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Design and Evaluation of Pyrazole Herbicides: QSAR-Driven Synthesis for Effective Weed Control and Crop Safety in Rice

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ABSTRACT

A total of twenty pyrazole derivatives were synthesized using alkoxy or halo acetophenones in reaction with N, N-dimethylformamide dimethylacetal (DMF-DMA). These compounds were characterized through ¹H NMR, ¹³C NMR, and LC-HRMS techniques. Their herbicidal efficacy against barnyard grass (*Echinochloa crus-galli*) was evaluated via *in vitro* bioassays. Notably, compound **6a** (5-Methoxy-2-(1H-pyrazol-3-yl) phenol) and compound **6s** (3-(4-Fluoro-2-hydroxyphenyl) pyrazole) demonstrated inhibition rates of 30.6% to 54.1% and 26.9% to 50.6%, respectively, across concentrations ranging from 62.5 to 1000 µg mL⁻¹. In *in vivo* assessments, compound **6a** yielded the highest weed control index (WCI) of 51.32%, followed by compound **6s** with a WCI of 50.24%. These findings indicate that compound **6a** represents a promising herbicidal agent, effectively managing barnyard grass while exhibiting tolerance toward rice seedlings following both post-emergence and soil application. Toxicity predictions for the synthesized compounds were evaluated for fish (LC₅₀: 0.0001 to 38.1 mg/L), daphnids (LC₅₀: 0.0001 to 27.7 mg/L), and green algae (EC₅₀: 0.0001 to 1.70 mg/L), including chronic toxicity (ChV). Using the ECOSAR model, the assessment found that all synthesized compounds are within acceptable limits. The binding free energy of compound **6a** with HPPD was relatively low (-8.3), which was consistent with the findings of bioassay activity studies. As a result, compound **6a** could serve as the starting point for the development of novel HPPD inhibitors.

Keywords: Pyrazole derivatives, HPPD, *Echinochloa crus-galli*, Rice, Weed

1. INTRODUCTION

Rice (*Oryza sativa* L.) serves as a major staple food for approximately two-thirds of the global population. In India, rice is cultivated across more than 48 million hectares, resulting in an annual production of roughly 134 million tonnes (Dixit et al. 2024; USDA, 2024). Nevertheless, productivity is significantly impeded by various abiotic and biotic factors, among them weeds represent the highest potential loss (34%) or most substantial challenge (Behura et al. 2011; Gharde et al. 2018). Among these, barnyard grass (*Echinochloa crus-galli*) is recognized as one of the major serious weeds impacting rice cultivation and frequently demonstrates resistance to herbicides (Rao et al. 2007; Holm, 1991; Heap, 2023). This particular weed poses considerable difficulties in both transplanted and direct-seeded rice systems due to its ecological similarities to rice. While numerous herbicides are effective in controlling barnyard grass during its younger leaf stages, their efficacy markedly declines once the grass exceeds three leaf stages. Furthermore, fluctuations in environmental temperatures may influence the growth of barnyard grass, enabling it to evade control measures in specific regions (Singh et al. 2020).

There exists a significant need for the development of new herbicides capable of effectively controlling annual weeds, with particular emphasis on late-stage barnyard grass, utilizing a single application. Recent advances in HPPD-inhibiting herbicides have demonstrated potential in this domain, as they offer the ability to target all weed types simultaneously, commonly referred to as “one-shot” herbicides (Jeschke, 2016). Additionally, there is an increasing demand for herbicides that are environmentally sustainable, highly effective, low in toxicity, selective in action, and exhibit low persistence in the environment (Hasan et al. 2021).

Heterocyclic compounds, particularly pyrazole derivatives, are vital as effective pesticides in the field of chemical control. Their application in both pharmaceuticals and agrochemicals is significant and well-established (Liu et al. 2010; Kasiotis et al. 2014). Pyrazolynate and pyrazoxyfen (4-(2,4-dichlorobenzoyl)-1,3-dimethyl-5-hydroxypyrazole) herbicides are the pyrazole derivatives, specifically demonstrate decisive herbicidal activity against rice. These compounds function by inhibiting 4-hydroxyphenylpyruvate dioxygenase (HPPD), which disrupts carotenoid biosynthesis and unequivocally leads to bleaching effects in susceptible weeds (Jhala et al. 2023; He et al. 2022; Jhala et al. 2014; Kaundun, 2021; Jeschke, 2016).

Our team has been focused on developing new bioactive compounds for crop protection (Shakil et al. 2010; Shakil et al. 2013; Kaushik et al. 2019; Yadav et al. 2021; Kaushik et al. 2021; Yadav et

al. 2022). We explored a new chemical group based on the pyrazole moiety and evaluated the herbicidal effectiveness of these derivatives in a greenhouse. In addition to their herbicidal properties, these compounds show strong affinity for various biological targets, making them significant in modern medicinal chemistry (Yurttas et al. 2016). This study reports the synthesis and characterization of several pyrazole derivatives, along with their evaluation against *E. crus-galli*.

2 MATERIALS AND METHODS

2.1 Chemicals and instruments

The purity and identity of the synthesized pyrazole derivatives were verified using ultra-fast liquid chromatography with photodiode array detection (UFLC-PDA) (SHIMADZU, Japan), utilizing a C₁₈ Shim-pack column (5 μ m, 4.6 $\times$ 250 mm) in an isocratic solvent system of methanol-water (98:2). ¹H and ¹³C nuclear magnetic resonance (400 and 100 MHz NMR) spectra were recorded on a JEOL Spectrospin spectrometer, with tetramethylsilane (TMS) as the internal standard. The precise mass of the compounds was determined by liquid chromatography-high-resolution mass spectrometry (LC-HRMS, Singapore) using an AB SCIEX Triple TOFTM 5600+ (Singapore) system equipped with a TurboIonSpray (TIS) ion source, SCIEX ExionLC, coupled with a PDA detector and a C₁₈ column (2.7 μ m, 4.6 $\times$ 100 mm). The column was eluted with a methanol-water (98:2) mixture containing 0.1% formic acid at a flow rate of 0.5 mL/min, with the column oven maintained at 40°C. Melting points were determined using a melting point apparatus (Labcare LB-MPS8, India).

2.2 Synthesis

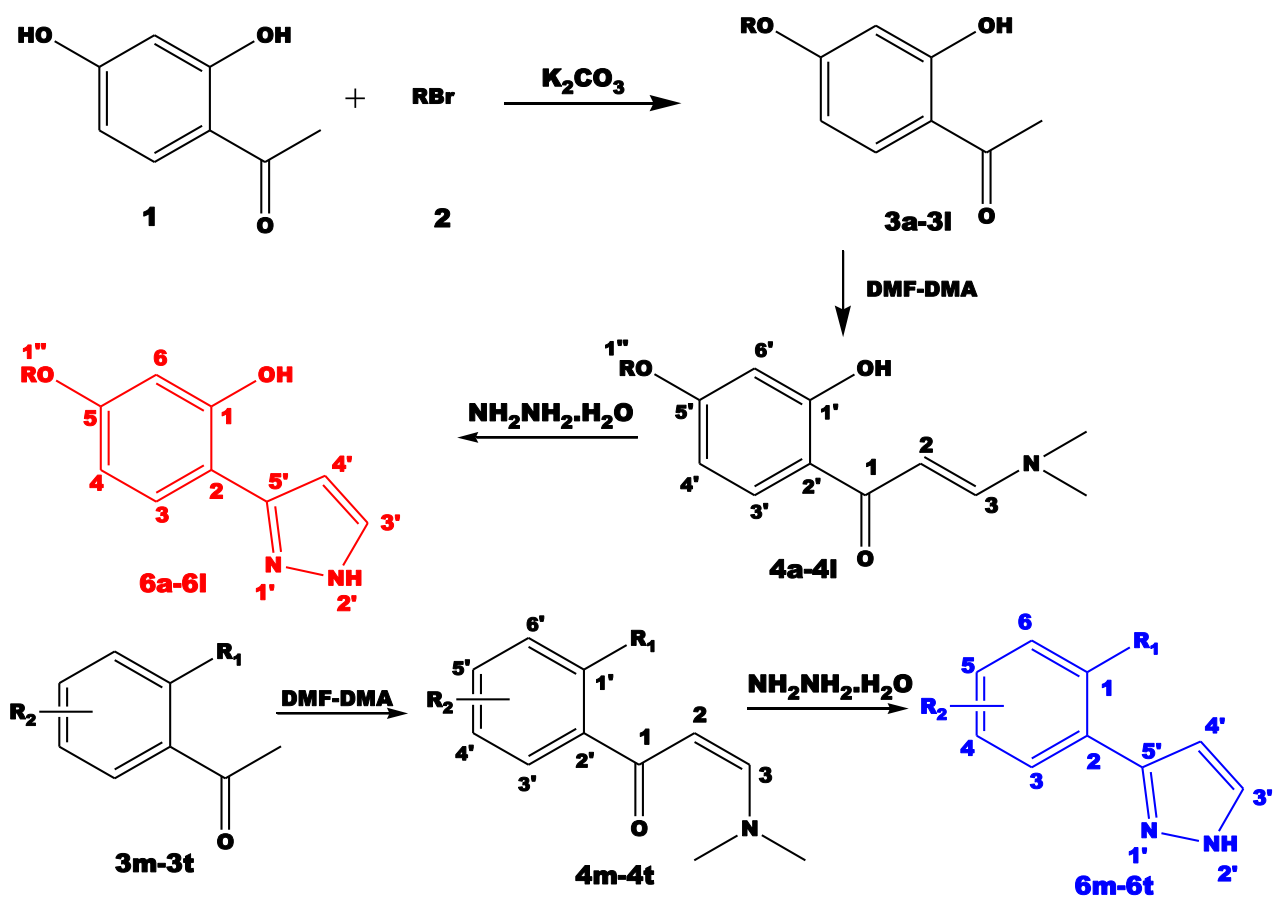
2.2.1 Synthesis of substituted 2-hydroxyacetophenones (3a–3t)

A molar ratio of 1:1.2 was established between iodoalkanes or bromoalkanes with varying carbon chain lengths and 2-hydroxyacetophenone. The reaction mixture was subjected to continuous stirring for a duration of 6 hours at a temperature of 60°C, utilizing K₂CO₃ and acetone as catalysts. The progression of the reaction was monitored through thin-layer chromatography (TLC) employing a solvent system composed of ethyl acetate and hexane in a 3:7 ratio.

