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Recent applications of pyrazole and its substituted analogs

V Kumar, V Sareen, V Khatri and S Sareen

Abstract
Pyrazole is a five membered heterocyclic ring which is a versatile leading compound for designing potent bioactive agents. This interesting group of compounds has diverse biological activities such as antimicrobial, anti-inflammatory, analgesic, anticonvulsant, anticancer, anthelmintic, antioxidant and herbicidal. Results of numerous derivatives of different pyrazole and their substitutions are reviewed in present article. Various methods for synthesizing pyrazole are discussed with their pharmacological activities.

Keywords: Pyrazole, antimicrobial, antibacterial, analgesic and anticancer

Introduction
Pyrazole is the name given by "LUDWIG KNORR" to this class of compounds in 1883. The doubly unsaturated compound containing two nitrogen and three carbon atoms in the ring, with the nitrogen atoms neighboring to each other, is known as pyrazole (fig.1). Being so composed and having pharmacological effects on human, they are classified as alkaloids, although they exit rarely in nature. The reduction products are pyrazoline and pyrazolidine, which are also used in medicine.

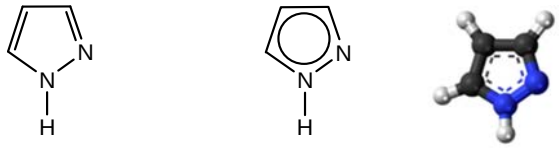


Fig 1

Pyrazole, like its structural isomer imidazole, contains a pyrrole-like and a pyridine-like N atom, but in the 1- and 2-positions (1,2-diazole). The pyrazole molecule is planar. Bond lengths and bond angles have been calculated from microwave spectra. Consistent with the structural formula, the bond between 3 and 4 atoms is the longest.
The ionization energy of pyrazole is 9.15 eV. When compared with pyrrole (8.23 eV). The pyridine-like N-atom reduces the energy of the HOMO, indeed even more so than in the case of imidazole (8.78 eV).
In 1954, Kosuge *et al.,* [1] isolated the first naturally occurring pyrazole derivative, 3-nonylpyrazole from *Hauttuynia Cordata,* a plant of "Piperaceae family". The compound was found to inhibit the growth of *Staphylococcus aureus*, *Bacillus subtilis, Trichophytons, Zygosaccharomycetes salsus* and *Aspergillus niger*.
For a long time no pyrazole derivatives has been found in nature, then in 1959 β-(1-pyrazolyl) alanine was isolated from the seeds of water melons (Citurllus lanatus) (L. Fowden) [2].

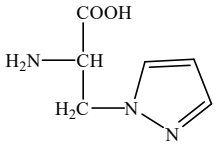


Fig 2

When pyrazole and its derivatives were developed, it was found that pyrazole structure acts as anti-inflammatory, [3] kinase inhibitors, [4] antimicrobial, [5, 6] antifungal, [7] antibacterial, [8, 11] DNA gyrase inhibitor, [11] antitubercular, [12] anti-mycobacterial [13] anticonvulsant [14] analgesic [15] anxiolytic [16] and antiviral agents [17, 21].

The pyrazole ring is present as the core moiety in a variety of leading drugs such as Celebrex, Viagra [22] or Rimonabant. They have also found use as bifunctional ligands for metal catalysis, [23, 24] and in various building blocks for pharmaceutical and agricultural research.

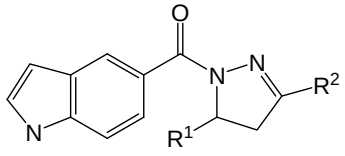
Numerous patents describe the use of the 3-aminopyrazole analogue (H30935) as building block to more complex moieties, such as potential drug candidates [25]. 5-Aminopyrazoles such as H32831 have been used in heterocyclizations involving N-arylmaleimides [26]. Studies involving H32918 as a building block showed that 3-aminopyrazole derivatives can be selective based MK-2 inhibitors [27]

Pyrazoline derivatives, possess a variety of significant and diverse pharmacological activities such as antimicrobial [28, 29] analgesic, [30] anti-inflammatory, [31, 32] anticancer [33] antibacterial [34] antifungal [35] Antimycobacterial [36] and antiamoebic [37] activity.

