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REVIEW ARTICLE

4,5-Dihydro-1*H*-pyrazole: an indispensable scaffold

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Abstract

Pyrazoles, categorized as nitrogen-containing heterocycles, are well known for their interminable participation in the field of perpetual research and development of therapeutical active agents. As a consequence pyrazoles became an inevitable core of numerous drugs having diverse activities. The broad spectrum of activities portrayed by the pyrazoles instigated the researchers to modify the pyrazole ring as 4,5-dihydro-1*H*-pyrazoles commonly known as 2-pyrazolines. The present review is a concerted effort to retrace compounds covered from 2009-till date which owe diverse biological activities to the 2-pyrazoline scaffold and also condenses the retro-synthetic approaches employed for their synthesis. This endeavor culminated in revelation that inhibitory potential varied when the substituents in particular *N*-substituents of 2-pyrazolines were altered.

Keywords

4,5-Dihydro-1*H*-pyrazole, biological activities, synthesis

History

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Introduction

Even though ''pyrazoles'' had been known since the 19th century when Ludwig Knorr coined the term, the first natural pyrazole β-(1-pyrazolyl) alanine, was isolated after 75 years in 1959 from the seeds of *Citurllus lanatus*. Pyrazoles (Figure 1) although are resistant to oxidizing and reducing agents, are known to undergo catalytic hydrogenation to pyrazolines (2-pyrazoline) in particular 4,5-dihydro-1*H*-pyrazole (Figure 1)[1].

Pyrazolines considered as cyclic hydrazine moiety[2] possess an endocyclic double bond[3,4]. In comparison to pyrazoles, pyrazolines are stronger bases, less stable and behaving more like unsaturated compounds. These nitrogen containing heterocycles[5] are colorless liquid which have their boiling point in the range of 120–150 °C[1]. Among various derivatives of pyrazolines, 4,5-dihydro-1*H*-pyrazole or 2-pyrazoline have been observed to be the most common derivatives[6] found to be insoluble in water but owing to its lipophilic character[7] soluble in propylene glycol. These electron rich nitrogen heterocycles[8] can be subjected to reduction or oxidation[9]. On reduction 2-pyrazolines either yield pyrazolidines or undergo ring cleavage; and when oxidized they form blue or red coloring matter[1]. The conjugated part of the ring (–N1–N2–C3–) includes an electron donating and electron withdrawing moieties within it. As observed from the X-ray analysis, all the atoms but C_5 of the pyrazoline ring adopt a planar system[10] and this deviated atom is known to play a crucial role in the development of theory in heterocyclic chemistry[11,12]. 2-Pyrazolines absorb light in the range 300–400 nm and emit blue fluorescence owing to the two nitrogen atoms in the heterocyclic ring[13,14] and also as a consequence of the double bond hindering which occur as a result of cyclization[15,16]. 2- Pyrazolines owing to these properties[17] have been exploited in the synthesis of synthetic fibers, fluorescent probes, in electro photography and electroluminescence.

The pyrazolines find their application as alkaloids, vitamins, pigments, and so on[18]. Antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) was the first pyrazoline derivative used in the management of inflammation and pain[19]. The presence of this moiety in several therapeutically active compounds encouraged the researchers in the direction of design and synthesis of novel pyrazoline derivatives possessing myriad activities. Some of the activities that pyrazolines exhibit are anticancer[20,21], antitumor[22], anti-androgenic[23], antioxidant[24], antimicrobial[25–27], antiviral[28], antitubercular[29,30], antimalarial[31], anti-amoebic[32,33], COX-II[34,35], monoamine oxidase[36,37], xanthine oxidase[38]and amine oxidase[39] inhibitory, and so on. With an incentive to improve the existing activities several modifications are being done on this scaffold and many of which are proved to be successful. The most extensive modification in 2-pyrazoline was the substitution of diaryl/hetroaryl groups mainly at -3, 5 position[40] since it was observed that heterocycles with functional groups greatly increased solubility in water[41,42]. The aryl substituted pyrazolines were detected to combine the activity of pyrazoline moiety with activity of heteroarene thus proving their usefulness[43]. The perpetual research carried out revealed the indispensable role *N*-substituents of pyrazoline play in exhibiting the biological activity. As the substituent changes, a particular activity is altered either completely or to a certain extent. Substitution on the carbon of pyrazoline also modified the biological activity but activity altered significantly with the variation in Y which may be acetyl, amide, phenyl, and so on. R_1, R_2 and R may be any alkyl, aromatic or hetero-aromatic substituent (Figure 2).

An exclusive review put forward by Suresh Kumar et al.[44] in the year 2009 encompassed the 2-pyrazoline derivatives

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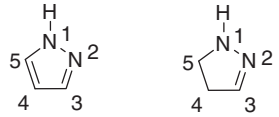


(1) (2)

Figure 1. Pyrazole and 4,5-dihydro-1*H*-pyrazole.

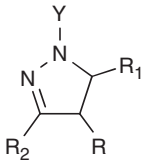


Figure 2. Various substitutions on pyrazoline ring.

synthesized from 2005 to 2009 giving a lucid picture of their biological activities. In 2010, Rahman et al.[11] comprehended the biological activities of 2-pyrazoline derivatives from 2000 to 2008. In 2011, M. Yusuf et al.[18] compiled together the biological activities and different synthetic strategies of the pyrazoline derivatives from 2007 to 2011. Recently, Dipankar Bardalai et al.[1] congregated the information on the pyrazoline derivatives synthesized (1993–2011) as anti-inflammatory and analgesic agents. The present review highpoints the pyrazoline derivatives synthesized from 2009 till date with an inducement to fathom the crucial role that substituents in particular *N*-substituents play in determining the biological activity. It also summarizes some of the retro-synthetic approaches employed for the synthesis of pyrazolines. In this manuscript, with the aid of SAR studies and inhibitory potential of the compounds, we have sought to establish the relationship between the *N*-substituents and the biological activities.

Synthetic strategies

Research over the years has led to the development and introduction of several synthetic routes for the efficient synthesis of pyrazolines. Mostly the starting materials required to prepare pyrazoline compounds are obtained either via Claisen-Schmidt condensation or through synthesis of 1,3-dicarbonyl compounds. Some of the retro-synthetic approaches for the construction of pyrazolines have been sketched in Figure 3. One of the strategies involved is the parallel solution phase synthesis of **1** which involves the use of polymer bound bases A and B as depicted in route **A**[45]. Although routes **B** and **G** use the same reactants **3**, route **B** follows microwave irradiation[46] unlike route **G** in which the reactants are subjected to heating at 120 °C. Route **B** employed an efficient, rapid, and green synthesis under solvent-free conditions in the presence of scandium triflate [$Sc(OTf)_3$] resulting pyrazoline (**1**) in yield ranging from 74 to 92% in 5 min and silica chloride (route **G**) catalyzed one pot cyclocondensation[47] afforded yield of 80% in 2 h. Suzuki-Miyaura reaction[48] exploiting Pd $(OAc)_2$ (5 mol %) as a catalyst in the presence of SPhos (10 mol %) in an aqueous solution of K_2CO_3 (2 M) (route **C**) afforded pyrazoline in 60–66% yield in 8 h. Yet another strategy employed included solvent-free synthesis[49] as in route **D** which used equivimolar concentration of methanesulphonic acid and **5** at 80 °C giving a yield of 95% in 45 min. Route **E** followed asymmetric synthesis[50] through an enantioselective phase transfer organocatalytic addition of *N*-Boc hydrazine to **2** followed by a transprotection sequence allowing *N*-Boc transformation into *N*-Ac or other functional groups resulting in **1**. Route **F** followed a simple yet highly efficient and environment friendly one-pot condensation reaction[51] of **6** with tosylhydrazide in water yielding 74–92%. Route **H** followed a region-selective synthesis of **1**[52] by acylation of *N*-Boc-*N*-methylhydrazones followed by TFA giving a yield of 95–98%.