2.2.2 Synthesis of substituted 3-dimethylamino-1-(2-hydroxyphenyl) propenones (4a–4t)

A mixture of substituted 2-hydroxyacetophenones (3a–3t) (1.2 mmol) and N, N-DMF-DMA (2.4 mmol, 2 moles) was heated at 90°C for 8 hours, then allowed to cool. After the reaction, the solvent

was removed. Separation of pure compound was done by the column chromatography with a hexane-ethyl acetate mixture (85:15), yielding 72% to 88% (Tripathi et al. 2025).



	R		R ₁	R ₂
a	5-CH ₃	m	OH	4-Cl
b	5-C ₂ H ₅	n	-	1-Cl
c	5-C ₃ H ₇	o	OH	4-Br
d	5-C ₄ H ₉	p	OH	2,4-Cl
e	5-C ₅ H ₁₀	q	OH	H
f	5-C ₆ H ₁₃	r	OH	3-F
g	5-C ₇ H ₁₅	s	OH	4-F
h	5-C ₈ H ₁₇	t	-	2,4-Cl
i	5-C ₉ H ₁₉	These acetophenone derivatives were purchased		
j	5-C ₁₀ H ₂₁			
k	5-C ₁₂ H ₂₃			
l	5-C ₁₃ H ₂₇			

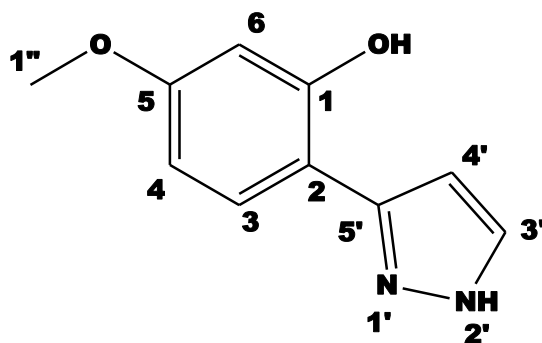
Scheme 1. Synthesis of pyrazole derivatives

2.2.3 General method for the synthesis of pyrazole derivatives (6a–6t)

The synthesis of pyrazole derivatives were done by reacting substituted 3-(dimethylamino)-1-(2-hydroxyphenyl) propenone (**4a–4t**) (5.6 mmol) with hydrazine monohydrate (10.47 mmol, 2 equivalents) in methanol (15 mL) at 65°C for 5 hours, as described in Scheme 1 (Zhang et al. 2017). The progress of the reaction was monitored using thin-layer chromatography (TLC) with an ethyl acetate-hexane (3:7) solvent system. after, the solvent was removed via rotary evaporation. The resulting pyrazole derivatives were purified using column chromatography, yielding pure pyrazoles with an efficiency of 85-90% (Tripathi et al. 2025).

5-Methoxy-2-(1H-pyrazol-3-yl) phenol (**6a**)

Light yellow to light red, Yield 87 %, m. p. 138-142°C; ¹H NMR (400 MHz, DMSO-d₆): δ 3.76 (3H, s, H-1"), 6.36 (1H, dd, *J*=6.8, 2.4 Hz, H-4), 6.62 (1H, s H-4'), 6.84 (1H, d, *J*=2.4 Hz, H-6), 7.49 (1H, d, *J*=8.8 Hz, H-3), 7.80 (1H, s, H-3'). ¹³C NMR (100 MHz, DMSO-d₆): 55.23 (C-1"), 100.59 (C-4), 101.59 (C-4'), 105.90 (C-6), 107.28 (C-2), 127.94 (C-3), 151.42 (C-5'), 156.29 (C-1), 161.65 (C-5) and 165.35 (C-3'). HR-MS for C₁₀H₁₀N₂O₂ [M + H]⁺ m/z: Calcd 190.0815; Observed 191.0863. The major mass fragments observed were C₁₀H₁₀NO₂⁺ (176), C₇H₃N₂O⁺ (131) and C₇H₇N₂⁺ (119)



2.3. Bio efficacy studies

2.3.1. Phytotoxicity Assessment

Phytotoxicity assessments were performed using a visual observation-based scoring system. The toxicity of the plants was evaluated through visual observation scores. Pyrazole derivatives and certain post-emergence herbicides were applied at 7, 14, and 21 days after spray (DAS). Five different observers independently evaluated treatments 6a through 6t, assessing each plot for symptoms such as necrosis, wilting, chlorosis, and leaf injury (including tip and surface damage). The mean phytotoxicity values were calculated by averaging the individual scores. Damage was rated on a scale of 1 to 10, where 1 indicated 1-10% damage and 10 represented 91-100% damage (Table 1).

2.3.2 Screening under seed germination chamber

The herbicidal activity against *E. crus-galli* was assessed by measuring percent germination, coleoptile length, and radical length (Song et al. 2021; Kumar et al. 2021). The seeds were sterilized in 1% sodium hypochlorite for 10 minutes and rinsed with autoclaved water. A 1% potassium nitrate (KNO₃) solution was used to break dormancy. A stock solution of 10000 µg mL⁻¹ of the test compounds was prepared in DMSO and serially diluted in double-distilled water. Various concentrations (62.5, 125, 250, 500, and 1000 µg mL⁻¹) of the solutions were applied to Petri dishes lined with germination paper, where twenty seeds were placed per dish. A 1% Tween-20 solution served as the negative control. Three replicates were prepared for each treatment in a completely randomized design at room temperatures of 25–28°C. After five days, germination rates, root lengths (cm) and shoot lengths (cm) were measured at 24, 48, 72, 96, and 120 hours. Water was used as a negative control and Pendimethalin (38.7 % CS, BASF) was used as a positive control. Germination percentages were calculated using the following formula:

149 Germination % = $\left(\frac{NT}{N}\right) \times 100$

150 where NT =Number of germinated seeds in each treatment; N= Number of seeds used in the
151 bioassay.

152 At the end of the 120 hr of incubation, the length of the shoot and root was measured. The formulae
153 used for determining the inhibition of shoot and root growth are as follows:

154 Inhibition of hypocotyl (shoot length) growth (% Inhibition) = $100 \times \left(1 - \frac{St}{Sc}\right)$

155 where St = Growth of shoot length in treatment and Sc = Growth of shoot length in control.

156 Inhibition of radicle (root length) growth (% Inhibition) = $100 \times \left(1 - \frac{Rt}{Rc}\right)$

157 where Rt = Growth of root length in treatment and Rc = Growth of root length in control.

158 **2.3.3 Screening under greenhouse conditions.**

159 The efficacy of synthesized pyrazole derivatives was evaluated under pot conditions and compared
160 with commercial formulation of Bispyribac-sodium (10% SC, Post-emergence herbicide, PI
161 Industries Ltd., Udaipur) under a controlled environment. The pots were maintained under flooded
162 conditions at a 3-cm depth of water at 28-33 °C (day) and 20-26°C (night) in a greenhouse. The
163 soil in the pots has been taken from the experimental farm of ICAR-Indian Agricultural Research
164 Institute, New Delhi, the soil was alluvial having a sandy loam texture with 0.54 % organic carbon
165 and pH 7.6. A completely randomized design (CRD) was used for the experiment with three
166 replications of each treatment with a pot size (12 x 16 cm). In each pot, 10 seeds of *E. crus-galli*
167 were initially sown, at 0.5-1.0 cm depths. Synthesized pyrazole and commercial herbicide were
168 applied to the pot after 13 days after sowing as post emergent herbicide. A total of 3 weeks after
169 the application, the herbicidal efficacy and rice injury were evaluated on a visual scale of 0
170 (inactive or no damage) to 100 (complete kill of weed or crop). Data on crop phytotoxicity were
171 recorded at 15 and 30 DAS. Three replications for each treatment (100, 75 and 50 µg mL⁻¹) were
172 maintained, while the commercial herbicide was applied at a single dose of 100 µg mL⁻¹(40 g ha⁻¹
173 ¹). Weed density and weed dry weight was monitored at 30 and 60 days after sowing. Thereafter,
174 weeds were collected, counted, and dried in a hot air oven at 65°C for about 72 hr to a constant
175 weight and the dry weight of weed from each pot was recorded. Weed control efficacy (WCE) and
176 weed control index (WCI) were determined with the following equations (Das, 2007).

$$WCE = \frac{WD_c - WD_t}{WD_c} \times 100$$

Where, WD_c and WD_t are weed density (number of weeds/pot) in control and treated plot, respectively.

$$WCI = \frac{WDM_c - WDM_t}{WDM_c} \times 100$$

Where, WDM_c and WDM_t are weed dry weight (g/pot) in control and treated plot, respectively

2.4 Aquatic toxicity predictions

ECOSAR (Ecological Structure Activity Relationships) predicts the aquatic toxicity of chemicals using SARs and QSARs. Developed by the EPA, this standalone program estimates both acute and chronic toxicity for organisms such as fish, *Daphnia*, and green algae, with freely available software.