Azopyrazoles exhibited a wide variety of biological and pharmaceutical activities and therefore they play important role in medicinal chemistry. An exciting development in the synthesis of nitrogen heterocycles like azopyrazoles has commenced in last few years. Pyrazoles having azo group have been found to exhibit a wide range of biological activities like antibacterial, CNS depressant, antitumor, potent local anesthetics.

Pyrazole as Anti-Microbial Agent

K. N. Sharma *et al.,* [38] synthesized a series of pyrazole derivatives by esterification of indole-5-carboxylic acid. All the newly synthesized compounds were evaluated for antimicrobial activities. The compounds 3a and 3d exhibited good antibacterial activity against *E. coli* and compounds 3c and 3f showed good activity against *P. aeruginosa* and compounds 3b, 3e and 3h showed good activity against *S. aureus.* The compounds 3a and 3f exhibited excellent antifungal activity against *A. niger* and compounds 3b and 3h exhibited good activity against *A. flavus* and compounds 3d and 3g showed a good activity against *A. terrus.*



R^1	R^2	R^1	R^2
3 a = -C_6H_5	-C_6H_5	3 e = -C_6H_5	-p-tolyl
3 b = -p-tolyl	-C_6H_5	3 f = -p-tolyl	-p-tolyl
3 c = 4-CH_3O-C_6H_4	-C_6H_5	3 g = 4-CH_3O-C_6H_4	-p-tolyl
3 d = 4-Cl-C_6H_4	-C_6H_5	3 h = 4-Cl-C_6H_4	-p-tolyl

Fig 3

M. M. Youssef *et al.,* [39] synthesized a series of some new pyrimidine, thiazolopyrimidine and pyrazole derivatives using diarylepoxypropaneone as precursors. The antimicrobial activity of the compounds considered was tested on i) *Escherichia coli,* ii) *Pseudomonas puticle,* iii) *Bacillus subtilis*, iv) *Streptococcus lactus,* v) *Aspergillus niger,* vi) *Penicillium sp.* and vii) *Candida albicans.* Out of all the synthesized compounds (fig.4) showed good activity against all micro-organism.

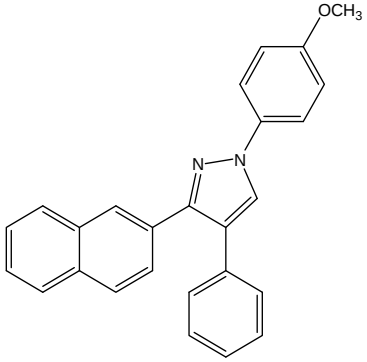


Fig 4

S. Bondock *et al.,* [40] synthesized a series of substituted pyrazole derivatives. Compound, 1-[5-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2-methylfuran-3-yl]ethanone (fig.5a) has showed equal activity with chloramphenicol against *B. subtilis* (MIC 3.125 µg/mL), while its activity was 50% lower than of chloramphenicol against *B. thuringiensis* and compound 2-(5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-furo-[3,2-c]chromen-4-one (fig.5b) has found to exhibit the most potent *In vitro* antifungal activity with MICs (6.25 µg/mL) against *B. fabae* and *F. oxysporum.*

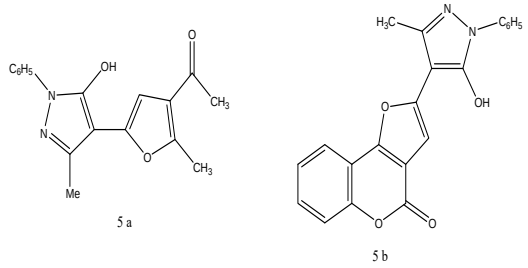
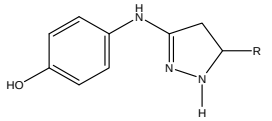


