-d_6 solvent at Mangalore University, Mangalore, Karnataka, India. Mass spectra of the synthesized compound were obtained using an Acquity UPLC system (USA-made) at a facility in Mysore, Karnataka, India.



Scheme 1. The detailed synthesis of 3-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(furan-3-yl)prop-2-en-1-one derivatives **3(a-f)**; Reagents and conditions :i)1,3-diphenyl-1H-pyrazole-4-carbaldehyde,2-acetylfuran, Ethanol, 40%NaOH.

2.1. General procedure for the Synthesis of 1-(furan-3-yl)-3-(1,3-diphenyl-1H-pyrazol-4-yl)prop-2-en-1-one derivatives **3(a-f)**.

In a 100mL round-bottom flask, 2-acetylfuran (**1**) (1mmol) and 1,3-diphenyl-1H-pyrazole-4-carbaldehyde **2(a-f)** (2mmol) were dissolved in ethanolic sodium hydroxide (10mL, 40%), and the mixture was stirred. The reaction mixture was refluxed at 80-90°C for 5–6 hours. The progress of the reaction was monitored by thin- layer chromatography(TLC). Upon completion, the reaction mixture was poured into ice-cold water. The resulting precipitate was filtered, dried, and recrystallized from ethanol to obtain the pure compounds **3(a-f)**.

2.1.1. 3-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(furan-3-yl)prop-2-en-1-one(**3a**).

Yellow Solid, Yield 90%, R_f :0.53 (CH₂Cl₂/C₆H₆, v/v 8:2), MP 221-223°C; IR (KBr, ν cm⁻¹) 3091(CH),1655(C=O),1592(C=C),1500 (Pyrazole-C=N); as shown in Figures.S1. ¹H-NMR (400MHz, DMSO-d₆, δ ppm): 8.6(s,1H,Pyrazole-CH), 7.32-7.8 (m, 15H, Ar-H) 6.61-6.62 (d-d, 2H, -CH=CH-); as shown in Figures.S2. ¹³C-NMR, (100MHz, DMSO-d₆, δ ppm): 186 (C=O), 112-151 (20C, Aromatic-Carbons); as shown in Figures.S3. (HRMS) (EI)m/z 341(M⁺); as shown in Figure S4. Anal.% calcd for C₂₂H₁₆N₂O₂; C,77.59; H,4.70; N,8.19. Found:C,77.63;H,4.74;N,8.23.

2.1.2. 1-(furan-3-yl)-3-[3-(4-methylphenyl)-1-phenyl-1H-pyrazol-4-yl]prop-2-en-1-one(**3b**).

Yellow solid, yield 78%, R_f : 0.42 (C₈H₁₀/C₆H₆, v/v 7:3), MP 266–268 °C; IR (KBr, ν cm⁻¹): 2990 (CH), 1646 (C=O), 1583 (C=C), 1499 (pyrazole, C=N), 1454 (CH₃); as shown in Figure S4. ¹H-NMR (400 MHz, DMSO-d₆, δ ppm): 9.20 (s, 1H, pyrazole-CH), 6.91–8.58 (m, 18H, Ar-H), 6.61–6.77 (dd, 2H, CH=CH), 2.36 (s, 3H, CH₃); as shown in Figure S5. ¹³C-NMR (100 MHz, DMSO-d₆, δ ppm): 186 (C=O), 117–153 (19C, Aromatic-carbons), 112 (CH₃); as shown in Figures.S7. HRMS (EI) m/z 335 (M⁺); as shown in Figure S8. Anal. calcd for C₂₃H₁₈N₂O₂: C, 77.91; H, 5.08; N, 7.86. Found: C, 77.95; H, 5.08; N, 7.86.

2.1.3. 1-(furan-3-yl)-3-[3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl]prop-2-en-1-one(**3c**).

Yellow solid, yield 82%, R_f : 0.50 (CH₂Cl₂, v/v 6:4), MP 235–237 °C. IR (KBr, ν cm⁻¹): 1649 (C=O), 1587 (C=C), 1529 (pyrazole-C=N), 688 (Cl); as shown in Figure S9. ¹H-NMR (400 MHz, DMSO-d₆, δ ppm): 9.38 (s, 1H, pyrazole-CH), 6.84–7.95 (m, 15H, Ar-H), 6.77–6.78 (dd, 2H, -CH=CH-); as shown in Figure S10. ¹³C-NMR (100 MHz, DMSO-d₆, δ ppm): 176.47 (C=O), 112–152 (16C, Aromatic-carbons); as shown in Figures.S11. HRMS (EI) m/z:

375.13 (M^+), 377.1214 ($M+2^+$); as shown in Figure S12. Anal. % calcd for $C_{22}H_{15}ClN_2O_2$: C, 70.46; H, 3.99; N, 7.43. Found: C, 70.55; H, 4.72; N, 7.50.

2.1.4. 3-[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1-(furan-3-yl)prop-2-en-1-one(**3d**).

Yellow solid, yield 82%, R_f : 0.50 (CH_2Cl_2 , v/v 7:3), MP 235–237 °C. IR (KBr, ν cm^{-1}): 1649 (C=C), 1587 (C=O), 1529 (pyrazole-C=N), 688 (Cl); as shown in Figure S13. 1H NMR (400 MHz, $DMSO-d_6$, δ ppm): 9.38 (s, 1H, pyrazole-CH), 6.84–7.95 (m, 15H, Ar-H), 6.77–6.78 (dd, 2H, –CH=CH–); as shown in Figure S14. ^{13}C NMR (100 MHz, $DMSO-d_6$, δ ppm): 176 (C=O), 112–152 (16C, Aromatic-carbons); as shown in Figures.S15. HRMS (EI) m/z : 375.1301 (M^+), 377.1214 ($M+2^+$); as shown in Figure S16. Anal. % calcd for $C_{22}H_{15}ClN_2O_2$: C, 70.46; H, 3.99; N, 7.43. Found: C, 70.55; H, 4.72; N, 7.50.

2.1.5. 1-(furan-3-yl)-3-[3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one(**3e**).

Yellow solid, yield 90%, R_f : 0.44 (C_6H_{14}/C_6H_6 , v/v 5:5), MP 260–263 °C. IR (KBr, ν cm^{-1}): 1659 (C=O), 1597 (C=C), 1539 (pyrazole-C=N), 1333 (NO_2); as shown in Figure S17. 1H -NMR (400 MHz, $DMSO-d_6$, δ ppm): 9.44 (s, 1H, pyrazole-CH), 7.44–8.10 (m, 14H, Ar-H), 6.78–6.79 (dd, 2H, CH=CH); as shown in Figures.S18. ^{13}C -NMR (100 MHz, $DMSO-d_6$, δ ppm): 186 (C=O), 120–140 (19C, Aromatic-carbons). HRMS (EI) m/z : 386.32 (M^+). Anal. % calcd for $C_{22}H_{15}N_3O_4$: C, 68.53; H, 3.83; N, 10.56. Found: C, 68.17; H, 3.52; N, 10.50.

2.1.6. 1-(furan-3-yl)-3-[3-(4-hydroxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one(**3f**).

Yellow solid, yield 78%, R_f : 0.40 ($CH_3COOC_2H_5/C_6H_6$, v/v 5:5), MP 280–281 °C. IR (KBr, ν cm^{-1}): 3138 (–OH), 1680 (C=O), 1597 (C=C), 1504 (pyrazole-C=N); as shown in Figures.S19. 1H -NMR (400 MHz, $DMSO-d_6$, δ ppm): δ 12.80 (s, 1H, –OH), 8.59 (s, 1H, pyrazole-CH), 7.26–7.77 (m, 14H, Ar-H), 6.62–6.63 (dd, 2H, –CH=CH–). ^{13}C -NMR (100 MHz, $DMSO-d_6$, δ ppm): 196 (C=O), 113–138 (19C, Aromatic-carbons); as shown in Figures.S20. HRMS (EI) m/z : 357.39 (M^+). Anal. % calcd for $C_{22}H_{16}N_2O_3$: C, 74.11; H, 4.49; N, 7.82. Found: C, 73.15; H, 4.53; N, 7.86.

2.2. Anti-breast cancer.

Breast cancer remains a significant global health challenge, necessitating the continued exploration of novel therapeutic strategies [36]. Although conventional chemotherapeutic agents are often effective, they are frequently associated with severe side effects and the emergence of drug resistance. This highlights the urgent need for more targeted and less toxic anti-cancer therapies [37]. Among the various compounds under investigation, pyrimidine and pyrazole derivatives have attracted considerable attention due to their wide range of biological activities and structural versatility [37]. Pyrimidine and pyrazole scaffolds are considered privileged structures in medicinal chemistry and are present in numerous biologically active molecules, including several FDA-approved drugs [38]. Investigating their anticancer properties, especially against breast cancer cell lines such as MCF-7, is critical for identifying promising drug candidates. The MTT assay, a well-established colorimetric technique, is commonly used to assess cell viability and drug cytotoxicity [39]. This assay quantitatively measures the reduction of yellow tetrazolium MTT to purple formazan crystals by metabolically active cells, offering insights into cell survival and proliferation [40].

Cisplatin, a widely used platinum-based chemotherapeutic agent, is effective against various cancers including breast cancer. However, its clinical utility is often limited by adverse effects and the development of resistance [41]. Investigating the anticancer potential of

pyrimidine and pyrazole derivatives in combination with cisplatin may yield synergistic effects, potentially lowering the required cisplatin dose and reducing associated toxicities [42,43].

Furthermore, the inherent structural diversity of pyrimidine and pyrazole scaffolds facilitates the design of compounds with improved selectivity toward cancer cells, thereby reducing off-target effects on normal tissues. Hybrid molecules that combine two or more pharmacophores within a single entity have the potential to interact with multiple biological targets, thereby enhancing therapeutic efficacy while mitigating the side effects associated with individual components [44]. Such multi-targeted strategies are particularly promising for the treatment of cancers that develop resistance to conventional monotherapies [45]. The present study presents a comparative analysis of the anticancer potential of a series of pyrimidine and pyrazole derivatives, evaluated against the human breast cancer MCF-7 cell line using a dose-dependent cytotoxicity assay. All tested compounds exhibited a progressive reduction in cell viability as the concentration increased from 10 $\mu\text{g/mL}$ to 50 $\mu\text{g/mL}$, indicating their capacity to inhibit cancer cell proliferation. Notably, the extent of cytotoxicity varied among the different derivatives, enabling a comparative assessment of their relative potencies.

