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A COMPREHENSIVE REVIEW OF SYNTHESIS, DOCKING TARGETS AND PHARMACOLOGICAL ACTIVITIES OF PYRAZOLINE DERIVATIVES

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Keywords:

Pyrazoline, Claisen-Schmidt condensation, Molecular Docking, Docking Targets, Biological Activity

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ABSTRACT: Pyrazolines, among the various 5-membered heterocyclic compound derivatives, have drawn attention towards it because of their various pharmacologic activities. They are nitrogenous heterocyclic compounds containing two nitrogens in the adjacent position, which possess considerable biological activity. The synthesis of pyrazolines was initiated after the pioneering work of Fischer and Knoevenagel in the late 19th century. Later, Claisen-Schmidt condensation, and Aldol-condensation, became the most popular methods for the preparation of pyrazolines nowadays. It has been an exciting area of pharmaceutical chemistry to research the biological evaluation of pyrazoline derivatives. The review provides different methods for the synthesis of pyrazolines by Claisen-Schmidt condensation, Aldol-condensation, 1,3-Dipolar Cycloaddition and its biological activities like anti-inflammatory, anti-tubercular, hypotensive, Cannabinoid CB1 Receptor Antagonist activity, anti-viral, *etc*. It also gives information regarding different possible docking targets and examples in figures. This review article will help explore novel pyrazoline analogues for challenging pathophysiological conditions.

INTRODUCTION: In the field of medicinal chemistry, heterocyclic compounds play an essential role by displaying different biological activities. Pyrazolines are emerging compounds with a range of variable properties based on the synthesis methods and molecular structure. Generally, pyrazolines can be synthesized by Claisen-Schmidt condensation of substituted aldehydes and ketone to form intermediate chalcones, which on reaction with appropriate hydrazine derivative undergo cyclization to form pyrazoline nucleus.

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Pyrazoline derivatives are electron-rich compounds in which 3-substituted pyrazolines are the most commonly seemed one. These derivatives are intramolecular charge transfer compounds and they are a kind of fluorescent brightening agents because they have a strong blue fluorescence in solutions. A large number of pyrazoline compounds are used in different synthetic methods for the preparation of other compounds. They widely occur in nature in the form of alkaloids, pigments, vitamins etc[1].

There are three known tautomeric structures for pyrazolines namely: 1-pyrazoline, 2-pyrazoline and 3-pyrazoline. Among these tautomeric structures, 2-pyrazoline is the most common and better biological activities including anti-inflammatory, anticancer, anti-diabetic, hypotensive, anti-viral, anti-malarial, anticancer *etc*.

MATERIALS AND METHODS:

Structure of Pyrazoline: Pyrazoline is a dihydropyrazole, 5-membered Heterocyclic ring with two nitrogen atoms at adjacent positions and possessing only one endocyclic double bond with a molecular formula of $C_3H_6N_2$. It is a cyclic Hydrazine moiety which is basic in nature. Modification of carbon at C_3, C_4, C_5 or nitrogen at N_1 expands the spectrum of pharmacological activity.

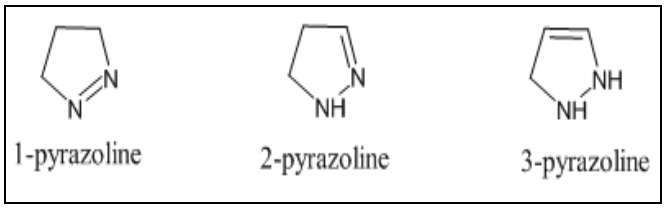

FIG. 1: DIFFERENT FORMS OF PYRAZOLINE

The structure of 5 membered dihydropyrazole ring has an envelope conformation. C_5 atom is deviated from the almost planar system of the other four atoms of the pyrazoline ring. In the conjugated part of the ring (-N_1-N_2-C_3-), the N_1 and C_3 are electron-donating and electron-withdrawing moieties respectively. The C_4 and C_5 do not conjugate with the above-conjugated part [2]. Among different forms of pyrazolines, 2-pyrazoline is the most stable because it does not lose nitrogen easily. The nitrogen atom in the ring has 2 lone pairs of electrons, so it acts as an electron donor moiety.

Physical Properties:

TABLE 1: PHYSICAL PROPERTIES OF PYRAZOLINE

Chemical Formula	$C_3H_6N_2$
Colour	White
Solubility	Insoluble in water Soluble in propylene glycol
Boiling point	10.4±23.0 °C at 760 mmHg
Density	0.9±0.1 g/cm^3
Molar refractivity	20.1±0.3 cm^3
Refractive index	1.456

Synthetic Methods for Preparation of Pyrazolines:

Claisen-Schmidt Condensation: Nahed M Eid and Riham F George synthesized various pyrazoline derivatives by the condensation reaction of 1,5-bis(5-methylfuran/thiophen-2-yl) penta-1,4-dien-3-ones and substituted hydrazine compounds [3].

