



Pharmacological Activities of Pyrazoline Derivatives

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ABSTRACT

The review of the literature shows diverse pharmacological activities of pyrazoline moiety. Pyrazoline derivatives display various pharmacological activities such as antimicrobial, anti-inflammatory, antitumor, antioxidant, anti-analgesic, anti-depressant etc. The purpose of this review was to collect literature on research work reported by various researchers on pyrazolines for their various pharmacological activities and also report recent efforts made on this moiety.

Keywords: Pyrazoline derivatives, pharmacological activities, anti-microbial, anti-inflammatory.

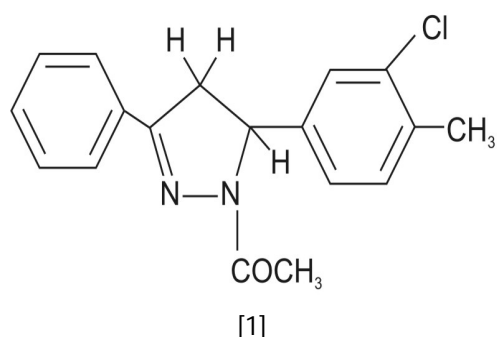
INTRODUCTION

Pyrazolines are five member ring heterocyclic compounds having two adjacent nitrogen atom within the ring. It has only one endocyclic double bond and is basic in nature. The study of biological evaluation of pyrazoline derivatives has been an interesting field of medicinal chemistry. Pyrazoline exhibit biological activities such as antimicrobial, antitumor, antiviral, antitubercular, antioxidant, anticonvulsant activity etc. Several pyrazolines have shown promising results as chemotherapeutic agents.

PHARMACOLOGICAL ACTIVITIES OF PYRAZOLINE DERIVATIVES

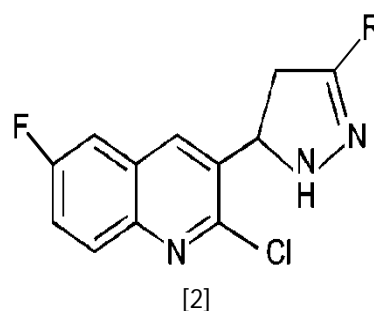
Antibacterial Activity

Vijayvergiya et al., synthesized some new 3,5-diaryl-1-phenyl/isonicotinoyl-2-pyrazolines [1] and evaluated their antibacterial activity against gram+ve bacteria *S. aureus*, *S. albus*, *S. pyogenes*, *S. viridans* and gram-ve bacteria *E. coli* and *S. typhosa*.¹

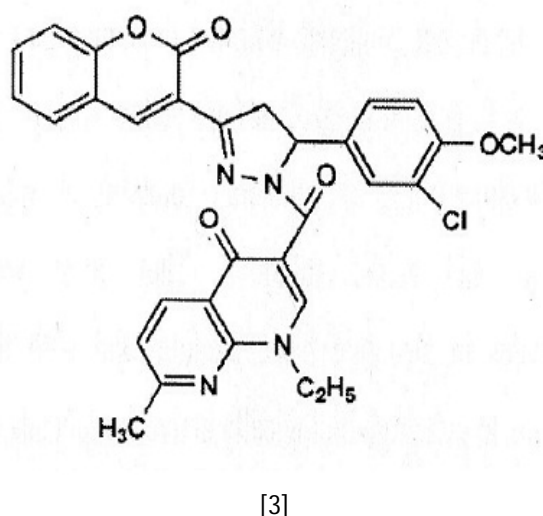


Baluja and Chandra synthesized a series of pyrazoline derivatives [2] and their antibacterial activities were evaluated against gram +ve bacteria viz. *Bacillus cereus*, *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Micrococcus luteus*, and gram-ve bacteria viz. *Proteus mirabilis*, *E. coli*, and *Klebsiella aerogenes*. The pyrazoline

derivatives which had nitro group at para position showed best antibacterial activity.²



Waheed and Khan synthesized certain substituted 1,2-pyrazolines [3] from nalidixic acid as antibacterial agents. They were found to have significant antibacterial activity against gram-ve bacteria.³