Morphological studies revealed that the untreated MCF-7 cells appeared healthy, forming a dense monolayer with well-defined borders, features characteristic of viable cells. In contrast, cells treated with cisplatin exhibited pronounced cytotoxic effects, including cell shrinkage, membrane blebbing, and detachment, which are indicative of apoptosis or necrosis. Compounds **3(a-f)**, representing various synthesized derivatives, also induced noticeable morphological changes. Most notably, derivatives **3a**, **3b**, and **3c** caused severe morphological disruption, characterized by reduced cell density and the presence of cellular debris, suggesting strong cytotoxic potential. Compound **3f** showed evidence of cell rounding and detachment, indicating a possible dose-dependent or structure-related influence on cytotoxic potency. These morphological changes are illustrated in Figure 1.

2.3. Molecular docking.

2.3.1. Ligand generation.

The ChemDraw Ultra tool was used to draw the 2D structure of ligands, and SMILES were generated. The energy of the ligand was minimized by employing a force field (AMBER) and transformed into a PDB file using USCFC ChimeraV2023 [46].

2.3.2. Preparation of macromolecule.

The 3D crystal structure of human 17-beta-hydroxy steroid-dehydrogenase type1 mutant H221Q protein (PDB:1FDW) [47] was accessed. It was accessed through the database (<https://www.rcsb.org>) [42], and the co-crystallized ligand was removed from the protein. Using the USCF ChimeraV2021 tool, optimization of hydrogen, refinement of the protein, and minimization of energy were executed.

2.3.3. Gridbox selection and visualization.

Around the active sites VAL143, SER222, PHE226, and GLU282, a grid box was arranged and run with an exhaustiveness value of eight [43]. The grid box center dimensions are $x=46.0612\text{\AA}$, $y=8.9856\text{\AA}$, $z=42.3979\text{\AA}$, and the volume of the box was $x=21\text{\AA}$, $y=19\text{\AA}$,

$z=19\text{\AA}$. The ligands were docked against the protein as per the docking module of AutoDock Vina [48], in the PyRx 0.8 platform [49]. The choice of the best conformation of a ligand with a target is based on the most negative binding energy. The docked protein and hit were converted into PDB file format using the Schrödinger PyMolV.2.3.4 [50] tool, and 3D ligand plots were visualized by BVStudio V.2020 software [51].

2.3.4. Validation of docking protocol.

The RC plot was employed to check the stability of the protein using BIOVIA Discovery Studio V.2020. The protocol of the molecular docking procedure was validated by calculating the RMSD values of designed ligands with the cocrystal and Carboxy amidotriazole via PyMolV.2.3.4 tool [52,53].

3. Results and Discussion

3.1. Chemistry.

The novel chalcone derivatives were synthesized by condensing 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde with 2-acetylfuran in the presence of ethanolic sodium hydroxide under reflux conditions for 7-8 hours. The reaction yielded the target compounds, 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1-(furan-3-yl)prop-2-en-1-one derivatives **3(a-f)**, in pure form. All newly synthesized compounds were characterized using physicochemical procedures (TLC), Melting Point, and spectroscopic methods (IR, ¹H-NMR, ¹³C-NMR, and mass spectrometry). The synthesized compounds were evaluated for biological properties, focusing on anti-breast cancer activity using the MCF-7 cell line, and molecular docking studies were conducted to understand the interactions with target proteins. Scheme 1 describes the entire synthesis strategy. The experimental part includes analytical and spectral data for the produced chemical.

3.2. Anti-breast cancer.

Among the synthesized series, compounds **3d** and **3f** demonstrated the strongest antiproliferative activity against MCF-7 cells, reducing cell viability to 1.72% and 14.62%, respectively, at 50 $\mu\text{g/mL}$, with compound **3d** emerging as the most potent. In contrast, compound **3c** exhibited weaker activity, maintaining 22.06% cell viability at the same concentration. Compound **3e** showed moderate efficacy, with cell viability ranging between 19–22%. These variations highlight the significant influence of structural features—particularly substitutions on the pyrimidine and pyrazole rings—on anticancer activity. Therefore, compounds **3d** and **3f** may serve as promising candidates for further optimization and preclinical development.

The synthesized pyrazole and pyrimidine derivatives showed IC_{50} values ranging from 19.39 to 34.02 $\mu\text{g/mL}$ against MCF-7 cells, with compounds **3a**, **3d**, and **3f** exhibiting the highest cytotoxicity, highlighting their potential as lead candidates for anticancer drug development. The IC_{50} results are shown in Table 1, Table 2, Figure 1, and Figure 2.

Table 1. Percentage of cell viability of test samples on the breast cancer MCF-7 cell line.

Sl.no	Conc.	3a	3b	3c	3d	3e	3f
1	10 μg	74.90 $\pm$ 1.6393	78.31 $\pm$ 1.7654	90.16 $\pm$ 1.0088	62.79 $\pm$ 1.3871	83.35 $\pm$ 1.7654	70.23 $\pm$ 0.0056
2	20 μg	58.13 $\pm$ 1.7654	63.17 $\pm$ 1.0088	70.23 $\pm$ 1.5132	50.44 $\pm$ 1.6393	68.34 $\pm$ 1.1349	52.71 $\pm$ 0.0035
3	30 μg	46.91 $\pm$ 0.8827	48.92 $\pm$ 0.3783	61.66 $\pm$ 1.7654	39.34 $\pm$ 1.1349	55.35 $\pm$ 2.0176	36.31 $\pm$ 0.0077
4	40 μg	26.98 $\pm$ 2.3959	33.54 $\pm$ 0.6305	39.47 $\pm$ 1.2610	25.97 $\pm$ 0.8827	36.94 $\pm$ 1.2610	24.21 $\pm$ 0.0056

Sl.no	Conc.	3a	3b	3c	3d	3e	3f
5	50 µg	14.24±0.5044	16.89±1.3871	22.06±0.7566	11.72±0.7566	19.29±1.0088	14.62±0.0063

Results are expressed as mean±standard error.

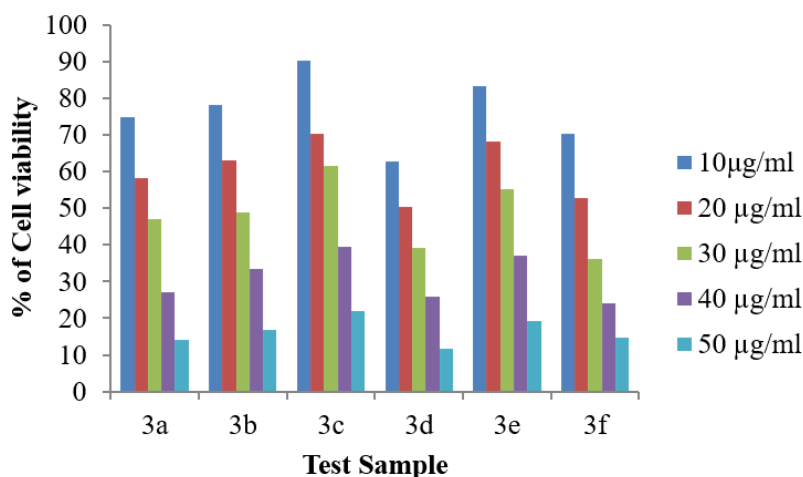


Figure 1. Percentage of cell viability in breast cancer cell line MCF-7 treated with sample 3(a-f).

Table 2. IC₅₀ details of test Samples.

Test sample	IC ₅₀ in µg/ML
3a	19.39
3b	28.80
3c	34.02
3d	20.56
3e	31.67
3f	22.57
cisplatin	22.86

Results are expressed as mean±standard error.

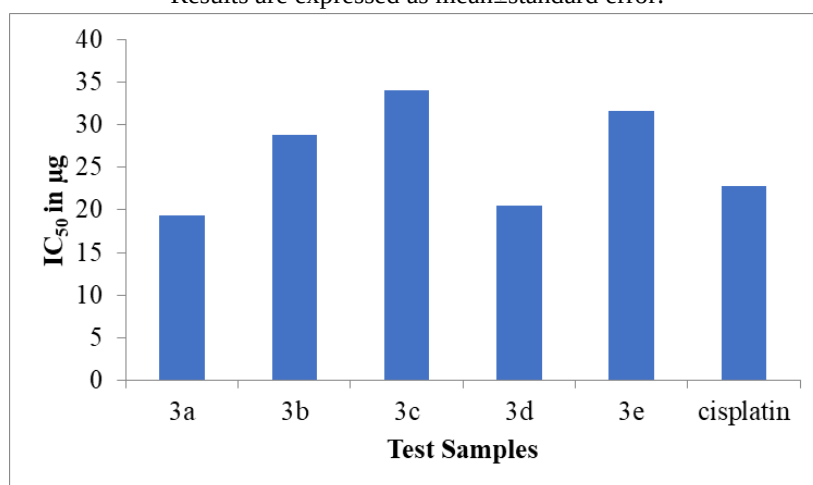


Figure 2. IC₅₀ of test compounds 3(a-f).