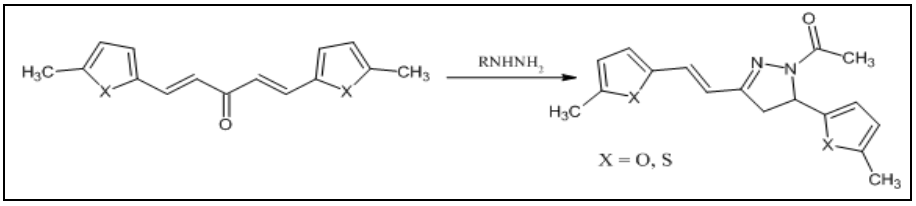

FIG. 2: SCHEME 1

Mohd. Imran Ansari and Suroor Ahmad Khan prepared quinoline-pyrazoline-based coumarinyl thiazole derivatives by the condensation of 3-(2-bromoacetyl)-6-H/halo-2H-chromen-2-ones and 5-(2- chloroquinolin-3-yl)-3-substituted phenyl-4,5-dihydro-1Hpyrazole-1-carbothiamide. The initial compound was synthesized using salicyldehyde and ethyl acetoacetate whereas the later compound was synthesized using 2-Chloroquinoline-3-carbaldehyde as the starting compound [4].

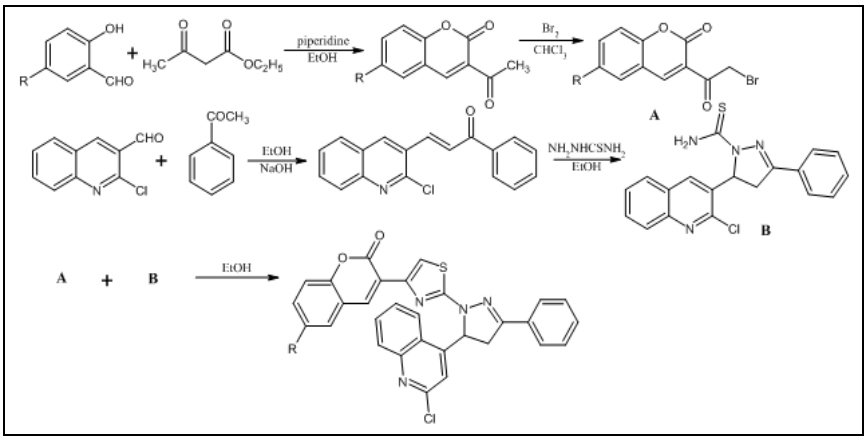

FIG. 3: SCHEME 2

Sharad C. Karad, Vishal B. Purohit synthesized pyrazoline derivatives by refluxing 2-chloroquinoline-3-carbaldehydes and morpholine to form 2-morpholinoquinoline-3-carbaldehyde subjected to base catalysed Claisen-Schmidt condensation reaction with 4- substituted acetophenones to produce the required (E)-1-(4-substituted phenyl)-3-(2- morpholino quinolin-3-yl) prop-2-en-1-ones. These chalcones were treated with hydrazine hydrate/ acetic acid to form the required product [5].

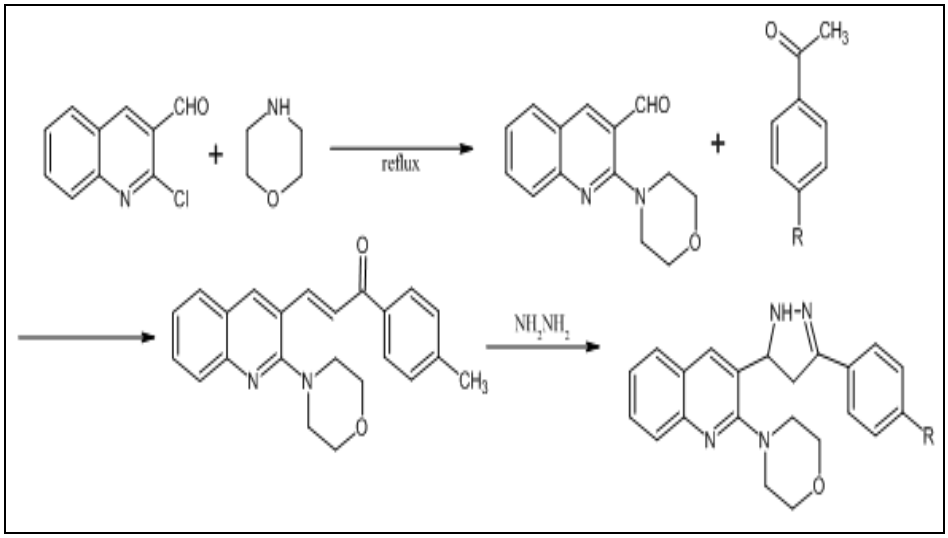

FIG. 4: SCHEME 3

A. Ahmad *et al.* synthesized 16 new pyrazolines analogues from isoniazid and phenyl hydrazine with chalcones, which in turn were prepared from p-acetamido phenol. The starting material, 3-acetyl-4-hydroxyphenyl acetamide, was prepared by heating N-(4-hydroxyphenyl) acetamide with acetic anhydride in the presence of dry pyridine followed by heating with anhydrous $AlCl_3$ [6].