2.5 Molecular Docking

To compare docking metrics with bioassay results and investigate the relationship between synthesized pyrazole derivatives (6a-6t) and 4-hydroxyphenylpyruvate dioxygenase (HPPD), a key target for herbicidal activity, we utilized AutoDock Vina as the primary software for the docking study. The protein target selected was the HPPD enzyme from *Arabidopsis thaliana* (PDB ID: 1TG5). The protein was prepared for docking by adding hydrogen bonds after removing water molecules and heteroatoms. Additionally, the three-dimensional structures of the ligands, specifically compounds 6a-6t, were optimized. Key active site residues identified for interaction were Tyr144, His287, and Phe254. The docking process involved specific parameters: ten independent docking runs were conducted, the grid was centered on the active pocket, and the exhaustiveness was set to 8.

2.6 QSAR Methodology

2.6.1 Computational Descriptor Generation and Validation

Molecular descriptors for the QSAR study were selected based on their relevance to herbicide bioavailability and target-site affinity. Log Kow (octanol-water partition coefficient) was calculated using the atom-contribution method to represent the lipophilic character influencing

cuticular penetration. Binding Free Energy (ΔG) was obtained via AutoDock Vina 1.1.2 using a grid box centered on the native ligand binding site of HPPD (size $22.5 \times 22.5 \times 22.5$ Å).

2.6.2 Multiple Linear Regression (MLR) Parameters

The MLR model was developed using a training set of structurally diverse derivatives to ensure broad chemical space coverage. The statistical significance of the regression coefficients was evaluated using the t-test, and the overall model validity was confirmed via the F-test. The exclusion of outliers was based on Cook's distance to ensure that no single compound disproportionately influenced the model slope.

2.7 Statistical analysis:

A robust multiple linear regression model was meticulously constructed to illuminate the relationship between percentage inhibition and key molecular parameters, namely Binding Energy and Log Kow. This analysis utilized data from six carefully selected pyrazole derivatives (6a, 6s, 6c, 6j, 6m, 6t), providing a diverse representation of structural variations. The regression analysis was conducted using Microsoft Excel (v. 365) and underwent rigorous validation through the statistical programming language R (v. 4.3).

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2$$

Where: Y = % inhibition, X_1 = Binding Energy, X_2 = Log Kow, β_0 = intercept and β_1 , β_2 = coefficient

3 RESULTS AND DISCUSSIONS

3.1 Synthesis

In this study, 20 compounds (6a–6t) were synthesized, out of which, 11 compounds (6b, 6c, 6d, 6e, 6g, 6h, 6i, 6j, 6k, 6l and 6m) were reported were novel. The compounds were synthesized by the multistep reaction protocol. β -dimethylaminovinyl ketones (4a–4t) were used as an intermediate for the synthesis of various pyrazole derivatives according to the literature reported and the yield ranged from 85 to 90% (Rosa et al. 2008; Tripathi et al. 2025).

3.2 Bio-efficacy studies

3.2.1. Phytotoxicity Assessment

The assessment of crop phytotoxicity due to herbicide application revealed no adverse effects on crop growth at 7, 14, and 21 days following the pre-emergence herbicide spray (Table 1). This aligns with findings reported by Ratnam et al. (2011), which indicated that the pre-emergence herbicides used in their study did not result in any crop damage. Similarly, the crop phytotoxicity score showed no harm at 7, 14, and 21 days after the application of post-emergence herbicides, except for Pendimethalin 38.7 CS at a rate of 1.5 kg a.i. ha⁻¹ and bispyribac sodium 10 SC at 200 g a.i. ha⁻¹. Pendimethalin 38.7 CS and Bispyribac sodium 10 SC received a 1.00 rating on a 10-point scale for causing some stand loss, leaf stunting, or discolouration seven days after application. A minor discolouration, injury, or stunting was observed 14 days after spraying, with ratings ranging from 0.67 to 1.00. However, the crop had completely recovered by the 21st day after the herbicide application. The observed phytotoxicity in rice may have been attributed to the higher dosage of the post-emergence herbicide Pendimethalin and bispyribac sodium (Table 2). This conclusion is consistent with the findings of Meena et al. (2020), who noted that wheat exhibited phytotoxicity after receiving 1.5 kg a.i. ha⁻¹ of post-emergence Pendimethalin but later recovered. Similar results were reported by Rao and Rao (2006) and Mahapatra et al. (2017). Figure 4 illustrates that the synthetic pyrazole derivatives (6a and 6s) did not induce any phytotoxicity in rice, as noted by Kumar and Rana (2013).

3.2.2. *in-vitro* herbicidal Activity

The inhibition of seed germination in *E. crus-galli* decisively indicates the herbicidal activity of the tested compounds. As the concentration of pyrazole derivatives increased, there was a clear decline in the average number of seeds that germinated. For compound **6a** (5-Methoxy-2-(1H-pyrazol-3-yl) phenol), the average number of seeds germinated on day 1 at increasing concentrations from 62.5 to 1000 µg mL⁻¹ was 9, 7.2, 6.8, 5.6, and 5.2, respectively. By the final day of the experiment (120 hours), germination rates dropped significantly to 12.56, 10.64, 10.22, 9.44, and 8.3. The percent inhibition was 30.6% at the lowest concentration of 62.5 µg mL⁻¹ and increased to an impressive 54.1% at 1000 µg mL⁻¹ (Table 3).

For compound **6s** (3-(4-Fluoro-2-hydroxyphenyl) pyrazole), the germination results on day 1 were 8.4, 7.6, 6.6, 6.0, and 5.6 with rising concentrations from 62.5 to 1000 µg mL⁻¹. On the final day

of the experiment, the numbers declined to 17.1, 15.3, 15.0, 14.7, and 13.0, resulting in percent inhibition figures of 26.9% at 62.5 $\mu\text{g mL}^{-1}$ and 50.6% at 1000 $\mu\text{g mL}^{-1}$ (**Figures 1, 2, and 3**). In comparison, Pendimethalin, a commercial herbicide serving as a positive control, exhibited strong performance. At the lowest concentration (62.5 $\mu\text{g mL}^{-1}$), it achieved 70.4% inhibition, soaring to 93.5% at the highest concentration (1000 $\mu\text{g mL}^{-1}$). This performance clearly surpassed the inhibition levels observed with compounds **6a** and **6s**. The final measurements of shoot and root lengths of *E. crus-galli* revealed a definitive inverse relationship with concentration. For compound **6a**, the mean shoot length reached 9.10 cm, while the mean root length was 4.2 cm at 1000 $\mu\text{g mL}^{-1}$. Similarly, for compound **6s**, the lengths were 8.85 cm for the shoot and 4.3 cm for the root at the same concentration, further demonstrating the compounds' efficacy against seed germination and growth.

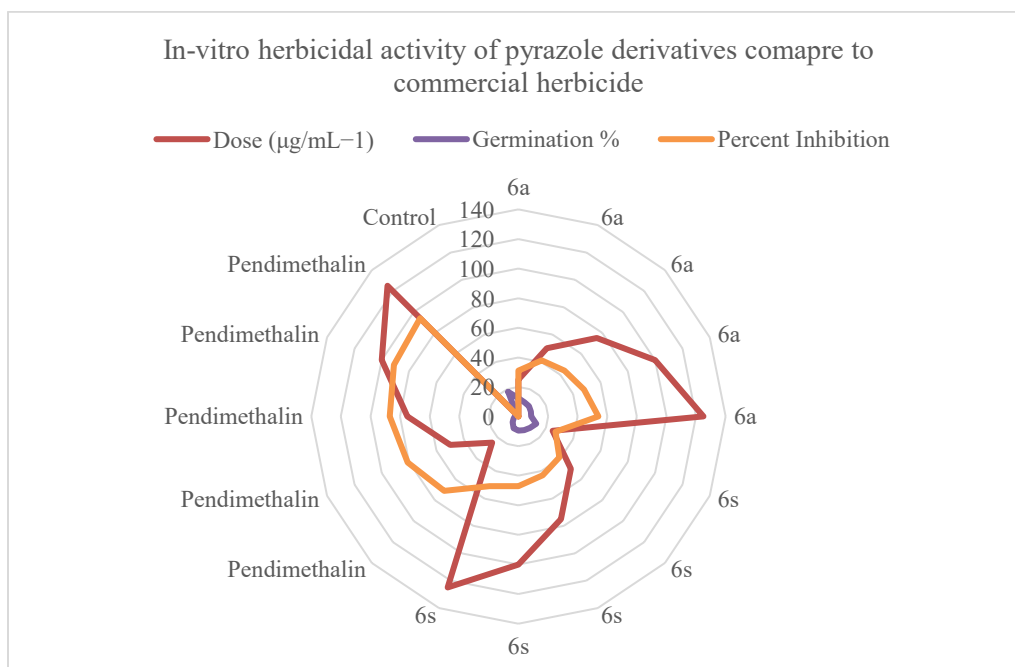


Figure.1: *In-vitro* herbicidal activity of pyrazole derivatives against *E. crus-galli* (Bars are corresponding to concentration)

