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Biogenic Synthesis of Pyrazole-Based Pharmacophores Using Onion Extract: A Sustainable Strategy for Antibacterial Drug Development

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ABSTRACT

Purpose: *The aim of the present study was to develop an eco-friendly and sustainable approach for the synthesis of substituted pyrazole derivatives using Allium cepa (onion) juice as a natural, green catalyst. The synthesized compounds were evaluated for their antimicrobial activity against selected Gram-positive and Gram-negative bacterial strains.*

Methods: *Fresh onion juice was extracted and used as a biocatalyst in the synthesis of various substituted pyrazole derivatives via condensation reactions. The structures of the synthesized compounds were confirmed by IR, NMR and mass spectrometry. Antibacterial screening was performed using the agar well diffusion method against Staphylococcus aureus, Bacillus subtilis (Gram-positive) and Escherichia coli, Pseudomonas aeruginosa (Gram-negative) bacteria. In silico studies, including molecular docking and ADME predictions, were also carried out to evaluate potential biological interactions and drug-likeness.*

Results: *All synthesized compounds were obtained in good yields with high purity. Antibacterial studies revealed that certain pyrazole derivatives exhibited significant activity, particularly against Gram- positive strains. Structure–Activity Relationship (SAR) analysis suggested that electron-donating substituents enhanced antibacterial potency. Molecular docking confirmed good binding affinities with target bacterial enzymes, while ADME predictions indicated acceptable pharmacokinetic profiles.*

Conclusion: *The study demonstrates that Allium cepa juice is an effective green catalyst for the synthesis of biologically active pyrazole derivatives. These compounds show promising antibacterial activity and favourable in silico drug-likeness, suggesting their potential as lead molecules for further pharmaceutical development.*

Keywords: Flavonoids; Flavone; Acacetin; Anticonvulsant; Pentylenetetrazole (PTZ) induced seizure; 4COF

INTRODUCTION

Pyrazoles, five-membered heterocyclic compounds containing two adjacent nitrogen atoms, are widely recognized for their broad spectrum of pharmacological activities and serves as a valuable template for both combinatorial and medicinal chemistry. The pyrazole ring system is a common scaffold in numerous biologically active compounds due to its structural versatility, ease of functionalization and favorable pharmacokinetic properties. Pyrazole derivatives have shown diverse biological activities, including antibacterial, antifungal, anticancer, antitubercular, anti-inflammatory antiviral and antiandrogenic properties. Additionally, some pyrazole derivatives have exhibited analgesic, antidiabetic, antioxidant, anthelmintic and analgesic activities. Beyond their biological significance, many pyrazoles are also known for their luminescent and fluorescent properties, this wide range of therapeutic applications has led to increased interest in the development of novel pyrazole-based molecules.

Traditionally, the synthesis of pyrazole derivatives often involves the use of harsh chemicals, toxic solvents and energy-intensive conditions, raising environmental and safety concerns. In response to the growing emphasis on sustainable chemistry, green synthetic methodologies have emerged as efficient and eco-friendly alternatives. These approaches focus on minimizing hazardous reagents, reducing energy consumption and employing renewable or natural resources [1].

Allium cepa (onion), a common kitchen ingredient, contains natural acids and sulfur-containing compounds such as sulfenic acid, phosphoric acid and citric acid, which can act as mild cyclo-dehydrating agents and natural catalysts. Leveraging these components, the present study explores the use of Allium cepa extract as a natural, non-toxic and biodegradable catalyst for the green synthesis of substituted pyrazole derivatives under microwave irradiation. Microwave-assisted synthesis is a well-established technique that offers rapid reaction rates, enhanced yields and cleaner product profiles compared to conventional thermal methods. The combination of microwave irradiation and a natural catalyst such as onion juice represents a highly attractive strategy for achieving green and efficient heterocyclic synthesis.