Classification of pyrazolines

We have categorized various 2-pyrazolines into three classes on the basis of the nature of substituents (Y) at *N*1 position of pyrazoline as shown in Figure 4. An effort has been made to put forward certain examples in this review portraying the modification in bioactivity as a consequence of alteration of the substituents.

Class I

The compounds pertaining to this class are shown to exhibit the following activities:

Anticancer activity

Zeinab H.I. and her group[53] synthesized and evaluated 3,5-diaryl-Δ^2-pyrazoline derivatives for their anticancer activity against the human colon (HCT-116) and breast (MCF-7) cancer cell lines. The structure–activity relationship studies of these compounds (Table 1) threw light on how substituents affect the change in biological activity. On one hand where the phenyl substitution on *N*1 decreased the anticancer activity (**5C1**, **5C2**), the *N*-acetyl substitution (**5B1**) showed promising results for HCT-116 cell line. In the absence of substitution on *N*1 of the pyrazoline ring, these compounds owed their anticancer activity to the phenyl ring and its substitution placed at C5 of the pyrazoline ring. If the presence of an electron withdrawing group (**5A1**) on the phenyl ring increased the activity towards MCF-7 cancer cell line, the electron donating group (**5A2**) shifted the spectrum of activity towards HCT-116 cell line.

A.H. Banday et al.[54] synthesized 17-pyrazolinyl derivatives of pregnenolone and evaluated the same against a panel of cancer cell lines - HT-29, HCT-15, 502713, HOP-62, A-545, MCF-7, SF-295. The structure–activity relationship studies along with the data obtained through IC_{50} values (Table 2) indicated *m*-fluro (**6C**) substitution to be significant for the anticancer activity against HT-29, HCT-15, 502713, HOP-62, *o*-chloro (**6E**) substitution to be promising against HT-29 and HCT-15 and similarly good activity against 502713, MCF-7 and SF-295 was attained when the phenyl ring at C5 of the core moiety was left unsubstituted (**6A**). An increase in IC_{50} values resulted as a consequence of substituted heterocyclic ring at C5 (**6B**) or with *p*-OMe (**6D**) thus leading to decrease in anticancer activity.

T. Liu et al.[55] synthesized a series of *cis*-restricted 4,5-diaryl-3-aminopyrazole and tested these compounds for their anticancer potential against five human cancer cell lines namely K562, ECA-109, A-549, SMMC-7721 and PC-3 (Table 3). Substitution of trimethoxy group on ring A (**7A**) led to a greater increase in anticancer activity than when present on ring B (**7B**). Replacement of 3,4,5-trimethoxy phenyl ring (**Ring B**) with 4-chloro phenyl ring (**7C**) resulted in a substantial increase in the activity as exhibited by the IC_{50} values. The substituted phenyl ring proved to be indispensable for activity because when ring B was substituted with a thiophene ring the activity was reduced considerably.

C. Congiu et al.[56] synthesized and put efforts to test a series of novel 4, 5-dihydro pyrazole based combretastatin analogs for their anticancer potential. The structural–activity relationship and IC_{50} values (Table 4) helped in concluding that 3,4,5-trimethoxy group at the C5 (**8B**) showed better activity than when it was present at C3 of the dihydropyrazole core (**8A**), that is, when the moiety is in the same plane as the *N*-acetyl group. Thus, the modifications

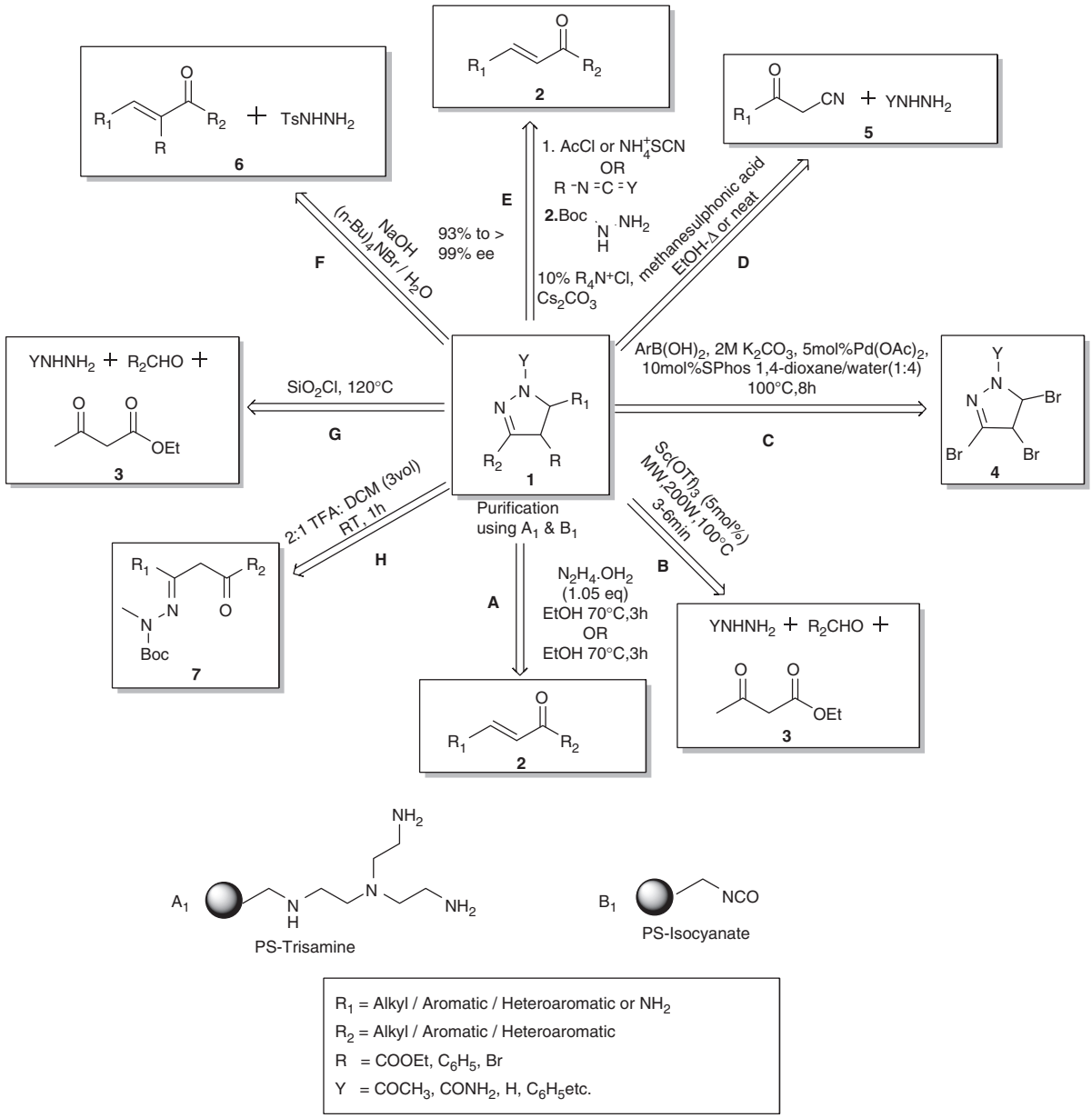


Figure 3. Retrosynthetic approach for the synthesis of pyrazoline derivative.

were carried out on ring A keeping the substituent on ring B constant. Some of these modifications led to increase the activity whereas others shifted the spectrum of activity in the opposite direction. Substitutions involving the amino group (**8B3**, **8B4**, **8B7**), methyl group (**8B5**, **8B2**) and halogens (**8B6**) showed promising activity. The derivatives with methoxy substituent (**8B1**) were found to be devoid of any activity. Hydroxyl substitution at C4 of ring A (**8B9**) furnished the most active compound of the series.