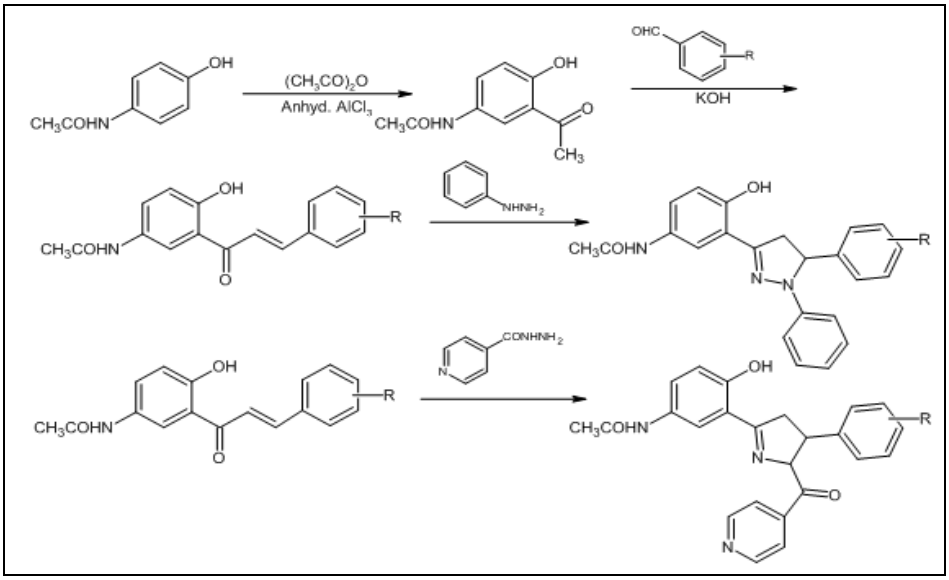

FIG. 5: SCHEME 4

N. C. Desai, Darshan Pandya, and Darshita Vaja developed benzimidazole bearing pyrazoline derivatives from naphthol with hydrazine hydrate followed by reaction of benzimidazole bearing chalcone [7].

Safaa I. Elewa *et al.* synthesized 3-(2-Thienyl)-5-aryl-1-thiocarbamoyl-2-pyrazolines by the reaction of 1-(2-thienyl)-3-aryl-2- propen-1-ones with thiosemicarbazide and sodium hydroxide in ethanol [8].

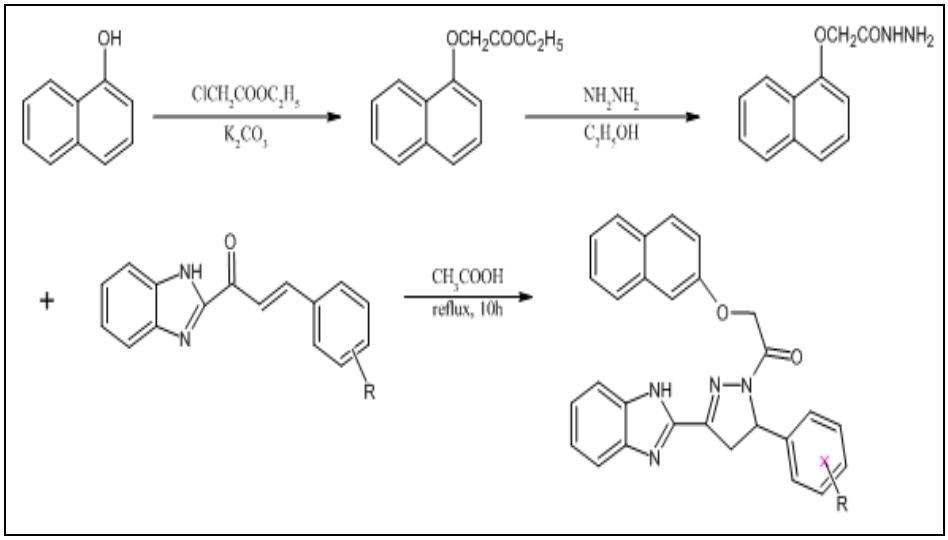

FIG. 6: SCHEME 5

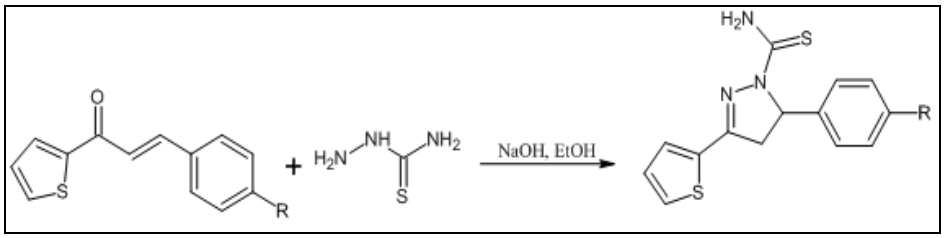

FIG. 7: SCHEME 6

Aldol Condensation: Natália Marceli Stefanes *et al.* synthesized chalcones by reacting acetophenones with aldehydes in ethanol and KOH (50% v/v), at room temperature and magnetic stirring for 24 h, and neutralized with HCl (10%v/v). The obtained chalcones were treated with acetic acid and hydrazine hydrate, refluxed under stirring for 6 h, and then poured in ice bath and neutralized with NaHCO3(aq). The formed precipitate was filtered, washed with cold water, and recrystallized in ethanol/EtOAc (80:20v/v) to give pyrazoline derivatives [9].