This study reports a simple, eco-friendly and efficient method for synthesizing various substituted pyrazole derivatives using chalcones and phenyl hydrazine in the presence of Allium cepa extract under microwave irradiation. The synthesized compounds were structurally characterized using IR and 1H NMR spectroscopy and evaluated for their antibacterial activity against Staphylococcus aureus and Escherichia coli. The results demonstrate the potential of natural catalysts in the development of sustainable synthetic methodologies for bioactive heterocycles.

MATERIALS AND METHODS

All chemicals used were of synthetic grade and were purchased from S. D. Fine Chem. Ltd., Mumbai, India. Fresh onions (Allium cepa) were procured from the local market. The melting points of the compounds were recorded on an electro-thermal apparatus and are uncorrected. For the synthesis of the compounds, a domestic microwave from ONIDA Company was utilized. The purity of the synthesized compounds was verified using Thin-Layer Chromatography (TLC). TLC was performed on precoated SiO_2 gel (HF254, 200 mesh) aluminium plates from E. Merk, employing a solvent system of hexane and ethyl acetate. Visualization was done in an iodine chamber. Infrared (IR) spectra were recorded in KBr on a PerkinElmer model-983 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on a varian mercury 300 MHz instrument using $CDCl_3$ and DMSO-d6 as solvents, with tetramethyl silane (TMS) as an internal standard. Chemical shifts are reported in δ ppm. Ultraviolet (UV) spectra were recorded in ethanol on a Beckmann DK-1 spectrophotometer [2].

Extraction of *Allium cepa* (Onion) juice

Fresh *Allium cepa* (onions) were procured from the local market. The onions were peeled, washed thoroughly and finely chopped using a clean stainless-steel knife. The chopped onion pieces were then subjected to manual pressing using a domestic juicer to extract the juice at ambient temperature. The crude extract obtained was initially filtered through a clean cotton or muslin cloth to remove coarse solid residues. Subsequently, the filtrate was passed through Whatman filter paper to ensure complete removal of any fine particulates. The resulting clear onion juice was collected and stored in a clean, airtight container. This freshly prepared juice was used immediately as a natural, eco-friendly catalyst in the green synthesis of pyrazole derivatives.

Synthesis of Chalcones (Ia-If):

Equimolar quantities of substituted benzaldehyde (0.01 mol) and acetophenone were dissolved in a minimum amount of alcohol. Sodium hydroxide solution (0.02 mol) was added slowly with stirring. The mixture was stirred for 2 hours until it became very cloudy, then poured into 400 ml of water with constant stirring and refrigerated for 24 hours. The precipitate was filtered, washed and recrystallized from ethanol. The reaction's completion was monitored by TLC [3].

Synthesis of Pyrazoles (IIa-IIf):

A mixture of chalcone (IIa) (0.01 mol), phenylhydrazine (0.01 mol) and 8-10 ml of Allium cepa extract was taken and the reaction was carried out in a microwave for 2-3 minutes. The resulting solid was filtered, washed, dried and recrystallized from ethanol. The completion of the reaction was monitored by TLC.

RESULTS AND DISCUSSION

In the present study, a green and efficient method for the synthesis of substituted pyrazole derivatives (IIa–IIf) was successfully developed using Allium cepa (onion) juice as a natural catalyst under microwave irradiation. The overall synthetic route involves two key steps: The Claisen-Schmidt condensation to yield chalcones (Ia–If), followed by cyclocondensation with phenylhydrazine to form the corresponding pyrazole derivatives.

The Allium cepa extract served as a mild, biodegradable and eco-friendly catalyst. It contains sulfur-based compounds and organic acids (e.g., sulfenic acid, phosphoric acid and citric acid) which facilitated the cyclo-dehydration step. Microwave irradiation further enhanced the reaction rate and yield by providing uniform and rapid energy transfer, reducing the overall reaction time to just 2-3 minutes. The proposed reaction involves initial condensation between chalcone and phenyl hydrazine to form a hydrazone intermediate, followed by intramolecular cyclization and dehydration to yield the desired substituted pyrazole ring.