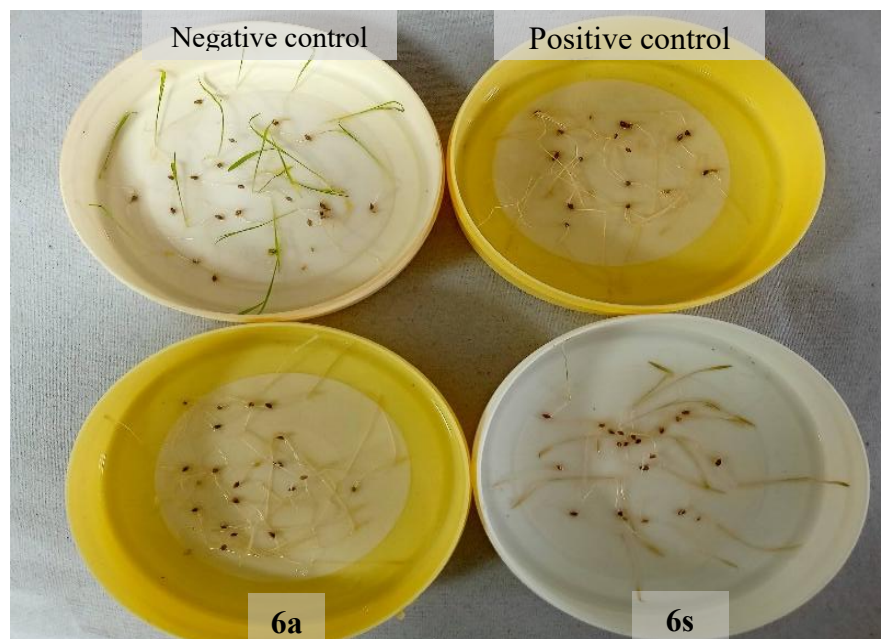


Figure 2: Herbicidal bioassay in plates containing *E. crus-galli* @ 1000 µg mL⁻¹ of test compounds 6a and 6s

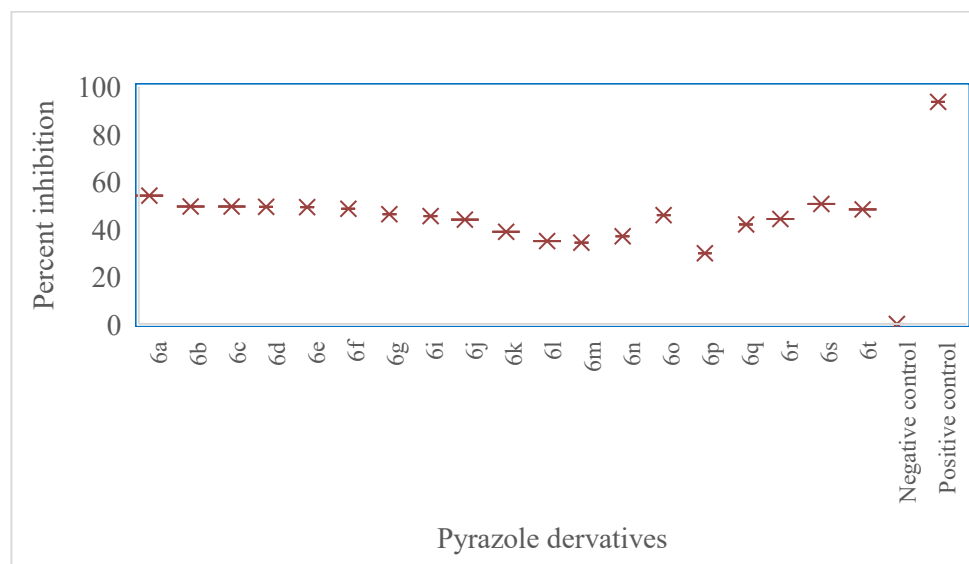


Figure 3: *in-vitro* herbicidal activity of pyrazole derivatives

3.2.3. Screening under greenhouse conditions.

Bio-efficacy studies revealed that pyrazole derivatives showed novel lead discovery with good herbicidal activity against *E. crus-galli* for weed control than the commercial formulation of

Bispyribac-sodium as post-emergence herbicides. In general, smaller alkoxy derivatives (**6a-6e**) showed better weed control than halogen substituted pyrazole (**6m- 6t**) derivatives. The highest weed control was observed at 30 DAS which significantly declined with time as observed at 60 DAS (Thakur et al. 2023). At 30 DAS the WCE of **6a** (5-Methoxy-2-(1H-pyrazol-3-yl) phenol), **6s** (3-(4-Fluoro- 2-hydroxyphenyl) pyrazole) and commercial formulations with Bispyribac-sodium @ 100 µg mL⁻¹, were 46.88, 45.73 and 61.55, respectively. Further, **6a** @ 75µg mL⁻¹ showed WCE of 41.11 which was lower than that of commercial formulation @ 100 µg mL⁻¹ of Bispyribac-sodium which confirmed the novel lead discovery with good activity of pyrazole derivatives over commercial formulation (**Table 4**). At 30 DAS, @ 100 µg mL⁻¹ WCI for **6a** was 51.32 which was higher than that of 6s and lower than the commercial formulations at the same dose i.e. 67.78. There was no phytotoxicity of synthesized compounds on rice (**Figure 4**) (Kumar and Rana, 2013).



Figure 4: Phytotoxicity of synthesized compounds (6a) on rice in 30 DAS

Table 1: Qualitative description of treatment effects on weeds and crop in the visual scoring scale of 0 to 10” (Rao, 1986)

Effect	Rating	Weed Description	Crop Description
None	0	No control	No injury, normal
	1	Very poor control	Slight stunting, injury or discolouration
	2	Poor control	Some stand loss, stunting or discolouration

Slight	3	Poor to deficient control	Injury more pronounced but not persistent
Moderate	4	Deficient control	Moderate injury, recovery possible
	5	Deficient to moderate control	Injury more persistent, recovery doubtful
	6	Moderate control	Near severe injury, no recovery possible
Severe	7	Satisfactory control	Severe injury, stand loss
	8	Good control	Almost destroyed, a few plants surviving
	9	Good to excellent control	Very few plants alive
Complete	10	Complete control	Complete destruction

319 **Table 2: Crop phytotoxicity ratings in rice following applications of pyrazole derivatives**

S N	Herbicide Treatment	Pre-Emergence			Post-Emergence		
		7 DAS	14 DAS	21 DAS	7 DAS	14 DAS	21 DAS
1.	6a	0.00	0.00	0.00	0.00	0.00	0.00
2.	6b	0.00	0.00	0.00	0.00	0.00	0.00
3.	6c	0.00	0.00	0.00	0.00	0.00	0.00
4.	6d	0.00	0.00	0.00	0.00	0.00	0.00
5.	6e	0.00	0.00	0.00	0.00	0.00	0.00
6.	6f	0.00	0.00	0.00	0.00	0.00	0.00
7.	6g	0.00	0.00	0.00	0.00	0.00	0.00
8.	6i	0.00	0.00	0.00	0.00	0.00	0.00
9.	6j	0.00	0.00	0.00	0.00	0.00	0.00
10.	6k	0.00	0.00	0.00	0.00	0.00	0.00
11.	6l	0.00	0.00	0.00	0.00	0.00	0.00
12.	6m	0.00	0.00	0.00	0.00	0.00	0.00
13.	6n	0.00	0.00	0.00	0.00	0.00	0.00
14.	6o	0.00	0.00	0.00	0.00	0.00	0.00
15.	6p	0.00	0.00	0.00	0.00	0.00	0.00
16.	6q	0.00	0.00	0.00	0.00	0.00	0.00
17.	6r	0.00	0.00	0.00	0.00	0.00	0.00
18.	6s	0.00	0.00	0.00	0.00	0.00	0.00
19.	6t	0.00	0.00	0.00	0.00	0.00	0.00
20.	Pendimethalin 38.7CS @ 1 kg a.i ha ⁻¹ (PE)	0.00	0.00	0.00	0.00	0.00	0.00
21.	Pendimethalin 38.7CS @ 1.5 kg a.i ha ⁻¹ (PE)	0.00	0.00	0.00	1.00	0.67	0.00
22.	Bispyribac Na 10 SC @ 100 g a.i ha ⁻¹ (PoE)	0.00	0.00	0.00	0.00	0.00	0.00
23.	Bispyribac Na 10 SC @ 200 g a.i ha ⁻¹ (PoE)	0.00	0.00	0.00	1.00	0.67	0.00
24.	Weedy check	0.00	0.00	0.00	0.00	0.00	0.00

320 *Days After Spray, PE – Pre-Emergence, PoE – Post-Emergence

Table 3: *in-vitro* herbicidal activity of pyrazole derivatives against *E. crus-galli*

Test compound (1000 µg mL ⁻¹)	Percent inhibition (%)	Mean root length (cm)	Mean shoot length (cm)
6a	54.1	4.2	9.1
6b	49.5	4.35	9.2
6c	49.4	4.4	9.95
6d	49.35	4.55	10.5
6e	49.25	4.6	10.55
6f	48.55	5.3	10.95
6g	46.25	5.4	11.37
6i	45.45	5.95	11.65
6j	43.95	6.1	12.35
6k	38.85	6.2	13.65
6l	34.95	6.3	14.5
6m	34.25	5.85	11.7
6n	36.95	5	12.5
6o	45.85	4.5	11.55
6p	29.75	4.7	9.65
6q	41.95	5.75	11.37
6r	44.15	5.45	12.35
6s	50.6	4.3	8.85
6t	48.25	5.75	13.65
Negative control	0	11.2	18.3
Positive control	93.5	1.6	5.6
SEm±	0.32	0.25	0.72
Sd	1.5	1.6	3.3
LSD (P≥ 0.05)	0.74	0.82	0.76

