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Synthetic Strategies, Structural Insights, and Pharmacological Versatility of Chalcone-Derived Pyrazolines: A Review.

Rakesh Choudhary[1], Hemant Dhakne[2], Sandhya Dhurve[3],
Diksha Dandge[4], Diksha Dandge[5], Sonal Dhonnar[6]
[1,2,3,4,5,6]Mumbai University

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Abstract—**The alteration of flexible molecular structures is a key to the drug discovery in modern medicinal chemistry. The review gives in-depth analysis of pyrazoles derivatives obtained in the reaction of chalcone precursors, which point out there. relevance as a privileged group of heterocyclic compounds. As alpha, beta ketone intermediates, chalcones are subject to cyclization with several hydrozaine reagents to produce pyrazolines- a reaction that greatly increases structure rigidity, metabolic stability, and target selectivity. We discuss the development of synthetic procedures, starting with the long-established Claisen-Schmidt condensation to modern day green chemistry procedures, such as the microwave-assisted chemistry, and solvent-free approaches. Additionally, the review explains the complicated structural description of these compounds, which was done using sophisticated spectroscopic methods (FT-).**

Tautomeric behaviors and molecular connectivity to elucidate tautomeric behaviors and molecular connectivity, IR, NMR, FT-Raman) and computational DFT methods are used to elucidate tautomeric behaviors and molecular connectivity. The important element of this work is the critical one, Investigation of Structure-Activity Relationships (SAR), whereby the position of substituents can cause changes in biological activity. The review concludes by Appraising the vast pharmacological scope of these derivatives, namely, their potential to serve as powerful antimicrobial, anti-inflammatory, antioxidant and anticancer agents, chalcone-derived pyrazolines are promising agents to be used in, treating chronic therapeutic problems and multi-drug resistance.

Index Terms— **(Chalcones, Pyrazoline Derivatives, Heterocyclic Synthesis, Structure-Activity Relationship (SAR), Tautomerism, Pharmacological Potential, Green Chemistry, Drug Discovery).**

I. INTRODUCTION.

Rational design of new therapeutic agents has frequently been applied in the high-paced discipline of medicinal chemistry, which possesses an initial point of synthetically accessible molecular scaffolds, which inherently contain pharmacological potential. The Chalcones are multipurpose 2-unsaturated ketones [2]. privileged family of compounds, which has been broadly studied within the context of the general biological applications, encompassing the use of anticancer, antioxidant, antimicrobial, analgesic, and anti-inflammatory [1, 2]. The chalcones can as well be closed-looped to offer rigid and more stable heterocyclic systems; it is also probable to enhance potency, selectivity and metabolic stability [3, 4]. In fact, these pharmacological and structural benefits render chalcone-based pyrazolines desirable development molecules and these 3-pyrazolines may be employed against multi-drug-resistant pathogens, chronic inflammatory illnesses, metabolic sickness, and cancer [3, 5].

1.1.1 Chalcone.

The chalcones are simple 2-propen-1-ones with unsaturated aromatic ketones (alpha, beta unsaturated), considered some of the simplest organic compounds, whose general formula can be expressed as 1, 3-diaryl-2-propen-1-ones, and, owing to their accessibility (both natural and synthetic) and diversity of pharmacological actions (including anticancer, anti-inflammatory, antimicrobial, antioxidant, antidiabetic, etc.) are of great interest over recent One of the prime reactive centers of this group of compounds is its enone functionality, this allows the formation of numerous heterocyclic systems.

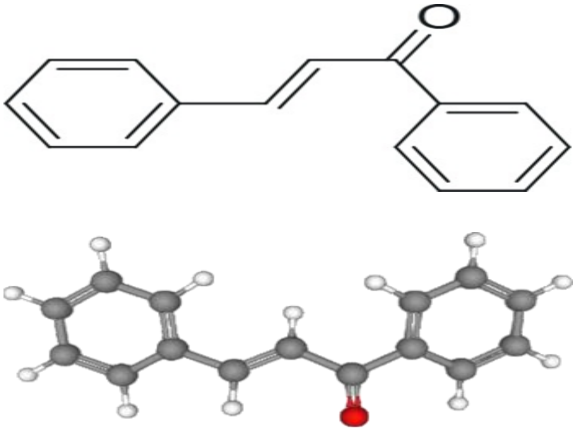


Figure 1: General Structure of Chalcone Along with Balls and Stick Model.

They are naturally present compounds of flavonoid family that are abundantly found in edible plants including fruits, vegetables, spices, tea, and foods based on soy [7]. The compounds can be used in a wide range of other heterocyclic derivatives, such as 1,3,4-thiadiazoles, isoxazoles, indoles, and quinazolines formed by cyclization of the reactive Ket ethylenic group (- CO-CH=CH-), which comprises two hydrogen lone pairs in the molecule [8].

1.1.2 Pyrazoline.

Among the most important value-added modifications of chalcones is that the chalcones can be subjected to cyclization to obtain pyrazole derivatives that give rise to a more rigid and stable heterocyclic core with increased biological performance [5]. The pyrazolines are 5 membered heterocyclic compounds with two adjacent nitrogen atoms and one endocyclic double bond and are known to have anticancer, antidepressant, antimicrobial and anticonvulsant properties. Additional advantages regarding this structural change are metabolic stability and selectivity to the target, and thus chalcone-derived pyrazolines have been instrumental in the process of discovering lead molecules. Recent research studies have added to this.

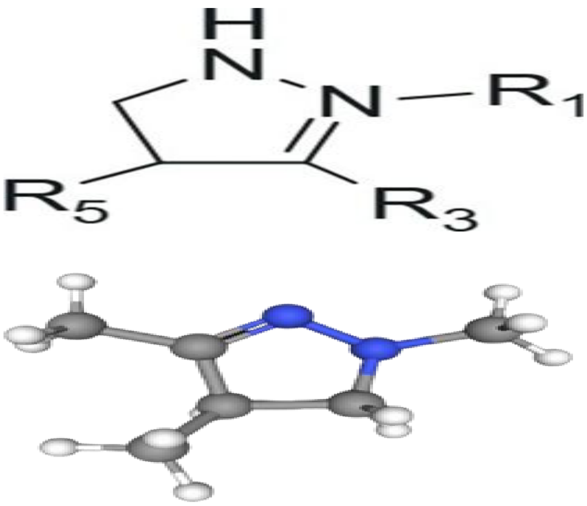


Figure 2: General Structure Of 2-Pyrazoline Along with Balls and Stick Model.

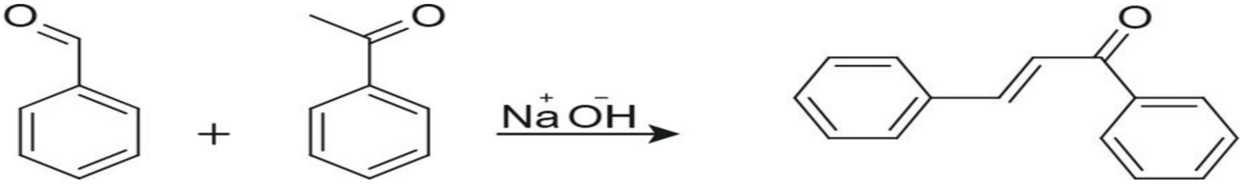
The reports of chalcone-pyrazoline hybrids in Bioorganic C Medicinal Chemistry Letters 2005 have been reported to be highly cytotoxic to leukemia cells [9]. The new synthetic methods to improve yields and selectivity were unveiled in the 2021 Chemistry Select and both tumor and microbial systems were attacked [10]. The combination of all these reports confirms the role of chalcone-derived pyrazolines as second generation pharmacophores.

1.2 Synthesis Methodologies.

The interest in conducting research on chalcone-born pyrazolines is highly inspired by the fact that they are easily accessible to produce. Typical preparative schemes include simple and rich responses; an enormous repertoire of experience in classical schemes is now effectively applied. enhanced and better with up-to-date, efficient, and long-term pathways of green chemistry [11, 12].

1.2.1 Preparation of Chalcone Precursors:

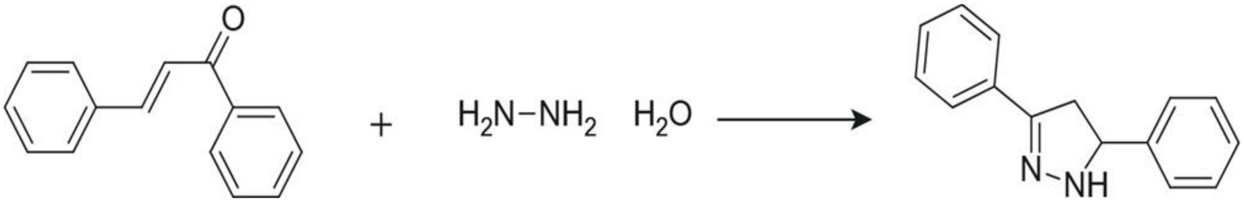
The most popular process of synthesizing chalcones as a type of the aldol reaction involving aromatic aldehydes and ketones in a basic or acidic solution to form good yields of 1, 8-unsaturated ketones is called the Claisen-Schmidt condensation. Sustainable alternatives were created to reduce reaction time and maximize atom economy, but these include microwave-assisted synthesis, solvent-free grinding, ionic liquid based and water-mediated methods [13].



Scheme 1: Claisen-Schmidt Condensation Reaction for Chalcone Formation.

1.2.2 Preparation of Derivatives of Pyrazolines:

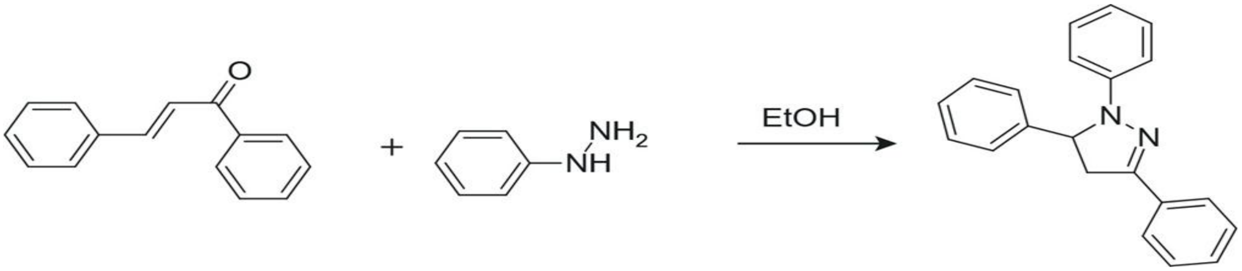
Classical The cyclocondensation of chalcones to hydrazine hydrate or hydrazines modified by either of the two under reflux, most usually in ethanol or acetic acid; the result is mainly 2-pyrazolines. The scaffold is also expanded using phenylhydrazine and thiosemicarbazone and other derivatives [12].



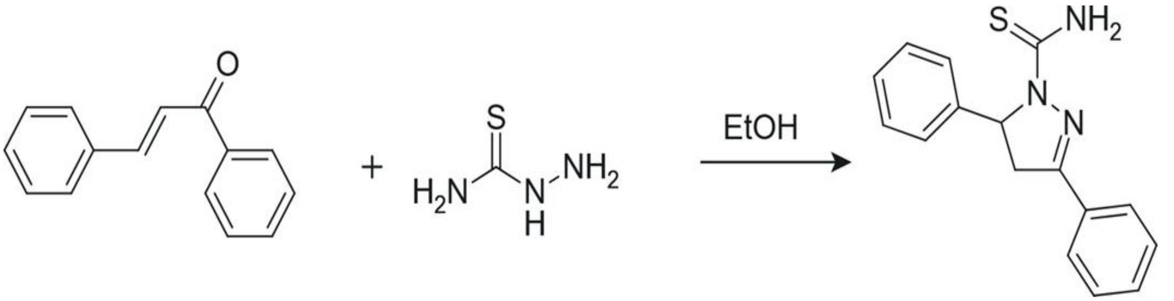
Scheme 2: General Pyrazoline Synthesis Reaction.

The classical method of making pyrazolines is the cyclo-condensation of hydrazines with chalcones under reflux temperature, usually in ethanol or acetic acid, to give the most common 2-pyrazolines. With phenylhydrazine, thiosemicarbazide and other derivatives, other scaffold diversities are also attained [14, 15]. To favor productivity, there were microwave-assisted, PEG-mediated and ultrasound- assisted cyclization techniques which lowered reaction time, and advocated the tenets of green chemistry [16, 17]. Contemporary reagents like 1,3- dipolar cycloaddition, Michael addition, and CuCl2 catalyzed Atwal reactions permit to multi-functional pyrazoline hybrids which are progressively being examined in fluorescent probe, bioimaging and multi-target therapeutic applications [18].