FabH inhibitory activity

Fifty-six analogues of 1-acetyl-3,5-diphenyl-4,5-dihydro-(*1H*)-pyrazole were synthesized by P.C. Lv et al.[57] and evaluated for their potential to be used as FabH inhibitors. The minimum inhibitory concentration (MIC) values and the SAR studies (Table 5) highlighted electron releasing group on ring A and electron donating groups on the ring B essential for FabH inhibitory activity of *E. coli* (**9A** and **9B**) and MIC value decreased if these substitutions were interchanged (**9C**). Dihalogen substitution on ring A (**9D**) showed significant FabH inhibition of *Bacillus subtilis*. These observations were further confirmed by carrying out molecular docking of the potent inhibitor into the active site of FabH of *E.coli*.

COX-II inhibitory activity

R. Fioravanti et al.[58] synthesized 18 analogous of 1-*N*-substituted-3,5-diphenyl-2-pyrazoline derivatives and evaluated the cyclooxygenase activity of these compounds. They synthesized compounds in which the *N*1 of pyrazoline was substituted with either acetyl moiety or thiocarbamoyl moiety. The SAR studies and the IC_{50} values (Table 6) revealed that compounds with *N*-acetyl group were more potent than those having thiocarbomyl group (**10A** and **10B**). The molecular docking studies conducted highlighted the importance of 4-methanesulphonyl group on the phenyl ring at C5 for the COX-II inhibitory activity.

Anti-inflammatory activity

B.P. Bandgar et al.[59] synthesized 3-(substituted)-aryl-5-(9-methyl-3-carbazole)-1*H*-2-pyrazolines and screened these compounds for

Figure 4. Various N-substitutions on the pyrazoline ring.

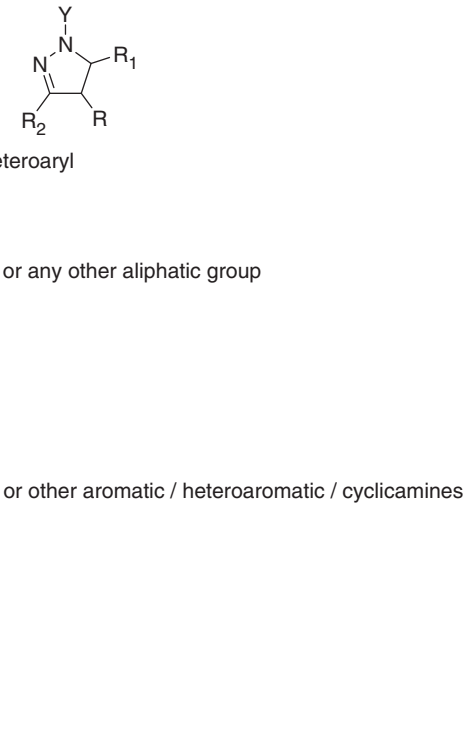
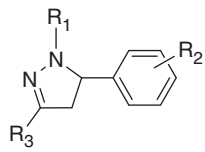
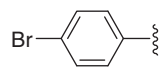
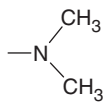
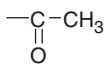


Table 1. Structural modification on 2-pyrazolines.



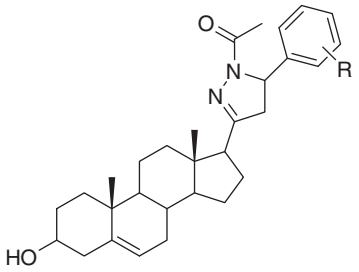
Compound	R_1	R_2	R_3	IC_{50} (μM) HCT-116	IC_{50} (μM) MCF-7
5A1	H	F		–	3.43
5A2				7.09	–
5B1		*o*-CI		6.8	12
5C1		F		–	16.5
5C2		NO_2		10.3	–

their antioxidant and anti-inflammatory potential (Table 7). The selectivity of these compounds for COX-II and commendable activity shown by these compounds were attributed to the presence of carbazole moiety. Substitution of electron withdrawing group on the aryl ring enhanced the antioxidant activity resulting via the DPPH radical scavenging (**11D** and **11E**) while the presence of electron donating group resulted in an increase of the anti-inflammatory effect (**11A** and **11B**). These studies also outlined the fact COX-II inhibitory activity increased tremendously in substituting the aryl ring at C5 with a thiophene (**11C**) or pyridine ring. Molecular docking studies accompanied by the team proved the credibility of these observations.

Antidepressant and anticonvulsant activity

N-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivative synthesized by Z. Ozdemir and his team[60] proved their potential as antidepressants and anticonvulsants by Porsolt's behavioral despair and maximal electroshock (MES) & subcutaneous pentylenetetrazole (scMet), respectively.

Table 2. Structural modification on steroidal based 2-pyrazolines.



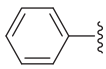
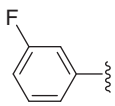
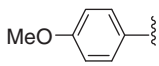
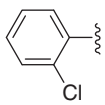
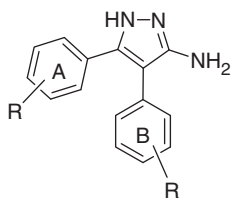
Compound	R	IC_{50} (μM) HT-29	HCT-15	502713	HOP-62	A-545	MCF-7	SF-295
6A		6.35	2.31	0.56	1.46	11.0	0.43	0.63
6B		11.8	23.4	44.2	50.0	48.1	ND	50.6
6C		0.44	0.53	0.32	0.50	1.42	1.60	3.79
6D		2.37	21.8	28.5	32.9	29.2	23.1	49.5
6E		0.24	0.25	37.0	50.0	32.2	17.5	30.2

Table 3. Structural modification on 3-amino based pyrazole derivatives.



Compound	Ring A	Ring B	Cytotoxicity (IC_{50}, μM) K562	ECA-109	A549	SMMC-7721	PC-3
7A	3,4,5-$(OCH_3)_3$	4-OCH_3	0.08 ± 0.04	12.01 ± 2.45	1.38 ± 0.94	12.07 ± 2.66	6.95 ± 0.74
7B	4-OCH_3	3,4,5-OCH_3	ND	25.04 ± 6.25	40.38 ± 3.21	ND	7.68 ± 5.27
7C	3,4,5-$(OCH_3)_3$	4-Cl	0.31 ± 0.16	8.00 ± 1.35	6.03 ± 2.51	13.79 ± 5.24	0.61 ± 0.53

The compounds in the series owed their antidepressant and anticonvulsant activity to the thiocarbamoyl substitutent at *N*1 of the pyrazoline. Furthermore, anticonvulsant activity was enhanced several folds by substituting 2-furyl ring at C5 of pyrazoline with (**12B** and **12C**) as represented in Table 8.