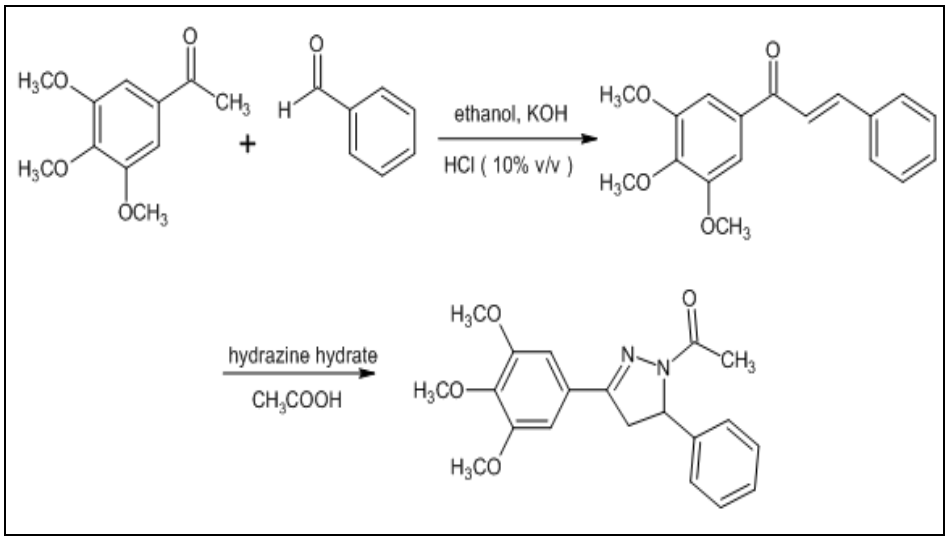

FIG. 8: SCHEME 7

Ioanna Kostopoulou, Antonia Diassakou, and Eleni Kavetsou discovered several quinolinone–chalcone and quinolinone–pyrazoline hybrids via Aldol condensation. 3-Acetyl-4-hydroxy-2-quinolinone was used as the starting material which was treated with substituted aldehydes followed by reaction with phenyl hydrazine hydrochloride to form pyrazoline hybrids [10].

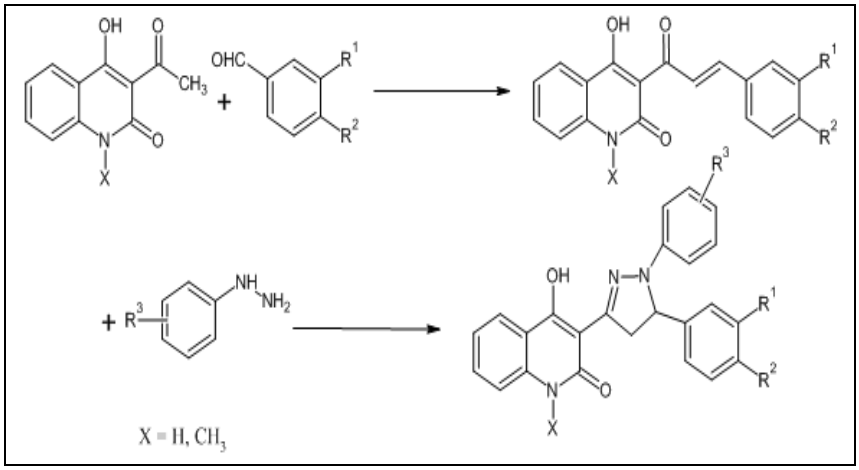

FIG. 9: SCHEME 8

Yali Songa, Siran Fenga, Jiajia Fenga Jinjiao Donga, and Kan Yang developed series of pyrazoline with thiochromen moiety contain indole skeleton using thiochroman-4-one as the reagent followed by treatment with phenyl hydrazine in the presence of triethylamine [11].