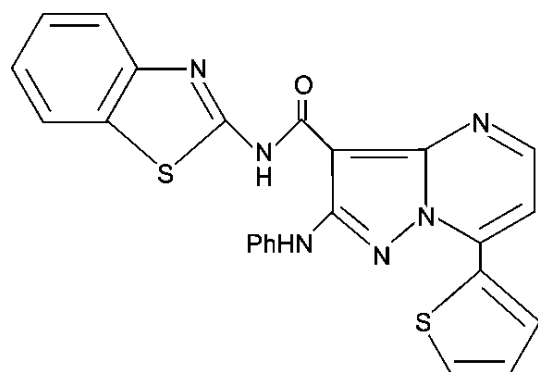


Chimenti et al., synthesized a series of N 1-substituted 3,5-diphenyl pyrazolines [4] and evaluated their *in vitro* antibacterial activity against *H. pylori*. Among the prepared compounds those with an N1-acetyl group and

a 4-methoxy substituent in the 5-phenyl ring showed the best activity against *H. pylori* metronidazole resistant strains in the 1-4 $\mu\text{g}\cdot\text{ml}^{-1}$ MIC range.⁴

Antifungal Activity

Bondock et al., prepared a series of substituted pyrazole derivatives [4]. The compound was found to exhibit the most potent *in-vitro* antifungal activity with MICs (6.25 $\mu\text{g}/\text{ml}$) against *A. fumigatus* and *F. oxysporum* comparable with chloroamphenicol.⁵

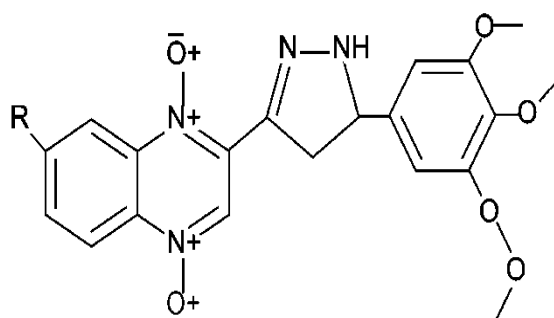


[4]

Lamani and Kotresh synthesized a series of 2-pyrazolines by reaction with quinoline and acetyl syndone derivatives as the starting materials. The synthesized compounds have shown promising activities towards the fungal strains viz, *A. niger* and *A. sereus*.⁶

Anti-inflammatory Activity

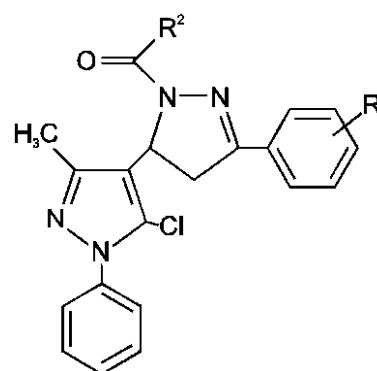
Burguete et al., prepared substituted pyrazole derivatives [5] and evaluated them for their anti-inflammatory activities. These compounds showed good anti-inflammatory activity against Carrageenan induced rat paw edema test.⁷



[5]

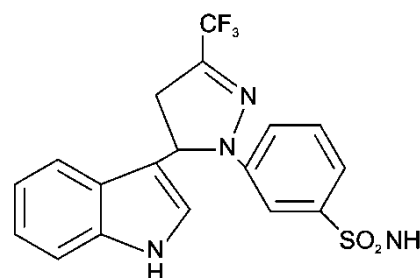
Girisha et al., synthesized a series of 1-acetyl/ propyl-3-aryl-5-(5-chloro-3-methyl-1-phenyl-1Hpyrazol-4-yl)-2-pyrazolines [6] in one step by condensing suitably substituted propenones, hydrazine and acetic/ propionic acid.

The newly synthesized compounds were screened for analgesic and anti-inflammatory activity and most of them showed good activity comparable with that of standard drugs pentazocin and diclofinac sodium respectively.⁸



[6]

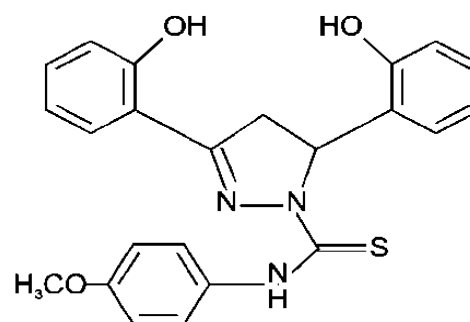
Reddy et al. designed and synthesized a series of novel 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-indolyl pyrazolines [7] and screened their *in vitro* anti-inflammatory activity. These compounds were designed for evaluation as dual inhibitors of cyclo-oxygenase (COX-1 and COX-2) and lipoxygenases (LOX-5, LOX-12 and LOX-15) that are responsible for inflammation and pain.⁹