Fig 5

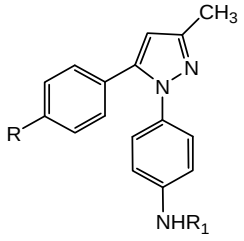
S. K. Sahu *et al.* [41] synthesized novel pyrazoline derivatives. The derivatives 6c, 6e and 6f (fig.6) showed potent antimicrobial activity: Antibacterial activity; by muller hinton agar (Hi-media) plates by agar diffusion cup-plate method for *Staphylococcus aureus, Staphylococcus feacalis, Salmonella typhi* and *Escherichia coli*. Antifungal activity; was tested on sabouraud dextrose agar plates by cup-plate method against *Candida albicans* and *Aspergillus niger*. In both of these assays Ciprofloxacin and Cotrimazole were used as standard drugs. Also the compounds 6c and 6e (fig.6) showed effective analgesic (by Tail flick method) and anti-inflammatory (by Carageenan induced rat paw oedema method).



Compounds	R
6 c	-4-NO_2-C_6H_4
6 e	-2-OH-C_6H_4
6 f	-4-Cl-C_6H_4

Fig 6

V. Gautam *et al.* [42] synthesized a series of 1, 3, 5-trisubustituted pyrazole derivatives and screened for their antimicrobial activity. The activity of the derivatives is more pronounced for gram -ve microorganisms than for the gram +ve ones. The compounds (fig.7) were evaluated against two gram +ve and two gram -ve bacteria and one fungus, at concentrations of 10 µg/mL and 50 µg/mL. The compounds were found to be inactive against *P. aeruginosa* and *A. niger* but exhibited moderate activity against *B. subtilis*, *E. coli* and *S. aureus*. It can be concluded that the newly synthesized compounds possess promising antimicrobial activity.



	R	R_1
7 a)	$-CH_3$	$-CH_3$
7 b)	$-C_2H_5$	$-CH_3$
7 c)	-Cl	$-CH_3$
7 d)	$-CH_3$	$-C_2H_5$
7 e)	$-C_2H_5$	$-C_2H_5$
7 f)	-Cl	$-C_2H_5$

Fig 7

G. Saravanan *et al.,* [43] synthesized a series of novel pyrazole derivatives. These compounds were screened for antibacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, and *Klebsiella pneumoniae* ATCC 11298) and antifungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique. Most of the synthesized compounds exhibited significant antibacterial and antifungal activities. Among the synthesized compounds, 2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (fig.8) was found to exhibit the highest antibacterial activity and 2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl) acetamide (fig.9) exhibited highest antifungal activity.

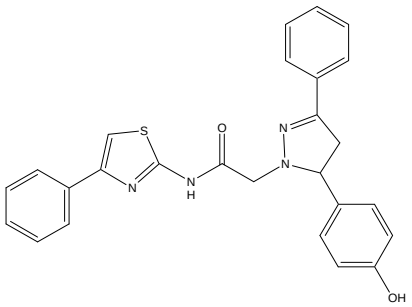


Fig 8

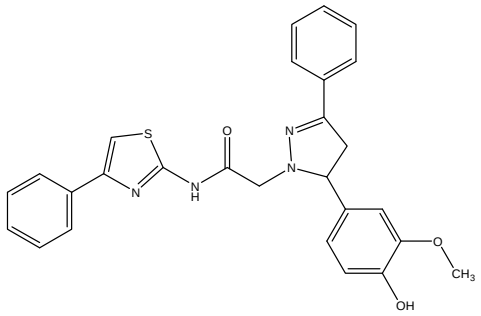
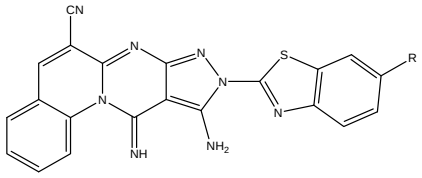