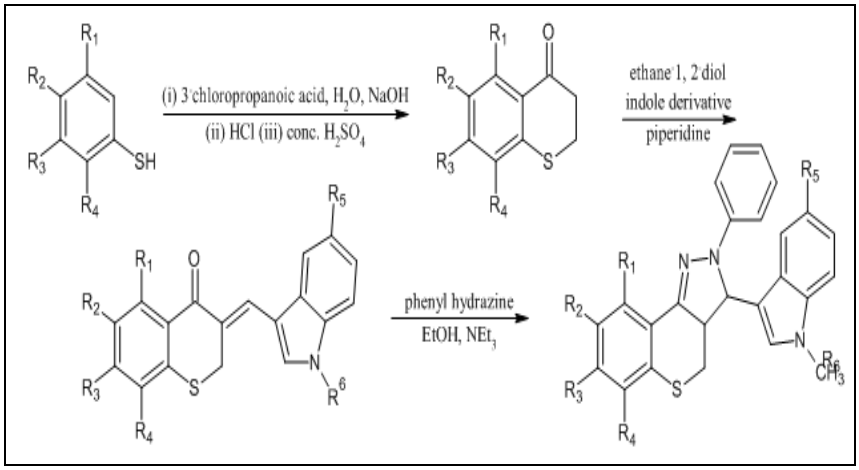

FIG. 10: SCHEME 9

Coupling Reactions: Fikret Turkan and Adnan Cetin synthesized a series of pyrazoline derivatives. Initially, the starting material, ethyl 2-((4-bromophenyl) diazenyl) -3-oxo- phenyl propanoate, was prepared as a coupling reaction of ethyl benzoyl acetate and tetra azotized solution, which was obtained 4-bromoaniline with sodium nitrite solution on the ice bath [12].

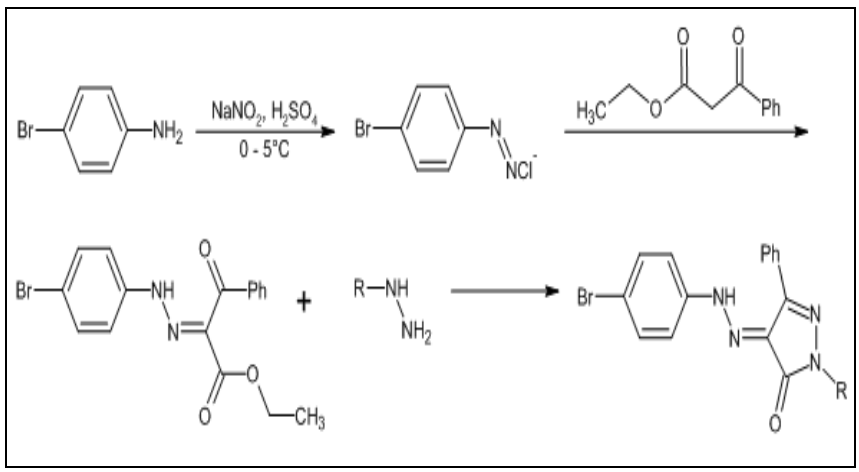

FIG. 11: SCHEME 10

Hawaiz *et al.* synthesized azo-pyrazoline derivatives using azo-benzyloxy acetophenone as the starting material which was coupled with m-cresol and benzylated with p-chlorobenzyl chloride followed by condensation with substituted benzaldehyde and phenylhydrazine in the presence of NaOH [13].

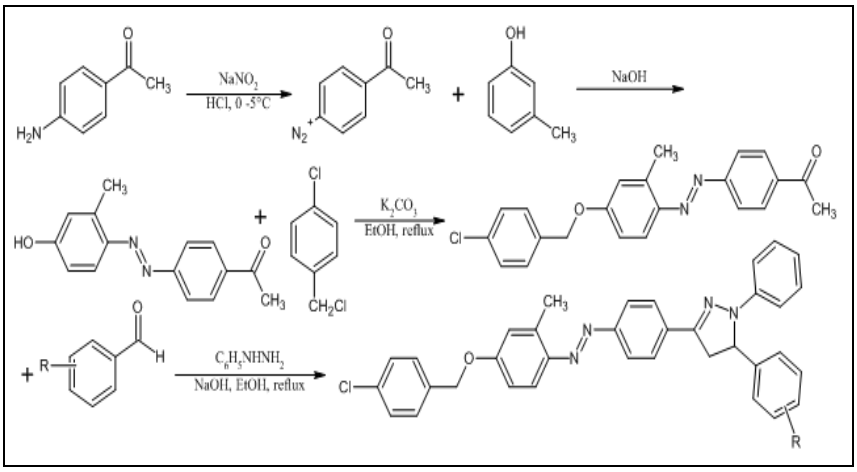

FIG. 12: SCHEME 11

1, 3-Dipolar Cycloaddition: Yi Zhong Wang, Claudia I. Rivera Vera, and Qing Lin developed mild, photoactivated polysubstituted pyrazolines between nitrile imine dipoles and alkene dipolarophiles [14].