1.2.3 Synthesis Using Different Hydrazine Reagents:



Scheme 3: Using Phenylhydrazine: Product 1,3,5-Triphenyl-2-Pyrazoline.



Scheme 4: Using Thiosemicarbazide: Product 3,5-Diphenyl-2-Pyrazoline-1 Carbothioamide.

1.3 Pharmacological Potential.

Chalcones and pyrazolines are two scaffolds that possess the most distinctive and varied pharmacological activity. Merging both of these scaffolds invariably yields compounds with robust antibacterial, antifungal, anticancer, and anti-inflammatory activities among others [3, 10]. Very potent activity is a universal common denominator in literature reports for the derivatives of pyrazoline; careful selection of substituents is called for in balancing efficacy versus toxicity.

1.3.1 Anticancer: A large number of analogues have been reported to inhibit VEGFR-2 and EGFR signaling, induce apoptosis, and arrest cell proliferation [19, 20].

Substituents including -NO2, halogens, and methoxy groups enhance cytotoxic potency [21].

1.3.2 Antimicrobial: They exhibit both antibacterial and antifungal action, electron- withdrawing substituents enhance lipophilic nature and microbial cell penetration [22, 23].

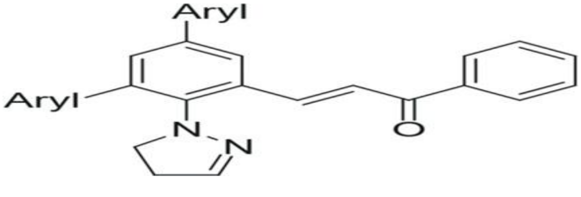
1.3.3 Anti-inflammatory s Analgesic: Inhibition of COX-2 and suppression of pro- inflammatory cytokines make these analogues a potential alternative to NSAIDs [24].

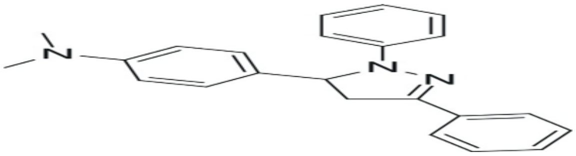
1.3.4 Neuroprotective s Anticonvulsant: Some pyrazolines modulate GABAergic transmission, hence holding promise in the management of epilepsy [25].

1.3.5 Antioxidant s Antidiabetic: They neutralize free radicals and inhibit alpha- glucosidase, demonstrating potential in diabetes therapy [26, 27].

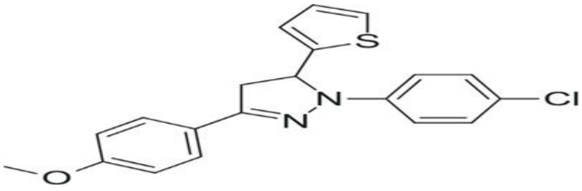
1.4 Preclincial Drugs In Research.

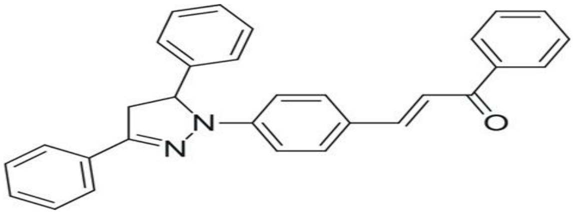
Preclinical drugs in research. Several drugs in clinical use have influenced the design of chalcone-derived pyrazolines, which are currently under extensive preclinical investigation due to their wide pharmacological scope. Consequently, these hybrid compounds have illustrated potent anticancer, anti-inflammatory, antimicrobial, and antioxidant potencies. For instance, 4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl)-N, N-dimethylaniline (PPA) has displayed weak antimicrobial activity with lower cytotoxicity [28], while 4-(3,5-diphenyl-4,5-dihydro-1H-pyrazol-1-yl) chalcones have demonstrated potent anti-inflammatory and antimicrobial activities [28]. Additionally, other N-(4- chlorophenyl)-3-(4-methoxyphenyl)-5-(2-thienyl)-2-pyrazoline chalcone hybrids are under study for anticancer and antioxidant activity, as drug candidates displaying the therapeutic potential of this new class [24].





4-(1,3-diphenyl-4,5-dihydro-1H-pyrazol-5-yl) 3,5-diaryl-2-pyrazoline-chalcone. -N, N-dimethylaniline (PPA).





4-(3,5-diphenyl-4,5-dihydro-N-(4-chlorophenyl)-3-(4-
1H-pyrazol-1-yl) Chalcone. methoxyphenyl)-5-(2-thienyl)-2-pyrazoline Figure 3: Some Clinically In Research Drugs.

II. TAUTOMERISM.

Complex tautomeric behavior of pyrazoline derivatives has been studied using a combined approach of spectroscopic and computational methods. The phenomenon includes migration of one proton, resulting in structural isomers that can be in equilibrium. [29, 30]

Figure 3: General Pyrazoline Core Structure.

2.1 Computational and Spectroscopic Investigation.

The study of tautomerism in pyrazolines heavily relies on computational chemistry and experimental spectroscopy.

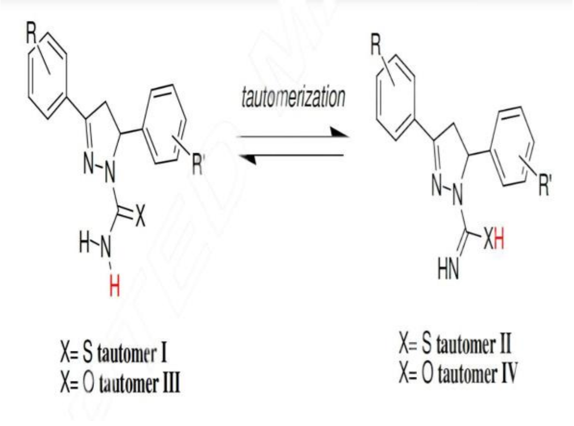
The Computational Methods DFT calculations of tautomers in the gas phase and in different environments were performed using methods such as B3LYP and M06-2X. The DFT calculations enable the determination of the minimum potential energy surface, the theoretical prediction of the stability of the tautomeric forms, and the simulation of different spectra, Raman and NMR, for comparison with experimental data [31].

Semiempirical (AM1, PM3) and ab initio (HF, MP2) methods have also been employed to study this behavior [32].

Spectroscopic Analysis: The presence and stability of tautomers are experimentally verified. X-ray crystallography identifies the solid-state dominant tautomer, but for solution-state behavior, ^{1}H and ^{13}C NMR spectroscopy are most frequently used, in which chemical shifts point to the prevalent structure [4]. FT-IR and FT-Raman spectroscopy is also used to observe tautomeric equilibria.[31].

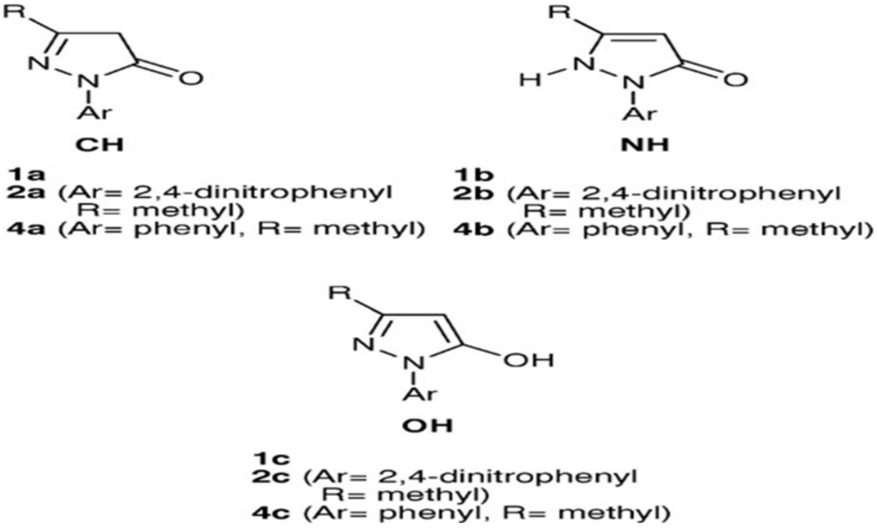
2.2 Tautomeric Forms and Stability.

Pyrazolines, depending on the substituents, can exist in several tautomeric forms. Carboxamide/Carbothioamide Tautomerism: Pyrazolines bearing these functional groups can undergo tautomerization in the solid and solution states. Thermodynamic estimations provide evidence that the amide $R(CO)NH_2$ and thioamide $R(CS)NH_2$ forms are more stable than their corresponding imidic acid $R(CNH)OH$ and thioimidic acid $R(CNH)SH$ tautomers.



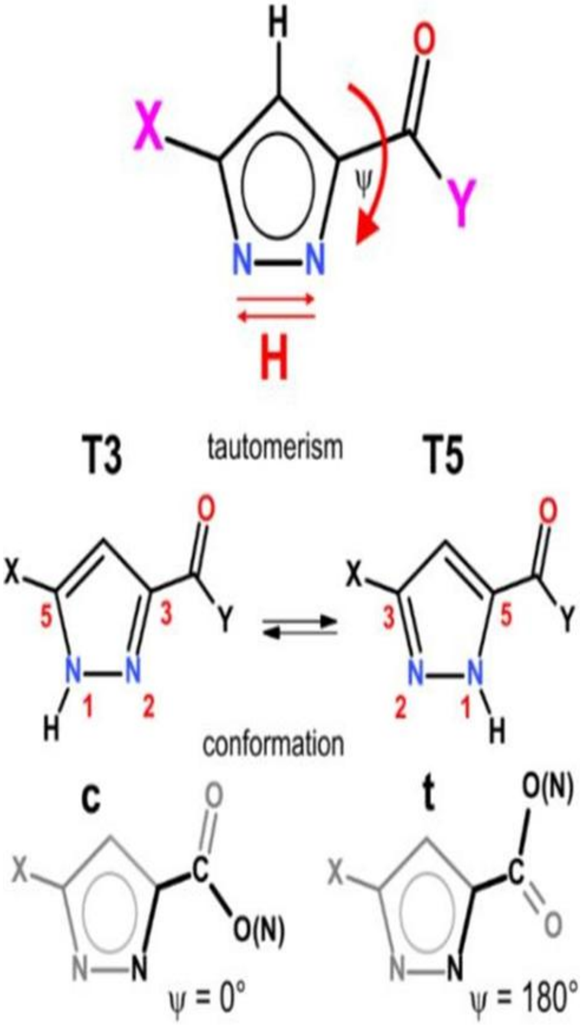
Scheme 5: Tautomeric forms of Carboxamide/Carbothioamide.

Pyrazolinone Tautomerism: Pyrazolinones can exist as CH, NH, and OH tautomers, out of which pyrazolinones with NH and CH7H9 are the most stable ones [30,32].



Scheme 6: Different tautomeric forms for 1-aryl-2-pyrazolin5-ones.

Annular Tautomerism: Annular tautomerism of disubstituted 1H-pyrazoles with ester and amide groups has been studied by methods involving X-ray crystallography, theoretical calculations, NMR, and FT-IR. X-ray experiments in the crystal state indicated that methyl and amino group-substituted compounds favored tautomer 3, with ester or amide groups at position 3, while the nitro groups favored tautomer 5. Similar results were obtained in solution by NMR NOE experiments in $CDCl_3$, DMSO-d_6, and CD_3OD solvents.[33].



Scheme 7: Representation Of Tautomers In 3(5)-1H-pyrazoles, Conformation of the 3(5)-Carbonyl Group.

2.3 Factors affecting Tautomeric Equilibrium.

The balance of different tautomers is sensitive and depends on several factors. Solvent and Physical State: The most stable tautomer may vary substantially in the gas phase, in the solid state, and in solution. The nature of the solvent used-DMSO, $CDCl_3$, or CD_3OD-may shift the equilibrium and determine which form is predominantly present [33].

Temperature: The tautomeric equilibrium can be affected by a change in temperature. To illustrate, the proportion of CH tautomer of a solution of 1-phenyl-3-methylpyrazolinone increases with the temperature of the solution [30].

Structural and Electronic Effects: The electronic properties of substituents are also important in defining which tautomer is preferred in a reaction [33].