Fig 9

S. P. Vartale *et al.,* [44] synthesized and evaluationed antimicrobial activity of 3-amino-11-cyano-4-imino-pyrazolo [4, 5-E]-*4H*-pyrimido [2, 1-B] quinoline and their derivatives. They reported synthesis of 3, 11-dicyano-4-imino-2-methylthio-*4H*-pyrimido [1, 2-*a*] quinoline, imino pyrazolo pyrimido quinoline nucleus which showed promising antimicrobial activity. It was found that 10h, 10i, and 10j derivatives (fig.10) have encouraging antifungal activity.



Compounds	R
10 h	$-OCH_3$
10 i	-Cl
10 j	$-NO_2$

Fig 10

S. Bondock *et al.,* [45] synthesized a series of substituted pyrazole derivatives. These compounds were screened for their antibacterial activity against gram +ve bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes*), gram -ve bacteria (*Pseudomonas phaseolicola* and *Pseudomonas fluorescens*) and antifungal activity against *Aspergillus fumigatus* and *Fusarium oxysporum*. The given compound (fig.11) was found to exhibit the most potent *in-vitro* antifungal activity with MICs (6.25 µ/mL) against *A. fumigatus* and *F. oxysporum* strains.

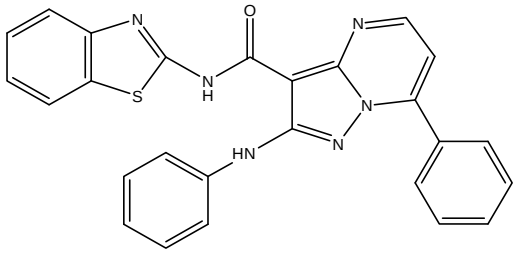


Fig 11

A. Saxena and R. Saxena [46] prepared, characterized and evaluated transition and inner transition metal complexes of ligands derived Schiff's Base from 1-phenyl-2,3-dimethyl-4-(4-iminopentan-2-one)-pyrazole-5-one and 2-aminophenol. The ligand and selected transition metal complexes (12a) MoO (V) and (12b) MoO_2 (VI) (fig.12) had also been evaluated for highest antimicrobial activity against *S. aureus* and *B. subtilis*.

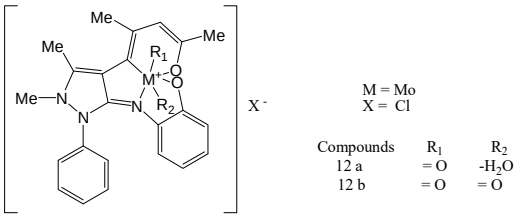
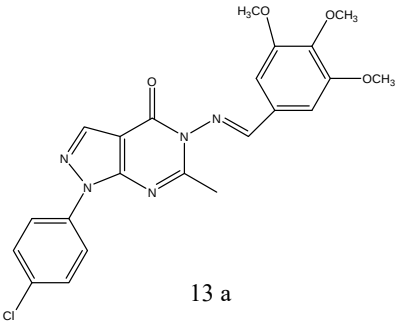


Fig 12

Pyrazole as Antiproliferative Agent

G. S. Hassan *et al.,* [47] synthesized new series of pyrazolo[3,4-d]pyrimidines and pyrazole hydrazones and evaluated them (fig.13) for their antiproliferative activity against human breast adenocarcinoma MCF-7 cell line. Most of the tested compounds exploited potent to moderate growth inhibitory activity, in particular compound 13a exhibited superior potency to the reference drug cisplatin (IC_{50} = 7.60 and 13.29 μM, respectively).



13 a

Fig 13

P. C. Lv *et al.,* [48] synthesized and evaluated a series of pyrazole derivatives containing thiourea skeleton as anticancer agents. The compound (fig.14) shows high antiproliferative activity against MCF-7 with IC_{50} of 0.08 μM. Therefore, compound with potent inhibitory activity in tumor growth inhibition would be a potential anticancer agent.