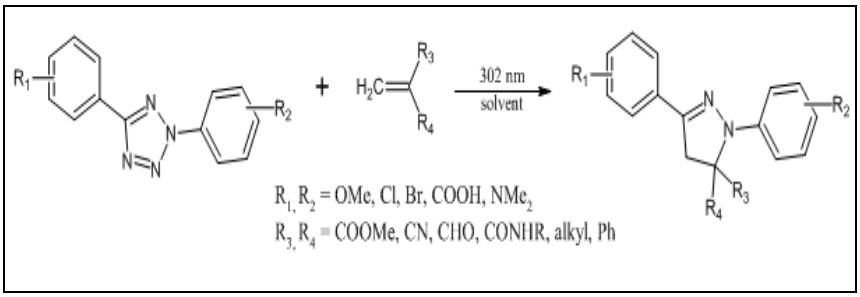

FIG. 13: SCHEME 12

Pyrazolines and their Docking Targets:

TABLE 2: DOCKING TARGETS OF PYRAZOLINE

Sl. no.	Target	PDB: ID	Activity
1	Human Carbonic anhydrase inhibitor I (hCA I)	2FW4	Carbonic anhydrase inhibitory activity [12]
	Human Carbonic anhydrase inhibitor II (hCA II)	5AML	
	Acetylcholinesterase (AChE)	4TVK	
2	EGFR kinase	1M17	Anticancer activity [15]
3	Monoamine oxidase (MAO)	2BYB; 2BXR	Antidepressant activity [16]
4	Tyrosine kinases (RTKs)	1UOM	Anticancer activity [17]
5	Monoamine oxidase-A (MAO-A)	2BXS	Antidepressant activity [18]
	Monoamine oxidase-B (MAO-B)	1S3E	
6	Cyclooxygenase-2 (COX-2)	1CX2; 4COX	Anti-inflammatory activity [19]
7	Cyclin-dependent kinase 2 (CDK2)	2A4L	Anticancer activity [20]
8	Soybean LOX	3PZW	Anti-inflammatory activity; Antioxidant [10]
9	COX-2	1CX2	Anticancer activity [21]
10	Arylamine n-acetyltransferase	1W6F	Antimicrobial activity [22]
	Dihydrofolate reductase	4HOE	
	Cobalamin-independent methionine synthase	4L6H	
11	Topoisomerase	ISC7	Anticancer activity [23]
12	Enoyl-acyl carrier protein reductase (ENR)	4TZK	Antibacterial and Antitubercular activity [24,25]

13	DNA topoisomerase I	5GWK	Anticancer activity [11]
14	VEGFR-2 kinase	4ASD	Anticancer activity [26]
15	Oestrogen receptor (ERα and ERβ)	3ERT	Anticancer activity [27]
16	PfATP4	2DQS	Anti-malarial activity [28]
17	DNA Topoisomerase IV	4EMV	Antimicrobial activity [29]

Pharmacological Activity of Pyrazoline Containing Compounds:

Anti-inflammatory Activity: N. A. Khalil *et al.* synthesized 5-aryl-3-cyclopropyl-4,5-pyrazoline derivatives and investigated their anti-inflammatory/antioxidant activities. The developed structures were characterised by elemental and spectral analysis. The free radical scavenging activity toward superoxide was determined. All the results showed that 1a and 1b **Fig. 14** showed highest free-radical scavenging and anti-inflammatory activities which can be further useful for the prevention of oxidative stress and inflammation-related disorders [30].

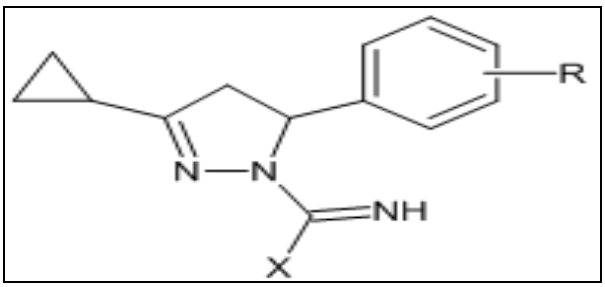

FIG. 14: 1A AND IB, CYCLOPROPYL PYRAZOLINE DERIVATIVE

TABLE 3:

No.	R
1a	-4-Cl, X= S
1b	-4-$(CH_3)_2$N, X = O

Suman *et al.*synthesized 1-acetyl-3,5-diaryl-2-pyrazolines using substituted benzaldehyde and acetyl indole. These acetylated pyrazolines, 2a **Fig. 15** were evaluated for anti-inflammatory activity by membrane stabilization method, which showed good stabilization of RBC membrane [31].

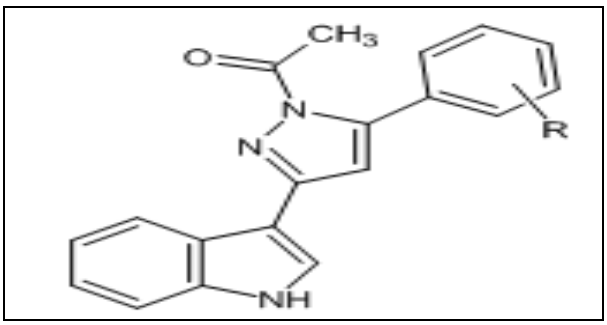

FIG. 15: 2A, ACETYLATED PYRAZOLINES

Rathish *et al.* synthesized 2-pyrazoline-bearing benzene sulphonamide derivatives and screened them for their anti-inflammatory activity. These synthesized derivatives, **3a Fig. 16,** were more active than the standard celecoxib [32].