3.3. Molecular docking.

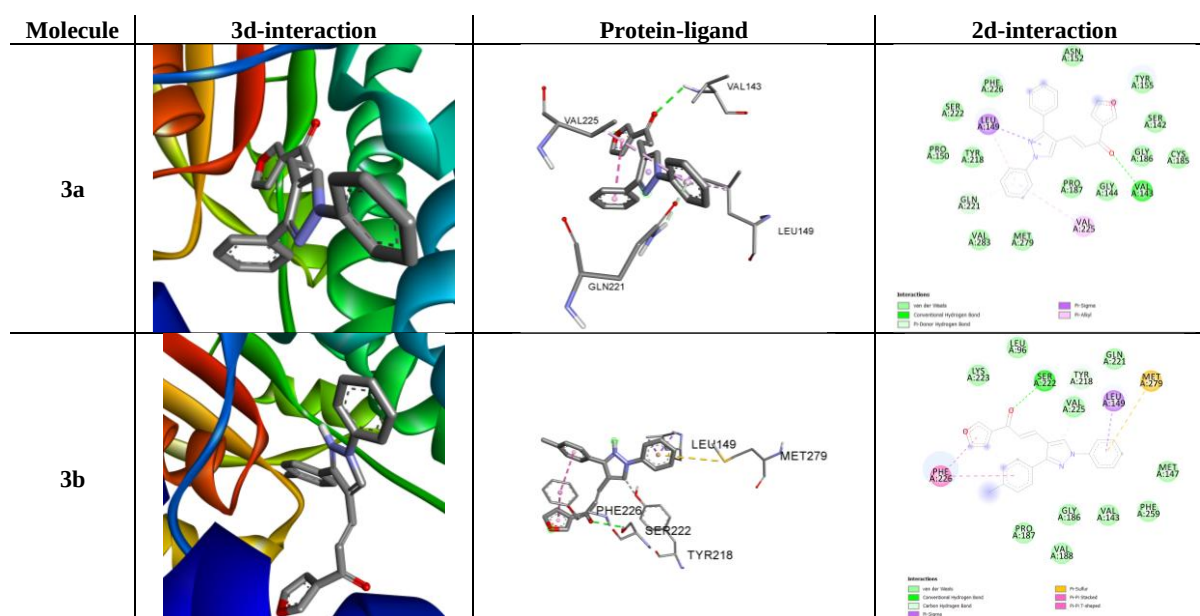
To analyze and understand the results of *in vitro* studies, molecular docking serves as an exceptionally effective tool. This method is commonly used in computer-aided drug design to predict how a compound will bind to a specific target protein and to estimate its binding affinity. The molecular docking results of IMD (1-6) **3(a-f)** ligands against the human 17-beta-hydroxysteroid dehydrogenase type-1 mutant H221Q reveal significant binding affinities and diverse interactions with key residues. The binding affinities of the ligands range from -8.3 to -8.7 kcal/mol, with IMD4 **3d** exhibiting the highest affinity at -8.7 kcal/mol. The ligands commonly form hydrogen bonds with residue VAL143, showing variations in bond lengths. For instance, IMD 2 (**3b**) exhibits the shortest hydrogen bond length of 1.95 Å with SER222. The ligands do not share identical hydrogen bonding patterns, indicating diversity in their

interactions. For example, TRI 2 shows a hydrogen bond length of 2.55 Å with GLN221. Additionally, the ligands commonly form hydrogen bonds with residues such as GLY144, GLY186, and ASN152, with varying bond lengths; for instance, TER shows the shortest hydrogen bond length of 2.84 Å with SER142.

In terms of hydrophobic and other interactions, all ligands interact with key residues including LYS223, LEU96, TYR218, VAL225, GLN221, LEU149, MET147, PHE259, VAL143, GLY186, VAL188, PRO187, and PHE226. However, notable differences are observed in their specific interaction profiles. IMD4 and IMD6, which exhibit higher binding affinities (-8.7 and -8.6 kcal/mol, respectively), show more extensive interactions. In comparison, IMD1 and IMD3, with lower binding affinities (-8.3 kcal/mol), also interact with multiple residues but lack certain key interactions present in the higher-affinity ligands. For comparison, the reference ligand 5-fluorouracil shows a binding affinity of -5.1kcal/mol and forms multiple hydrogen bonds with LYS644 and ASP829. The results are shown in Table 3 and Figures 3 and 4.

Table 3. Molecular docking studies of compounds **3(a-f)**.

Molecule	Binding affinity (kcal/mol)	'H'-Bonding	'H'-Bond length(Å)	E-interaction	H-phobicandotherinteractions
3a	-8.3	VAL143	2.13	-	ASN152,TYR155,SER142,CYS185,GLY186,GLY144,PRO187,MET279, VAL283,GLN221,TYR218,PRO150,SER222,PHE226,LEU149
3b	-8.4	SER222	1.95	MET279	LYS223,LEU96,TYR218,VAL225,GLN221,LEU149,MET147,PHE259, VAL143,GLY186,VAL188,PRO187,PHE226
3c	-8.3	VAL143	2.42	-	PHE226,TYR155,GLY186,SER142,CYS185,PRO187,GLY144,PHE259, MET279,VAL283,GLN221,TYR218,VAL225,SER222,LEU149,ASN152, LEU96
3d	-8.7	VAL143	2.21	-	LEU96,ASN152,GLY186,SER142,CYS185,TYR155,GLY144,PRO187, VAL225,GLN221,MET279,VAL283,PRO150,SER222,LEU149,TYR218, SER222,PHE226
3e	-8.5	SER142	2.39	-	TYR155,LEU96,PHE226,LYS223,SER222,TYR218,GLN221,VAL225, VAL283,MET279,PHE259,LEU149,PRO187,VAL143,GLY186
3f	-8.6	VAL143	2.87	-	SER142,GLY186,CYS185,GLY144,PHE226,PRO187,TYR218,LEU149, TYR155,PRO150,VAL283,VAL225,GLN221,MET279,SER222,ASN15, LEU96



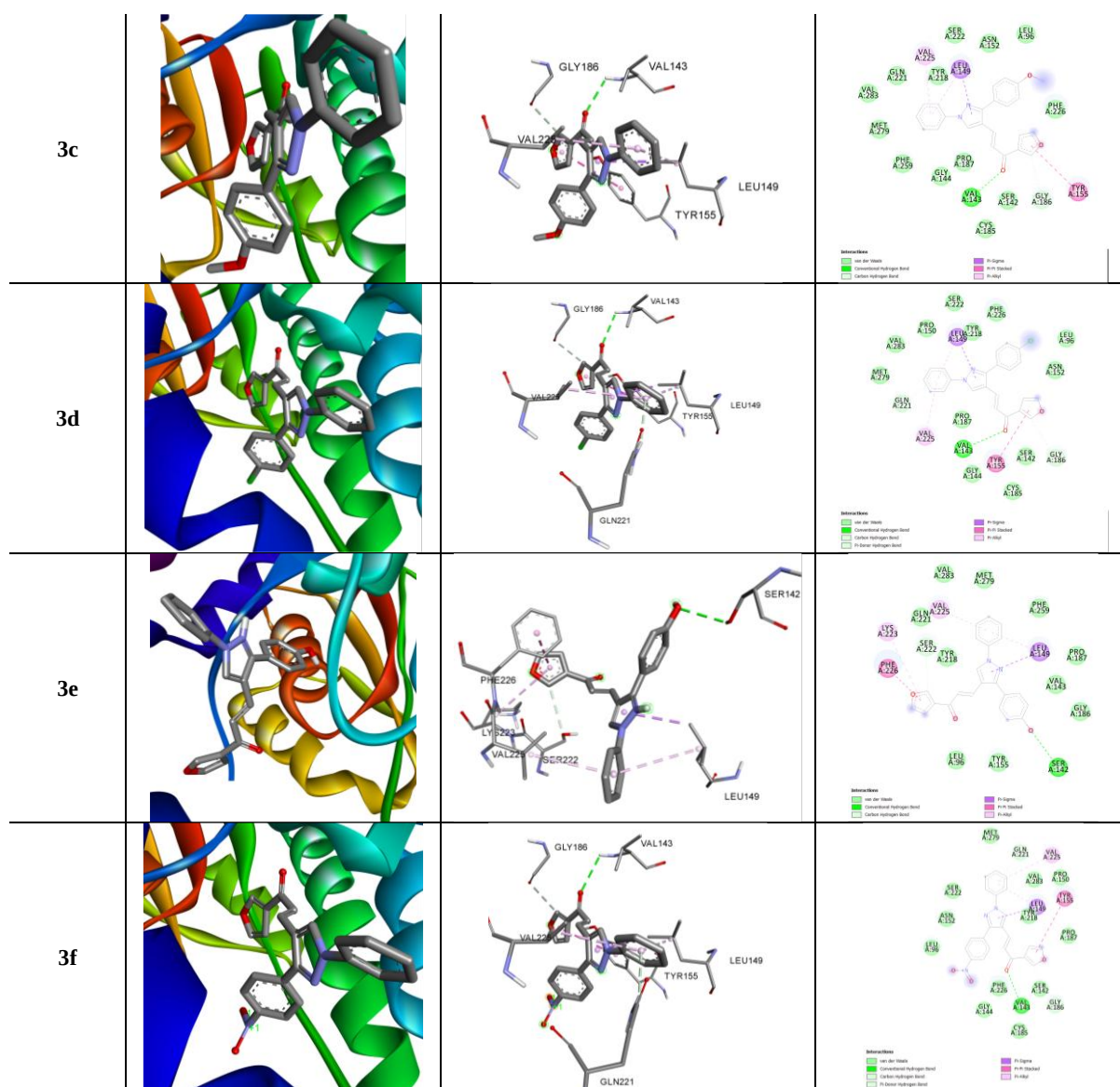


Figure 3. Molecular docking of compound 3(a-f).

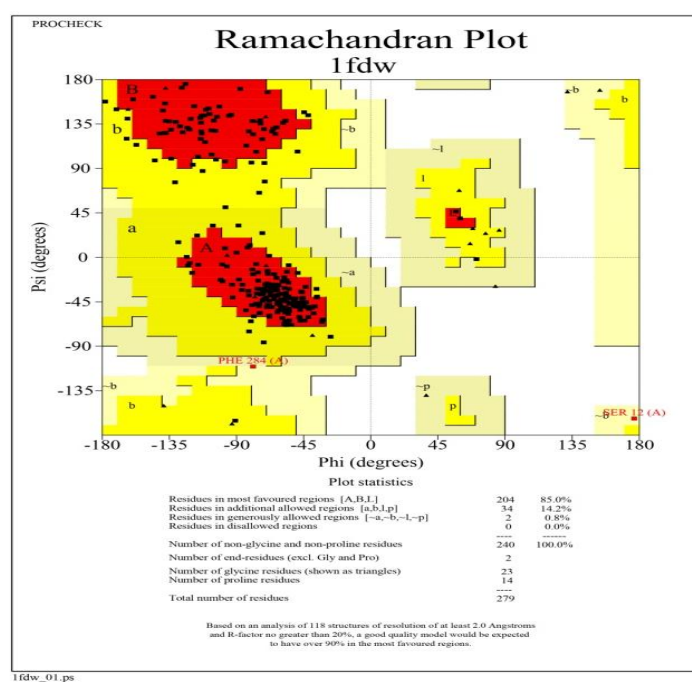


Figure 4. Gridbox selection and visualization 3(a-f).