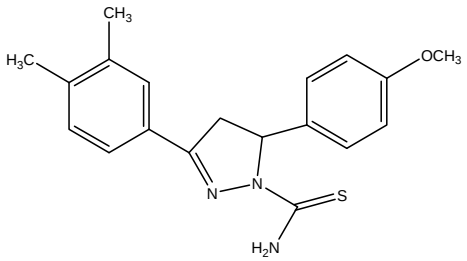


Fig 14

G. M. Nitulescu *et al.,* [49] synthesized a series of functionally substituted pyrazole compounds and evaluated *In vitro* for their antiproliferative effects on a panel of 60 cellular lines, according to the National Cancer Institute screening protocol. Three of the 12 tested compounds showed moderate antitumor activity, one of them (fig.15) being chosen for the 5-dose assay and presented $logGI_{50}$ values up to -5.75.

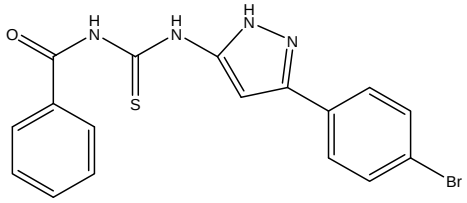


Fig 15

B. Insuasty *et al.,* [50] synthesized novel pyrazolic analogues of chalcones and their 3-aryl-4-(3-aryl-4, 5-dihydro-1*H*-pyrazol-5-yl)-1-phenyl-1*H*-pyrazole derivatives. Several of these compounds were screened by the US National Cancer Institute (NCI) for their ability to inhibit 60 different human tumor cell lines, where (fig.16) showed remarkable activity mainly against leukemia (K-562 and SR), renal cancer (UO-31) and non-small cell lung cancer (HOP-92) cell lines, with the most important GI_{50} values ranging from 0.04 to 11.4 μM, from the *In vitro* assays.

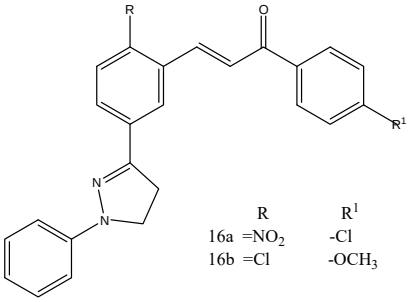


Fig 16

Pyrazole as Antibecterial agent

V. Nadaraj and S. T. Selvi[51] synthesized and characterized a series of condensed pyrazole derivatives *in* one pot by condensing various quinolines and semicarbazide in presence of catalytic amount of PTSA. The compounds (fig.17) showed excellent *In vitro* activity against *Escherichia coli,* and displayed moderate inhibition against other bacteria such as *Pseudomonas aeruginosa, Klebsiella aerogenes*, *Bacillus subtilis* and *Staphylococcus albus.*

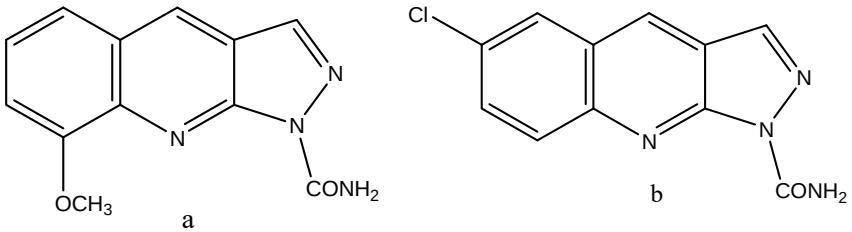
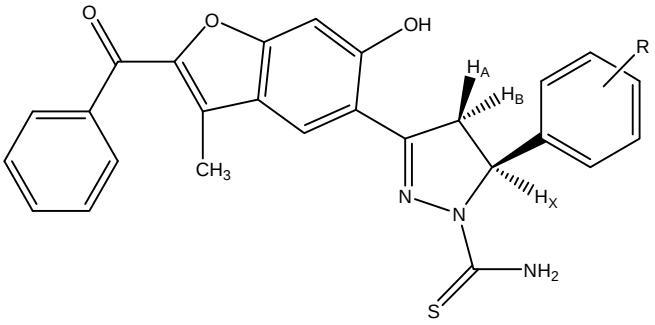