[7]

Anti-depressant Activity

Jayaprakash et al., synthesized several 3, 5-diaryl carbothioamide pyrazolines [8] designed as mycobactin analogs (Mycobacterial siderophore) and evaluated their antidepressant activity.¹⁰



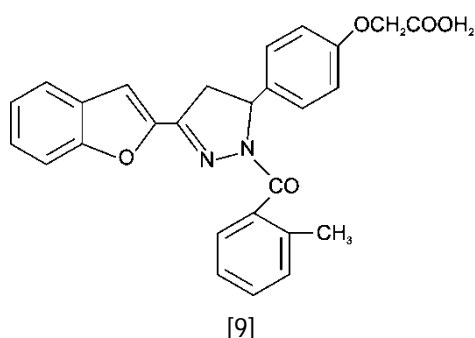
[8]

Palaska et al., synthesized new 3, 5-diphenyl-2-pyrazoline derivatives by reacting 1, 3- diphenyl-2-propen-1-one with hydrazine hydrate. The chemical structure of the compounds was proved by means of their IR, ¹H-NMR spectroscopic data and microanalysis. The antidepressant activities of these compounds were evaluated by the Porsolt Behavioural Despair Test on Swiss-Webster mice. In addition, it was found that 4-methoxy and 4-chloro substituents on the phenyl ring at position 3 of the pyrazoline ring increased the antidepressant activity.¹¹

Prasad et al., synthesized new 1, 3, 5-triphenyl-2-pyrazolines and evaluated their antidepressant activity by the Porsolt behavioural despair test on Swiss-Webster mice. In addition, it was found that the compounds possessing electron-releasing groups such as dimethylamino, methoxy and hydroxyl substituents on both the aromatic rings at position 3 and 5 of pyrazolines, considerably enhanced antidepressant activity when compared to the pyrazoline having no substituent on the phenyl rings.¹²

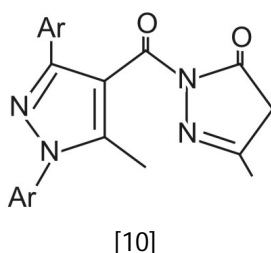
Antioxidant Activity

Babu et al., synthesized a series of pyrazoline derivatives viz. 2-(4-(3-(benzofuran-2-yl)-1-(2-methyl benzoyl)-2-pyrazolin-5-yl) phenoxy) acetic acid [9] and evaluated their antioxidant activity at 100, 500, 250, 100, 50, 25 and 10mg/ml concentrations against standard drug ascorbic acid.¹³



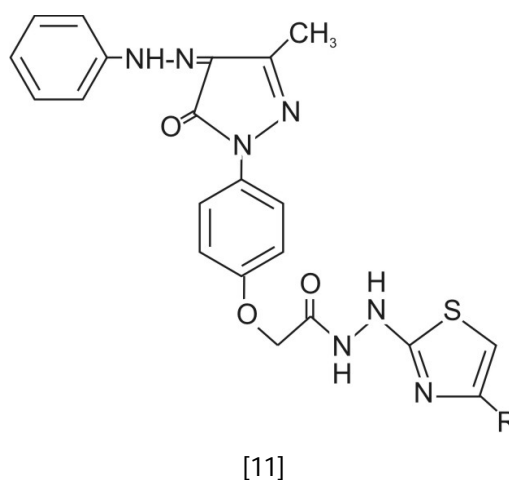
Jagdish et al., synthesized mannich base of pyrazolines under both conventional and microwave irradiation and purified by recrystallisation, characterized on the basis of UV, IR and NMR spectroscopy and further supported by mass spectroscopy. The synthesized compounds were subsequently evaluated for the antioxidant activity and showed better antioxidant activity as compared to ascorbic acid.¹⁴