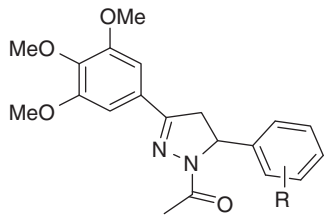
Xanthine oxide inhibitory activity

Our research group[40,61] synthesized 53 analogues of 1-acetyl-3,5-diaryl-4,5-dihydro (1*H*) pyrazoles and evaluated their xanthine oxidase activity using bovine milk xanthine oxidase enzymatic assay. Structure–activity relationships study and IC_{50} values (Table 9) observed and confirmed by the molecular docking studies revealed that the replacement of phenyl (**Ring A**, **13A**) with naphthalene ring (**13B**) increased the activity, which on replacement with 2-furyl ring resulted in further enhancement of XO inhibitory activity (**13C**). Replacement of ring B with 1-naphthyl (**13F**) resulted in decrease in activity. Replacement of phenyl with anthranyl ring resulted in complete loss of activity. Moreover, substituents on ring B also influenced the extent of activity. Deactivating groups such as nitro (**13E**) and halogens increased the xanthine oxidase inhibitory activity whereas activating group such as methoxy (**13D**) or *N, N*-dimethyl resulted in decrease in activity. Absence of *N*-acetyl substitution led to loss of the biological activity of the compound, thus making the importance of this moiety irrefutable.

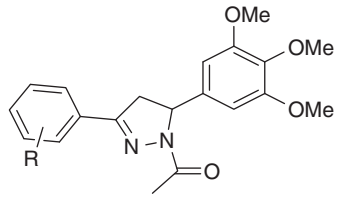
MAO inhibitory activity

N-substituted-3-[(2′-hydroxy-4′-prenyloxy)-phenyl]-5-phenyl-4,5-dihydro-(*1H*)-pyrazolines in particular pyrazoline N-substituted with either thiocarbamoyl or acetyl group, synthesized and

Table 4. Structural modifications on N_1-acetyl derivative of pyrazolines and their anticancer activity against NCIH-460 cancer cell line.



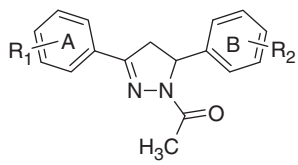
A



B

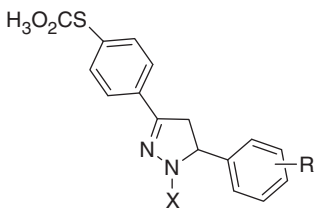
Compound	R	NCIH-460 IC_{50} (μM)
8B1	4-MeO	>20
8B2	4-MeS	8.0 ± 0.1
8B3	4-NH_2	2.6 ± 0.1
8B4	4-Me_2N	1.8 ± 0.06
8B5	4-Me	1.3 ± 0.05
8B6	3-Br	0.35 ± 0.01
8B7	3-NH_2	0.74 ± 0.33
8B8	3-OH	2.3 ± 0.06
8B9	3-MeO-4-OH	0.21 ± 0.005

Table 5. Antimicrobial activities of N_1-acetyl pyrazolines.



			MIC (μg/mL)					
			Gram positive			Gram negative		
Compound	R_1	R_2	*B. subtilis ATCC 6633*	*S. aureus ATCC 6538*	*S. faecalis ATCC 9790*	*P. aerug-inosa ATCC 13525*	*E. coli ATCC 35218*	*E. cloacae ATCC 13047*
9A	4-OCH_3	4-F	6.25	6.25	1.562	12.5	0.39	12.5
9B	4-OCH_3	4-Cl	6.25	25	6.25	25	0.78	25
9C	4-Cl	4-OCH_3	12.5	>50	25	25	25	>50
9D	3,4-Cl	4-Cl	0.78	25	6.25	25	25	>50

Table 6. COX-II inhibitory activity of some N_1-substituted pyrazoline.



Compound	R	X	IC_{50} (μM)
10A	2-OCH_2Ph	$COCH_3$	3.20 ± 0.24
		$CSNH_2$	Inactive at a conc. 25μM
10B	4-CH_3	$COCH_3$	6.77 ± 0.48
		$CSNH_2$	31.85 ± 2.57

evaluated by R. Fioravanti et al.[62] for their potential to inhibit monoamine oxidase (Table 10). Compounds bearing acetyl substitution at *N*1 exhibited better activity (**14A** and **14B**) than with thiocarbamoyl group (**14C** and **14D**). SAR studies highlighted that irrespective of the *N*1 substituent; benzyloxy substitution enhanced the MAO inhibition (**14A** and **14C**) whereas methyl or methoxy group led to a complete loss of activity (**14B** and **14D**).

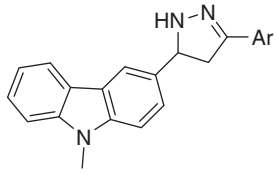
Class II

The compounds bearing these substitutions exhibited activity against various microorganisms such as bacteria, fungi, viruses and parasites such as *Plasmodium* species in addition to possessing analgesic activity.

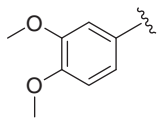
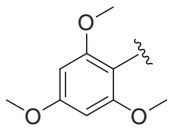
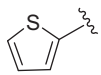
Antimicrobial activity

B.C. Revanasiddappa et al.[63] synthesized and determined the pyrazoline derivatives for their *in-vitro* antimicrobial activity against different Gram-negative and Gram-positive bacterial strains as well as fungal strains. Although these compounds showed comparable antibacterial and antifungal activity, the activity (Table 12) is seen mainly due to the presence of electron withdrawing groups (Table 11) at R_1 on the C2 phenyl ring. Substitution of a thiophene ring at R on the phenyl ring at C5 along with an electron withdrawing group at R_1 on the phenyl ring at C3 led to an increase in the antibacterial activity especially

Table 7. Anti-inflammatory & antioxidant activities of 2-pyrazolines.



Anti-inflammatory activity

Compounds	Ar	% Inhibition COX-I	% Inhibition COX-II	COX-2 enzyme inhibition assay *In vitro* % inhibition (100 μM)	COX-2 enzyme inhibition assay *In vivo* % inhibition
Indomethacin		63.87	28.43	28.43	47.0 ± 1.1
11A		24.15	88.43	88.43	60.3 ± 4.5
11B		23.49	86.85	86.85	54.3 ± 1.1
11C		18.50	48.43	48.43	42.2 ± 11.8

Antioxidant activity

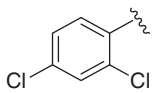
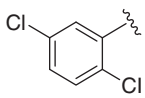
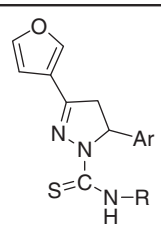
Compound	Ar	% Radical scavenging activity				
				DPPH radical	SOR radical	OH radical
Ascorbic acid			91.52	51.95	88.34	
11D		24.15	40.53	92.08	81.67	69.34
11E		8.85	10.15	91.74	86.26	78.64

Table 8. Anticonvulsant and antidepressant activities of N1-thiourea derivatives of pyrazoline.



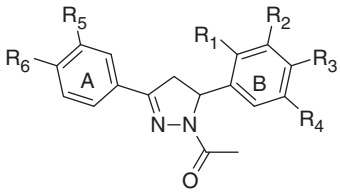
Antidepressant

Compound	R	Ar	Antidepressant activity (Duration of immobility) (mean ± S.E.M.)
12A	C_2H_5	Phenyl	139 ± 12
12B	C_3H_5	2-furyl	144 ± 21.4

Anticonvulsant

Compound	R	Ar	MES Time (hrs)	MES Conc (mg/kg)	scMET Time (hrs)	scMET Conc (mg/kg)
12C	Phenyl	2-furyl	1/2	100 & 300	No activity	
12D	2-furyl	C_2H_5	4	300	1/2	30,100,300

Table 9. XO inhibitory activity of N_1-acetyl pyrazolines.