3.4. DFT studies.

The DFT calculations provided insights into the electronic structure and reactivity of the synthesized compounds. The HOMO–LUMO energy gap (ΔE) values ranged from 3.57 to 3.66 eV, indicating a favorable charge transfer characteristic. Compound **3f** exhibited the lowest ΔE (3.57 eV) and the highest electrophilicity index (5.02), suggesting strong electron-accepting ability and enhanced biological reactivity. Higher dipole moment values observed for compounds **3c** and **3e** correlated with their improved polar interactions and potential for stronger binding affinity in the docking analysis. These theoretical results supported the experimental cytotoxicity trends and highlighted the significance of electronic factors in modulating anticancer activity. The DFT data of compounds **3(a–f)** are presented in **Table 4**.

Table 4. DFT parameters compounds 3(a–f).

Compounds	EHOMO (eV)	ELUMO (eV)	ΔE (Gap) (eV)	Dipole Moment (D)	Hardness η $= (\Delta E/2)$	Electronegativity (χ)	Electrophilicity Index (ω)
3a	-5.82	-2.21	3.61	3.41	1.81	4.01	4.44
3b	-5.75	-2.15	3.60	3.88	1.80	3.95	4.34
3c	-5.68	-2.02	3.66	4.22	1.83	3.85	4.06
3d	-5.95	-2.38	3.57	2.96	1.78	4.16	4.86
3e	-5.64	-1.98	3.66	4.78	1.83	3.81	3.96
3f	-6.02	-2.45	3.57	2.54	1.78	4.23	5.02

3.5. Structure-activity relationship (SAR) and correlation with IC_{50} and docking results.

The SAR analysis demonstrated a clear relationship between substituent electronic and steric effects, binding affinity, and *in vitro* anticancer potency (IC_{50}). Compounds bearing electron-donating and hydrophobic substituents exhibited the lowest IC_{50} values and the most favorable docking energies, confirming that substituent-controlled electronic density and steric orientation play a critical role in receptor recognition and cytotoxic response.

Derivatives bearing electron-donating substituents ($-OCH_3$, $-CH_3$) showed significantly lower IC_{50} values and stronger docking scores. This can be attributed to increased electron density on the aromatic system, enhanced π – π stacking interactions, improved hydrogen-bonding contributions from methoxy oxygen, and favorable charge distribution, as supported by a smaller HOMO–LUMO gap in DFT analysis. These molecules formed stable interactions with active-site amino acids, correlating well with their observed biological activity.

Improved biological activity. Stronger binding, Lower IC_{50} , and better docking score, and demonstrated synergistic steric and electronic advantage, reflected in docking and biological activity trends. Chloro-substituted derivatives displayed moderate to good cytotoxicity and docking scores, which can be attributed to Halogen-induced lipophilicity increase. Halogen bonding and van der Waals interactions with binding pocket residues enhanced membrane permeability, aiding cellular uptake. Compounds containing extended aromatic or fused systems showed lower cytotoxicity due to increased surface area for π -stacking.

Table 5. SAR conclusion.

Substitution features	Effect on docking	Effect on IC_{50}	Overall impact
$-OCH_3/-CH_3$	$\uparrow$ H-bonding + π -stacking	$\downarrow$ (better)	Most Active
Halogens	$\uparrow$ lipophilicity + halogen bonding	$\downarrow$ / Moderate	Good Activity
Bulky Aromatics	Better cavity fit	$\downarrow$ (enhanced)	Highly Active
Unsubstituted	Weak interactions	Higher IC_{50}	Least Active

Better binding activity, favorable docking energy, and higher polarizability enhance electron communication (DFT). Electronic properties correlated with activity (DFT Insight). Activity consistency showed a lower HOMO-LUMO gap, indicating high chemical reactivity, higher dipole movement, and enhanced biological interaction potential. Favorable orbital distribution near pharmacophoric regions. These computational parameters aligned with strong binding and superior IC₅₀ performance; Table 5 showed the SAR conclusion of all compounds.

The successful synthesis and structural confirmation of chalcone derivatives **3(a–f)** established a reliable chemical platform for subsequent biological assessment. MCF-7 cytotoxicity results revealed notable structure–activity relationships, particularly highlighting electron-withdrawing substituents as key contributors to enhanced anticancer potency. Compounds **3d** and **3f** demonstrated the highest cytotoxicity, correlating with their favorable binding affinity and interaction profiles in molecular docking studies. These findings suggest that specific substituents on the pyrazole ring not only promote molecular recognition at the active site of 17 β -HSD1 but also translate to stronger *in vitro* antiproliferative activity. Thus, integrating synthetic chemistry, cell-based assays, and docking analysis provides a comprehensive rationale for the lead potential of compounds **3d** and **3f**, supporting further optimization and mechanistic exploration.

The current results section presents synthetic, biological, and computational findings; however, a cohesive interpretation linking these data strengthens the scientific narrative. The successful synthesis and structural confirmation of chalcone derivatives **3(a–f)** established a reliable chemical platform for subsequent biological assessment. MCF-7 cytotoxicity results revealed notable structure–activity relationships, particularly highlighting electron-withdrawing substituents as key contributors to enhanced anticancer potency. Compounds **3d** and **3f** demonstrated the highest cytotoxicity, correlating with their favorable binding affinity and interaction profiles in molecular docking studies.

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4. Conclusions

In the present study, a series of novel 1,3-diphenyl-1*H*-pyrazol-4-yl)prop-2-en-1-one hybrids **3(a–f)** were synthesized and evaluated for their anti-breast cancer activity and molecular docking properties. Among the compounds, **3a** exhibited significant anti-breast cancer activity with an IC₅₀ value of 34.21 μ g/mL. Compound **3d**, which contains a hydrogen atom at the C-4 position of the phenyl ring, showed the highest binding affinity in molecular docking studies, with a binding energy of –8.7 kcal/mol. Additionally, the introduction of a chloro group at the C-4 position of the phenyl ring further influenced the activity. The SAR analysis suggested that electron-donating substituent's and heteroaromatic frameworks significantly contributed to the observed biological effects. Complementary *in silico* studies, including molecular docking and DFT calculations, provided additional molecular insights into the binding interactions and electronic behavior of the synthesized compounds. These results indicate that structural modifications in the pyrazole-furan chalcone framework can significantly impact biological activity. Overall, these newly developed frameworks represent promising candidates for further lead optimization and biological development. Future work

will focus on *in vivo* studies, mechanistic evaluation, and pharmacokinetic profiling to establish their clinical relevance.

Author Contributions

Conceptualization, N.D.S.; methodology, A.A.B.; formal analysis, A.A.B.; resources, P.C.; data curation, N.D.S.; writing—original draft preparation, A.A.B.; writing—review and editing, P.C.; supervision, P.C.; project administration, P.C.; funding acquisition, P.C. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

The authors declare no conflict of interest.

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Supplementary materials

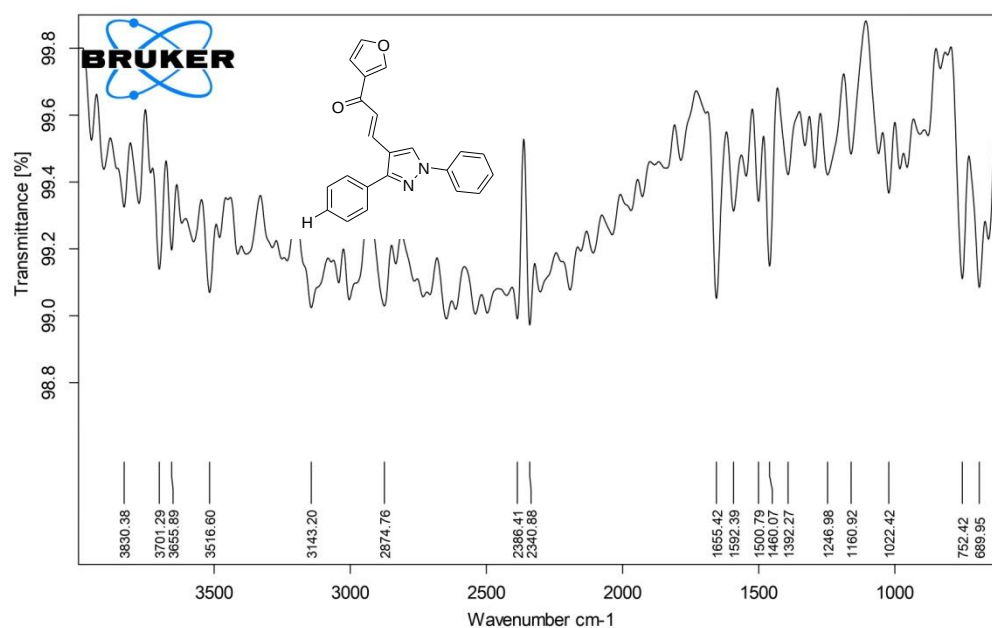


Figure S1. IR Spectrum of Compound 3a.

