

EXPERT OPINION

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Recent advances in the therapeutic applications of pyrazolines

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Introduction: Pyrazolines are well-known and important nitrogen-containing five-membered ring heterocyclic compounds. Various methods have been worked out for their synthesis. Several pyrazoline derivatives have been found to possess diverse biological properties, which has stimulated research activity in this field.

Areas covered: The present review sheds light on the recent therapeutic patent literature (2000 – 2011) describing the applications of pyrazolines and their derivatives on selected activities. Many of the therapeutic applications of pyrazoline derivatives have been discussed, either in the patent or in the general literature areas in this review. In addition to selected biological data, a wide range of pharmaceutical applications and pharmaceutical compositions are also summarized.

Expert opinion: Pyrazoline derivatives have numerous prominent pharmacological effects, such as antimicrobial (antibacterial, antifungal, antiamebic, antimycobacterial), anti-inflammatory, analgesic, antidepressant and anticancer. Further pharmacological effects include cannabinoid CB1 receptor antagonists, antiepileptic, antitrypanosomal, antiviral activity, MAO-inhibitory, antinociceptive activity, insecticidal, hypotensive, nitric oxide synthase inhibitor, antioxidant, steroidal and antidiabetic. Lastly, they also effect ACAT inhibition, urotensin II and somatostatin-5 receptors, TGF- β signal transduction inhibitors and neurocytotoxicity inhibitors activities. Many new pyrazoline derivatives have been synthesized and patented, but there are still new aspects to explore and work on.

Keywords: 2-pyrazolines, biological activity, dihydropyrazoles, pharmacological activity

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1. Introduction

Pyrazoline is a five-membered ring heterocycle having two adjacent nitrogen atoms within the ring. It has only one endocyclic double bond and is of basic in nature [1]. They are also known as dihydropyrazoles and their chemistry are closely related to pyrazoles. According to heterocyclic nomenclature, pyrazolines require that the nitrogen atoms to be numbered 1 and 2 in each structure. There are three well-known tautomeric structures for pyrazolines namely: 1-pyrazoline, 2-pyrazoline and 3-pyrazoline (Figure 1). However, among these tautomeric structures, 2-pyrazoline is the most common.

Pyrazoline derivatives are electron-rich nitrogenous heterocycles, which play an important role in the diverse biological activities. Among its derivatives, 3-substituted pyrazolines seem to be the most attractive pyrazoline-type derivatives [2]. These heterocyclic compounds are widely occurring in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cell.

Article highlights.

- Pyrazoline heterocycle provides a structural core for building huge variety of biologically active compounds.
- The pharmacological activity of pyrazoline-based compounds extends from central nervous system (CNS) applications to antimicrobials.
- The most predominant pharmacological activity was observed for the class of 'antimicrobials'.
- Cannabinoid receptor type 1 (CB1) pyrazoline modulators are very useful in treatment of obesity and schizophrenia.
- Pyrazoline-containing cytotoxic compounds are not only useful in treatment of cancer, but also some of them act as cancer chemopreventive agents.
- There are many reports centered on the antimycobacterium activity of pyrazoline-containing compounds, most of them have been assayed versus the vaccine-strain H37Rv.

This box summarizes key points contained in the article.

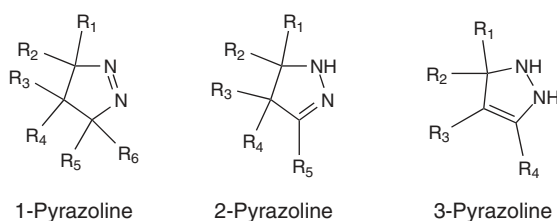


Figure 1. Tautomeric structures for pyrazolines.

According to the X-ray analysis, pyrazoline ring has the structure of the five-membered dihydropyrazole ring and it has an envelope conformation [3]. The carbon atom at position-5 is deviated from the almost planar system of the other four atoms of the heterocyclic ring [4]. 2-Pyrazoline is insoluble in water but soluble in propylene glycol because of its lipophilic character [4].