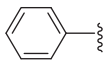
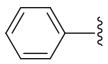
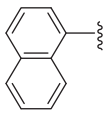
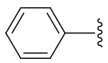
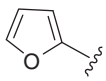
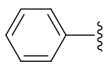
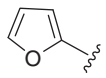
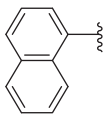
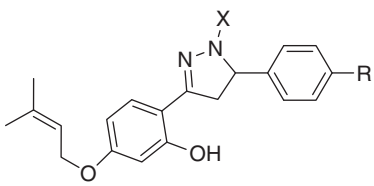
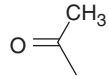
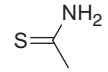
Compound	Ring A	Ring B	R	XO inhibitory activity IC_{50} (μM)
13A			H	61.4
13B			H	41.3
13C			H	26.4
13D			$R_2 = –OCH_3$	21.3
13E			$R_2 = NO_2$	13.1
13F			–	91.4

Table 10. MAO inhibitory activity of some pyrazolines.



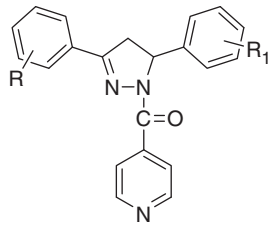
Compound	X	R	MAO inhibitory activity (pIC_{50}) hMAO-A	hMAO-B
Clorgyline (MAO-A inhibitor)			8.35	4.21
Deprenyl (MAO-B inhibitor)			4.17	7.70
14A		OCH_2Ph	6.50	6.76
14B		CH_3	–	–
14C		OCH_2Ph	–	6.57
14D		CH_3	–	–

against *Bacillus subtilis* and *Psuedomonas aerogenosa* (**15A**) but the substitution of a deactivating group at R and R_1 (**15C**) shifted the spectrum of activity towards antifungal activity. Co-relation of SAR studies and the data retrieved from the antimicrobial evaluation also featured that the presence of an activating group at R and deactivating group at R_1 led to a decrease in both antibacterial as well as antifungal activity.

Anti-tubercular activity

M.A. Ali et al.[64] synthesized pyrazoline derivatives and tested their anti-tubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$. Compound with 2,6-dichloro group substitution [**16A**, anilino-3-(4-hydroxy-3-methylphenyl)-5-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-1-pyrazolylmethanethione] (Table 13) produced highest efficacy and exhibited >90% inhibition at very low concentration. 2,6-Dichloro substituted derivatives exhibited relatively higher inhibitory activity although the presence of electron rich groups such as, 4-chloro, 2-chloro, and 3-nitro substituted analogue (**16B**) led to significant decrease in inhibitory activity against *M. tuberculosis* H37Rv. Pyrazoline analogues with 3,4-dimethoxy phenyl substitution (**16C**) and 3,4,5-trimethoxy phenyl substitution (**16D**) showed relatively moderate anti-tubercular activity. Compounds having $R = CH_3$ (**16E**) and $R_1 = 3,4,5$-trimethoxy phenyl presented relatively low inhibitory activity against *M. tuberculosis* H37Rv.

Table 11. Various of N_1-pyridamide pyrazoles.



Compound	R	R_1
15A	2-Thiophene	*p*-NO_2
15B	*p*-$(CH_3)N$	*p*-Br
15C	*p*-Cl	*p*-Cl
15D	*p*-OCH_3	*p*-Cl

Anti-amoebic activity

A team of A.R. Bhat[32] synthesized thiocarbamoyl bis-pyrazoline derivatives and assessed these compounds for their potential as anti-amoebic against HM1: IMSS strain of *Entamoeba histolytica* via the microdilution technique. The SAR studies (Table 14) carried out helped in inferring that the aromatic ring on *N*-thiocarbamoyl (**17A** and **17B**) proved to have better activity than the cyclic groups (**17C** and **17D**). The electron withdrawing substituent on the aromatic ring also contributed to the activity. Among the compounds containing the cyclic group, increase in activity was proportional to the ring size.

M.Y. Wani et al. (65) synthesized and subjected 1,3,5-trisubstituted pyrazoline derivatives to *in-vitro* anti-amoebic screening to assess their potential against growth of *Entamoeba histolytica*. The information drawn from SAR studies (Table 15) revealed that compounds having methyl groups at R_1 and R_2 possessed the highest activity (**18C**). Replacing the methyl group at R_2 with methoxy group ensued in a small decrease in activity (**18D**). Activity was further decreased when methyl group from **18D** was removed. Compounds with electron withdrawing group at R_1 (**18A** and **18B**) resulted in higher IC_{50} values thus indicating lower activity. The team also determined the safety profile for the synthesized compounds which held an inverse relation to the IC_{50} values measured.

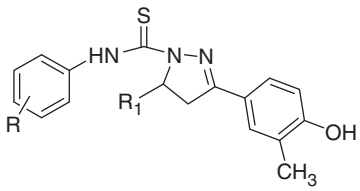
Anti HIV activity

Mohamed A. Ali and his group[66] synthesized and assessed nicotinoyl substituted pyrazolines for their activity against HIV strains IIIB and ROD (Table 16). Among the series, the compound having a phenyl ring bearing electron donating groups at C5 of the pyrazoline (**19A**) showed the highest activity. Derivatives with heteroaromatic ring (**19B**) showed moderate activity. In addition, the SAR studies signified that presence of

Table 12. Antimicrobial activity of various of N_1-pyridamide pyrazoles.

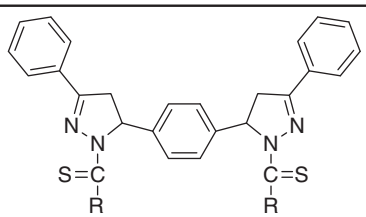
	Diameter of the zone of inhibition (mm) at 10 μg/mL concentration					
	Anti-bacterial activity				Anti-fungal activity	
Compound	*S. aureus*	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
15A	12	16	13	16	15	14
15B	13	13	16	14	15	14
15C	14	14	15	12	16	16
15D	14	14	14	13	15	15
Streptomycin	24	21	22	22	–	–
Griseofulvin	–	–	–	–	23	22
Control (DMF)	–	–	–	–	–	–

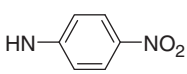
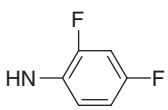
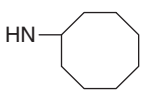
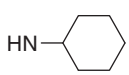
Table 13. MIC values for antituberculer activity.



Compound	R	R_1	Antituberculer activity MIC (μg/mL)
16A	2-OCH_3	2,6-Dichloro phenyl-	1.66
16B	2-OCH_3	3-Nitro phenyl-	–
16C	2-OCH_3	3,4-Dimethoxy phenyl-	5.67
16D	2-OCH_3	3,4,5-Trimethoxy phenyl-	–
16E	2-CH_3	3,4,5-Trimethoxy phenyl-	–

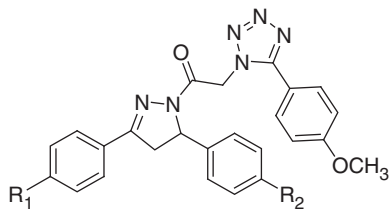
Table 14. Anti-amoebic activity of bispyrazolines.