All synthesized pyrazole derivatives (IIa–IIf) were characterized using standard spectroscopic techniques such as IR and 1H NMR spectroscopy. The results confirmed the formation of the desired products and provided insight into the structural features of the molecules. The characteristic absorption bands for the pyrazole ring were observed consistently in all compounds. The N-H stretching vibration appeared around 3160-3290 cm^{-1}.The azomethine (>C=N-) group exhibited strong absorptions near 1617-1640 cm^{-1}.In case of nitro-substituted compounds (IIe, IIf), strong symmetric and asymmetric -NO_2 stretching bands appeared near 1430 and 1020 cm^{-1}, respectively. For compound IIc (with m-COOH), a strong >C=O stretch appeared at 1708 cm^{-1}, confirming the presence of a carboxylic group. The NMR shows, singlet at δ 8.5 ppm due to -NH proton of the pyrazole ring and at δ 6.2 ppm representing the pyrazole ring -CH proton. The aromatic protons were observed at their expected position. The hydroxyl proton in compound IIc appeared as a singlet at δ 10.5 ppm, confirming the presence of a free -COOH group. These spectral data corroborate the successful formation of the substituted pyrazole derivatives and support the structural assignments [4].

Antibacterial activity

The antibacterial activity of the synthesized pyrazole derivatives (IIa-IIf) was evaluated against both Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacteria by using the agar well diffusion method Ciprofloxacin was used as the standard reference drug. The results demonstrated that all synthesized pyrazole derivatives possessed notable antibacterial activity, though none surpassed ciprofloxacin. Among them, compound IIf (p-NO_2) exhibited the highest antibacterial potency with inhibition zones of 20.0 ± 0.6 mm against *S. aureus* and 18.0 ± 0.5 mm against *E. coli*. The compounds IIe (o-NO_2) and IIc (m-COOH) also showed significant antibacterial activities. The enhanced activity of nitro and

carboxyl-substituted pyrazoles may be attributed to their increased electron-withdrawing (EWG) nature, which possibly enhances interaction with bacterial enzymes or membranes. On the other hand, unsubstituted (IIb) and Electron-Donating Group (EDG)-substituted compounds (IIa, IId) exhibited moderate to low antibacterial activity (Table 1). This suggests that the nature and position of substituents on the phenyl ring significantly influence biological activity [5].

Table 1: Structure-Activity Relationship (SAR).

Compound	Substituent	Type (EDG/EWG)	Gram positive bacteria (mm)	Gram negative bacteria (mm)	Relative activity (%) (Gram +ve/ Gram-ve)
IIa	o-CH_3	EDG	15	13	60% / 52%
IIb	-H	Neutral	17	14	68% / 56%
IIc	m-COOH	EWG	19	18	76% / 72%
IId	p-OCH_3	EDG	16	15	64% / 60%
IIe	o-NO_2	Strong EWG	18	17	72% / 68%
IIf	p-NO_2	Strong EWG	20	22	80% / 88%

The Structure Activity Relationship (SAR) revealed that, the electron-withdrawing groups like -NO_2 and -COOH increased antibacterial activity, particularly when present at the para-position (as in IIf). The electron-donating groups such as -CH_3 and -OCH_3 reduced antibacterial potential. The ortho-substitution (IIa, IIe) resulted in slightly reduced activity compared to meta or para substitution. These results highlight the critical influence of both electronic and steric effects on the bioactivity of pyrazole derivatives (Tables 2-5) [6-8].

Table 2: Zone of inhibition (mm) of substituted pyrazole derivatives against gram-positive and gram-negative bacteria (Mean ± SEM).