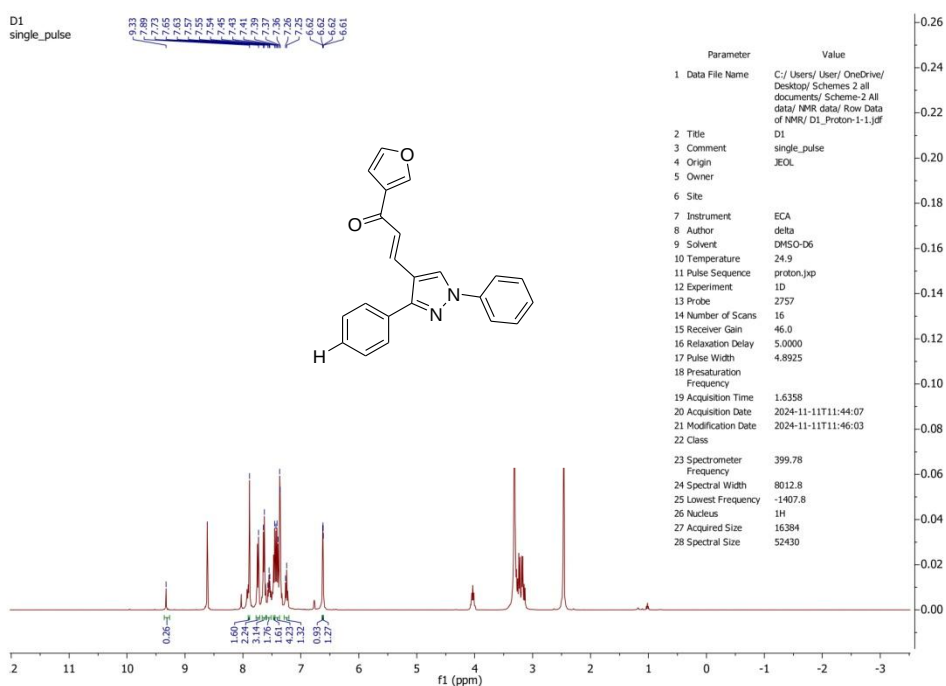


Figure S2. ¹H-NMR spectrum of compound 3a.

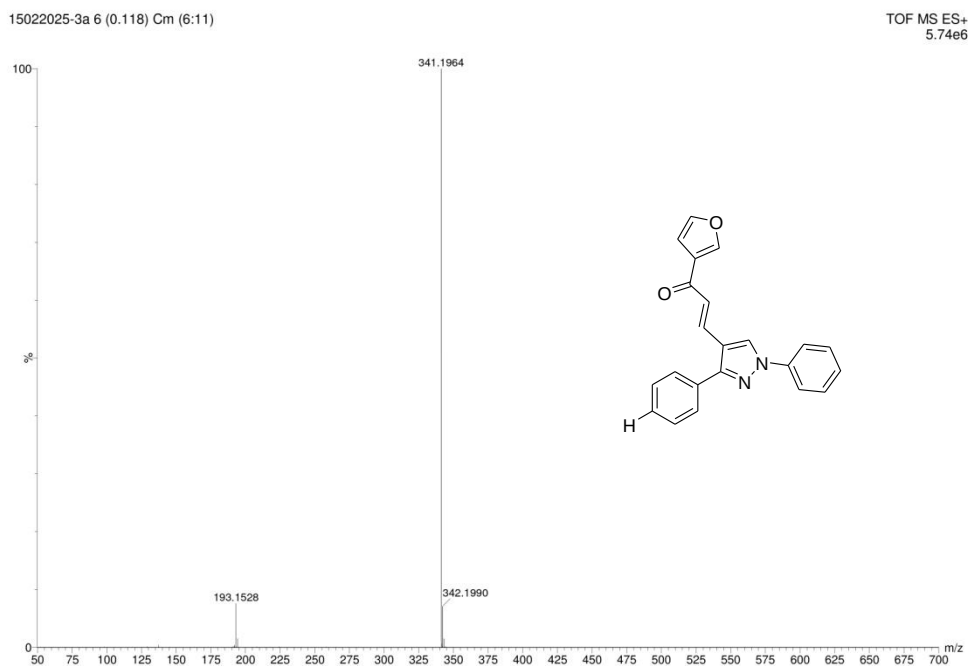


Figure S3. Mass Spectrum of Compound 3a.

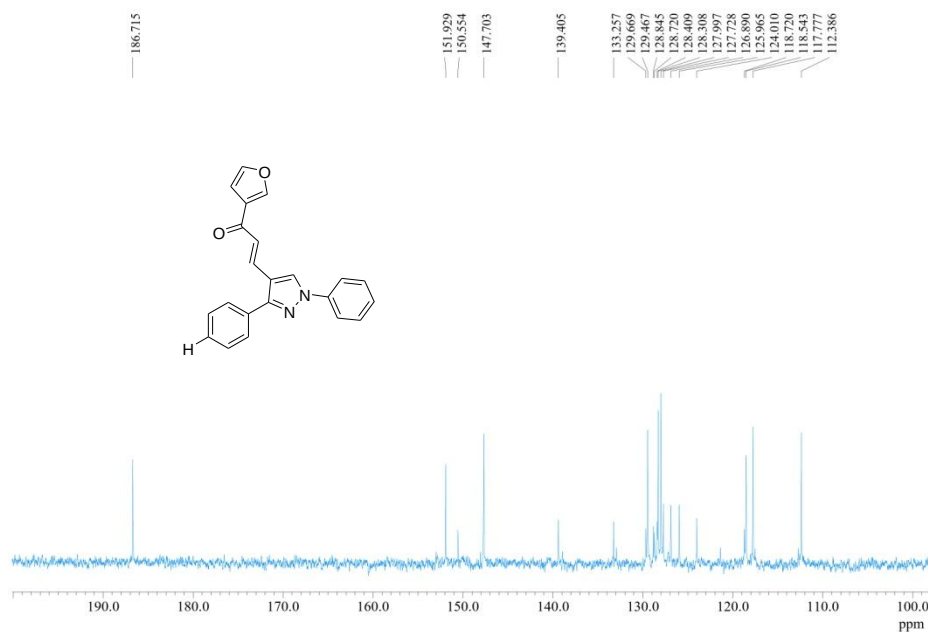


Figure S4. ^{13}C -NMR Spectrum of Compound 3a.

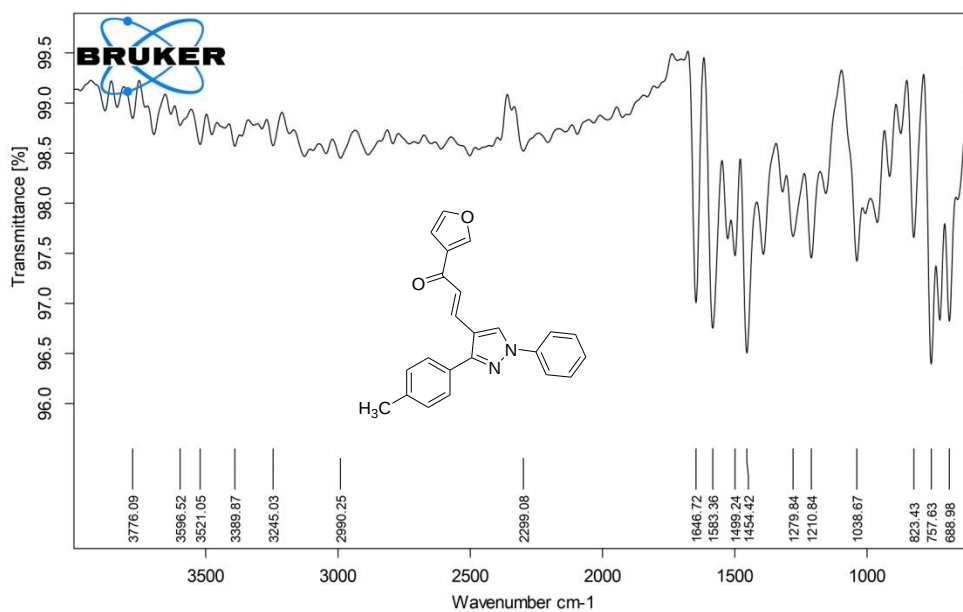


Figure S5. IR Spectrum of Compound **3b**.

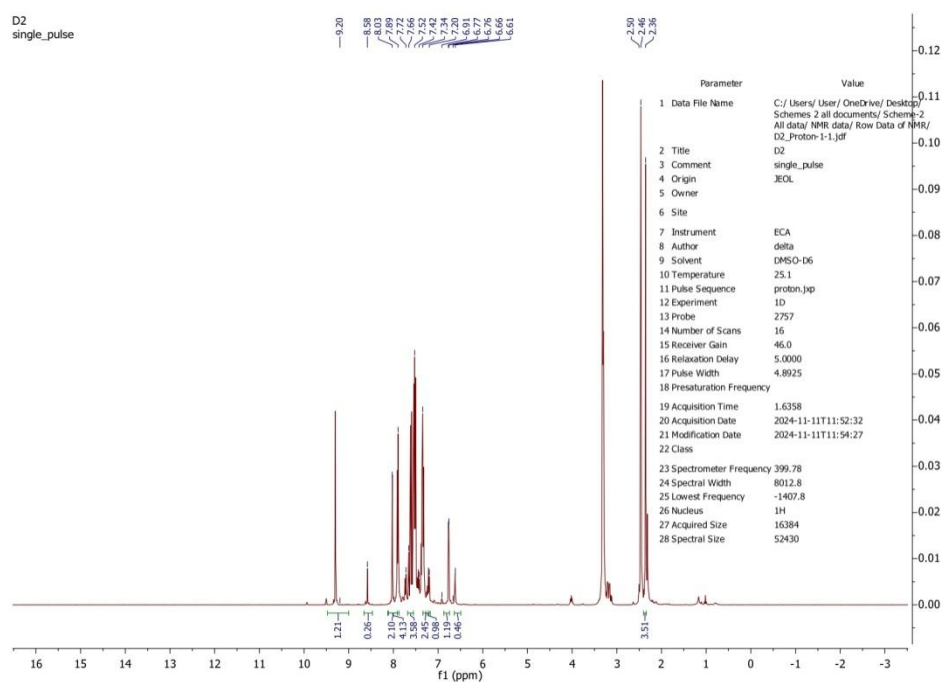


Figure S6. ^1H -NMR Spectrum of Compound **3b**.