Compound	R	Anti-amoebic activity IC_{50} (μM)
17A		0.42
17B		0.62
17C		0.92
17D		1.16
Metronidazole		1.8

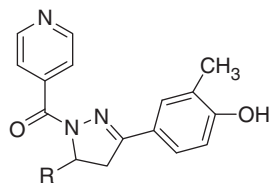
electron withdrawing groups resulted in fall of activity and this was found to be inversely proportional to the number of substitutions, that is dihalogen substitution showed better activity than monohalogen (**19C** and **19D**).

Table 15. *In-vitro* anti-amoebic activity of compounds against HM1: IMSS strain of *Entamoeba histolytica* and their toxicity profile.



			Anti-amoebic activity	
Compound	R_1	R_2	IC_{50} (μM)	Safety Profile (SI)
18A	Cl	H	3.15	28.76
18B	Cl	OCH_3	2.63	>38.02
18C	CH_3	CH_3	0.86	>116.27
18D	CH_3	OCH_3	1.08	>92.59
Metronidazole			1.80	>55.55

Table 16. Anti-HIV activity of N_1-pyridamide pyrazoles.



Compound	R	IC_{50} (μM)
19A	4-Dimethylaminophenyl-	5.7
19B	Furyl-	6.8
19C	4-Chlorophenyl-	>36.1
19D	2,6-Dichlorophenyl-	>13.83

Anti-malarial activity

B.N. Acharya et al.[67] synthesized and evaluated a series of nicotinoyl substituted pyrazolines for their potential as antimalarials against chloroquine sensitive (MRC-02) and chloroquine resistant (RKL 9) strains of *Plasmodium falciparum*. Among these derivatives, the SAR studies (Table 17) assisted in inferring that the compounds possessing electron withdrawing groups at either *ortho* or *para* (**20B**) or both (**20A**) showed commendable activity against both the strains. Substitution involving electron releasing group resulted in abolishing of the activity to a small extent for chloroquine sensitive strains although it retained good activity for chloroquine resistant strains.

Analgesic activity

R. S. Joshi et al.[68] synthesized a series of 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1*H*-pyarazol-3-yl) phenols and its

N-phenylpyrazol-1-carbothioamide and evaluated them for their analgesic activity by acetic acid induced writhing response in mice and anti-inflammatory activity against carrageenan induced rat paw edema model in rats. The compounds (Table 18) having the *N*-phenylpyrazol-1-carbothioamide moiety (**21D**) disclosed better activity than the pyrazoline compound. Although the presence of a halogen (Br) (**21B**) resulted in improvement of the activity but there was no direct correlation between enhancement of the anti-inflammatory activity and the presence of electron donating and electron withdrawing group. This might be owing to the fact that substitution of a dihalogen doesn't produce any significant activity when compared to monohalogen substitution.

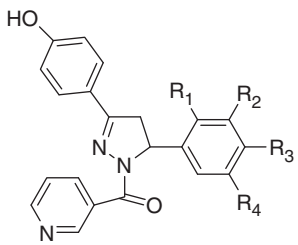
Class III

The compounds bearing these substituents at the pyrazoline *N*1 showed antimicrobial activity mainly against bacteria and fungi in addition to anti-inflammatory, anti-infective and anticancer activity.

Antimicrobial activity

Zeinab H. I. et al.[53] synthesized pyrazoline derivatives (Table 19) and tested them for their *in-vitro* antimicrobial activity against Gram-positive bacteria *Staphylococcus aureus*, *Bacillis subtilis*, the Gram-negative bacteria *Pseudomonas aeruginosa*, *Escherichia coli* and fungi *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum and Candida albicans*

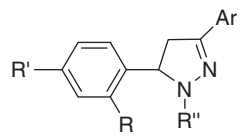
Table 17. Antimalarial activity of some N_1-pyridamide pyrazoles.



					Antimalarial activity	
Compound	R_1	R_2	R_3	R_4	MRC-02	RKL9
20A	Cl	H	Cl	H	0.0375 ± 0.005	0.0680 ± 0.019
20B	Br	H	H	H	0.0272 ± 0.005	0.0640 ± 0.003

The data obtained from the SAR studies projected that dinitrophenyl ring substitution on the *N*1 of pyrazoline indicated more commendable activity than an unsubstituted phenyl ring (Table 20). Phenyl ring bearing electron withdrawing groups (**22A**, **22B**, **22C**) at C3 and C5 of the pyrazoline ring displayed excellent activity against Gram-positive bacteria and also *E. coli* whereas phenyl ring with electron donating groups (**22C**) displayed only moderate activity against the Gram-positive bacteria. Derivatives in which the pyrazoline ring is substituted with thiophene ring (**22D**) at the C3 of the pyrazoline ring were seen to act against only *Escherichia coli*. Moreover, it was observed that the compounds that possessed significant antibacterial activity also displayed commendable antifungal activity (Table 21). Akin to the antibacterial activity, phenyl rings bearing electron withdrawing groups (**22A**) at C3 and C5 of the pyrazoline ring demonstrated excellent antifungal activity.

Table 19. Structural modification of some N-substituted pyrazolines.



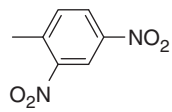
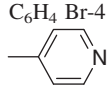
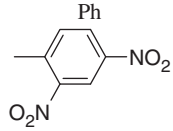
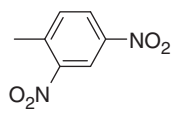
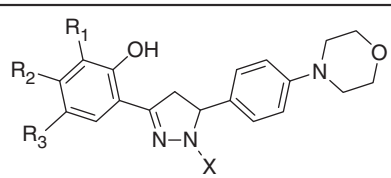
Compound	Ar	R	R′	R″
22A	C_6H_4 Br-4	H	$N(CH_3)_2$	
22B	C_6H_4 Br-4	Cl	H	Ph
22C		$-OCH_3$	H	
22D		H	Cl	Ph
22E	C_6H_5	H	H	

Table 18. Anlgesic and anti-inflammatory activities of morpholine containing pyrazolines.



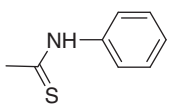
						Increase in paw volume (mL) after carageenan administration			
Compound	X	R_1	R_2	R_3	Number of writhings	2 h	3 h	4 h	24 h
Control					71 ± 3	1.49 ± 0.20	1.64 ± 0.15	1.57 ± 14	1.92 ± 0.12
Diclofenac					08 ± 2	0.18 ± 0.03	0.18 ± 0.015	0.18 ± 0.02	0.03 ± 0.01
21A	H	H	H	Cl	53 ± 4	1.52 ± 0.12	1.60 ± 0.18	1.61 ± 0.12	1.92 ± 0.18
21B		H	H	Br	15 ± 4	0.86 ± 0.15	0.52 ± 0.14	0.64 ± 0.10	0.98 ± 0.12
21C		H	H	Cl	09 ± 2	0.64 ± 0.10	0.72 ± 0.14	0.72 ± 0.12	0.86 ± 0.12
21D		H	H	Br	13 ± 3	0.87 ± 0.12	0.69 ± 0.13	0.91 ± 0.17	0.92 ± 0.16

Table 20. Antibacterial activity of **22A–22E**.