III. SPECTROSCOPIC CHARACTERIZATION OF CHALCONE-DERIVED PYRAZOLINES.

Structural confirmation of newly synthesized chalcone-derived pyrazolines is typically done through various spectroscopic methods with computational analysis frequently being used to back up the method. [31]

3.1. Fourier Transform Infrared (FT-IR) Spectroscopy.

The FT-IR spectroscopy will be a valuable instrument in the determination of functional groups in the pyrazolines synthesized. Confirmation of the occurrence of the targeted cyclization reaction is highly essential since it identifies specific absorption bands of the pyrazoline ring and injected side chains. [34,35].

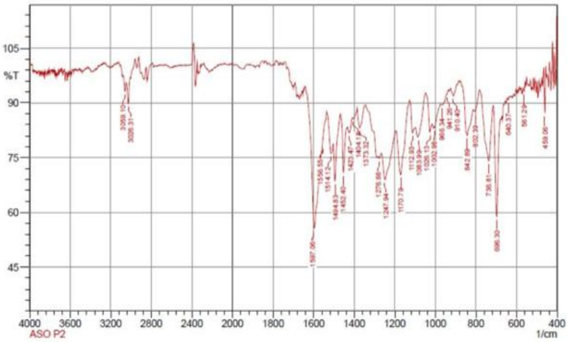


Figure 4: Representative FT-IR spectrum of a synthesized pyrazoline showing characteristic functional group absorptions.

3.2. Nuclear Magnetic Resonance (NMR) Spectroscopy.

NMR provides detailed information about the molecular structure of pyrazolines in solution.

^{1}H NMR Spectroscopy: Proton NMR is indispensable in mapping the hydrogen environment within the molecule. It confirms the formation of the pyrazoline ring by characteristic signals of its protons and helps in determining the substitution pattern. It is also a very important technique for the identification of the prevailing tautomeric form present in a given solvent. [31]

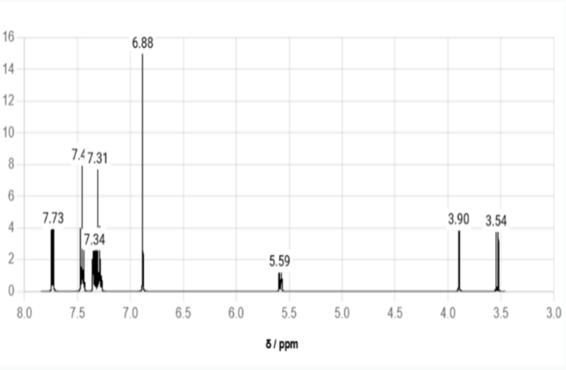
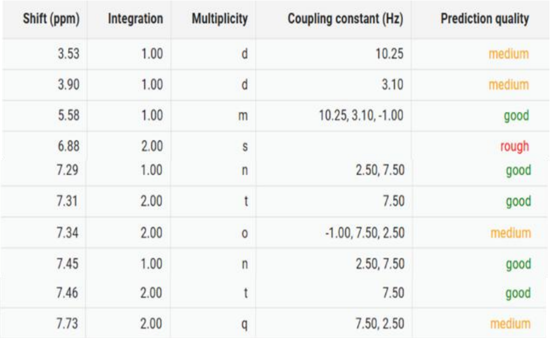


figure 5: Representative ^{1}H NMR spectrum of a pyrazoline, highlighting thecharacteristic signals of the C4 and C5 ring protons.



Shift (ppm)	Integration	Multiplicity	Coupling constant (Hz)	Prediction quality
3.53	1.00	d	10.25	medium
3.90	1.00	d	3.10	medium
5.58	1.00	m	10.25, 3.10, -1.00	good
6.88	2.00	s		rough
7.29	1.00	n	2.50, 7.50	good
7.31	2.00	t	7.50	good
7.34	2.00	o	-1.00, 7.50, 2.50	medium
7.45	1.00	n	2.50, 7.50	good
7.46	2.00	t	7.50	good
7.73	2.00	q	7.50, 2.50	medium

^{13}C NMR Spectroscopy: Carbon-13 NMR, sometimes enhanced with techniques like DEPT (Distortionless Enhancement by Polarization Transfer), complements ^{1}H NMR data by providing a map of the carbon skeleton [34,35].

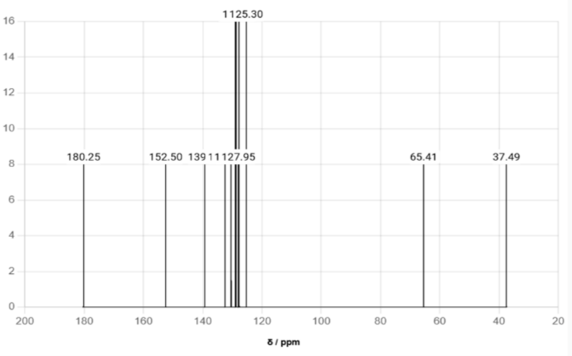
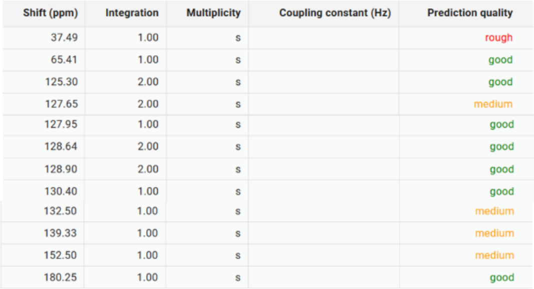


Figure 7: Representative ^{13}C NMR spectrum of a pyrazoline, with keyringcarbons(C3, C4, C5) assigned.



Shift (ppm)	Integration	Multiplicity	Coupling constant (Hz)	Prediction quality
37.49	1.00	s		rough
65.41	1.00	s		good
125.30	2.00	s		good
127.65	2.00	s		medium
127.95	1.00	s		good
128.64	2.00	s		good
128.90	2.00	s		good
130.40	1.00	s		good
132.50	1.00	s		medium
139.33	1.00	s		medium
152.50	1.00	s		medium
180.25	1.00	s		good

3.3. FT-Raman Spectroscopy.

The FT-Raman analyzer has proven to be a highly functional instrument in the study of the vibration of molecules. The deep dynamics of the pyrazolines are also obtained when they are coupled with the DFT calculations. This method has been particularly successful in the examination of the equilibrium between tautomeric forms of pyrazoline derivatives of carboxamide and carbothioamide groups, the outcomes of the computations by Raman spectrophotometry being quite in harmony with the experimental outcomes [31].

3.4. Computational and Integrated Approaches.

The present-day characterization method comprises computational methods such as DFT. Theoretical calculation of NMR and Raman spectrums can be done and hence the existence of the theoretical result. Experimental results. Besides this, the DFT technique is also used to ensure that the structure which is synthesized is a minimum of the potential energy surface and by implication, justifies the structure which has been experimentally determined. This type of combination of experimental spectroscopy along with calculations modelling facilitates the full and accurate explanation of the pyrazine compounds [31].

IV. STRUCTURE ACTIVITY RELATIONSHIP.

The derivatives of pyrazines based on chalcones have been involved in the production of pyrazine derivatives with various pharmacological activities such as anti-microbial, anti-inflammatory, antioxidant, and anticancer activities. The structure-
The activity relationship of such compounds is related directly with the strategic arrangement of substituents on the pyrazoline skeleton and the rings to which they are conjugated thus controlling their biological actions.

Antimicrobial Activity.

Cell wall microbiological penetration of pyrazolines. determines their antimicrobial potential. One example is the presence of halogen e.g., -Cl or -F in the para-position of aryl rings raises lipophilicity and improves. Permeability and antimicrobial effect of membrane [22,36]. Furthermore, an additional inhibition of ionization at physiological pH within the N1-position of the pyrazoline ring by non-ionizing groups such as an acetyl moiety is added to enhance bioavailability. and increases antimicrobial effect [37]. These mutations have been found to cause a huge reduction in MIC of bacterial strains due to increased membrane transport.

Anti-inflammatory Activity.

One of the major therapeutic approaches to inhibiting inflammation is the selective inhibition of the COX-2 enzyme. Specifically, the para-sulfonamide moiety (-SO 2 NH 2) on the C5-aryl ring can bind certain amino acid residues on the COX-2 side pocket, and it has a greater binding affinity. The steric interference of the smaller COX-1 active site inhibits this interaction. selectivity and a reduced number of side effects on gastrointestinal tract with non-selective COX inhibition. Molecular docking studies experimentally confirmed the findings which have emphasized the role of sulfonamide group in selective potent COX-2 inhibition [38].

Antioxidant Activity.

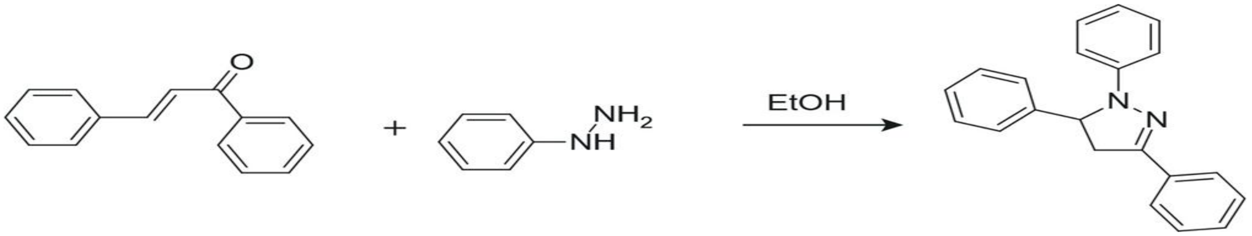
Pyrazoline derivatives, acting as free radical scavengers, are highly effective against oxidative stress. Hydroxyl groups on the aryl rings enhance electron density and, therefore, the ability of hydrogen atom donation to neutralize ROS via the formed phenoxy radical, which is further resonance-stabilized over the aromatic system, hence making an effective and efficient hydrogen donor from the parent molecule. Other
electron-donating groups like methoxy groups increase the electron density of aryl rings, thus enhancing their antioxidant potential through resonance and radical stabilization [26,39].

Anticancer Activity.

Among the anticancer methods, to which pyrazoline analogs can be applied, it is necessary to inhibit cell division that is necessary due to the polymerization of tubulins. The pyrazole structure has a 3,4,5 - trimethoxyphenyl group at the C3 - position, which provides high-position.
binding to the colchicine binding site of 8 -tubulin. This binding destabilizes the microtubules 권 [19] that inhibits cell proliferation by blocking the cell cycle at the G2/M phase and causing cell death. Optimization of pharmacologic profiles can be done using pharmacological profiles.
The replacement at the N1 position with other substitutions, such as the thiocarbamoyl group, increases the cytotoxicity and uptake by cells [38].

V. SYNTHESIS

Microwave-Assisted Synthesis of Pyrazoline Reaction:



Microwave, solvent-free
Chalcone+Phenylhydrazine

Mechanism:
1,3,5 − Triphenyl − 2 − pyrazoline
Microwave irradiation provides rapid heating, enhancing the nucleophilic attack of phenylhydrazine on the chalcone's carbonyl group, leading to cyclization and pyrazoline formation.

Procedure:
Mix equimolar chalcone and phenylhydrazine in a

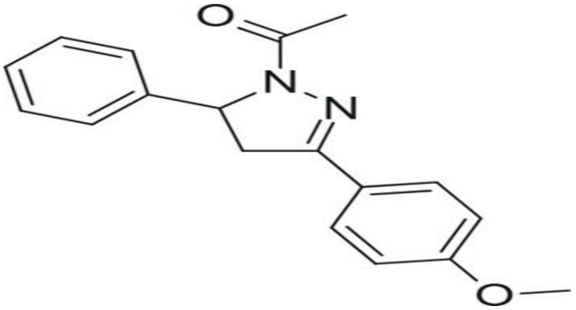
mortar. Grind and irradiate in a microwave oven for 2–5 minutes. Cool and dissolve crude product in ethanol. Filter and recrystallize from ethanol.

Materials: Chalcone, Phenylhydrazine, Microwave, Mortar and pestle, Ethanol [10].