Fig 17

D. Ashok *et al.,* [52] synthesized a series of 3-(2-benzoyl-6-hydroxy-3-methylbenzo [b] furan-5-yl)-5-(aryl)-4,5-dihydro-1*H*-pyrazole carbothioamides (fig.18) by the reaction of (*E*)-1-(2-benzoyl-6-hydroxy-3-methylbenzo [b] furan-5-yl)-3-aryl-2-propen-1-ones with thiosemicarbazide in the presence of sodium hydroxide under microwave irradiation. This methodology provides an easier, facile and environmentally benign synthesis in which the reaction time is reduced with better yields. The compounds 18b, 18e and 18g exhibited good antibacterial activity.



Compounds	R
18 b	2–Cl
18 e	4–OCH_3
18 g	2–furyl

Fig 18

S. Mohan *et al.,* [53] synthesized a series of some novel sulphur bridged pyrazole derivatives. The synthesized pyrazole derivatives were tested for antibacterial activity against both gram +ve and gram -ve bacteria such as *Staphylococcus aureus, Bacillus subtilis* from gram +ve organisms and *Escherichia coli, Pseudomonas aeruginosa* from gram -ve organisms as well as for antifungal activity against *Candida albicans*. The pyrazole derivative (fig.19) showed activity against *Bacillus subtilis* from gram +ve organisms and *Escherichia coli* from gram -ve organism.

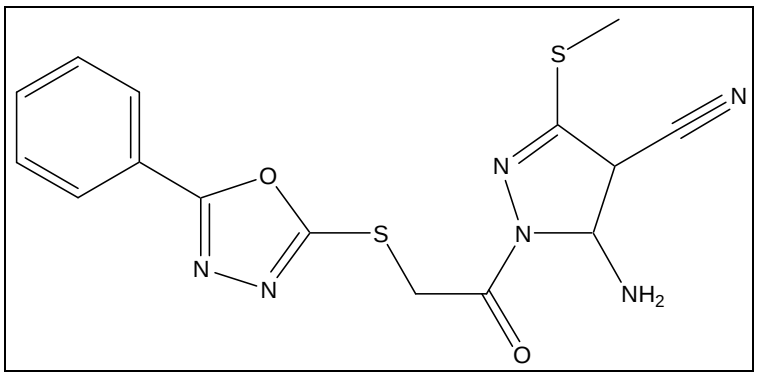


Fig 19

Synthesis and *In vitro* antibacterial activity of [5-(furan-2-yl)-phenyl]-4,5-carbothioamide pyrazolines was done by M. Rani *et al.* [54] *In vitro* antibacterial activity of these compounds were evaluated by the disk diffusion assay and then the minimum inhibitory concentration (MIC) strain of two gram + ve and two gram -ve bacteria like *Aeromonas hydrophila, Yersinia enterocolitica, Listeria monocytogenes* and *Staphylococcus aureus*, among all the compounds, alkoxy [5-(furan-2-yl)-2-(benzyloxy)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (20a) and 5-(furan-2-yl)-1-[2-(naphthalen-2-ylmethoxy)phenyl]-4,5-dihydro-1*H*-pyrazole-1-carbothio amide (20b) showed the most promising antibacterial activity when compared to gentamicin and tetracycline