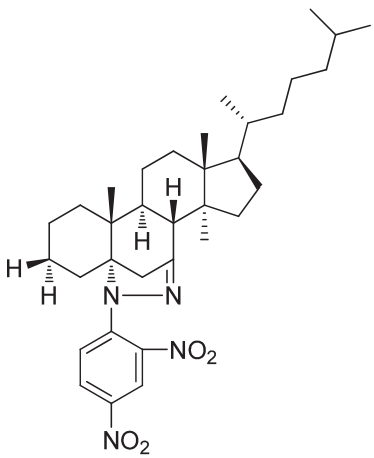
	Gram-positive bacteria						Gram-negative bacteria					
	S. aureus			*B. subtilis*			*E. coli*			*P. aeruginosa*		
Compound	1.25	2.5	5.0	1.25	2.5	5.0	1.25	2.5	5.0	1.25	2.5	5.0
22A	+	+	++	+	++	++	+	+	++	0	0	+
22B	0	0	+	0	0	+	+	+	+	0	0	0
22C	0	+	+	0	+	+	0	+	+	0	0	0
22D	0	0	0	0	0	0	0	+	+	0	0	0
22E	+	+	++	+	++	++	+	++	++	0	0	+

Chloramphenicol is the standard antibacterial control.
Inhibition values = 0.1–0.5 cm beyond control = +; Inhibition values = 0.6–1.0 cm beyond control = ++; and 0 = not detected.

Table 21. Antifungal activity of **22A** and **22B**.

	A. fumigatus			*P. italicum*			*S. racemosun*			*C. albicans*		
Compound	1.25	2.5	5.0	1.25	2.5	5.0	1.25	2.5	5.0	1.25	2.5	5.0
22A	+	+	++	+	+	0	+	++	++	0	+	+
22B	0	0	0	0	+	+	0	0	0	0	+	+

Table 22. Antimicrobial activity of steroidal pyrazolines.

Compound	MIC (Antibacterial)		
	E. coli	*C. xerosis*	*S. epidermidis*
	3.125	0.781	0.195
	MIC (Antifungal)		
	M. azygosporus	*C. purpurea*	*A. niger*
	3.125	6.250	1.562

2′-(2″,4″-dinitrophenyl)-5a-cholestano [5,7-*c d*] pyrazolines

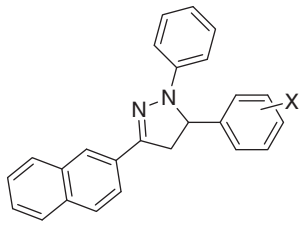
Shamsuzzaman and his coworkers[69] synthesized and screened 2′-(2″, 4″-dinitrophenyl)-5a-cholestano [5, 7-*c d*] (Table 22) to assess their antimicrobial activity against different bacterial strains (*Corynebacterium xerosis*, *Staphylococcus epidermidis* and *Escherichia coli*) method and fungal strains (*Mucor azygosporus, Claviceps purpurea and Aspergillus niger*) employing the broth dilution and agar diffusion method, respectively. The promising antifungal and antibacterial activity shown by the compound was attributed to the dinitrophenyl ring substituted at the *N*1 of the pyrazoline ring.

S. P. Shaktinathan and his research group[43] synthesized a series of novel 2-naphthyl pyrazolines and also evaluated these compounds for their antimicrobial activity against bacterial strains (Gram-positive *Micrococcous luteus*, *Bacillus substilis*, *Staphylococcus aureus* and Gram-negative *Escherichia coli and Klebsiella*) and against fungal strains (*Aspergillus niger* and *Trichoderma viride*) by utilising the well-known disc diffusion technique (Table 23). The activity was confirmed by measuring the diameter of the zone of inhibition. Among the electron withdrawing groups substituted, chlorine (**23C**) showed better activity against Gram-negative strains especially against *E. coli* and fluorine substitution (**23A**) exhibited moderate antibacterial activity against *E. coli* and *B. subtilis*. The electron releasing groups (**23D**) showed no activity against Gram-positive strains but showed the highest activity against Gram-negative *E. coli* strain. Antifungal activity more or less followed the same trend; chlorine substitution rendered the compound active against *T. viride* but not against *A. niger.*

Antibacterial activity

Mamta Rani and her research group[70,71] synthesized three series of pyrazoline derivatives with the same basic framework but different substituent and assessed their antibacterial activity against strains of *Aeromonas hydrophila*, *Yersinia enterocolitica*, *Listeria monocytogenes and Staphylococcus aureus* with the help of Halo Zone Test[72] and also compared their activity by measuring the zone of inhibition (Table 24). Derivatives having

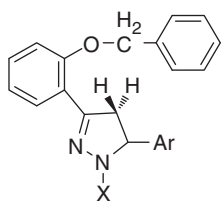
Table 23. Antimicrobial activity of **23A–23D**.



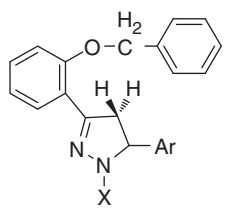
Antibacterial activity (mm)						
		Gram-positive bacteria			Gram-negative bacteria	
Compound	X	*B. subtilis*	*M. luteus*	*S. aureus*	*E. coli*	*K. pneumoniae*
23A	4-F	9	7	6	9	7
23B	4-Br	8	8	7	7	7
23C	4-Cl	8	7	–	10	7
23D	4-CH_3	6	–	–	12	7
Ampicillin		20	18	18	18	12

Antifungal activity (mm)			
Compound	X	*A. niger*	*T. viride*
23A	2-Cl	–	10
23B	3-Cl	–	10
23C	4-F	9	7
Miconazole		14	16

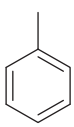
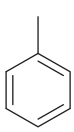
Table 24. Antimicrobial activity of **24A1–24B3**.



A



B

			Halo zone test (unit, mm)			
			Microorganisms			
Compound	Ar	X	*A. hydrophila*	*Y. enterocolitica*	*L. monocytogenes*	*S. aureus*
Gentamycin			21	–	–	17
24A1			21.5	24.4	21.3	22.8
24B1			25.3	18.6	20.8	24.5
24A2			22.3	21.4	24.3	22.8
24B2			21.7	25.2	19.4	23.6
24A3			20.5	22.4	24.3	22.8
24B3			21.7	18.4	21.2	19.4

furan ring at C5 of the pyrazoline ring were observed to possess better activity than the derivatives with thiophene ring.

Anti-inflammatory activity

S. Bano et al.[73] synthesized 2-pyrazolines bearing benzene sulphonamides (Table 25) and evaluated these compounds for their anti-inflammatory activity. The benzene sulphonamides substituted at the *N*1 of the pyrazoline ring attributed to these compounds their activity. *p-c*hloro substitution on the C5 phenyl ring increased the anti-inflammatory effect as compared to *o*-hydroxy substitution on the C5 phenyl ring.

S. Khode and his group[74] synthesized 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines and evaluated both their

Table 25. Anti-inflammatory activity of benzene sulphonamide derivative of 2-pyrazolines.