Umesha et al., synthesized 5-methyl-2-(5-methyl-1,3-diphenyl-1H-pyrazole-4-carbonyl)-2,4-dihydro-pyrazol-3-one [10] and evaluated their antioxidant activity.¹⁵

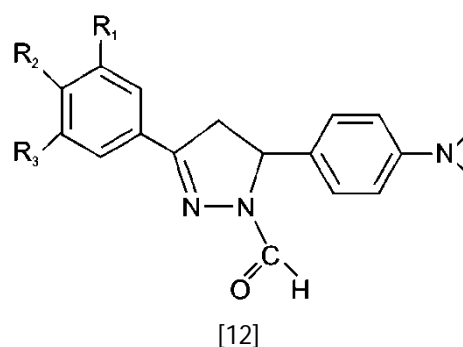


Antimicrobial Activity

Naik et al., synthesized a series of [4-(3-methyl-5-oxo-4-(phenyl hydrazono)-4,5-dihydro-pyrazol-1-yl)-phenoxy] – acetic acid N-(4-substituted – thiazole –2-yl)- hydrazide [11] and evaluated antibacterial activity against *Staphylococcus aureus*, *Bacillus cereus*, *E. coli* and *Pseudomonas aeruginosa* and antifungal activity evaluated against *Aspergillus niger*, *Candida albicans* by disc diffusion method.¹⁶

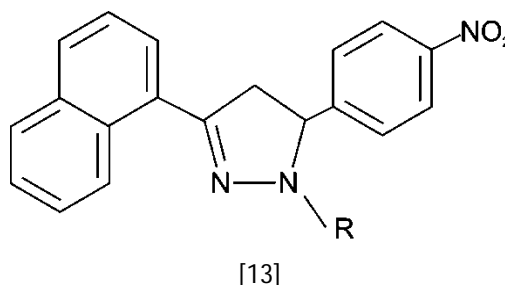


Kendre and Baseer have synthesized a new series of acetyl pyrazoline derivatives [12] by conventional method in excellent yield and in less reaction time using ethanol via cyclization reaction of chalcones, hydrazine hydrate and few drops of glacial acetic acid. These newly synthesized compounds were screened for their antimicrobial activities against different types of bacteria and fungi.¹⁷



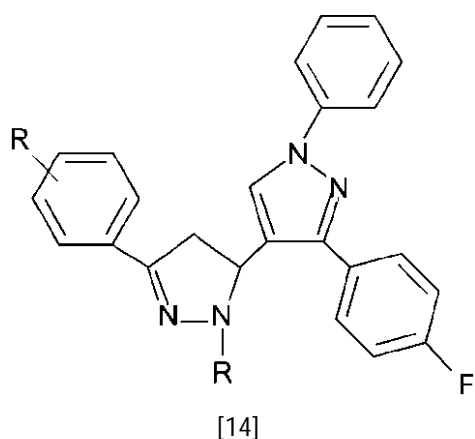
Dawane et al., synthesized some new 1-thiazolyl-2-pyrazoline derivatives by the base catalyzed condensation of 4-(2'-hydroxy-5'-chlorophenyl)-2-hydrazino-thiazole and pyrazole containing chalcones in polyethylene glycol (PEG-400) as a green reaction medium and tested their antimicrobial activities.¹⁸

Agarwal et al., synthesized 1,3,5-trisubstituted pyrazoline derivatives [13] and screened their antimicrobial activity.¹⁹

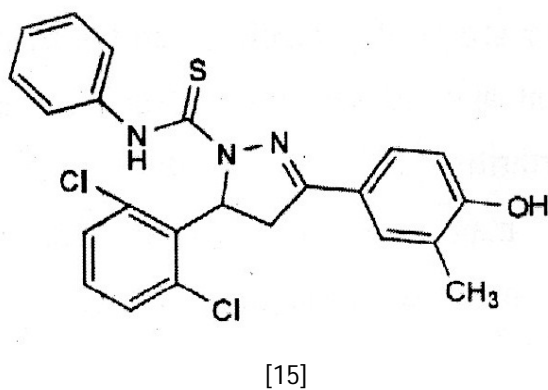


Antitubercular Activity

Coutinho et al., synthesized a series of N-phenyl-3-(4-fluorophenyl)-4-substituted pyrazole derivatives [14] and screened their antitubercular activity.²⁰