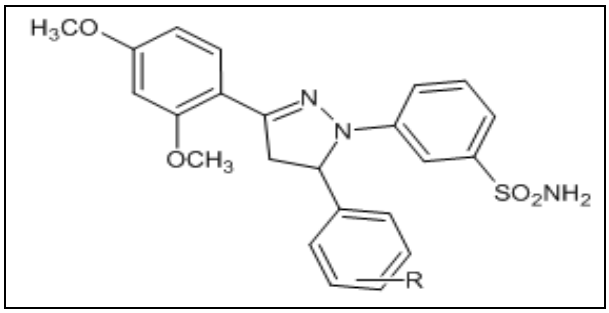

FIG. 16: 3A, PYRAZOLINE DERIVATIVES

Antioxidant Activity: Vidyashree H. S. Jois, Balakrishna Kalluraya and Kotathattu S. Girisha prepared a series of N-acetyl-3-aryl-5-(5-(p/o-nitrophenyl) - 2 - furyl// thienyl) - substituted pyrazolines in acidic medium and screened for their antioxidant activity. IR, 1H-NMR, mass spectra and a single-crystal X-ray study established the structures. Compounds 4a, 4b, 4c and 4d found moderate activity using DPPH scavenging assay [33].

TABLE 4:

No.	R	R_1
4a	p-NO_2	P-CH_3
4b	p-NO_2	p-NO_2
4c	o-NO_2	P-CH_3
4d	p-NO_2	m-NO_2

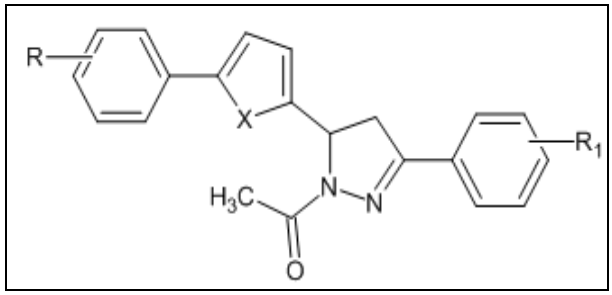

FIG. 17: 4A, 4B, 4C AND 4D, SUBSTITUTED PYRAZOLINES

Hypotensive Activity: Gülhan Turan-Zitouni developed 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazoline derivatives using phenyl acetyl bromide.

The structural characterization of developed compounds was done using IR, 1H-NMR and Mass spectral data and elemental analyses. Compound 5a showed better hypotensive activity in the tail-cuff method when compared to standard clonidine [34].

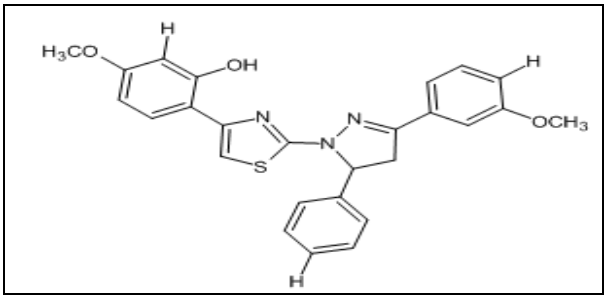

FIG. 18: 5A, THIAZOLYL PYRAZOLINES

Anti-tubercular Activity: M.A. Ali *et al.*developed novel pyrazoline derivatives by condensation reaction. The synthesized compounds evaluated for in vitro anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system. Compound 6a was found to be more active against *Mycobacterium tuberculosis* with minimum inhibitory concentration of 0.0034 µM [35].

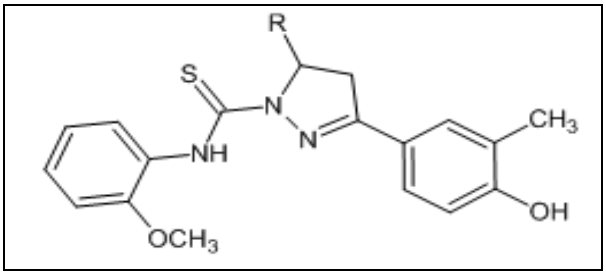

FIG. 19: 6A, PYRAZOLINE DERIVATIVES

Shivani Pola *et al.* developed naphthyl pyrazolines which were characterized by IR, NMR, and mass spectrometric analysis and screened for antimycobacterial activity against *Mycobacterium tuberculosis H37Rv* (ATCC 27924). Compound 7a showed significant antimycobacterial activity with MIC of 6.25 µM comparable to that of standard isoniazid [24].

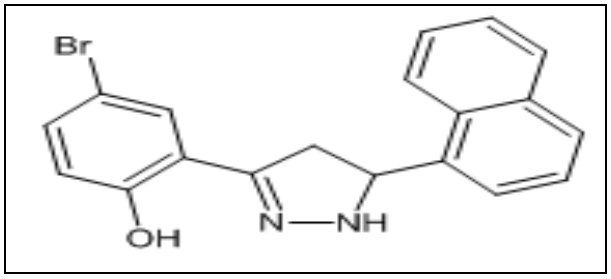

FIG. 20: 7A, NAPHTHYL PYRAZOLINE

Antiviral Activity: Yar *et al.* synthesized a variety of pyrazoline derivatives using phenoxy acetic acid which were evaluated for their *in-vitro* cytotoxicity and antiviral activity. Among them, compound 8a found to be maximum cytotoxicity [36].