324 **Table 4: Effect of pyrazole derivatives on weed density, WCE (%) and WCI (%) at**
325 **different days after sowing**

Treatments	Dose	30 Days				60 Days			
	$\mu\text{g mL}^{-1}$	Weed density	WCE%	Weed dry wt.	WCI ^a %	Weed density	WCE%	Weed dry wt.	WCI ^a %
6a	100	4.60	46.88	0.093	51.32	5.60	42.03	0.71	40.83
	75	5.10	41.11	0.105	44.74	6.10	36.85	0.724	39.67
	50	5.85	32.45	0.111	41.84	6.85	29.09	0.76	36.67
6b	100	4.75	45.15	0.101	47.11	5.75	40.48	0.724	39.67
	75	5.15	40.53	0.120	37.11	6.15	36.34	0.748	37.67
	50	5.95	31.29	0.128	32.89	6.95	28.05	0.78	35.00
6c	100	4.85	44.00	0.114	40.26	5.85	39.44	0.748	37.67
	75	5.15	40.53	0.125	34.21	6.15	36.34	0.76	36.67
	50	6.00	30.72	0.139	27.11	7.00	27.54	0.788	34.33
6d	100	4.90	43.42	0.120	36.79	5.90	38.92	0.795	33.75
	75	5.20	39.95	0.131	31.21	6.20	35.82	0.776	35.33
	50	6.10	29.56	0.145	23.95	7.10	26.50	0.916	23.67
6e	100	4.95	42.84	0.116	39.21	5.95	38.41	0.764	36.33
	75	5.20	39.95	0.155	18.42	6.20	35.82	0.84	30.00
	50	6.30	27.25	0.169	11.32	7.30	24.43	0.788	34.33
6f	100	5.10	41.11	0.124	35.00	6.10	36.85	0.748	37.67
	75	5.25	39.38	0.148	22.37	6.25	35.30	0.78	35.00
	50	6.35	26.67	0.153	19.74	7.35	23.91	0.98	18.33
6g	100	5.21	39.84	0.107	43.95	6.21	35.71	0.772	35.67
	75	5.65	34.76	0.110	42.37	6.65	31.16	0.796	33.67
	50	6.70	22.63	0.144	24.21	7.70	20.29	1.072	10.67
6h	100	5.25	39.38	0.108	43.42	6.25	35.30	0.78	35.00
	75	5.75	33.60	0.109	42.63	6.75	30.12	0.792	34.00
	50	6.75	22.06	0.145	23.68	7.75	19.77	1.08	10.00
6i	100	5.30	38.80	0.116	39.21	6.30	34.78	0.844	29.67
	75	5.75	33.60	0.123	35.53	6.75	30.12	0.9	25.00
	50	6.70	22.63	0.170	10.53	7.70	20.29	0.956	20.33
6j	100	5.40	37.64	0.115	39.47	6.40	33.75	0.84	30.00

	75	5.95	31.29	0.148	22.37	6.95	28.05	0.95	20.83
	50	6.80	21.48	0.173	9.21	7.80	19.25	0.1	91.67
6k	100	5.70	34.18	0.104	45.53	6.70	30.64	0.748	37.67
	75	6.67	22.98	0.108	43.42	7.67	20.60	0.78	35.00
	50	7.50	13.39	0.113	40.79	8.50	12.01	0.82	31.67
6l	100	6.10	29.56	0.141	25.89	7.10	26.50	0.784	34.67
	75	6.83	21.13	0.160	16.05	7.83	18.94	0.796	33.67
	50	7.67	11.43	0.166	12.89	8.67	10.25	0.844	29.67
6m	100	6.33	26.91	0.105	45.00	7.33	24.12	0.756	37.00
	75	7.50	13.39	0.109	42.63	8.50	12.01	0.792	34.00
	50	8.00	7.62	0.124	35.00	9.00	6.83	0.908	24.33
6n	100	5.90	31.87	0.105	45.00	6.90	28.57	0.756	37.00
	75	6.80	21.48	0.111	41.84	7.80	19.25	0.804	33.00
	50	7.85	9.35	0.116	39.21	8.85	8.39	0.844	29.67
6o	100	6.50	24.94	0.110	42.11	7.50	22.36	0.815	32.08
	75	7.33	15.36	0.112	41.32	8.33	13.77	0.812	32.33
	50	8.10	6.47	0.117	38.68	9.10	5.80	0.852	29.00
6p	100	6.17	28.75	0.105	45.00	7.17	25.78	0.756	37.00
	75	7.33	15.36	0.111	41.84	8.33	13.77	0.804	33.00
	50	7.95	8.20	0.141	26.05	8.95	7.35	1.044	13.00
6q	100	6.83	21.13	0.108	43.42	7.83	18.94	0.78	35.00
	75	7.50	13.39	0.118	38.16	8.50	12.01	0.86	28.33
	50	8.10	6.47	0.148	22.37	9.10	5.80	1.1	8.33
6r	100	5.40	37.64	0.103	45.79	6.40	33.75	0.792	34.00
	75	5.55	35.91	0.117	38.42	6.55	32.19	0.856	28.67
	50	8.20	5.31	0.149	21.58	9.20	4.76	1.112	7.33
6s	100	4.70	45.73	0.095	50.24	5.70	40.99	0.764	36.33
	75	5.10	41.11	0.102	46.18	6.10	36.85	0.9	25.00
	50	5.90	31.87	0.116	39.21	6.90	28.57	1.164	3.00
6t	100	5.30	38.80	0.108	43.42	6.30	34.78	0.804	33.00
	75	6.95	19.75	0.114	40.26	7.95	17.70	1.148	4.33
	50	7.70	11.09	0.118	38.16	8.70	9.94	1.164	3.00
Control		8.66	0.00	0.190	0.00	9.66	0.00	1.2	0.00

Bispyribac-sodium	100	3.33	61.55	0.058	67.78	3.33	61.55	0.22	68.57
SEm±	-	-	-	0.30	1.445	-	-	0.80	2.32
Sd	-	-	-	0.21	1.38	-	-	0.41	1.56
LSD (P≥ 0.05)	-	-	-	0.68	0.86	-	-	2.41	2.14

^aThe measured herbicidal activity against *E. crus-galli* [cd (<0.05) =0.97]

Table 5: Predicted aquatic toxicity data for the synthesized compounds

Compounds	Molecular weight	Log Kow (Kow Win estimate)	Water solubility (mg/L) (WsKow Win estimate)	LC ₅₀ /EC ₅₀ (mg/L)			ChV (mg/L)		
				Fish	Daphnid	Green Algae	Fish	Daphnid	Green Algae
6a	190.2	1.42	11351.16	38.1	27.7	1.70	0.244	0.476	0.756
6b	204.23	1.91	3667.97	13.4	15.0	1.09	0.158	0.259	0.505
6c	218.26	2.41	1179.66	4.69	8.14	0.690	0.102	0.140	0.336
6d	232.28	2.9	377.83	1.63	4.38	0.437	0.0655	0.0757	0.222
6e	246.31	3.39	120.57	0.567	2.35	0.276	0.0420	0.0407	0.147
6f	260.34	3.88	38.35	0.196	1.26	0.173	0.0268	0.0218	0.0963
6g	274.37	4.37	12.16	0.0677	0.672	0.109	0.0170	0.00116	0.0632
6h	288.39	4.86	3.85	0.0233	0.357	0.0679	0.0108	0.0062	0.0413
6i	302.42	5.35	1.21	0.008	0.190	0.0423	0.00685	0.0033	0.0269
6j	316.45	5.84	0.38	0.00274	0.101	0.0263	0.00433	0.00175	0.0175
6k	344.5	6.83	0.04	0.00032	0.0280	0.0101	0.00172	0.00048	0.00739
6l	358.53	7.32	0.01	0.0001.09	0.0148	0.00628	0.00108	0.000258	0.00478

6m	194.62	1.99	3560.68	1.08E01	1.30E01	9.59E-01	1.40E-01	2.23E-01	4.48E-01
6n	178.62	2.47	437.18	3.34E00	6.11E00	5.29E-01	7.84E-02	1.05E-01	2.59E-01
6o	239.07	2.23	1281.18	7.61E00	1.13E01	9.08E-01	1.33E-01	1.95E-01	4.34E-01
6p	229.07	2.63	662.43	2.94E00	6.24E00	5.70E-01	8.49E-02	1.08E-01	2.83E-01
6q	160.18	1.34	18539.73	3.86E01	2.61E01	1.56E00	2.23E-01	4.48E-01	6.88E-01
6r	178.17	1.54	10285.37	2.72E01	2.20E01	1.40E00	2.02E-01	3.78E-01	6.31E-01
6s	178.17	1.54	10285.0	2.72E01	2.20E01	1.40E00	2.02E-01	3.78E-01	6.31E-01
6t	213.07	3.11	82.43	9.19E-01	2.98E00	3.19E-01	4.82E-02	5.16E-02	1.66E-01

3.3 Aquatic toxicity

The synthesized pyrazole derivatives exploit Structure-Activity Relationships (SARs) and Quantitative Structure-Activity Relationships (QSARs) to estimate acute and chronic toxicity for organisms such as fish, Daphnia, and green algae (**Table 5**). Developed by the EPA. The ECOSAR analysis showed a strong negative correlation between acute and chronic toxicities and log K_{ow} values (**Figure 5 and 6**). Green algae had the lowest acute toxicity, while Daphnia exhibited the lowest chronic toxicity. Fish LC₅₀ values ranged from 0.0001 to 38.1 mg/L, with the highest toxicity linked to compound **6l** (C₁₃H₂₇O side chain). Alkoxy-substituted compounds were the most toxic, and the dichloro derivative was the most toxic among halogenated derivatives. All compounds fit within the ECOSAR model's applicability domain, consistent with prior research. (Kundu et al. 2024).