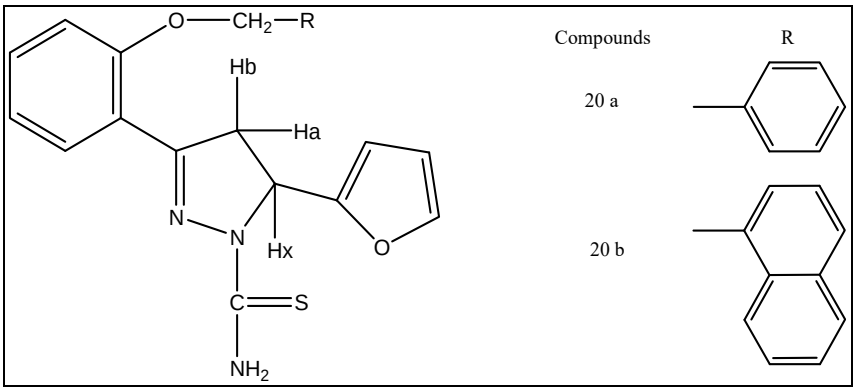


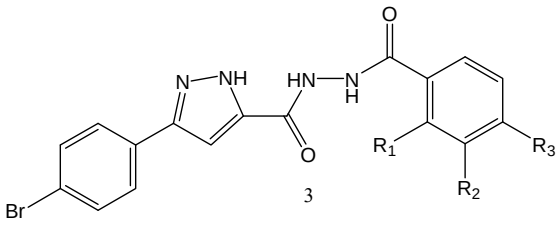
Fig 20

N. K. Shah *et al.,* [55] synthesized a new series of quinoline bearing pyrazole nucleus by condensation of arylidenemalononitriles and 3-aminocyclohex-2-en-1-ones in alcohol in the presence of a catalytic amount of piperidine and screened for their antimicrobial activities.

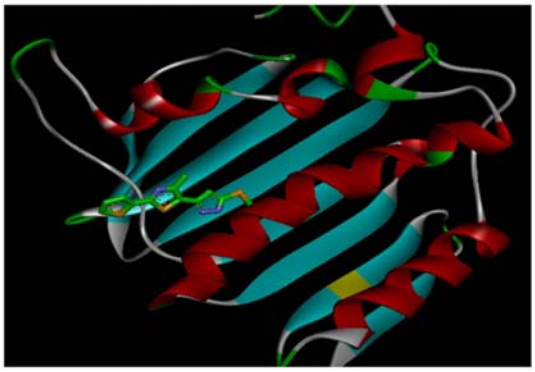
Novel (21a- 21f) N′-benzoyl-3-(4-bromophenyl)-1H-pyrazole-5-carbohydrazide analogs were designed and synthesized by J. Sun *et al.* [56] The results showed that compound (21d) can strongly inhibit *Staphylococcus aureus* DNA gyrase and *Bacillus subtilis* DNA gyrase (with IC_{50} of 0.15 µg/mL and 0.25 µg/mL, respectively). Structure activity relationships were also discussed based on the biological and docking simulation results.

The compounds (21a) and (21c) showed antibacterial activities against *B. subtilis* with the MIC of 3.66, 1.12 µg/mL, respectively, comparable to that of positive control penicillin. Compound 21d with MIC value of 0.78 µg/mL exhibited promising antibacterial activities against *B. subtilis* which were even better than that of the commercial penicillin. The compounds (21a-f) showed moderate antibacterial activities against *P. aeruginosa* with MIC of 12.50 µg/mL. Besides, compound (21f) also showed moderate antibacterial activities against *E. coli* with MIC of 12.50 µg/mL.

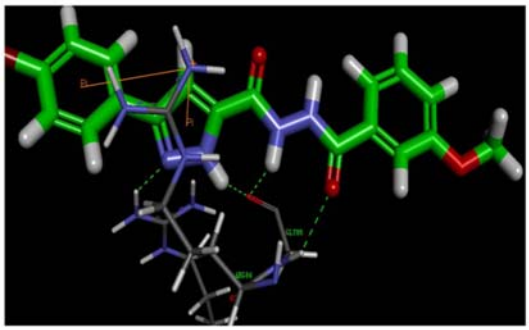
The compound (21f) showed the same activities against *S. aureus* and *B. subtilis* with the MIC of 10.56 µg/mL, but it showed different inhibition against the *S. aureus* DNA gyrase and *B. subtilis* DNA gyrase (IC_{50} = 3.25 µg/mL, 1.00 µg/mL respectively).