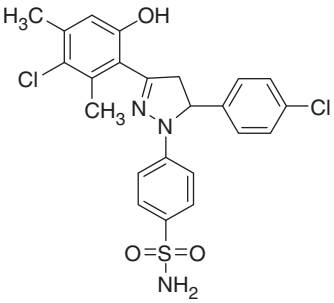
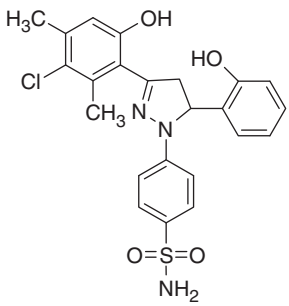
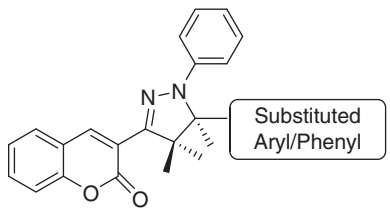
	Carrageenan-induced rat paw edema assay			
	3 h		5 h	
Compound	Increase in the paw volume (ml)	% Inhibition	Increase in the paw volume (ml)	% Inhibition
Celecoxib	0.12 ± 0.0041	79.59	0.09 ± 0.0031	82
	0.12 ± 0.004	80	0.09 ± 0.003	81.82
	0.125 ± 0.005	78.95	0.125 ± 0.004	75

Table 26. Anti-inflammatory activity of coumarin based 2-pyrazolines.



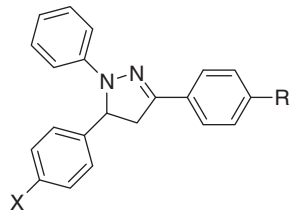
		Anti-inflammatory activity		
		In vitro % inhibition		
Compound	Ar	2 h	4 h	*In vivo* % inhibition after treatment
25A	2,4-Cl_2-C_6H_3	56.7 ± 0.030	67.5 ± 0.024	45.4 ± 1.63
25B	4-F-C_6H_4	44.9 ± 0.023	66.7 ± 0.011	40.5 ± 1.80
25C	4-Cl-C_6H_4	39.2 ± 0.026	64.7 ± 0.021	39.1 ± 0.81
25D	3-OMe-C_6H_4	38.3 ± 0.030	61.5 ± 0.013	20.9 ± 1.25
Diclofenac		63.7 ± 0.017	78.7 ± 0.013	53.0 ± 1.92

in vitro as well as *in-vivo* anti-inflammatory activity (Table 26). The IC_{50} activity exhibited by these compounds revealed that activity increased with the electron withdrawing group with fluro-substitution (**25B**) showing better activity than the chloro (**25C**) substitution although activity was also dependent on the number of groups (**25A**) substituted. Compound **25C** and **25D** showed good inhibitory activity at second and fourth hour, respectively, while the most active compounds **25A** and **25B** exhibited excellent inhibitory activity at second and fourth hour, respectively.

Anti-infective agents

P. M. Sivakumar and his team[75] synthesized 1, 3, 5-triphenyl-2-pyrazolines and screened these compounds for their anti-infective activities against *Mycobacterium tuberculosis* $H_{37}Rv$, bacterial and fungal strains. It was observed (Table 27) that sulfonylmethyl (**26A**) substitution increased the activity towards the $H_{37}Rv$ strain since it was observed to bring the log P value to 3 (ideal for penetration through mycobacterial cell). Compounds having thiomethyl substitution (**26C**) in the A-ring resulted in higher

Table 27. Antimicrobial activity of N_1-phenyl substituted pyrazolines.



Anti-tubercular activity (% reduction in rlu)

Compound	R	X	50 μg/ml	100 μg/ml
26a	SO_2CH_3	–	1.70	50.71
26b	SCH_3	–	0.00	17.65

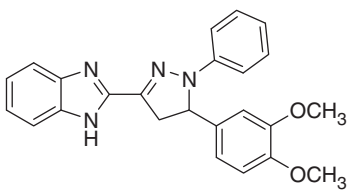
Antibacterial activity (mic in μm)

Compound	R	X	*E. coli*	*P. vulgaris*	*E. aerogenes*	*S. aureus*	*S. typhii*	*B. subtilis*
26a	SO_2CH_3	–	0.166	0.332	0.332	0.664	0.332	0.332
26c	SCH_3	Cl	0.152	0.304	0.304	0.608	0.304	0.304
26d	SCH_3	Br	0.148	0.295	0.295	0.591	0.295	0.295

Antifungal activity (% inhibition at 2mg/ml concentration)

Compound	R	X	*F. proliferatum*	*C. tropicalis*	*A. flavus*	*A. niger*
26a	SO_2CH_3	–	97.61 ± 0.47	30.64 ± 0.30	65.85 ± 1.82	47.20 ± 5.03
26c	SCH_3	Cl	88.26 ± 0.90	95.58 ± 1.05	88.44 ± 1.92	97.54 ± 0.07
26e	SCH_3	F	98.71 ± 0.16	97.41 ± 1.40	94.82 ± 0.16	97.28 ± 1.31

Table 28. *In-vitro* anticancer activity of compound NSC 748326.



Panel	Cancer cell lines	GI_{50} (μM)
Leukemia	CCRF-CEM	2.23
	RPMI-8226	2.76
Renal	CAKI-1	3.6
	UO-31	2.2
Prostate	PC-3	6.27
	DU-145	33.1
Colon	HCT-116	3.94
	HCT-15	4.1
Breast	MCF7	2.41
	MDA-MB-468	5.25

activity against the bacterial and the fungal strains. Activity possessed by the active compounds (**26C**, **26D** and **26E**) was attributed to the halogen substitution at the -*p* and/or -*m* position in the B-ring, thus, highlighting the importance of halogen substitution for antibacterial and antifungal activities.

Anticancer activity

M. Shaharyar et al.[76] synthesized series of benzimidazole bearing 2-pyrazolines and tested these compounds against various cancer cell lines belonging to different panels (Table 28) such as renal, breast, colon, melanoma, prostate, and so on. Most active compound of the series was found to be 2-[5-(3, 4-dimethoxyphenyl)-1-phenyl-4,5-dihydro-1*H*-3-pyrazolyl]-1*H*-benzimidazole. Based on close examinations of the substituent, it was concluded that the role of electron donating group on the phenyl ring at C5 of the pyrazoline ring had a great influence on anticancer activity.

Conclusion

Modifications on the pyrazole ring are rightly claimed to have inextricable contribution to the multifaceted activities projected by the pyrazoline moiety. The broad spectrum of activities exhibited by the 2-pyrazolines makes them an indispensable scaffold for the synthesis of numerous pharmacologically active compounds. The review was put forward with an incentive to congregate the 2-pyrazoline derivatives synthesized from 2009-till date and classifying them in a manner that would justify the activities portrayed by these derivatives. Although, the substituents on the pyrazoline ring, whether on nitrogen (N1, N2) or on the carbon (C3, C4, and C5) proved to be significant, the decisive role was played by the *N*1 of the pyrazoline. The plethora of information, retrieved from the structure–activity relationship studies, IC_{50} values, safety profiles and confirmation by the molecular docking studies, helped paint a lucid picture of the potential held by the substituents to influence the extend of inhibitory potential commendably. Amide, acetyl or thiocarbamoyl substitution on the *N*1 of the pyrazoline portrayed activity that varied over a wide range of activity such as anticancer activity, oxidase inhibitory activity, anti-inflammatory activity, antidepressant activity, and so on. On the contrary, aromatic or heteroaromatic substitution on the *N*1 contributed to synthesis of compounds which had the potential as antimicrobials, anti-HIV, anti-amoebic, antiparasitic, antitubercular and analgesic. Not many efforts have been made so far to isolate and separate the enantiomeric forms of *N*1-substituted 2-pyrazolines. An understanding of interactions of the resolved single isomer with the target in co-crystal structures may be beacon for offering the scope of tuning and having permutation and combination of a variety of *N*-substituents at 2-pyrazolines for the design of potential and specific inhibitors.

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Declaration of interest

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