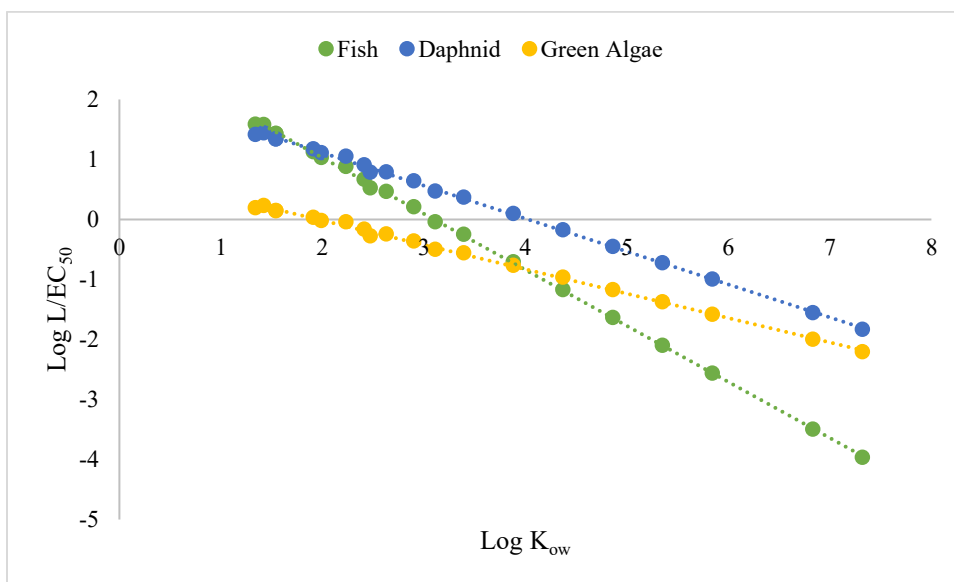


Figure 5: Plot of log LD/ED₅₀ values against Log K_{ow}

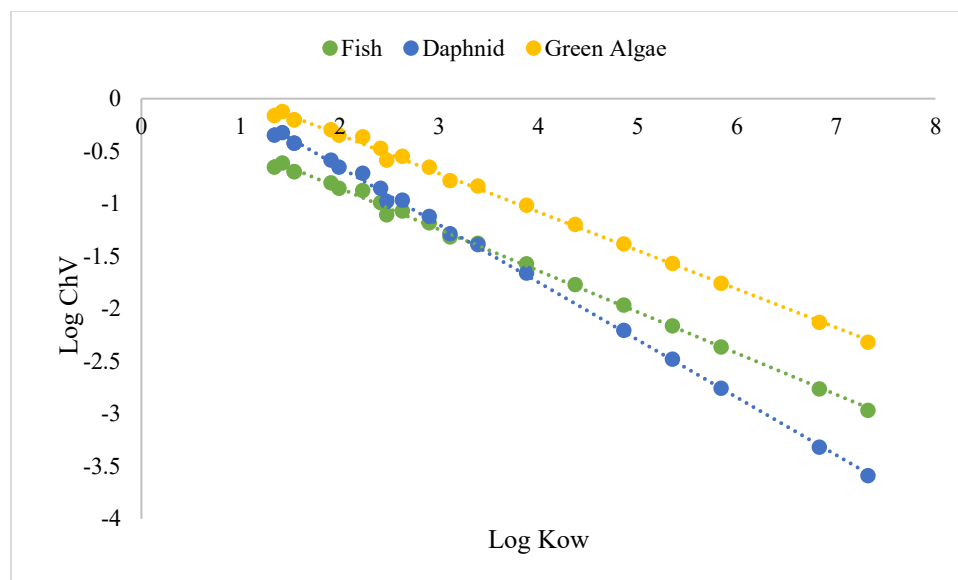


Figure 6: Plot of log ChV values against Log K_{ow}

3.4 Detailed Quantitative structure-activity relationship (QSAR) and Multiple Linear Regression (MLR) Analysis

To analyze the structural factors affecting herbicidal activity, a QSAR model was developed using Multiple Linear Regression (MLR). This model linked the percentage inhibition (Y) to two key physicochemical descriptors: molecular lipophilicity (Log K_{ow}) and binding free energy (ΔG) from AutoDock Vina. The model was trained with data from six diverse derivatives: 6a, 6s, 6c, 6j, 6m, and 6t. The resulting statistically validated equation is:

$$Y = 22.74 + 7.90(\Delta G) - 1.32(\text{Log Kow})$$

Where: Y= Predicted % Inhibition, ΔG = Binding Free Energy (kcal/mol) and Log K_{ow}= Octanol-water partition coefficient.

To validate the predictive power of the developed QSAR model, we constructed a parity plot comparing experimentally observed herbicidal inhibition with predicted values (Figures 7 and 8). The linear correlation yielded a coefficient of determination ($R^2 = 0.81$, $p < 0.01$), indicating that the model accounts for 81% of the total variance in the biological data. The closeness of the data points to the $y = x$ reference line demonstrates the reliability of using molecular docking scores (ΔG) and lipophilicity (Log K_{ow}) as primary descriptors for pyrazole-based HPPD inhibitors.

Statistically, the positive sensitivity toward binding energy ($\beta_1 = 7.90$) confirms that the thermodynamic stability of the enzyme-ligand complex is the dominant factor in growth suppression. In contrast, the negative coefficient for Log Kow ($\beta_2 = -1.32$) highlights a critical threshold in side-chain elongation. While hydrophobicity is essential for cellular uptake, the model suggests that exceeding a Log Kow of approximately 2.5 leads to reduced efficacy due to steric hindrance within the HPPD catalytic pocket. This is evident in the lower activity of long-chain analogs such as compounds 6j and 6l. For instance, compound 6j, which possesses a bulky C10 chain (Log Kow = 5.84), demonstrates reduced binding energy (-6.4 kcal/mol) and lower inhibition (43.95%) (Table 6).