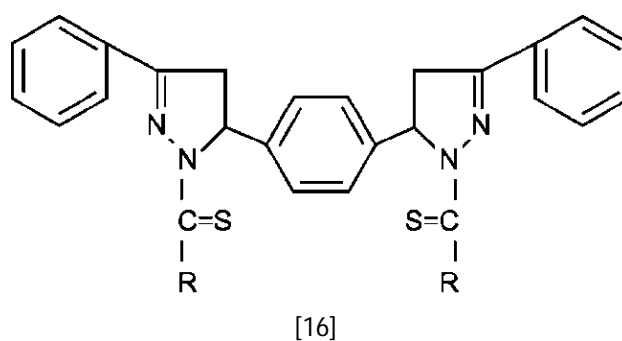


Ali et al., prepared a series of 5-(4-(substituted phenyl)-3-(4-hydroxy-3-methylphenyl)-4, 5-dihydro-1H-1-pyrazolyl)-2-toluidinomethan-ethione and 5-(substituted phenyl)-3-(4-hydroxy-3-methylphenyl)-4, 5-dihydro-1H-1-pyrazolyl-2-methoxyanilino methane thione by the reaction between hydrazine hydrate and chalcones followed by condensation with appropriate aryl isothiocyanate which yielded N-substituted pyrazoline derivatives. Newly synthesized compounds were tested for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H₃₇Rv using the bactec 460 radiometric system. Among the prepared compounds, anilino-3-(4-hydroxy-3-methylphenyl)-5-(2, 6-dichlorophenyl)-4, 5-dihydro-1H-1-pyrazolylmethanethione [15] was found to be the most active agent against *M. tuberculosis* H₃₇Rv with minimum inhibitory concentration of 0.0034 μ M.²¹

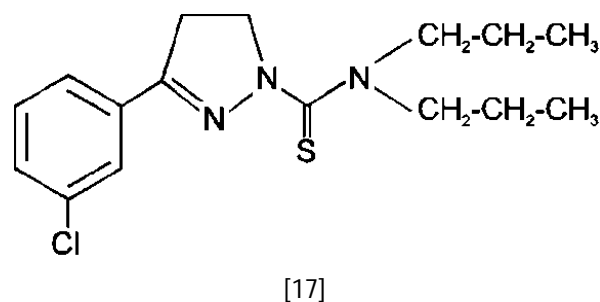


Antiamoebic Activity

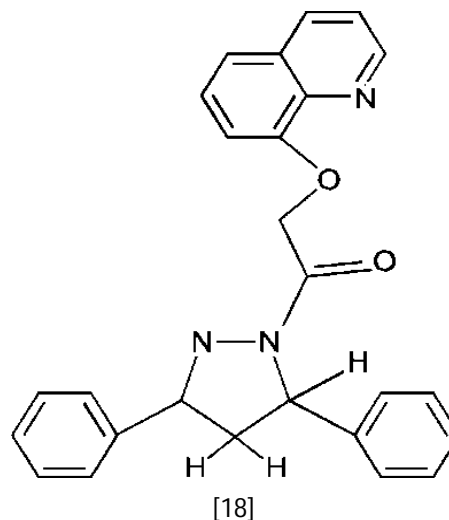
Athar et al. synthesized thiocarbamoyl bis-pyrazoline derivatives [16] by cyclization of chalcone with N-4 substituted thiosemicarbazides under basic condition. The structure of the compounds was elucidated by UV, IR, ¹H NMR, ¹³C NMR and ESI-MS spectral data and thermogravimetric analysis and their purities were confirmed by elemental analysis. The antiamoebic activity of these complexes was evaluated by microdilution method against HM1: IMSS strain of *Entamoeba histolytica* and the results were compared with the standard drug, metronidazole. Structure-activity relationship showed that the compounds with aromatic substituents at the thiocarbamoyl group was more active than those with the cyclic groups.²²



Abid and Azam synthesized a series of new 1-N-substituted cyclised pyrazoline analogues of thiosemicarbazones [17] by cyclization of mannich bases with thiosemicarbazides of variegated nature. The chemical structure of the compounds was proved by UV, IR, ¹H NMR, ¹³C NMR spectroscopic data and elemental analyses. The antiamoebic activities of these compounds were evaluated by micro-dilution method against HM1: IMSS strain of *Entamoeba histolytica*. It was found that 3-chloro and 3-bromo substituents on the phenyl ring at position 3 of the pyrazoline ring enhanced the antiamoebic activity as compared to unsubstituted phenyl ring.²³