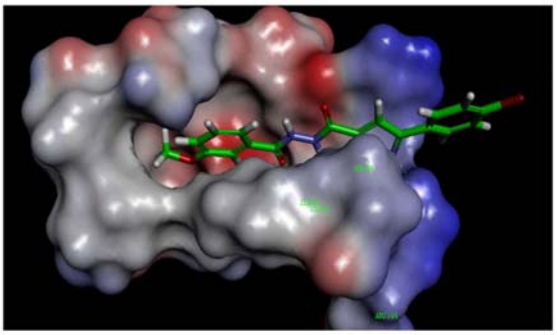
	a	b	c	d	e	f
R_1 =	H	H	H	H	OCH_3	H
R_2 =	H	H	CH_3	OCH_3	H	H
R_3 =	CH_3	OCH_3	H	H	H	H



Crystal structure of *Staphylococcus aureus* DNA gyrase co-complexed with inhibitor.



3D model of the interaction between compound 21d and DNA gyrase binding site.

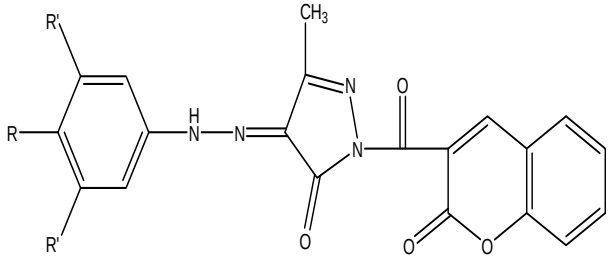


The receptor surface model with compound 21d.

Fig 21

Pyrazole as Analgesic Agent

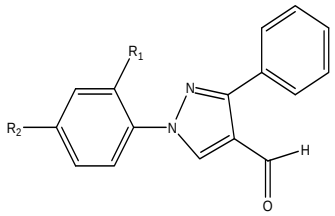
K. K. Sivakumar *et al.,* [57] synthesized a series of (4*Z*)-3-methyl-1-[(2-oxo-2*H*-chromen-4-yl)carbonyl]-1*H*-pyrazole-4,5-dione-4-[(4-substituted phenyl) hydrazone]. The synthesized compound (fig.22) exhibited significant analgesic activity with the standard drug (indomethacin 5 mg/kg) at the dose level of 50 mg/kg on oral administration.



R'	R
a = H	Cl
b = H	Br
d = H	CH3
h = H, Cl	Cl
i = H, Br	Br

Fig 22

A series of 1-(4-substituted phenyl)-3-phenyl-1*H*-pyrazole-4-carbaldehydes have been synthesized by T. P. Selvam *et al.*[58] Formation of the pyrazole derivatives was achieved by treating with Vilsmeier-Haack reagent. The newly synthesized compounds have been evaluated for their anti-inflammatory and analgesic activities compared to Diclofenac sodium as standard drug. Compounds 23a, 23b and 23c exhibited the maximum anti-inflammatory and analgesic activities.



Compound	R_1	R_2
23 a	–H	–F
23 b	–H	–Cl
23 c	–H	–Br

Fig 23

Pyrazole as Anti angiogenic Agent

M. S. Christodoulou *et al.,* [59] synthesized and reported a series of novel trisubstituted pyrazole derivatives and their PIFA-mediated conversion to molecules bearing the fused pyrazolo[4,3-c] quinoline ring system. The anti angiogenic activity of these compounds was evaluated by using *In vitro* assays for endothelial cell proliferation and migration, and in the chicken chorioallantoic membrane (CAM) assay. Compounds containing the fused pyrazolo[4,3-c]quinoline motifs emerged as potent anti angiogenic compounds, which also had the ability to inhibit the growth of human breast (MCF-7) and cervical (Hela) carcinoma cells *In vitro*.

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