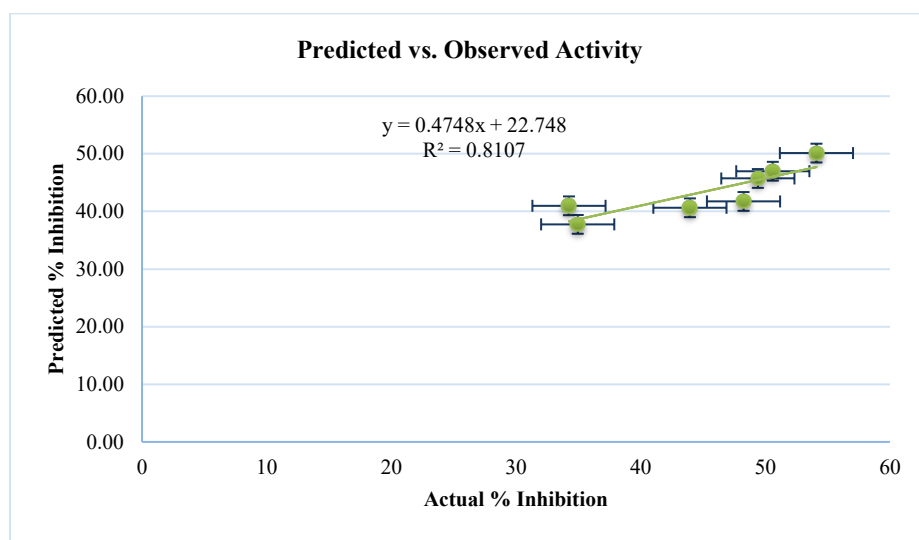


Figure 7. Quantitative Structure-Activity Relationship (QSAR) Parity Plot

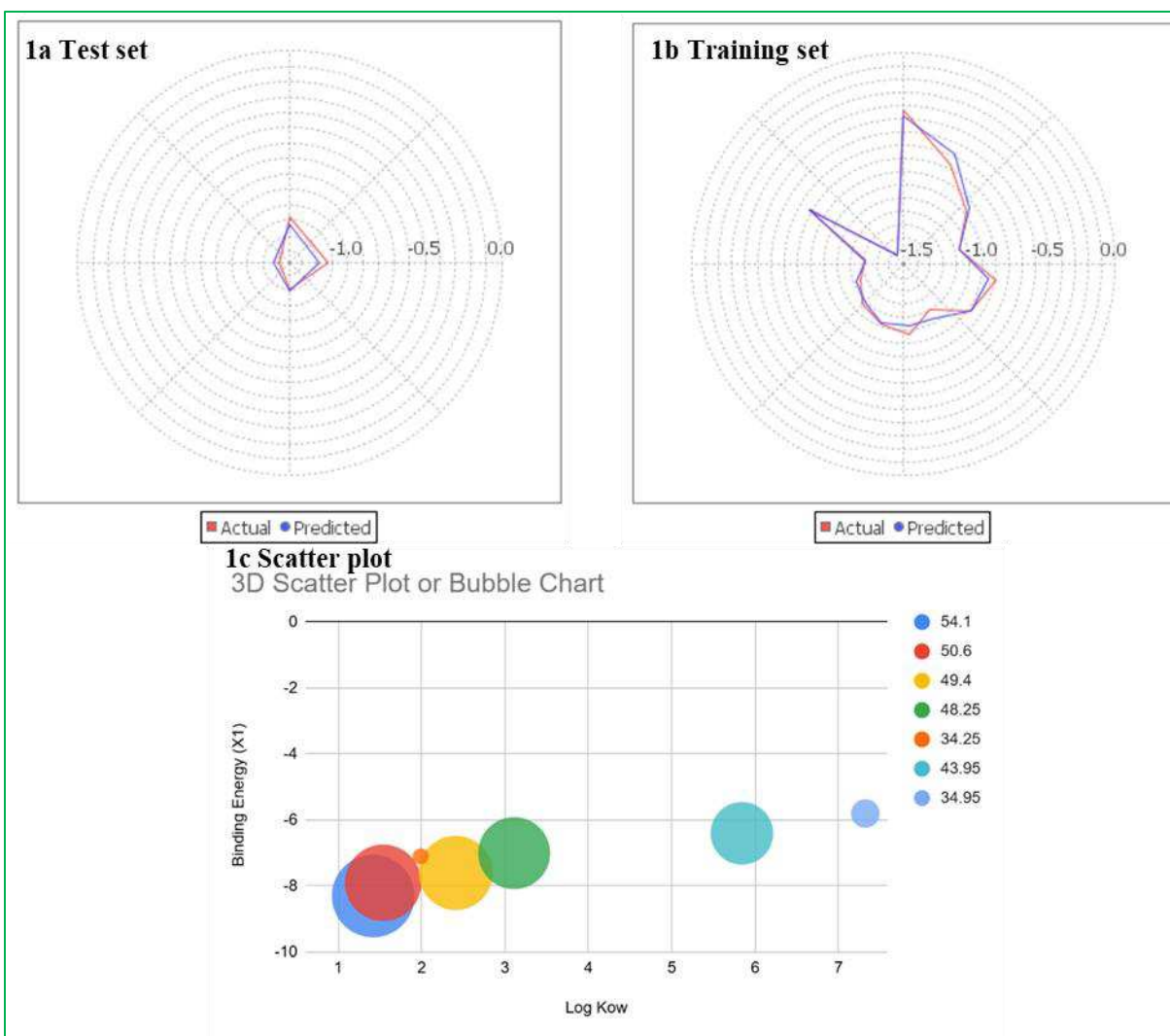


Figure 8. Graphs of experimental versus predicted herbicidal activity of MLR model and SAR Trend (3D Scatter Plot or Bubble Chart)

Table 6: Predicted toxicity data for the synthesized compounds

Compound	% Inhibition	Binding Energy)	Log Kow	MW	Predicted
6a	54.1	-8.3	1.42	190.2	50.13
6s	50.6	-7.9	1.54	178.2	46.98
6c	49.4	-7.6	2.41	218.3	45.72
6t	48.25	-7.0	3.11	213.1	41.74
6m	34.25	-7.1	1.99	194.6	40.98
6j	43.95	-6.4	5.84	316.5	40.63
6l	34.95	-5.8	7.32	358.6	37.75
Multiple R	0.904				

R Square	0.819	
Significance F	0.01	

As mentioned, pyrazoles having substitution with smaller alkoxy groups showing better herbicidal activity against barnyard grass in paddy in both conditions *in vitro* as well as *in vivo*. Also, when we substituted with the halogen groups in the phenyl ring and evaluated for herbicidal activity fluoro derivative were showing good activity compare to other halogen derivatives with good safety to rice. In general, the phenyl ring attached at the 5 positions of the pyrazole ring showed better herbicidal activity than the phenyl ring attached at the 3 position. The 5-position attachment likely provides a more favorable orientation or electronic environment for the interaction with HPPD, leading to more effective inhibition and thus better herbicidal activity. These findings are important for the design of new herbicides that are both effective and safe for use in rice cultivation (Fu et al. 2017).

3.5 Molecular Docking

Docking simulations reveal that compound 6a has the strongest interaction with HPPD, with a binding energy of -8.3 kcal/mol, owing primarily to strong hydrogen bonding with Tyr144. Compound 6a successfully enters the HPPD pocket, forming essential hydrogen bonds with Tyr144 and engaging in π - π stacking with Phe254 (Table 7). Meanwhile, compound 6s uses halogen bonding and hydrophobic interactions to maintain a stable orientation. These molecular interactions are completely consistent with the bioassay results, which strongly support our conclusions about structure-activity relationships (SAR). Similar findings by Fu et al. 2017 and Zeng et al. 2023 shows that pyrazole derivatives 6a, with short alkoxy chains and favorable HPPD docking profiles, significantly improve herbicidal effectiveness against *E. crus-galli* (Figure 9). The binding energies clearly show that short-chain alkoxy derivatives (6a-6e) interact much more effectively with HPPD than their bulkier halogenated counterparts. The binding energies clearly show that short-chain alkoxy derivatives (6a-6e) interact much more effectively with HPPD than their bulkier halogenated counterparts.

Table :7 The interaction analysis of the molecular docking study on 4-hydroxyphenylpyruvate dioxygenase (HPPD enzyme) with the pyrazole derivative-based structural isomers

4. CONCLUSION

In this study, twenty pyrazole compounds were synthesized, of which eleven were identified as novel. Among these, compounds **6a** (2-(isoxazol-5-yl)-5-(methoxy) phenol) and **6s** (3-(4-Fluoro-2-hydroxyphenyl) pyrazole) exhibited the highest levels of in vitro herbicidal activity. The average number of germinated seeds decreased as the concentration of the pyrazole derivatives increased. In pot experiments, compound **6a** (5-Methoxy-2-(1H-pyrazol-3-yl) phenol) demonstrated the most effectiveness against *E. crus-galli*, achieving a weed control index (WCI) value of 51.32%. These compounds exhibit specific modes of action of HPPD inhibitors and are environmentally safe. Compound **6a** demonstrated low aquatic toxicity and good tolerance for rice seedlings when applied post-emergence and in soil, as well as effective control of barnyard grass weeds in pot experiments.

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7. Data availability statement

The original contributions presented in the study are included in the article further inquiries can be directed to the corresponding author.

8. Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work the author(s) used MS-co-pilot to language editing in some places. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

Author Contribution declaration

Author Contributions

- **KT:** Conceptualization, Methodology, Synthesis, QSAR modeling, Writing – original draft.
- **RK:** Supervision, Project administration, Resources, Methodology.
- **PK:** Data curation, Formal analysis, Software, Validation.
- **VSR:** Investigation, Validation, Characterization of compounds.
- **TKD:** Methodology (Field evaluation), Weed control assessment, Resources.
- **NAS:** Investigation, Data collection, Writing – review & editing.

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REFERENCES

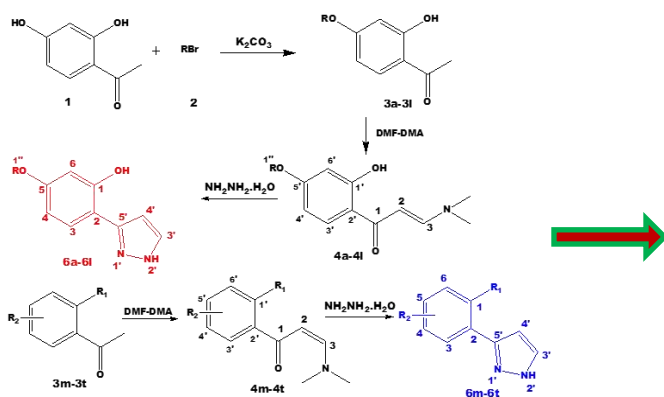
1. Behura N., Sen P., & Kar M.A. (2011). Introgression of yellow stem borer (*Scirpophaga incertulus*) resistance genes into cultivated rice (*Oryza sp.*) from wild species. *Indian Journal of Agricultural Sciences*, 81(4), 359-362.
2. Das T.K. (2008). Weed science basics and application, Jain Brothers, New Delhi, 797-800.
3. Dixit D., Siddiqui N., Bollinedi H., Malik A., Bhowmick P.K., Ellur R.K., & Singh A.K. (2024). Allele mining for Granule Bound Starch Synthase1 gene governing amylose content in aromatic rice (*Oryza sativa L.*) germplasm. *Indian Journal of Genetics and Plant Breeding*, 84(1), 38–45.
4. Fu Y., Wang M.X., Zhang D., Hou Y.W., Gao S., Zhao L.X., & Ye F. (2017). Design, synthesis, and herbicidal activity of pyrazole benzophenone derivatives. *RSC advances*, 7(74), 46858-46865.
5. Gharde Y., Singh P.K., Dubey R.P., & Gupta P.K. (2018). Assessment of yield and economic losses in agriculture due to weeds in India. *Crop Protection*, 107, 12-18.
6. Hasan M., Mokhtar A.S., Rosli A.M., Hamdan H., Motmainna M., & Ahmad-Hamdani M.S. (2021). Weed control efficacy and crop-weed selectivity of a new bioherbicide WeedLock. *Agronomy*, 11(8), 1488.
7. He B., Hu Y., Wang W., Yan W., & Ye Y. (2022). The progress towards novel herbicide modes of action and targeted herbicide development. *Agronomy*, 12(11), 2792.
8. Heap I.M. (2023) International survey of herbicide-resistant weeds: lessons and limitations. www.weedscience.org [Accessed January 2, 2024].