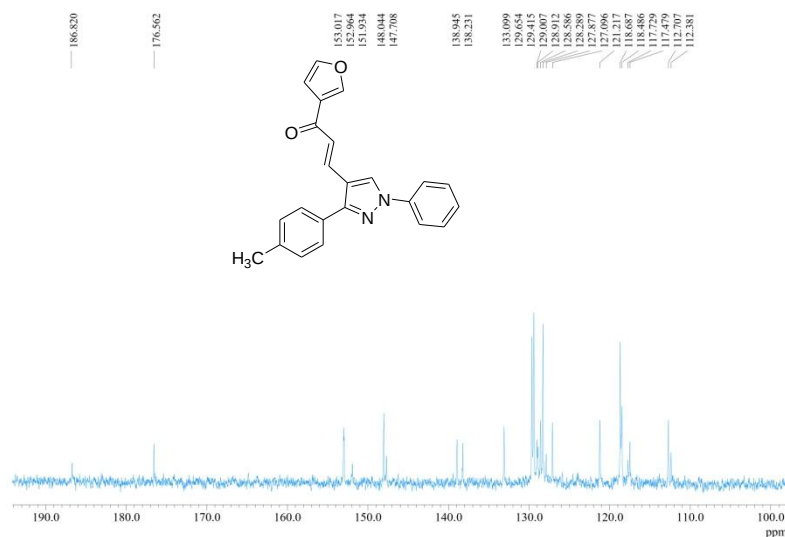


Figure S7. ^{13}C NMR Spectrum of Compound **3b**.

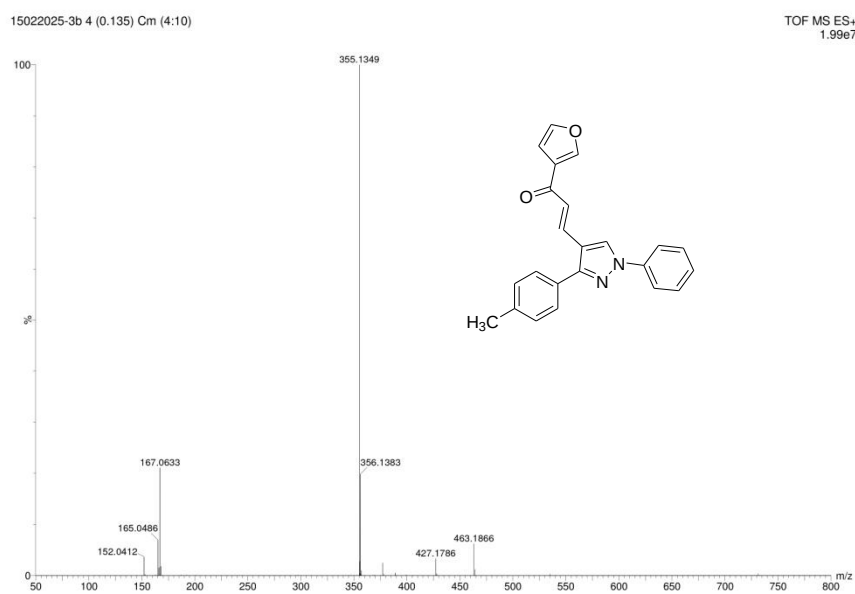


Figure S8. Mass Spectrum of Compound **3b**.

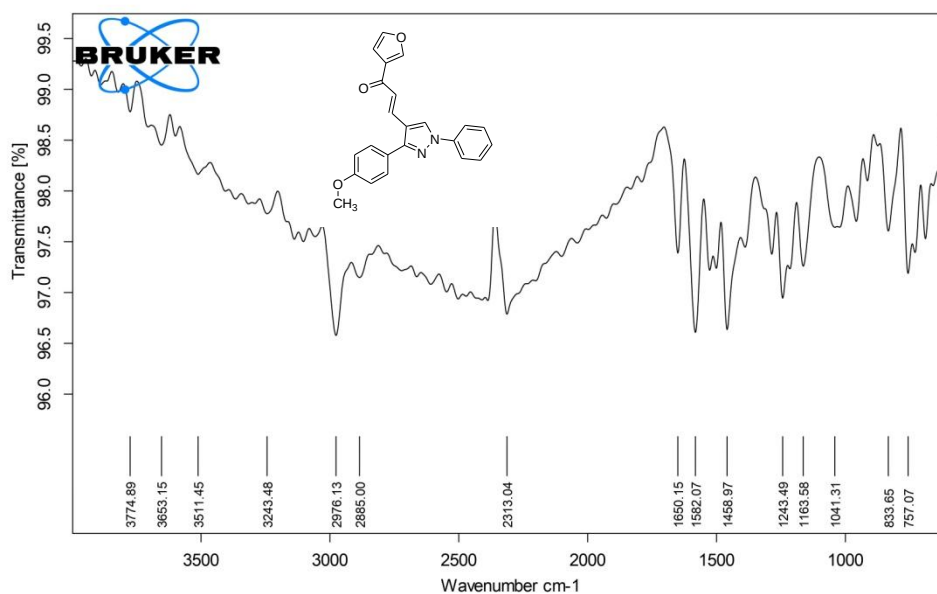


Figure S9. IR Spectrum of Compound **3c**.

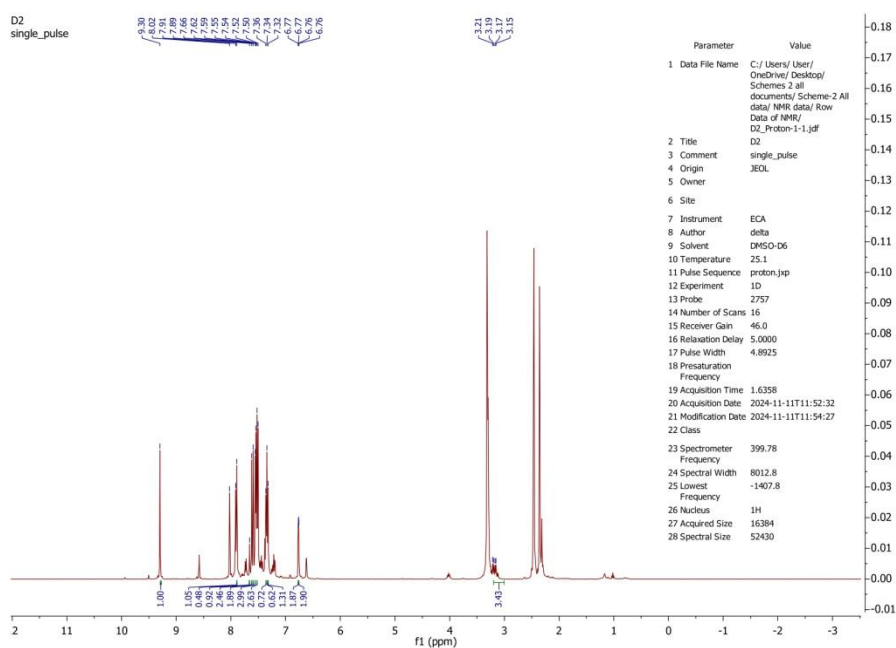


Figure S10. ¹H-NMR Spectrum Compound of **3c**.

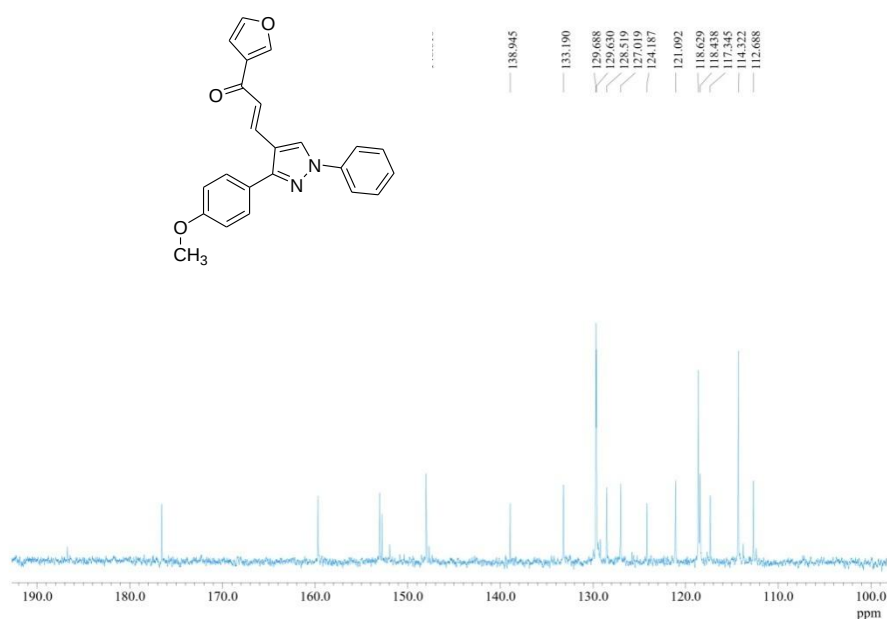


Figure S11. ¹³C NMR Spectrum Compound 3c.

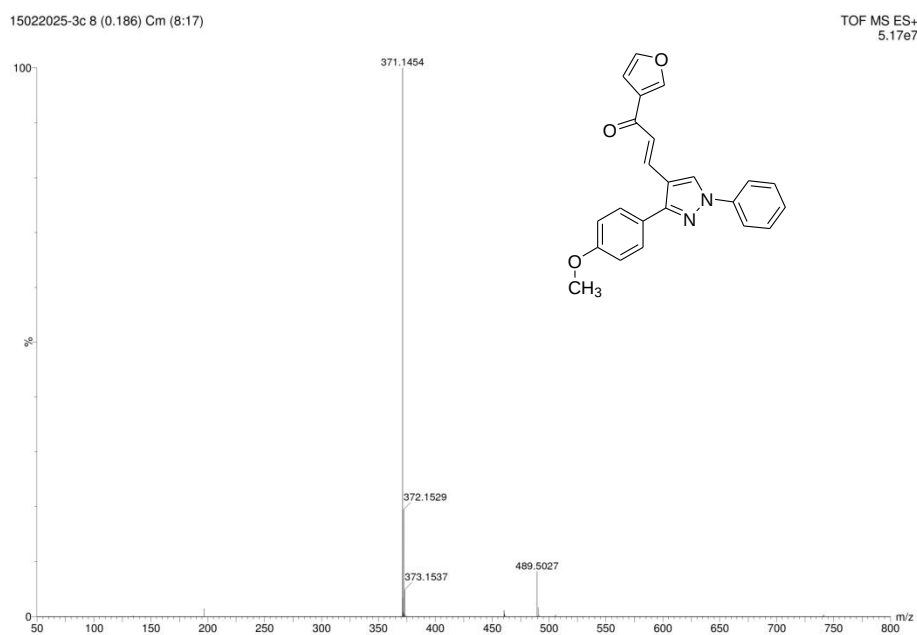


Figure S12. Mass Spectrum of Compound 3c.