Diversely substituted pyrazolines and their derivatives embedded with variety of functional groups are important biologically active agents and a huge amount of research activities have been directed toward this class of compounds. Pyrazoline derivatives are typical ICT (intramolecular charge transfer) compounds [5], and are known as a kind of fluorescent brightening agents because they have strong blue fluorescence in solution.

A classical synthesis of these compounds has been stimulated after the pioneering work of Fischer and Knöevenagel in the late 19th century [6]. The reaction of α,β -unsaturated aldehydes and ketones with hydrazines became one of the most popular methods for the preparation of 2-pyrazolines [7,8]. In this method, hydrazones are formed as intermediates, which can be subsequently cyclized to 2-pyrazolines in the presence of a suitable cyclizing reagent like acetic acid. An alternative route involves 1,3-dipolar cycloaddition of nitrileimines to

carbon-carbon double bond of arylmethylene (arylidene derivatives of active methylene) compounds as well as acrylic and cinnamic acid derivatives [9-15]. The discovery of this class of compounds and considering their efficiency as drugs provides an outstanding case history of modern drug developments and also points out the unpredictability of pharmacological activity from structural modification of a prototype drug molecule. In general, pyrazoline derivatives display a broad spectrum of potential pharmacological activities and have wide medical applications.

2. Pyrazoline patents

2.1 Overview of patent activity

In the last decade, a significant interest of research in heterocyclic chemistry has been directed to substituted 2-pyrazoline derivatives. Section 2.2 of this review focuses on the recent development on pyrazolines along with their biological properties in both regular literature and patents field. Recently, some important reviews have been published on pyrazoline compounds [16,17].

The present review casts light on the recent patents and literature that is directed toward the therapeutic applications of pyrazolines during the period 2000 – 2011. The patents activities that have been reviewed include the World Intellectual Proprietary Organization (WIPO), United States Patent Trademark Office (USPTO), The European Patent Office (EP), German Offen. (DE), Spain (ES), China (CN) and Korea (KR) patents. Figure 2 illustrates the distribution of patents over the period 2000 – 2010. Obviously, 2007 has the highest activity in the therapeutic applications of pyrazolines.

2.2 Biological and therapeutic applications of pyrazolines

2.2.1 Cannabinoid CB1 receptor antagonists

One of the most attractive subjects of intensive research on pyrazoline derivatives is cannabinoid receptor type 1 (CB1) antagonists due to their highly fruitful therapeutic features. CB1 receptor antagonists have good prospects in many therapeutic areas, such as smoking and alcohol addiction as well as cognitive impairment. Recently, new chemical entities (NCEs) with CB1 antagonistic properties, structurally related to rimonabant 1, have been disclosed by some academic research groups and several pharmaceutical companies as well. There are a considerable number of CB1 antagonists that are bioisosteres and derived from rimonabant (1) by replacement of the pyrazole moiety with other heterocyclic analogs like pyrazoline.

Recently, Marti *et al.* reported one-pot preparation of cinchonidine salt of (4*S*,5*S*)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-4,5-dihydro-1*H*-pyrazole-3-carboxylic acid (2), which is useful as an intermediate in the preparation of cannabinoid CB1 neutral antagonists. The method is efficient to avoid isolation of intermediates and produces product in good yield and enantiomeric excess [18].