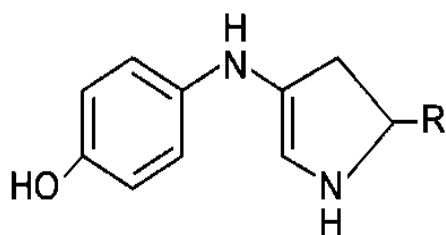


Azam et al., synthesized novel pyrazoline derivatives [18]. *In vitro* antiamoebic activity was performed against HM1: IMSS strain of *Entamoeba histolytica*. The results showed that the compounds exhibited promising antiamoebic activity than the standard drug metronidazole (IC₅₀= 1.84 μ M). The toxicological studies of these compounds done on human breast cancer MCF-7 cell line showed that all the compounds and metronidazole were non-toxic at the concentration range of 1.56 – 50 μ M.²⁴



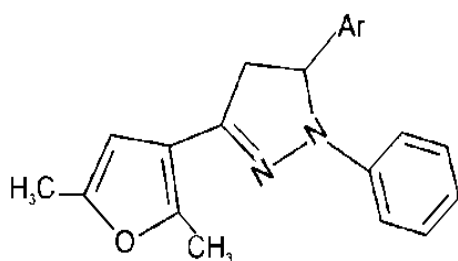
Analgesic Activity

Sahu et al., developed some novel pyrazoline derivatives [19] and observed potent analgesic activity. The compound showed effective analgesic and anti-inflammatory activities.²⁵



[19]

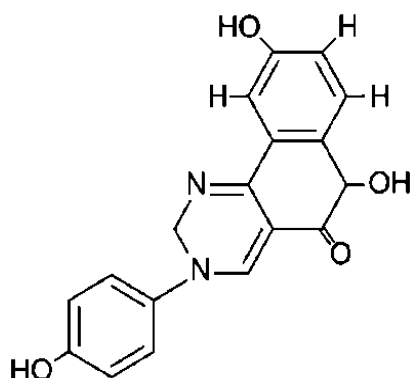
Sridhar and Rajendra Prasad synthesized a new series of 2-pyrazolines [20] and evaluated their analgesic activity.²⁶



[20]

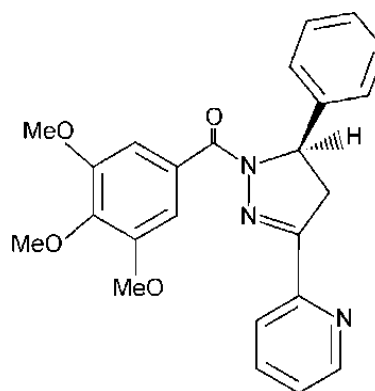
Anticancer Activity

Christodoulo et al., prepared a new series of trisubstituted pyrazole derivatives and screened the compounds for anti-angiogenic activity. Compounds containing the focused pyrazole 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. The compound [21] was found to be active eliciting 64% of inhibition ($P < 0.01$) by chicken chlorioallantoic membrane (CAM) assay.²⁷



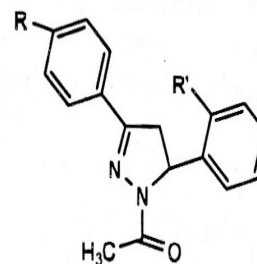
[21]

Caggiano et al., synthesized and investigated some 3-(pyrid-2yl)-pyrazoline [22] and their antiproliferative activities. The lead pyrazoline was selected from this preliminary study and further investigated against the NCI 60 cancer cell line and exhibits sub-micromolar activity in a number of cell lines.²⁸



[22]

Manna et al., synthesized a series of substituted pyrazoline (1-acetyl-3, 5-diphenyl-4, 5-dihydro-(1H)-pyrazole) and evaluated their anticancer activity and their ability to inhibit *P*-glycoprotein-mediated multidrug resistance by direct binding to a purified protein domain containing an ATP-binding site and a modulator interacting region. Compounds [23] have been found to bind to *P*-glycoprotein with greater affinity.²⁹



[23]

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