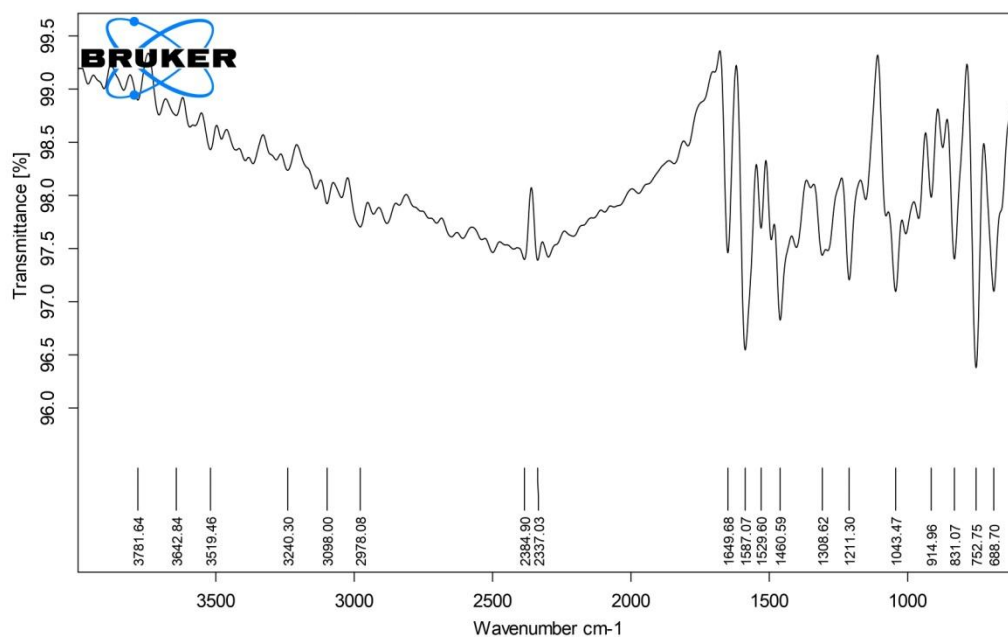


Figure S13. IR Spectrum of Compound 3d.

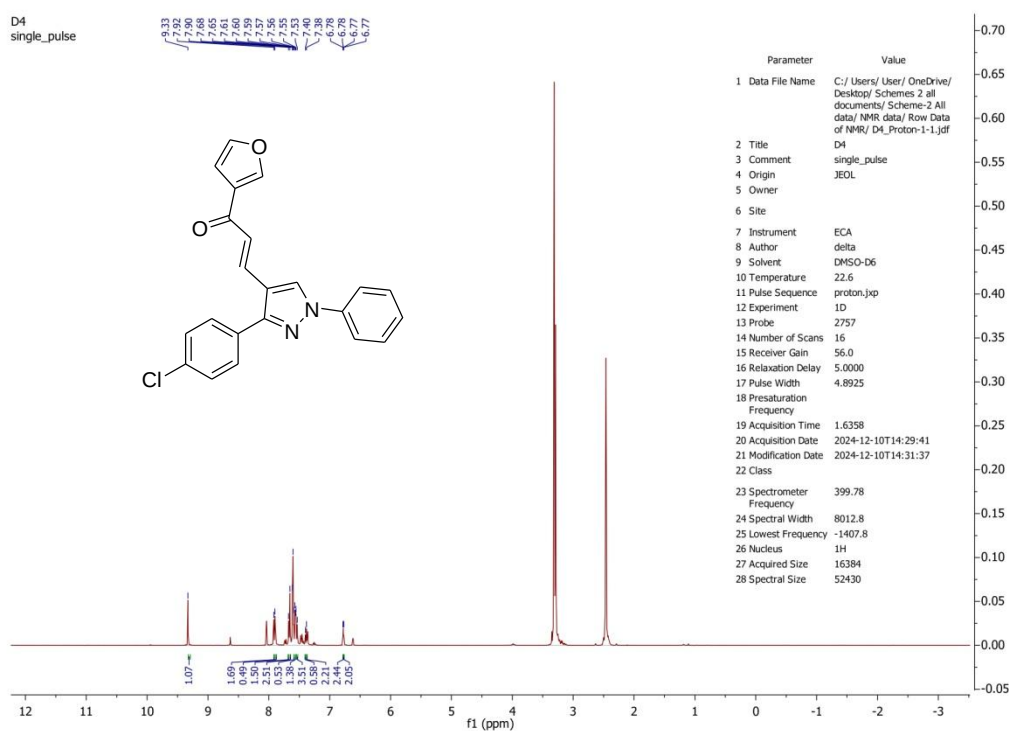


Figure S14. IR Spectrum of Compound 3d.

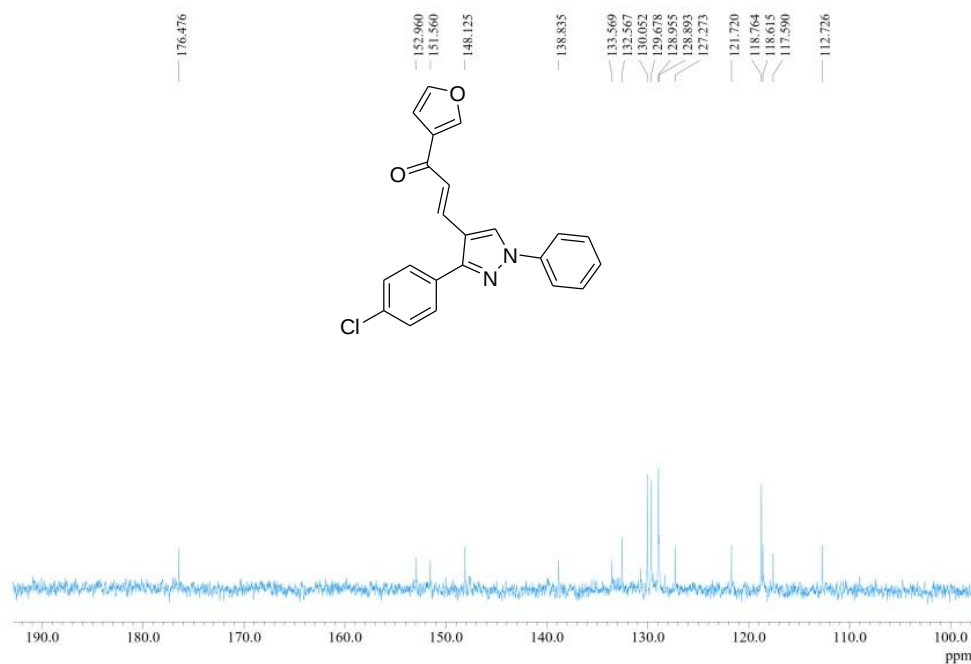


Figure S15. ¹³CNMR Spectrum of Compound **3d**.

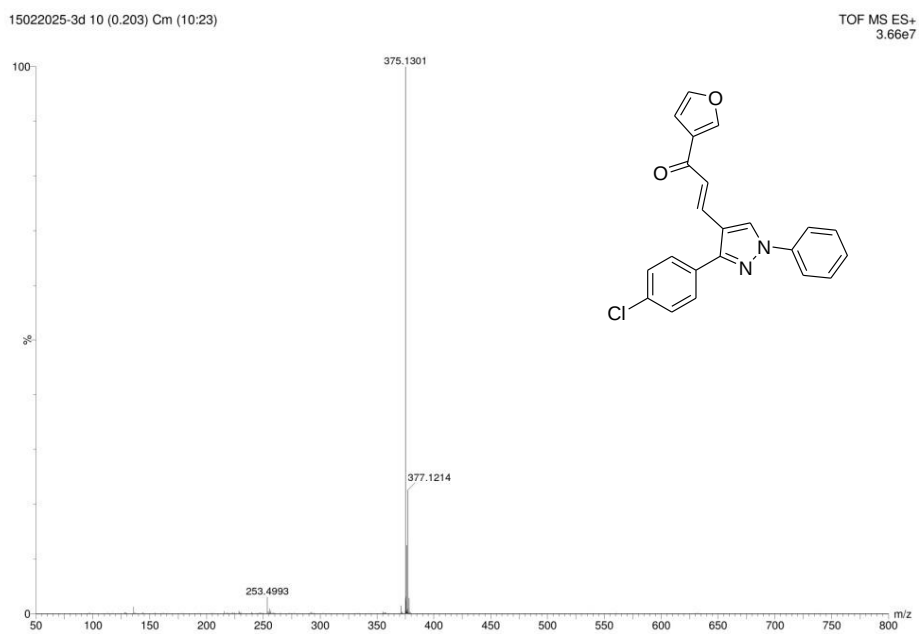


Figure S16. Mass Spectrum of Compound **3d**.