Compound	Substituent	Gram-positive bacteria	Gram-negative bacteria (Escherichia coli)	Standard drug (Ciprofloxacin)
IIa	o-CH3	15.0 ± 0.5	13.0 ± 0.6	25.0 ± 0.2
IIb	-H	17.0 ± 0.4	14.0 ± 0.5	25.0 ± 0.2
IIc	m-COOH	19.0 ± 0.6	18.0 ± 0.4	25.0 ± 0.2
IId	p-OCH3	16.0 ± 0.4	15.0 ± 0.5	25.0 ± 0.2
IIe	o-NO2	18.0 ± 0.5	17.0 ± 0.6	25.0 ± 0.2
IIf	p-NO2	20.0 ± 0.6	22.0 ± 0.5	25.0± 0.2

Table 3: Percentage inhibition relative to ciprofloxacin (Gram-Negative).

Compound	Zone (mm)	% of standard
IIa	13	52.00%
IIb	14	56.00%
IIc	18	72.00%
IId	15	60.00%
IIe	17	68.00%
IIf	22	88.00%

Table 4: Percentage inhibition relative to Ciprofloxacin (Gram-Negative).

Compound	Fold decrease=(25-est)/test
IIa	(25−13)/13 ≈ 0.92×
IIb	≈ 0.79×
IIc	≈ 0.39×
IId	≈ 0.67×
IIe	≈ 0.47×
IIf	(25−22)/22 ≈ 0.14× (least reduction)

Table 5: Docking results.

Compound	Substituent	Binding affinity (kcal/mol)	Key interactions	Binding score rank
IIa	o-CH_3	-6.2	Pi–Pi stacking with Tyr122	6th
IIb	-H	-6.4	Hydrogen bonding with Asp73	5th
IIc	m-COOH	-6.7	H-bonds with Arg76, Ser55	3rd
IId	p-OCH_3	-6.5	Pi–alkyl with Ile78	4th
IIe	o-NO_2	-6.8	Strong H-bond with Ser55	2nd
IIf	p-NO_2	-7.1	H-bonds with Arg76, Pi-stacking with Phe104	1st
Std (Ciprofloxacin)	-	-8.2	Metal coordination with Mg^{2+}, H-bonds with DNA gyrase pocket	Reference

Table 6: *In Silico* drug-likeness and ADME prediction.

Compound	MW (g/mol)	LogP	TPSA (Å²)	Lipinski's Rule	GI absorption
IIa	~290	2.56	65.3	Yes	High
IIb	~275	2.31	58.9	Yes	High
IIc	~305	1.1	97.6	Yes	Moderate
IId	~305	2.12	75.1	Yes	High
IIe	~320	1.45	89.5	Yes	Moderate
IIf	~320	1.37	88.3	Yes	Moderate
Std	331.3	–0.7	74.6	Yes	High

The above Table 5 and Table 6 shows that, the docking results align well with the antibacterial data, confirming that compound IIf (p-NO_2) exhibits the highest binding affinity (-7.1 kcal/mol) and the best antibacterial activity, likely due to strong hydrogen bonding and π- interactions at the active site of DNA gyrase. The Table 6 shows the LogP and TPSA values suggest that IIf strikes a favourable balance between lipophilicity and polarity, aiding in both membrane permeability and target binding. All compounds obey Lipinski's Rule of Five, indicating good drug-likeness. The combined *in vitro* and *in silico* results strongly support the hypothesis that electron-withdrawing groups, particularly p-NO_2, enhance antibacterial potency by improving interaction with bacterial DNA gyrase [9,11].

CONCLUSION

We have successfully carried out the microwave-assisted synthesis of different substituted pyrazoles using a natural catalyst, Allium cepa. The merits of this method include operational simplicity, the use of natural catalysts, readily available reagents, high yields, shorter reaction times and the avoidance of hazardous chemicals. The synthesized pyrazole derivatives displayed promising antibacterial activity, with compound IIf (p-NO2) showing the highest efficacy. While the standard drug ciprofloxacin remains more potent, the results suggest that these derivatives could serve as potential candidates for developing new antibacterial agents. Further optimization and testing are warranted to enhance their efficacy and broaden their application.

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