VI. ACTIVITIES

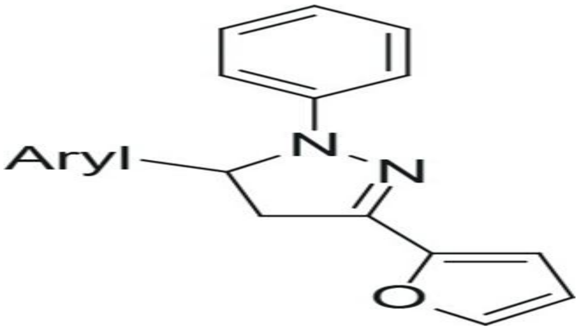
6.1 Anti-Microbial.

6.1.1 (2005a) - Chimenti et al. first synthesized N-acetyl-3-(4-methoxyphenyl)-5- (1,2) phenyl-4,5-dihydro-1H-pyrazole, showing strong inhibition against H. pylori (metronidazole-resistant) with MIC 1–4 μg/mL, marking a key early example of targeted potency [40].



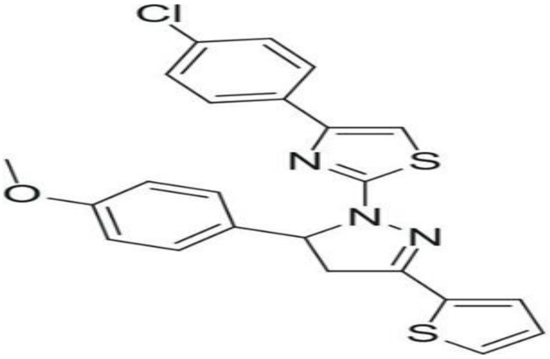
N-acetyl-3-(4-methoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazole.

6.1.2 (2005b) - Shivarama et al. developed 1-phenyl-3-(furan-2-yl)-5-aryl-4,5- dihydro-1H-pyrazole, which displayed broad-spectrum antibacterial and antifungal activity, highlighting pyrazoline's versatility [41].



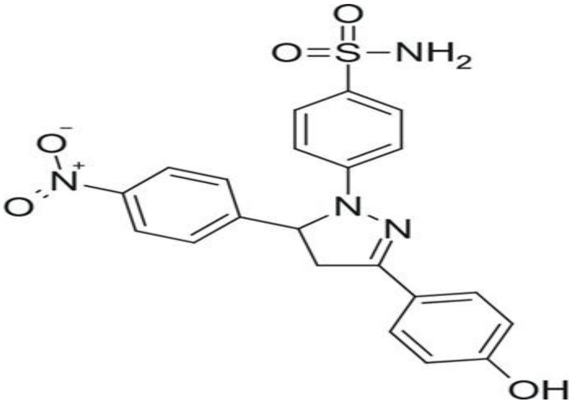
1-Phenyl-3-(furan-2-yl)-5-aryl-4,5-dihydro-1H-pyrazole.

6.1.3 (2007a) - Ozdemir et al. synthesized 1-(4-(4-chlorophenyl)-thiazol-2-yl)-3-(2- thienyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole, combining thiazole and thiophene moieties, resulting in synergistic action against E. coli, S. aureus, and C. albicans [42].



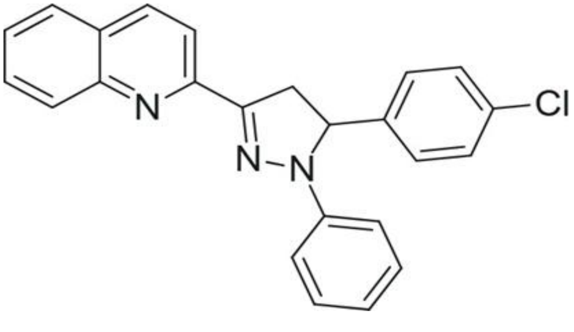
1-(4-(4-Chlorophenyl)-thiazol-2-yl)-3-(2-thienyl)-5-(4-methoxyphenyl)-4,5-dihydro- 1H-pyrazole.

6.1.4 (2007b) - Shaharyar et al. designed 4-(3-(4-hydroxyphenyl)-5-(4-nitrophenyl)- 4,5-dihydro-1H-pyrazol-1-yl) benzenesulfonamide, which showed favorable anti- tubercular activity against M. tuberculosis [43].



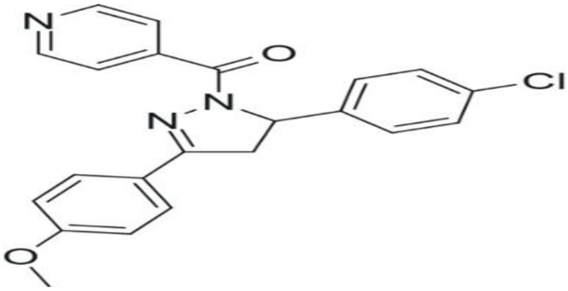
4-(3-(4-hydroxyphenyl)-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl) benzenesulfonamide.

6.1.5 (2008a) - Munawar et al. reported 1-phenyl-3-(quinolin-2-yl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole, where the chloro-substituted ring enhanced potency against S. aureus, S. typhi, and E. coli. [44].



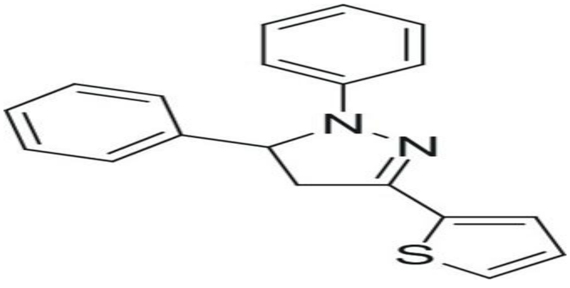
1-phenyl-3-(quinolin-2-yl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole.

6.1.6 (2008b) - Kini et al. synthesized 1-(isonicotinoyl)-3-(4-methoxyphenyl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole, which demonstrated significant antimicrobial activity across Gram-positive and Gram-negative strains (E. coli, P. aeruginosa, B. subtilis, S. aureus) [45].



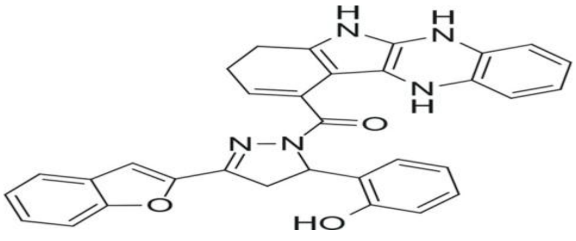
1-(isonicotinoyl)-3-(4-methoxyphenyl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole.

6.1.7 (200Ga) - Ramesh et al. developed 1,5-diphenyl-3-(thiophen-2-yl)-4,5-dihydro- 1H-pyrazole, which displayed antibacterial activity comparable to sparfloxacin[40].



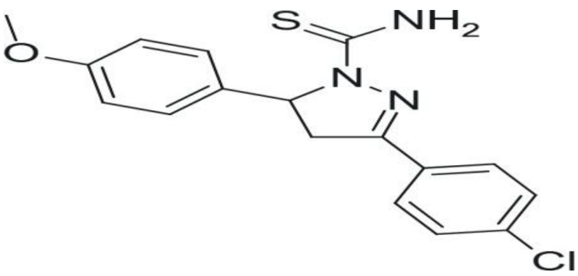
1,5-diphenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazole.

6.1.8 (200Gb) - Manna et al. synthesized 2-(1-(5,8-dihydroquinoxalino[2,3-b] indole- 10-carbonyl)-3-(1-benzofuran-2-yl)-4,5-dihydro-1H-pyrazol-5-yl) phenol, showing good activity against S. aureus, P. aeruginosa, and E. coli. [40]



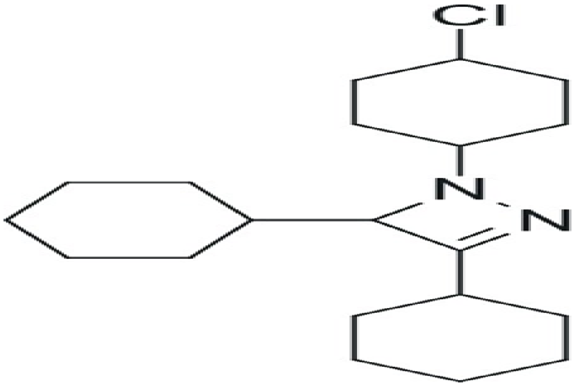
2-(1-(5,8-dihydroquinoxalino[2,3-b] indole-10-carbonyl)-3-(1-benzofuran-2-yl)-4,5- dihydro-1H-pyrazol-5-yl) phenol.

6.1.G. (2010a) - Chawla et al. introduced 3-(4-chlorophenyl)-5-(4-methoxyphenyl)- 4,5-dihydro-1H-pyrazole-1-carbothioamide, exhibiting strong antibacterial and antifungal effects against B. subtilis, E. coli, C. albicans, and A. niger[40].



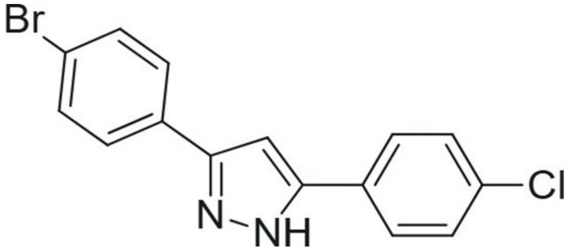
3-(4-chlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1- carbothioamide.

6.1.10. (2010) - Sivakumar et al. produced 1,3,5-triphenyl-2-pyrazoline with chlorine on Ring A, where chlorine substitution significantly enhanced antibacterial potency [40].



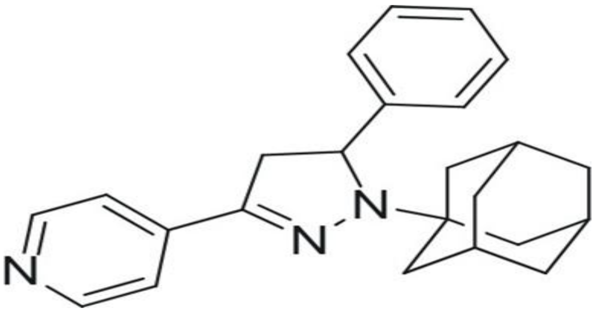
1,3,5-triphenyl-2-pyrazoline with chlorine on Ring A.

6.1.11. (2013) - Kendre and Baseer investigated 3-(4-bromophenyl)-5-(4-chlorophenyl)-1H-pyrazole, confirming that bromo- and chloro-substitutions on aryl rings were critical for antibacterial and antifungal activity [46].



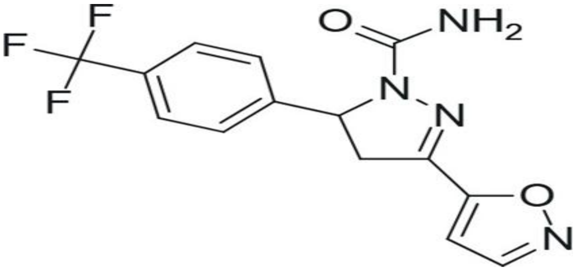
3-(4-bromophenyl)-5-(4-chlorophenyl)-1H-pyrazole derivative.

6.1.12. (2020a) - Al-saheb et al. synthesized 1-adamantyl-3-(pyridin-4-yl)-5-phenyl- 4,5-dihydro-1H-pyrazole, where the bulky adamantyl group improved lipophilicity and broadened Gram+/− activity, including activity against F. oxysporum [47].



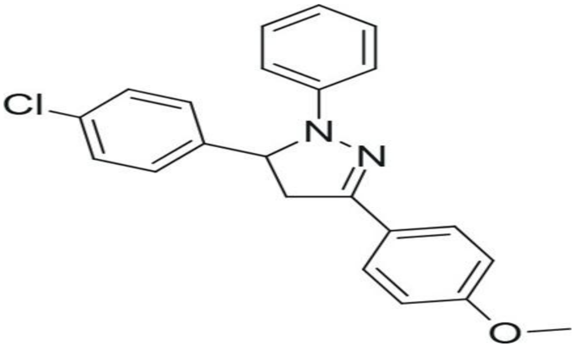
1-adamantyl-3-(pyridin-4-yl)-5-phenyl-4,5-dihydro-1H-pyrazole.

6.1.13. (2020b) - Shaik et al. reported (Compound 46) 1-carboxamide-3-(isoxazol-5- yl)-5-(4-(trifluoromethyl) phenyl)-4,5-dihydropyrazole with excellent antifungal
potency ($IC_{50} \approx 2 \pm 1$ µg/mL) against C. albicans, A. niger, and A. flavus [48].