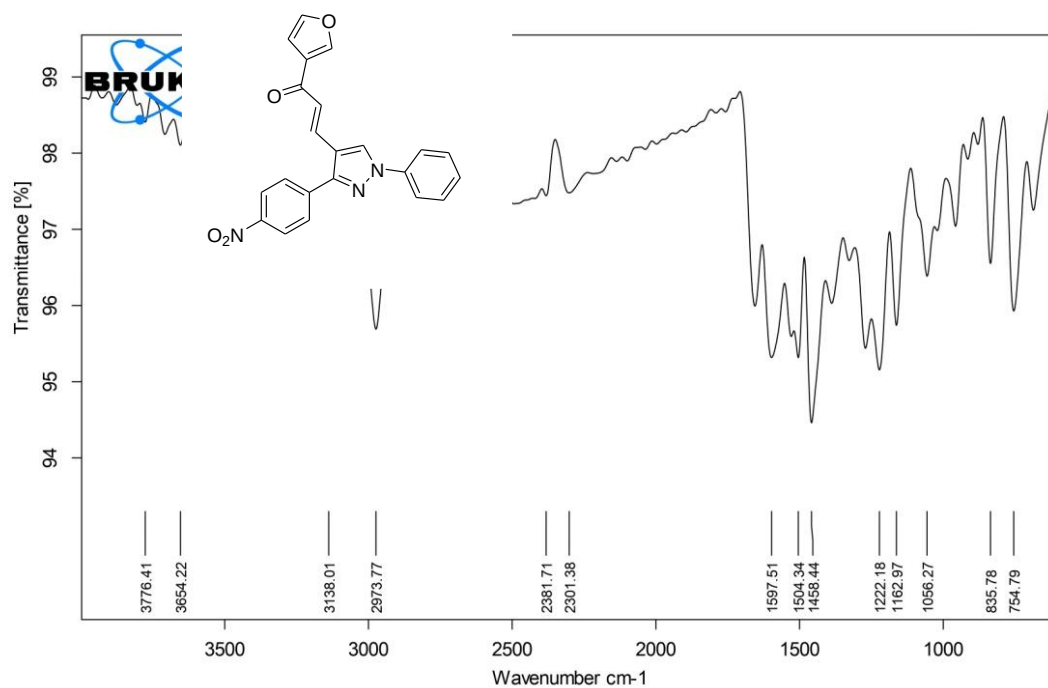


Figure S18. ¹H-NMR Spectrum of Compound 3d.

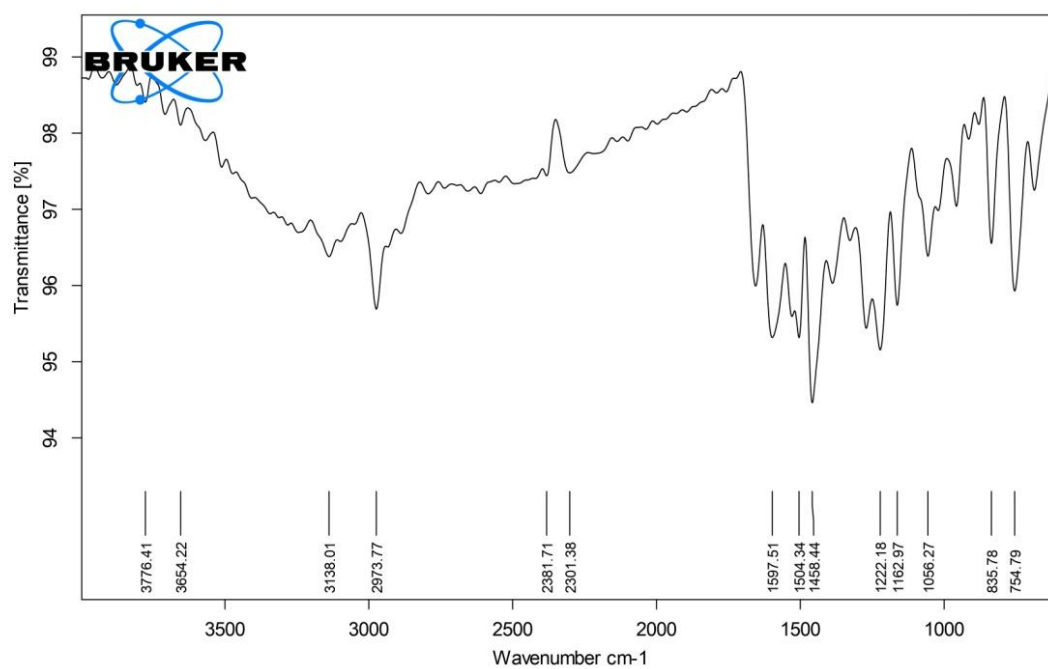


Figure S17. IR Spectrum of Compound 3e.

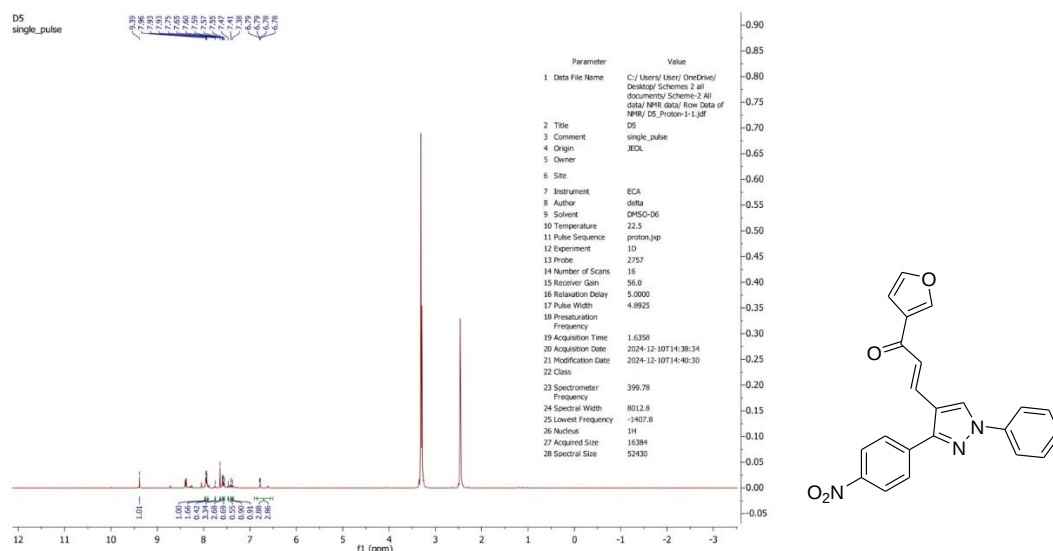


Figure S18. ¹H-NMR Spectrum of Compound 3e.

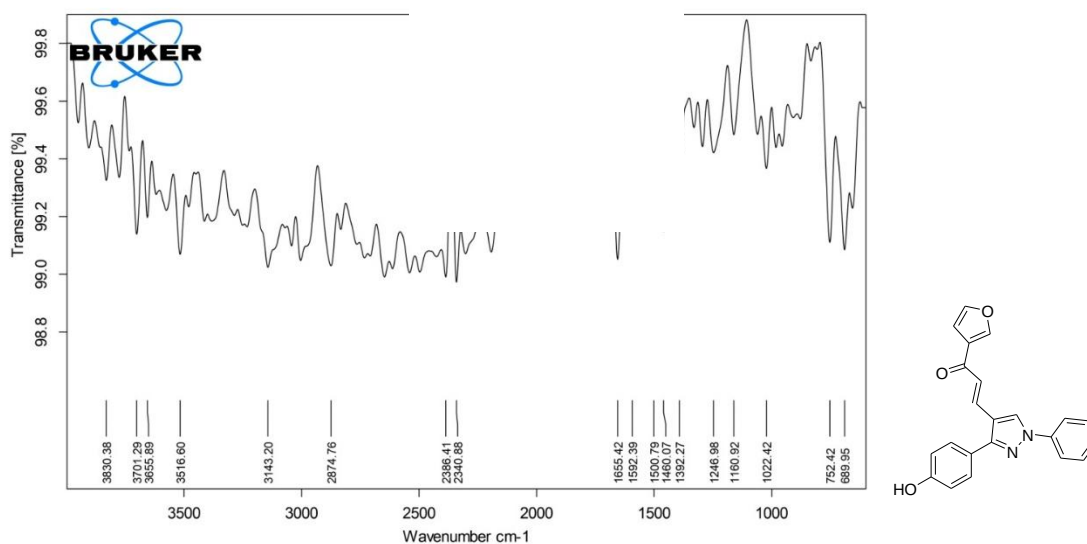


Figure S19. IR-Spectrum of Compound 3f.

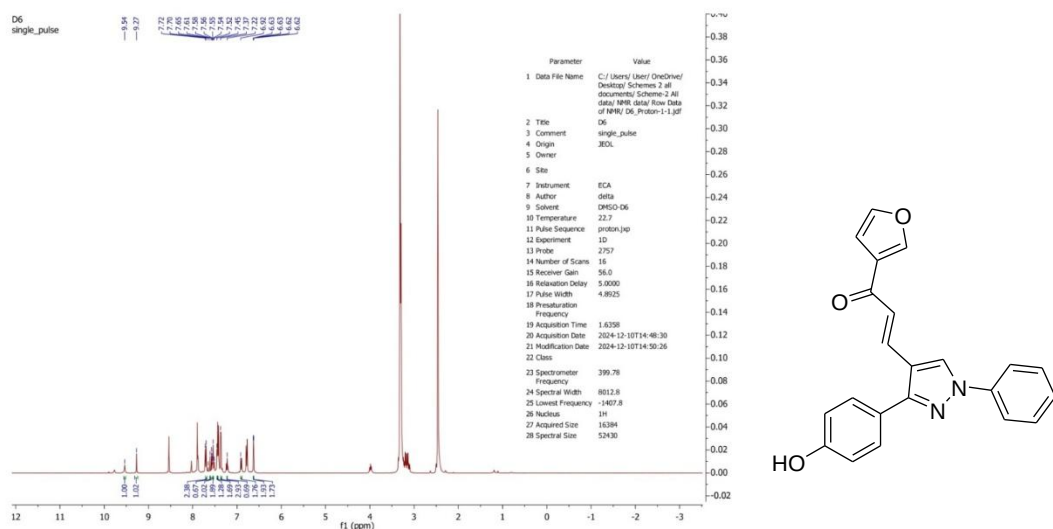


Figure S20. ¹H-NMR Spectrum of Compound 3f.