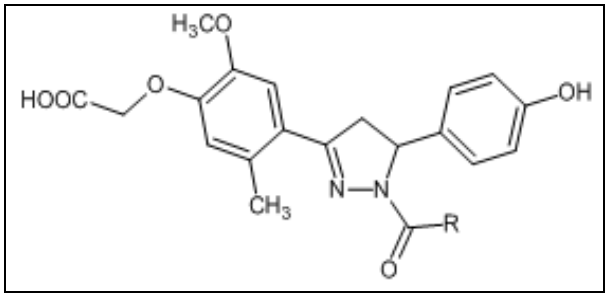

FIG. 21: 8A, PYRAZOLINE DERIVATIVE

Cannabinoid CB1 Receptor Antagonists: Lange *et al.* developed 3,4-diarylpyrazolines derivatives and evaluated their cannabinoid CB1 receptor antagonistic activity with lipophilicity lower than that of SLV319. Compound 9a exhibited the highest CB1 receptor affinity as well as potent CB1 receptor antagonist and selectivity [37].

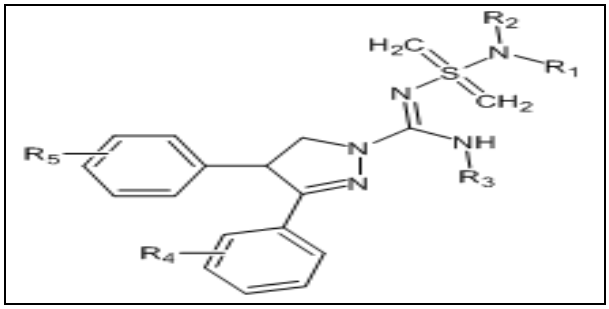

FIG. 22: 9A, DIARYL PYRAZOLINE DERIVATIVES

Srivastava *et al.* synthesized a series of diaryl dihydropyrazole-3-carboxamides and evaluated them for appetite suppression and body weight reduction in animal models *in-vivo*. Compound 10a reported the highest CB1 receptor affinity (Ki = 24 nM) and also potent CB1 antagonistic activity (pA_2 = 8.8) and a high CB1/CB2 subtype selectivity (∞147-fold) [38].

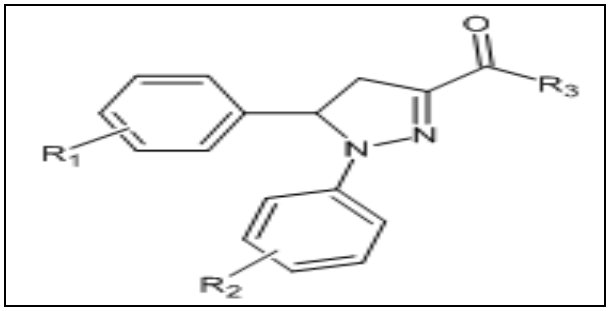

FIG. 23: 10A, PYRAZOLINE DERIVATIVES

Anti-candidal Activity: Mashooq Ahmad Bhat, Abdul Arif Khan, Mohamed A. Al-Omar and Azmat Ali Khan synthesized pyrazoline derivatives and evaluated their anti-candidal activity against various strains of Candida species. The structures were confirmed by FT IR, ^{1}H NMR, ^{13}C NMR and MS spectral data. Compound 11a was found to be most potent antifungal agent against Candida strains [39].

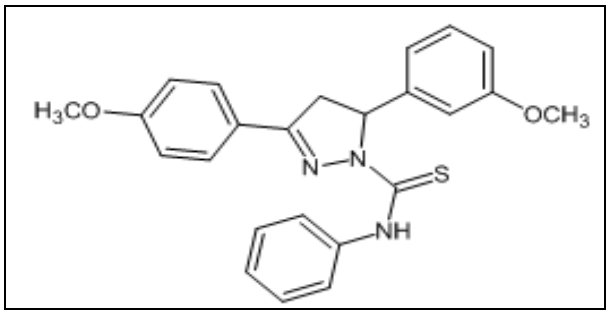

FIG. 24: 11A, PYRAZOLINE DERIVATIVES

CONCLUSION: Pyrazolines are compounds which having significant biological activities. There are many reactions for the synthesis of these compounds. Among them, Claisen-Schmidt condensation are used for the convenient synthesis. Pyrazoline nucleus plays very important role in the heterocyclic chemistry. It possesses various biological activity, including anti-inflammatory, anti-tubercular, antioxidant, anti-viral *etc*. Pyrazoline analogues show better therapeutic effect and less toxicity. The review provides different synthetic methods, diverse docking targets and biological activity.

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CONFLICTS OF INTEREST: There are no conflicts to declare.

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