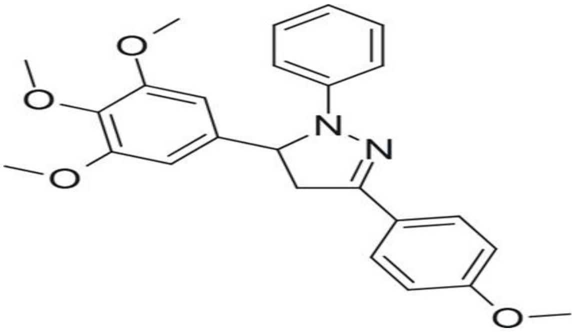


1-carboxamide-3-(isoxazol-5-yl)-5-(4-(trifluoromethyl) phenyl)-4,5-dihydropyrazole.

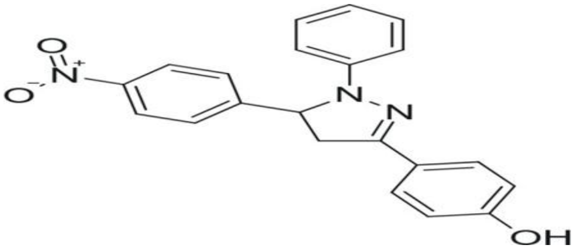
6.1.14. (2023a) - Kumar et al. synthesized multiple derivatives including Compound (4b) (1-phenyl-3-(4-methoxyphenyl)-5-(4-chlorophenyl)-pyrazoline) and Compound (4f) (3,4,5-trimethoxy-substitution), both showing remarkable activity against S.
aureus, B. subtilis, and S. typhi. Compound 4h (4-hydroxy/4-nitro substitution) extended activity to C. albicans [49].



(1-phenyl-3-(4-methoxyphenyl)-5-(4-chlorophenyl)-pyrazoline).

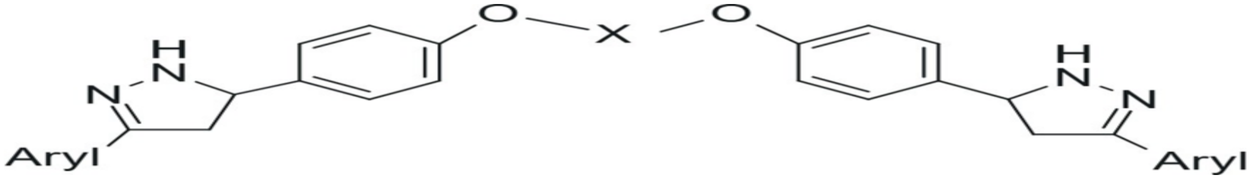


1-Phenyl-3-(4-methoxyphenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazole.

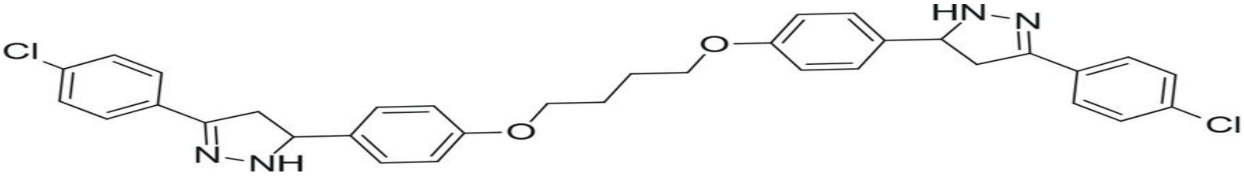


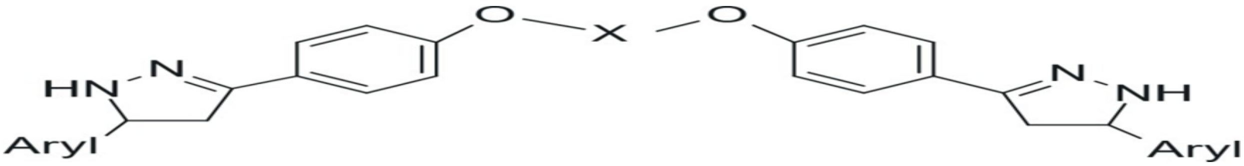
1-Phenyl-3-(4-hydroxyphenyl)-5-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole.

6.1.15. (2023b) - Kassab et al. designed bis-pyrazoline scaffolds Compound (5ad,
Gad, Gah) which were highly potent against MSSA, MRSA, and VRSA, with MICs as low as 0.17 µM (MSSA) and low micromolar activity against VRSA, highlighting bis- pyrazoline dimers as next-generation leads [50].

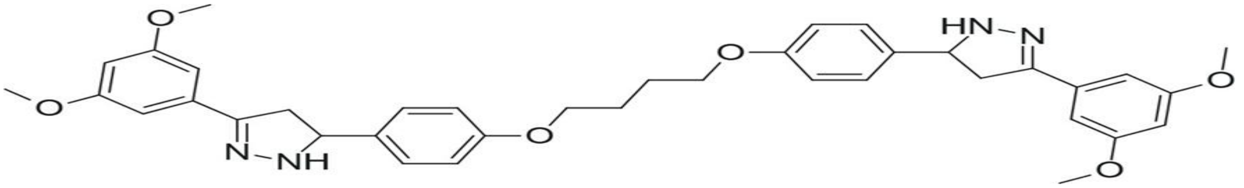


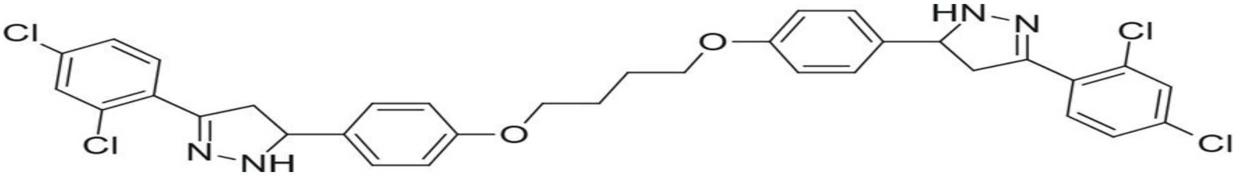
5ad aryl = 4-clc6h4



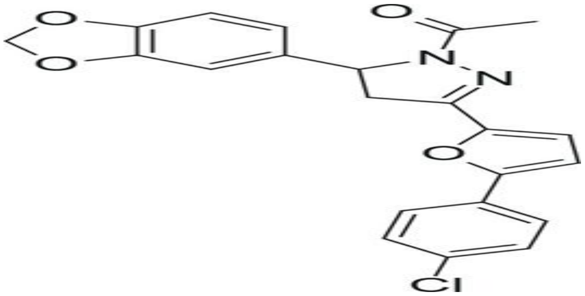


Gad aryl =3,5-och3c6h3 Gah aryl =2,4clc6h3





6.1.16. (2024) - Al-Ghorbani et al. synthesized Compound 3d (1-acetyl-3-(5-(4-chlorophenyl) furan-2-yl)-5-(3,4-methylenedioxyphenyl)-4,5-dihydropyrazole), which demonstrated selective activity against Gram-positive bacteria, particularly S. aureus and S. epidermidis, confirming structural tuning can yield spectrum-selective agents [51].

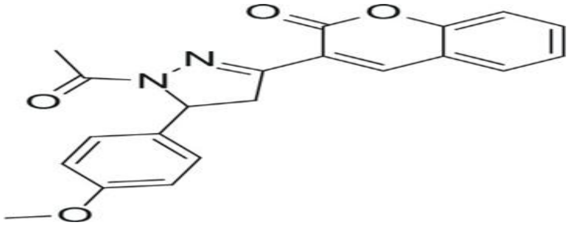


1-Acetyl-3-(5-(4-chlorophenyl) furan-2-yl)-5-(3,4-methylenedioxyphenyl)-4,5- dihydropyrazole.

6.2 Anti-Cancer /Cytotoxic.

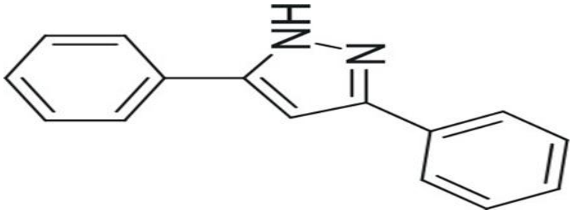
6.2.1 (200G) - Liu et al. developed a coumarin-pyrazoline hybrid compound,

compound G, 3-(Coumarin-3-yl)-5-(4-methoxyphenyl)-1-acetyl-4,5-dihydropyrazole. This molecule was identified as a potent inhibitor of telomerase (with an IC50 = 2.0 µM), an enzyme crucial for the immortalization of cancer cells. The compound demonstrated significant activity against the SGC-7G01 gastric cancer cell line, exhibiting an IC50 value of 2.6G µg/mL. This study established a clear and early link between a specific molecular target (telomerase) and the therapeutic potential of this chemical scaffold [52].



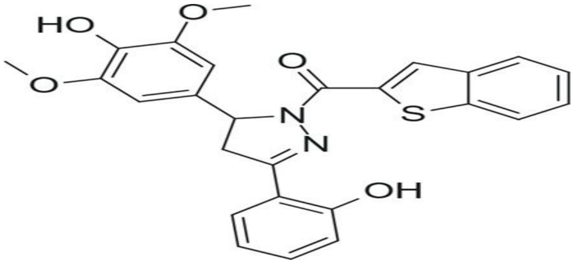
3-(Coumarin-3-yl)-5-(4-methoxyphenyl)-1-acetyl-4,5-dihydropyrazole.

6.2.2 (2015) - Havrylyuk et al. screened large numbers of pyrazole-based compounds. Their experiment identified a 3, 5-Diphenyl-1H-pyrazole analog L2 that possessed general cytotoxic action on the pancreatic cancer cells extending the overall antiproliferative properties of the scaffold [53].



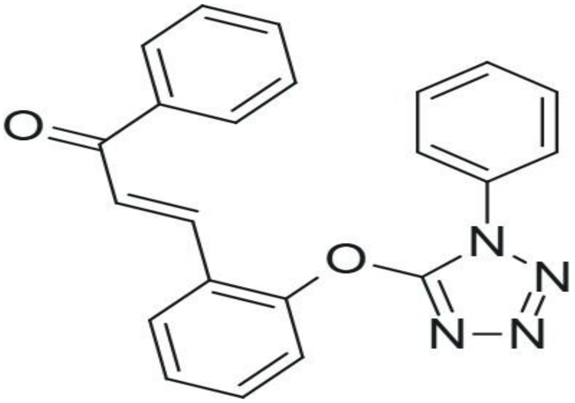
3,5-Diphenyl-1H-pyrazole.

6.2.3 (2017) - Xu et al. that synthesized a complex of benzo[b]thiophene-pyrazoline hybrid. This compound (b17) was an excellent inhibitor of the HepG-2 liver cancer cell line line (IC50 = 3.57 uM) which was more than twice as active as the active chemotherapy agent cisplatin. The effectiveness of its application in the mechanistic studies was because of its ability to induce a blockage at the G2/M phase in the cancer cell cycle and causecontrolled cell death (apoptosis) [21]

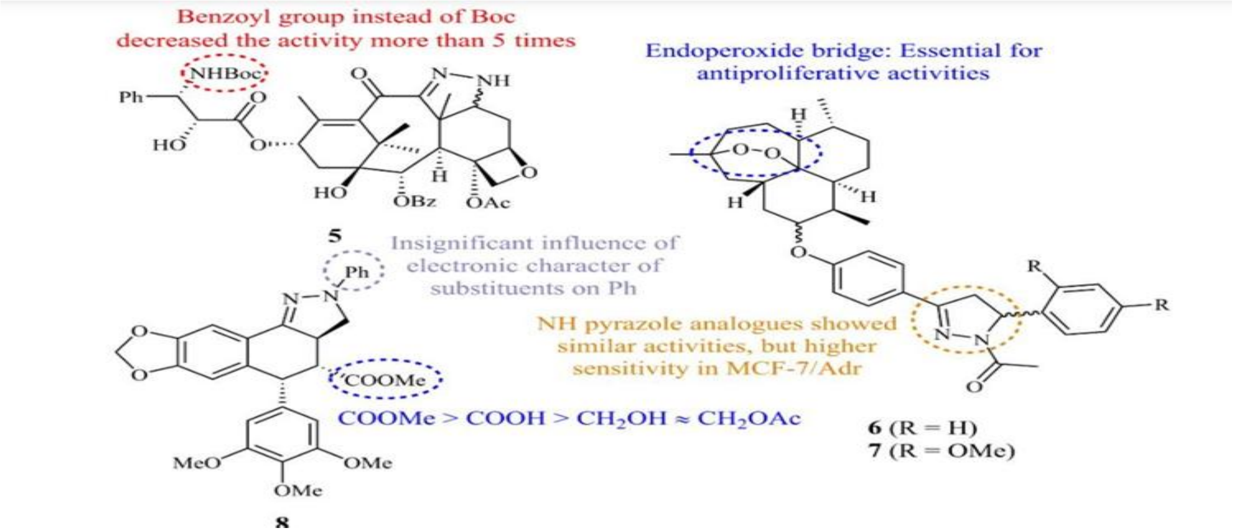


Benzo[b]thiophen-2-yl-(5-(4-hydroxy-3,5-dimethoxyphenyl)-3-(2-hydroxyphenyl)- 4,5-dihydropyrazol-1-yl) methanone.