9. Holm L.G., Plucknett D.L., Pancho J.V., & Herberger J.P. 1991. The world's worst weeds: Distribution and Biology. Malabar, FL: Krieger. The University Press of Hawaii, Honolulu. pp. 98–104.
10. Jeschke P. (2016). Progress of modern agricultural chemistry and future prospects. *Pest Management Science*, 72(3), 433-455.
11. Jhala A.J., Kumar V., Yadav R., Jha P., Jugulam M., Williams M.M., & Norsworthy J.K. (2023). 4-Hydroxyphenylpyruvate dioxygenase (HPPD)-inhibiting herbicides: past, present, and future. *Weed Technology*, 37(1), 1-14.
12. Jhala A.J., Sandell L.D., Rana N., Kruger G.R., & Knezevic S.Z. (2014). Confirmation and control of triazine and 4-hydroxyphenylpyruvate dioxygenase-inhibiting herbicide-resistant *Amaranthus palmeri* in Nebraska. *Weed Technology*, 28(1), 28-38.
13. Jiddimani, L., Chandranath, H.T., & Chogatapur, S.V. (2017). Phytotoxicity ratings and weed control ratings as influenced by chemical weed control treatments in greengram (*Vigna radiata* L.). *International Journal of Pure and Applied Bioscience*, 5(5), 1578–1581.
14. Kasiotis K.M., Tzanetou E.N., & Haroutounian S.A. (2014). Pyrazoles as potential anti-angiogenesis agents: a contemporary overview. *Frontiers in Chemistry*, 2, 78.
15. Kaundun S.S. (2021) Syngenta's contribution to herbicide resistance research and management. *Pest Management Science*, 77, 1564–1571.
16. Kaushik P., Sarkar D.J., Chander S., Rana V.S., & Shakil N.A. (2019). Insecticidal activity of phenolic acid amides against brown planthopper (BPH), *Nilaparvata lugens* (Stål) and their QSAR analysis. *Journal of Environmental Science and Health, Part B*, 54(6), 489-497.
17. Kaushik P., Shakil N.A., & Rana V.S. (2021). Synthesis, biological evaluation, and QSAR studies of 3-iodochromone derivatives as potential fungicides. *Frontiers in Chemistry*, 9, 636882.
18. Kumar R., Kumar R., & Prakash O. (2021). Evaluation of *in-vitro* herbicidal efficacy of essential oil and chloroform extract of *Limnophila indica*. *The Pharma Innovation Journal*, 10, 386–390.
19. Kumar S., & Rana S.S. (2013). Bioefficacy of Bispyricbac-sodium for Weed Control in Direct Seeded Rice. *Pesticide Research Journal*, 25(2), 123-127
20. Kundu R., Shakil N.A., Narayanan N., Kamil D., Rana V. S., Tripathi K.P., & Kaushik P. (2024). Novel indazolychromones: synthesis, fungicidal evaluation, molecular docking and aquatic toxicity prediction. *Frontiers in Chemistry*, 12, 1411187.
21. Liu C., Li M., Zhang H., Li L., Zhang M., Guan A., & Jia Y. (2010). U.S. Patent No. 7,795,179. Washington, DC: U.S. Patent and Trademark Office.
22. Liu C.L., & Chi B.S., (2013). New agrochemicals Discovery and Synthesis. Chemical Industry Press, Beijing, pp. 251–252.

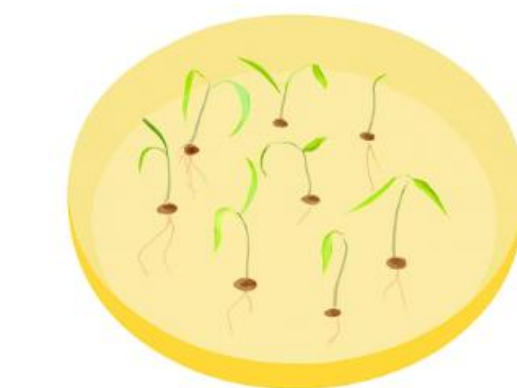
23. Mahapatra, A., Saha, S., Munda, S., & Shukla, R.K. (2017). Studies on phytotoxicity of herbicides and herbicide mixtures and their effect on yield of direct-sown rice (*Oryza sativa* L.). *International Journal of Bio-resource and Stress Management*, 8(6), 853–856.
24. Meena, M., Kumar, O., Rajput, R.K., Singh, A.K., & Dey, I. (2022). Phytotoxicity effect of different doses of pendimethalin on wheat and succeeding greengram. *The Pharma Innovation Journal*, 11(5), 2252–2254.
25. Rao A.N., Johnson D.E., Sivaprasad B., Ladha J.K., & Mortimer A.M. (2007). Weed management in direct-seeded rice. *Advances in Agronomy*, 93, 153–255.
26. Rao, A.S., & Rao, S.N. (2006). Effect of stage and dose of cyhalofop-butyl on *Echinichloa colona* control in blackgram grown as paira crop. *Indian Journal of Weed Science*, 38(1&2), 148–149.
27. Rao, V.S. (1986). *Principles of Weed Science*. Oxford and IBH Publishing Co. Pvt. Ltd., New Delhi, p. 349.
28. Ratnam, M., Rao, A.S., & Reddy, T.Y. (2011). Integrated weed management in chickpea (*Cicer arietinum* L.). *Indian Journal of Weed Science*, 43(1&2), 70–72.
29. Rosa F.A., Machado P., Bonacorso H.G., Zanatta N., & Martins M.A. (2008). Reaction of β -dimethylaminovinyl ketones with hydroxylamine: A simple and useful method for synthesis of 3- and 5-substituted pyrazoles. *Journal of Heterocyclic Chemistry*, 45, 879–885.
30. Shakil N.A., Singh M.K., Kumar J., Sathiyendiran M., Kumar G., Singh M.K., & Parmar V.S. (2010). Microwave synthesis and antifungal evaluations of some chalcones and their derived diaryl-cyclohexenones. *Journal of Environmental Science and Health Part B*, 45(6), 524–530.
31. Shakil N.A., Singh M.K., Sathiyendiran M., Kumar J., & Padaria J.C. (2013). Microwave synthesis, characterization and bio-efficacy evaluation of novel chalcone based 6-carbethoxy-2-cyclohexen-1-one and 2H-indazol-3-ol derivatives. *European Journal of Medicinal Chemistry*, 59, 120–131.
32. Singh K., Singh S., & Pannu R.K. (2020). Temperature, pH and light effect on germination and growth behavior of grassy weeds of direct-seeded rice. *Indian Journal of Weed Science*, 52(1), 21–26.
33. Song H.M., Zhao L.X., Zhang S.Q., Ye T., Fu Y., & Ye F. (2021). Design, synthesis, structure–activity relationship, molecular docking, and herbicidal evaluation of 2-cinnamoyl-3-hydroxycyclohex-2-en-1-one derivatives as novel 4-hydroxyphenylpyruvate dioxygenase inhibitors. *Journal of Agricultural and Food Chemistry*, 69 (43), 12621–12633.
34. Thakur A., Verma M., Setia P., Bharti R., Sharma R., Sharma A., & Bansal R. (2023). DFT analysis and *in vitro* studies of pyrazole derivatives as potent antioxidant and antibacterial agents synthesized via one-pot methodology. *Research on Chemical Intermediates*, 49(3), 859–883.

35. Tripathi K., Kaushik P., Yadav D.K., Kumar R., Misra S.R., Godara R., Bashyal B.M., Rana V.S., Kumar, R., Yadav J., & Shakil N.A. (2024). Synthesis, antifungal evaluation, 2D-quantitative structure activity relationship and molecular docking studies of pyrazole derivatives as potential fungicides, *Pest Management Science* (Doi:10.1002/ps.8152)
36. Tripathi K., Kumar R., Misra S.R., Kaushik P., Bashyal B.M., Yadav D.K., Rana V.S., Narayanan N., Shakil N.A. (2025). Synthesis, Antifungal Activity, Molecular Docking, Aquatic Toxicity Prediction, and 2D-QSAR of Pyrazole Derivatives as Potential Fungicides for Basmati Rice. *Chem Biodivers.* 22(12): e01550. doi: 10.1002/cbdv.202501550.
37. USDA 2024: <https://ipad.fas.usda.gov/countrysummary/Default.aspx?id=IN&crop=Rice>
38. Yadav D.K., Kaushik P., Tripathi K.P., Rana V.S., Yeasin M., Kamil D., & Shakil N. A. (2022). Bioefficacy evaluation of ferrocenyl chalcones against *Meloidogyne incognita* and *Sclerotium rolfsii* infestation in tomato. *Journal of Environmental Science and Health, Part B*, 57(3), 192-200.
39. Yadav D.K., Tripathi K.P., Pankaj, Kaushik P., Rana V.S., Khatri D., & Shakil N.A. (2021). Antinemic activity of ferrocenyl chalcones against *Meloidogyne incognita* infestation in tomato. *Indian Journal of Agricultural Sciences*, 91(2), 305-9.
40. Yurttas L., Kaplancıklı Z.A., Göger G., & Demirci F. (2016). Synthesis and anticandidal evaluation of new benzothiazole derivatives with hydrazone moiety. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 31, 714-720.
41. Zeng, H., Zhang, W., Wang, Z., & Gan, X. (2023). Discovery of novel pyrazole derivatives with improved crop safety as 4-hydroxyphenylpyruvate dioxygenase-targeted herbicides. *Journal of Agricultural and Food Chemistry*, 71(9), 3950-3959.

Graphical Abstract



Multistep synthesis using alkoxy/halo substitutions



6a and 6s inhibited germination of *E. crus-galli*