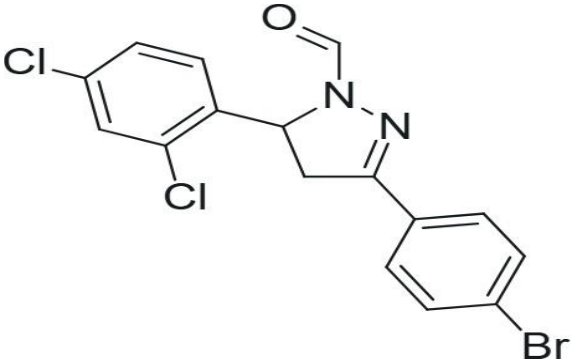
6.2.4 (2018) - Abd ElMonaem et al. evaluated the potential of the tetrazole-pyrazol hybrids. Their lead compound (5a) showed a phenomenal antiproliferative action to both HCT-116 colon cancer (IC50 = 0.6 ug/mL) and PC-3 prostate cancer cell lines suggesting the significance of molecular hybridization on the potency [54].



6.2.5 (2020a) - Matiadis s Sagnou showcased several landmark hybrids, including a Taxol-pyrazoline compound 5 with an exceptionally potent IC50 of 1.4 nM against MDA- MB-231 breast cancer cells by inhibiting tubulin polymerization. They also featured an artemisinin-pyrazoline hybrid compound (6) that not only showed broad-spectrum activity (GI50 = 0.025–0.42 uM) but critically, was able to overcome adriamycin resistance in the MCF-7/Adr breast cancer cell line [19].

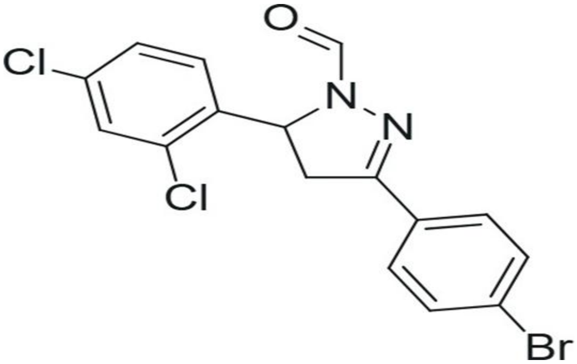


6.2.5. (2020b) - Salum et al. identified another pyrazoline derivative with notable cytotoxic effects against the MCF-7 breast cancer cell line (IC50 = 6.50 uM) [55].

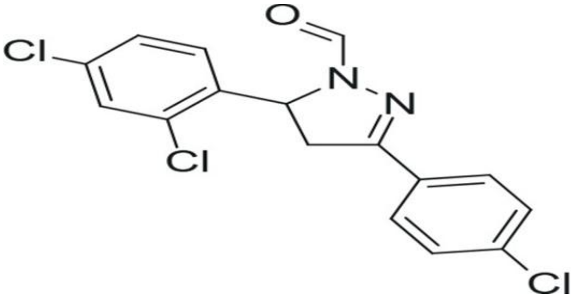


5-(2-Chlorophenyl)-3-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole.

6.2.6. (2021) - Rana et al. synthesized N-formyl pyrazolines and identified them as effective Topoisomerase II inhibitors. These compounds demonstrated excellent cytotoxicity against the A549 lung cancer cell line, with IC50 values of 12.47 uM and 14.46 uM, further diversifying the known mechanisms of action for this class of molecules [56].

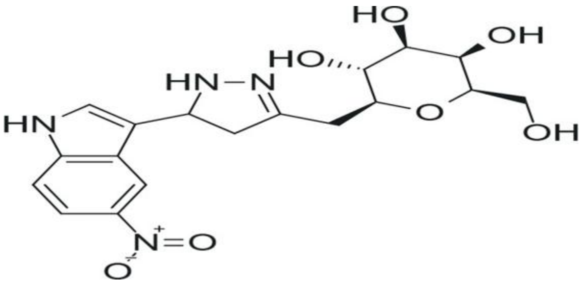


N-Formyl-3-(4-bromophenyl)-5-(2,4-dichlorophenyl)-4,5-dihydropyrazole.



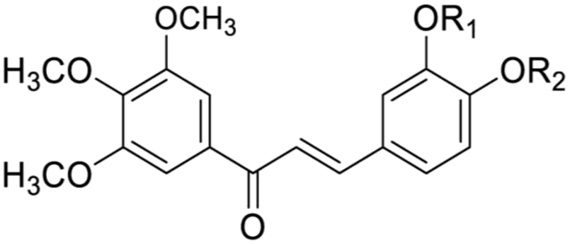
N-Formyl-3-(4-chlorophenyl)-5-(2,4-dichlorophenyl)-4,5-dihydropyrazole.

6.2.7. (2022) - Kumari et al. developed a novel pyrazoline-indole C-glycoside hybrid that functioned as a COX-2 inhibitor, a well-known target in inflammation and cancer, showing specific efficacy against the MCF-7 breast cancer cell line (IC50 = 4.67 uM) [57].

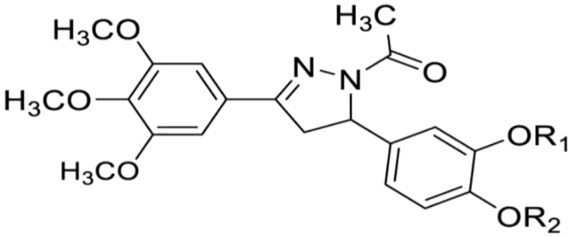


6.2.8. (2024a) - Hwang et al. successfully targeted a protein-protein interaction (PPI). They identified a parent chalcone and its pyrazoline derivatives as potent inhibitors of the ELF3-MED23 interaction, which in turn downregulated the HER2 oncogene. This led

to significant anticancer activity in both lab-based and animal models of HER2-positive NCI-N87 gastric cancer, including those resistant to the standard drug trastuzumab [58].



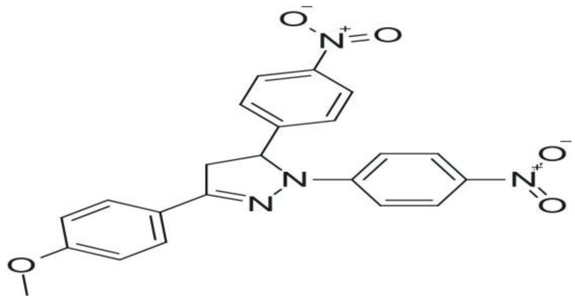
R1 = 3-methyl1-but-2-enyl R2 = CH3



R1 = Propenyl R2 = CH3

R1 = 2-Butenyl R2 = CH3

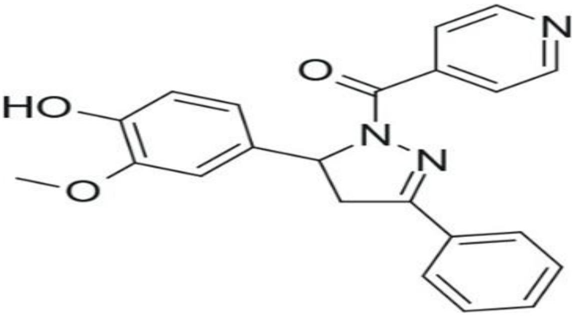
6.2.G. (2024b) - Kumar et al. identified a pyrazoline as a potent and selective inhibitor of the B-Raf kinase, another key oncogenic driver, showing effectiveness against A549 lung cancer (IC50 = 6.45 uM). Finally, Pérez-Rojas et al. investigated a series of pyrazoline derivatives that effectively targeted kinase signaling pathways in both MCF-7 (breast) and HT-2G (colon) cancer cells, with potencies in the IC50 = 28.8–124.6 uM range [59].



6.3 Anti-Oxidant.

(2014) - Yildiz et al. This was the pioneer study that conducted a systematic study on the antioxidant 1-(4-Nitrophenyl)-3-(4-methoxyphenyl)-5-(4-nitrophenyl)-4,5-dihydropyrazole

6.3.1 activity of pyrazolic chalcones. The researchers synthesized a series of compounds which contained pyrazolic chalcone with phenolic - OH groups and put them to test in regard to their free radical scavenging ability. They concluded that the existence and position of the phenolic hydroxyl (-OH) groups on the aromatic rings were a significant determinant of their major conclusion as this activity was directly associated with the -OH group. This established a fundamental structure- activity relationship. In such a case, it is evident that the methodology (SAR) must guide future research in the direction of the same area [60]

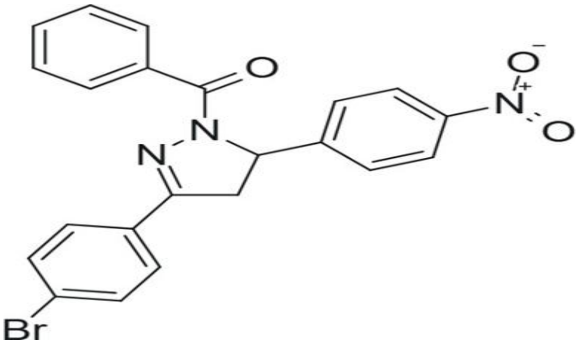


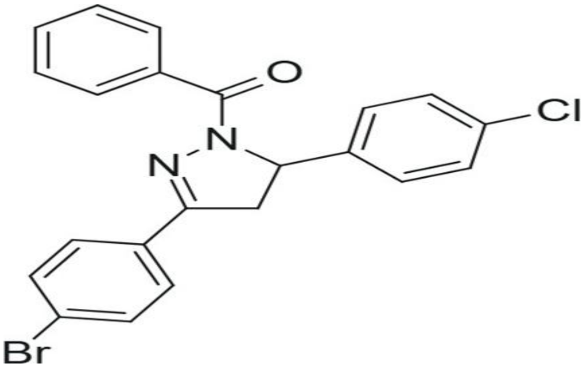
6.3.2 (2018a) - Bistuvalli et al. In accordance with the prior study, this group prepared a set of 1,3,5-trisubstituted pyrazolines. They discovered that the electron-withdrawing groups, that is, bromo genes contained in the compounds exhibited moderate but significant antioxidant in their characteristics. The lead compounds they possessed were:

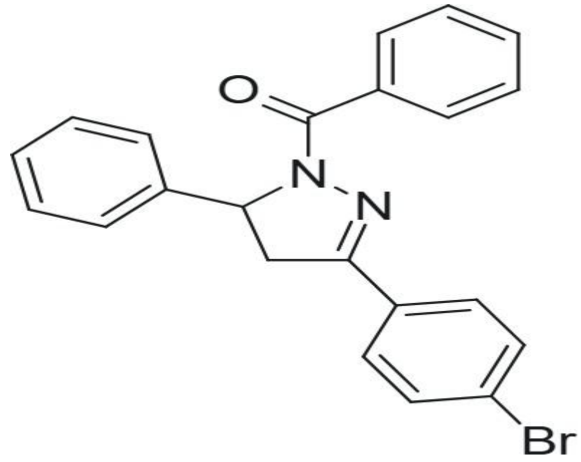
1-Benzoyl-3-(4-bromophenyl)-5-(4-nitrophenyl)-4,5-dihydropyrazole (Cpd 3e) with an IC50 = 28.22 uM.

1-Benzoyl-3-(4-bromophenyl)-5-(4-chlorophenyl)-

4,5-dihydropyrazole (Cpd 3f) with an IC50 = 34.22 uM.1-Benzoyl-3-(4-bromophenyl)-5-phenyl-4,5-dihydropyrazole (Cpd 3g) with an IC50 = 25.G2 uM. They employed a set of assessments (DPPH, superoxide, and nitric oxide scavenging) and therefore provided a distinct perspective of the radical-scavenging activities of the compounds in focus [61].

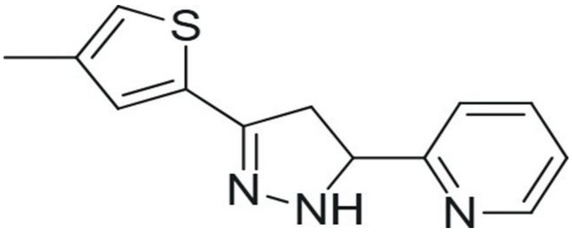




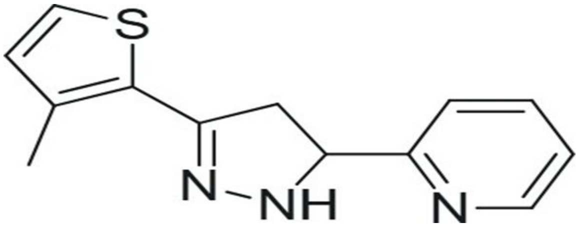


6.3.3 (2018b) - Usta et al. In one of the key findings of this group, there were 2- pyrazoline derivatives prepared with azachalcones. It was noted that these compounds were very potent for radical scavengers. These compounds were found to be exceptionally potent radical scavengers. Specifically, 3-(3-Methylthiophen-2-yl)-5- (pyridin-2-yl)-4,5-dihydro-1H-pyrazole (Cpd 2a) showed potent scavenging with an

SC50 = G.G1-15.16 ug/mL. Notably, 3-(4-Methylthiophen-2-yl)-5-(pyridin-2-yl)-4,5- dihydro-1H-pyrazole (Cpd 2b) was more powerful than the butylated hydroxytoluene (BHT) that is widely used as a synthetic antioxidant in the ABTS test [62].



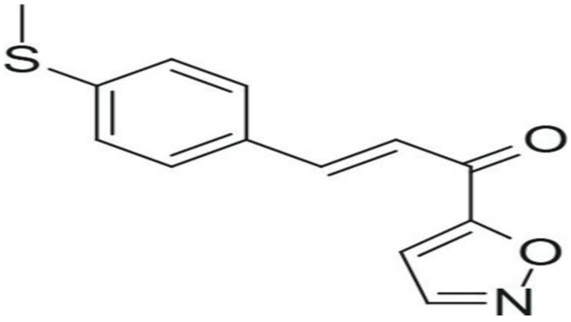
3-(3-Methylthiophen-2-yl)-5-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole.



3-(4-Methylthiophen-2-yl)-5-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole

6.3.4 (2020a) - Kumar et al. This piece of evidence brought about significant revelation since it revealed that cyclization is not necessarily good to possess a presence of antioxidant activity. The researchers found that precursors of chalcones were superior in their progression of isoxazole-based hybrids.

antioxidants to the cyclized pyrazoline derivatives. (E)-1-(Isoxazol-5-yl)-3-(4- (methylthio)phenyl) prop-2-en-1-one (47, Chalcone 28) was highly potent, with a DPPH scavenging IC50 of 5 ± 1 ug/mL [63].



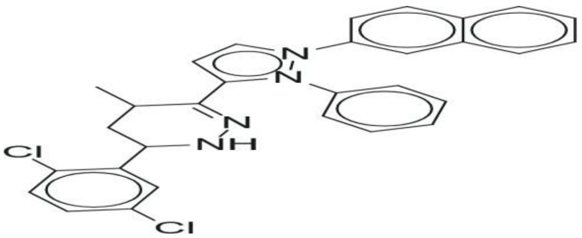
(E)-1-(Isoxazol-5-yl)-3-(4-(methylthio) phenyl) prop-2-en-1-one.

6.3.5 (2020b) - El-Sayed et al. This research group synthesized and evaluated three series of pyrazoline derivatives of naphthalenyl pyrazole chalcones. Their work identified the most potent compounds in each series, further refining the SAR for this class. The most active compounds were:

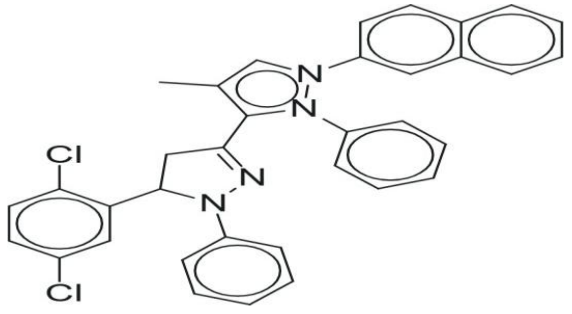
Compound 3e (5-(3,4-Dichlorophenyl)-3'-naphthalen-2-yl-1'-phenyl-3,4-dihydro- 2H,1'H- [3,4'] bipyrazole) with an IC50 = 21.3 uM.

Compound 4e (5-(3,4-Dichlorophenyl)-3'-naphthalen-2-yl-2,1'-diphenyl-3,4- dihydro-2H,1'H- [3,4'] bipyrazole) with an IC50 = 17.5 uM.

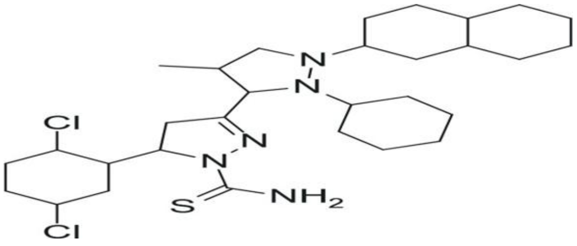
Compound 6e (5-(3,4-Dichlorophenyl)-3'-naphthalen-2-yl-1'-phenyl-3,4-dihydro-1'H- [3,4'] bipyrazolyl-2-carbothioic acid) with an IC50 = 15.2 uM [64].



5-(3,4-Dichlorophenyl)-3'-naphthalen-2-yl-1'-phenyl-3,4-dihydro-2H,1'H- [3,4'] bipyrazole.

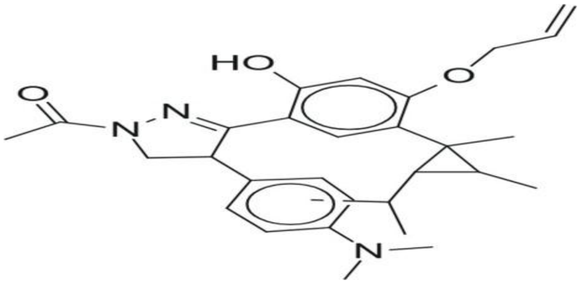


5-(3,4-Dichlorophenyl)-3'-naphthalen-2-yl-2,1'-diphenyl-3,4-dihydro-2H,1'H- [3,4'] bipyrazole

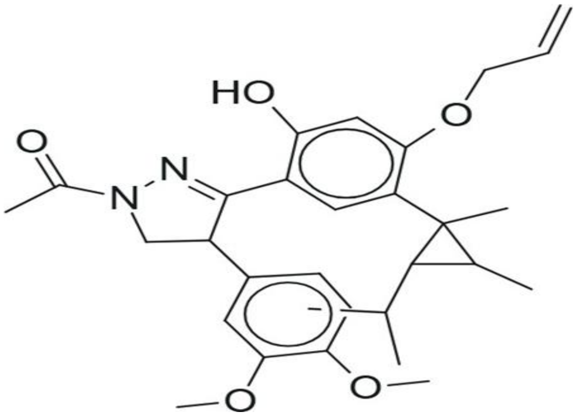


5-(3,4-Dichlorophenyl)-3'-naphthalen-2-yl-1'-phenyl-3,4-dihydro-1'H- [3,4'] bipyrazolyl-2-carbothioic acid

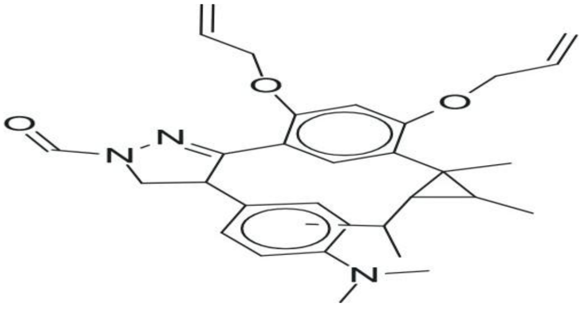
6.3.6 (2021a) - Popova et al. This team conducted a detailed investigation into diarylpyrazolines, concluding that the highest antioxidant activity was achieved by combining an electron-donating group (like dimethylamino, seen) with a hydroxyl group. Their most active compounds, 7i and Gi, featured a catechol (dihydroxy) moiety on Ring B and exhibited antioxidant activity comparable to standard reference compounds in the Fe2+/ascorbate LPO assay [27].



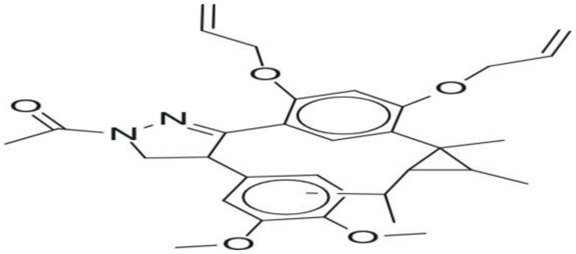
1-(5-(4-Dimethylaminophenyl)-3-(4'-allyloxy-2'-hydroxy-5'-isobornylphenyl)-4,5- dihydro-(1H)-pyrazole-1-yl)ethenone.



1-(5-(3,4-Dimethoxyphenyl)-3-(4'-allyloxy-2'-hydroxy-5'-isobornylphenyl)-4,5- dihydro-(1H)-pyrazole-1-yl) ethenone.

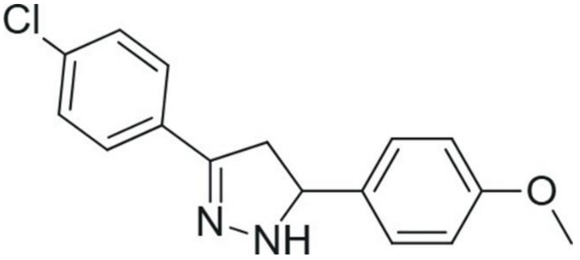


1-(5-(4-Dimethylaminophenyl)-3-(2',4'-diallyloxy-5'-isobornylphenyl)-4,5-dihydro- (1H)-pyrazole-1-yl) ethenone.



1-(5-(3,4-Dimethoxyphenyl)-3-(2',4'-diallyloxy-5'-isobornylphenyl)-4,5-dihydro-(1H)- pyrazole-1-yl) ethenone.

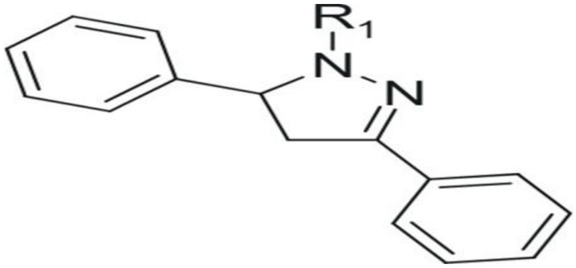
6.3.7 (2021b) - Pontiki s Hadjipavlou-Litina The following effect of the antioxidant explored in the present research was the inhibition of an enzyme lipoxygenase (LOX) a cause of oxidative inflammation. They have reported the strong selective LOX inhibitor (55, Cpd 2g) 3U-4uchlorophenyl-5-u4methoxyphenyl)-4-5-dihydro-1H -pyrazole with an IC50 = 80 uM [24].



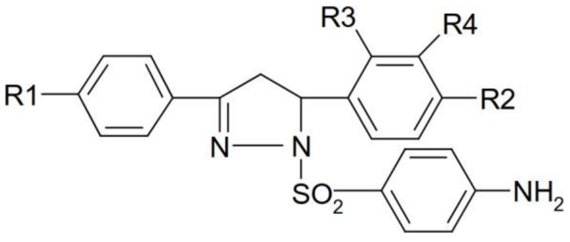
3-(4-Chlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole.

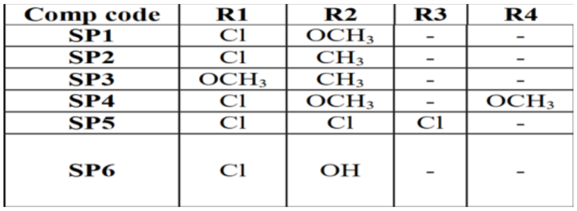
6.4 Anti-inflammatory.

6.4.1 (2010) - Bekhit et al. This first paper preconditioned that the pyrazoline skeleton would be a convenient starting point in the development of new anti-inflammatory agents. The authors conducted the synthesis of a group of N-substituted-3, 5-diphenyl-2-pyrazole derivativesmental skills in the desensing of enzymes cyclooxygenase (COX). In their discovery, they also found these compounds as the potential leads which were highly active in terms of inhibition against the COX-2 isozyme [65]



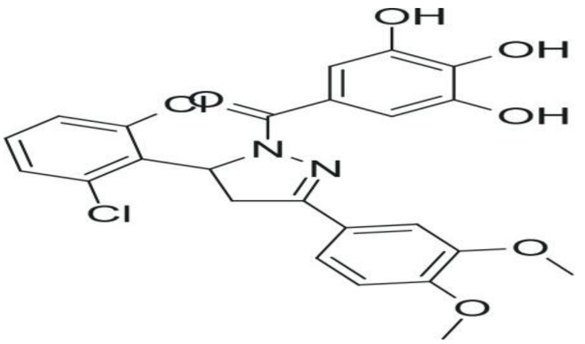
6.4.2 (2012) - Awati et al. The findings in this paper were very important in the structural component that was necessary to induce a potent anti-inflammatory effect. The researchers were able to develop p -amino benzene sulphonyl 1, 2-pyrazines derivatives that incorporate a p -amino- benzene-sulfonyl group on a 1, 2-pyrazoline backbone and are highly active. When these were applied on the rat paw edema model induced by carrageenan it was proven that they were effective. has proved to possess a tremendous anti-inflammatory activity [66]





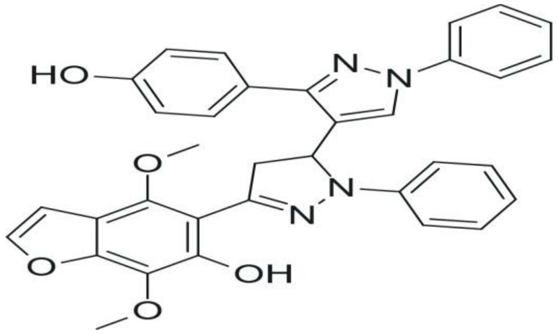
Comp code	R1	R2	R3	R4
SP1	Cl	OCH_3	-	-
SP2	Cl	CH_3	-	-
SP3	OCH_3	CH_3	-	-
SP4	Cl	OCH_3	-	OCH_3
SP5	Cl	Cl	Cl	-
SP6	Cl	OH	-	-

6.4.3 (2015) - Reddy et al. The article assumes of constructing fuzzy based algorithm on the combination of known bioactive motifs, since a group of galloyl pyrazolines were laid down. The strongest one was 5-(2, 6-Dichlorophenyl)-4, 5-dihydro- 1- (3,4, 5- trihydroxybenzoyl)- 3- (3, 4- dimethoxyphenyl)-1H-pyrazole, in which a 2, 6-dichlorophenyl group was inserted at C-5 position. This was an anti-inflammatory derivation that was highly effective in carragenan induced edema model [67].

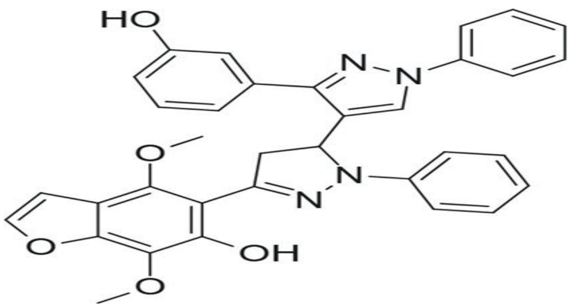


5-(2,6-Dichlorophenyl)-4,5-dihydro-1-(3,4,5-trihydroxybenzoyl)-3-(3,4- dimethoxyphenyl)-1H-pyrazole.

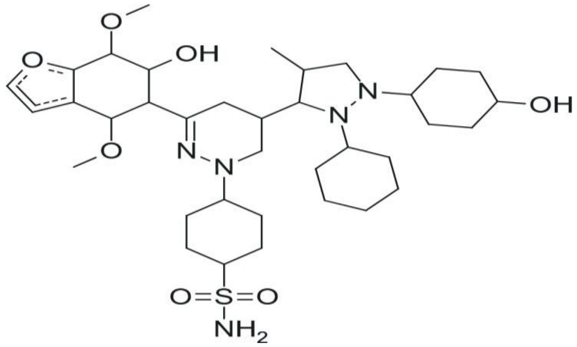
6.4.4 (2020) - Ragab et al. It was an innovative study that offered a methodological and systematic way of designing highly selective COX-2-inhibitors. The researchers could prepare multiple series of multifunctionally pyrazolylpyrazoline hybrids and concluded that those containing a benzenesulfonamide functional group were outstanding and remarkably effective selective for COX2. Compound 4d, a hybrid with hydroxy-benzo-furanyl and 4-sulfonamidophenyl groups, exhibited an outstanding COX-2 IC50 of 0.10 uM and a Selectivity Index (S.I.) of 253.00. Other highly potent analogs included Compound 4c (COX-2 IC50 = 0.11 uM, S.I. = 224.26), Compound 8e (COX-2 IC50 = 0.10 uM, S.I. = 218.3G), and Compound 8f (COX-2 IC50 = 0.0G uM, S.I. = 223.64). Crucially, these potent compounds showed strong in vivo anti-inflammatory activity, were devoid of ulcer-causing effects, and even demonstrated a significant gastroprotective effect [38].



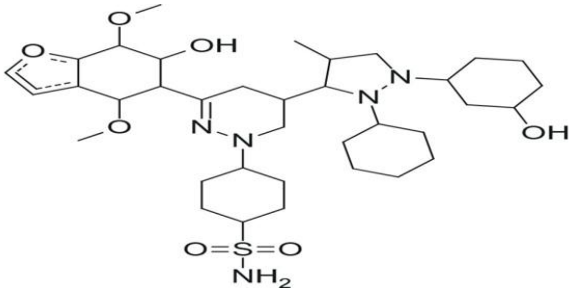
5-(4,5-Dihydro-5-(3-(4-hydroxyphenyl)-1-phenyl-1H pyrazol-4-yl)-1-phenyl-1H- pyrazol-3-yl)-4,7-di methoxybenzofuran-6-ol.



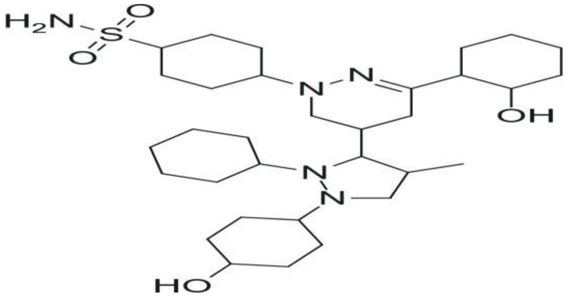
5-(4,5-Dihydro-5-(3-(3-hydroxyphenyl)-1-phenyl-1H pyrazol-4-yl)-1-phenyl-1H- pyrazol-3-yl)-4,7-di methoxybenzofuran-6-ol.



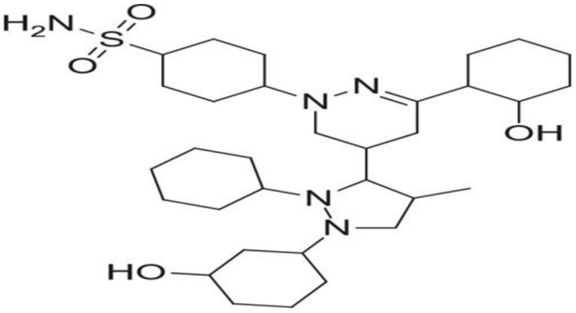
5-(1-(4-Sulfonamidephenyl)-4,5-dihydro-5-(3-(4-hydroxyphenyl)-1-phenyl-1H- pyrazol-4-yl)-1H-pyrazol-3-yl)-4,7-dimethoxybenzofuran-6-ol.



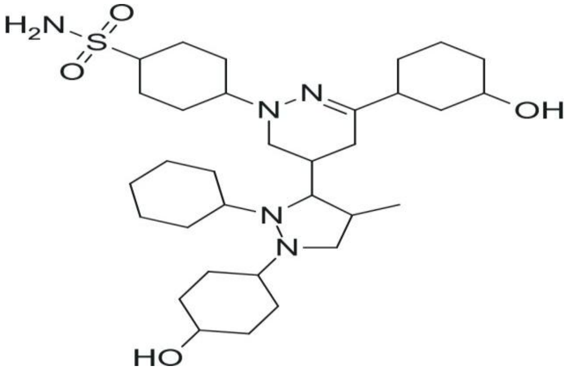
5-(1-(4-Sulfonamidephenyl)-4,5-dihydro-5-(3-(3-hydroxyphenyl)-1-phenyl-1H- pyrazol-4-yl)-1H-pyrazol-3-yl)-4,7-dimethoxybenzofuran-6-ol.



2-(1-(4-Sulfonamidephenyl)-4,5-dihydro-5-(3-(4-hydroxyphenyl)-1-phenyl-1H- pyrazol-4-yl)-1H-pyrazol-3-yl)phenol.

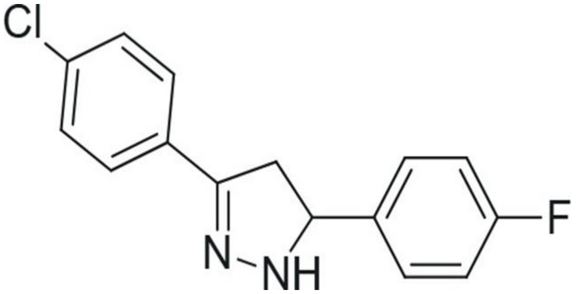


2-(1-(4-Sulfonamidephenyl)-4,5-dihydro-5-(3-(3-hydroxyphenyl)-1-phenyl-1H- pyrazol-4-yl)-1H-pyrazol-3-yl) phenol.

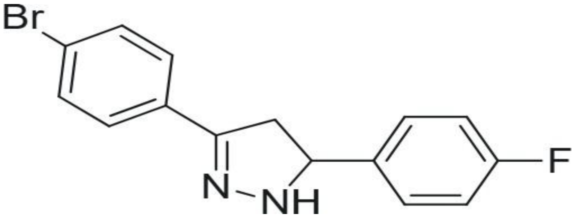


3-(1-(4-Sulfonamidephenyl)-4,5-dihydro-5-(3-(4-hydroxyphenyl)-1-phenyl-1H- pyrazol-4-yl)-1H-pyrazol-3-yl) phenol.

6.4.5 (2021) - Pontiki s Hadjipavlou-Litina This team synthesized and evaluated a series of simpler diaryl pyrazolines. They identified 3-(4-Chlorophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (Cpd 2d) and 3-(4-Bromophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole (Cpd 2e) as highly potent agents. In in vivo tests, both compounds exhibited greater anti-inflammatory and pain-relieving activity than the standard drug indomethacin [24].



3-(4-Chlorophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole.



3-(4-Bromophenyl)-5-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole.

VII. CONCLUSION

The other type of bioactive molecule rational design that has proved to be very efficient is the substitution of the chalcones with the derivatives of pyrazolines. The pyrazoline pharmacophore has distinct virtues compared to its precursors such as improved pharmacokinetic properties and increased spectrum of biological action as indicated in this review. The synthesis of experimental spectroscopy with computational modelling has been found to be fully necessary in the definition of the complex tautomeric equilibria of these forms, provisions of right structural identification.

The pyrazolines that are derived from chalcone are highly pharmacologically diverse. Their therapeutic capabilities are seen to be colossal, and this is confirmed by the literature especially where the electron- withdrawing or the electron- donating substituents are effectively located to boost the lipophilicity or the radical scavenging activity. Since this resistance to an attack on a specific microbial pathway (ex: tubulin polymerization and).

These chemicals inhibit body inflammation by the action of COX-2 and the kinase signal. portray vast proportions of elasticity. The future research should aim at enhancing such scaffolds to promote sustainable development through conducting more rigorous preclinical research and developing green synthetic paths. Finally, the chalcone pyrazolines are not yet to be stopped in this productive field in the era of the discovery of the next generation of therapeutics.

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