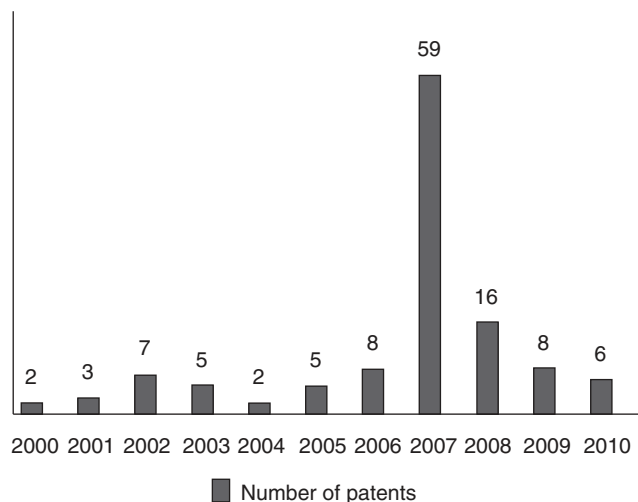
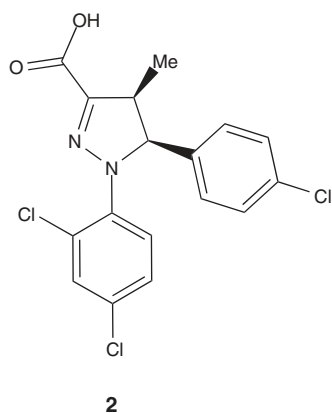
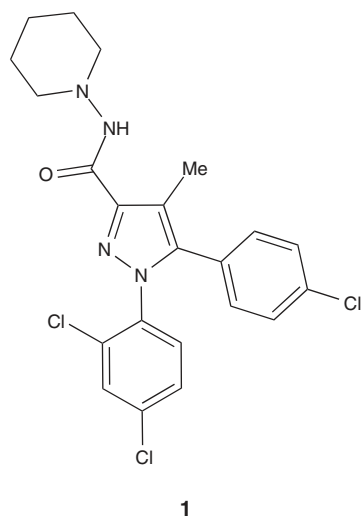


Figure 2. The distribution of patents on pyrazolines over the period 2000 – 2010.



Also, synthesis of 3,4-diphenyl-4,5-dihydro-pyrazole-1-carboxylic acid hydrazide **3**, which is used as CB1 modulators was achieved by Yoo *et al.* [19]. In CB1 receptor binding assay, pyrazoline **4** hydrochloride showed 97% affinity at 3 μ M. So far, pyrazoline derivatives of the general structure **5** are claimed to be useful for the treatment of obesity and schizophrenia.

Preparation of the cannabinoid CB1 receptor ligand 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1*H*-pyrazole-3-carboxamide (**6a**) have been reported by Soler *et al.* [20,21]. Solid solutions and/or solid dispersions of **6a** as racemate, or the (*S*)-enantiomer **6b** were prepared efficiently in such patents. The same results have been achieved by Vela Hernandez for the preparation of (4*S*,5*S*)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(*cis*-2,6-dimethylpiperidin-1-yl)-4-methyl-4,5-dihydro-1*H*-pyrazole-3-carboxamide (**6b**) as a cannabinoid CB1 neutral antagonist for treatment of food intake disorders [28,29].

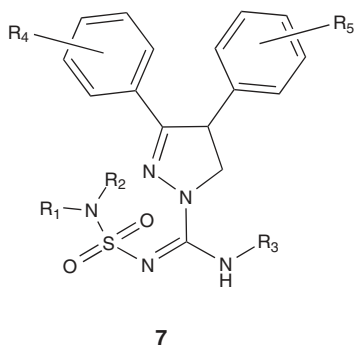
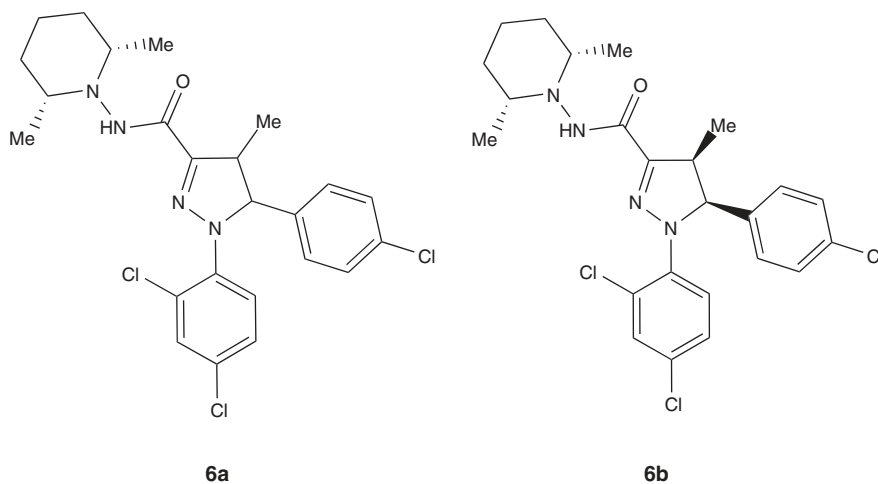
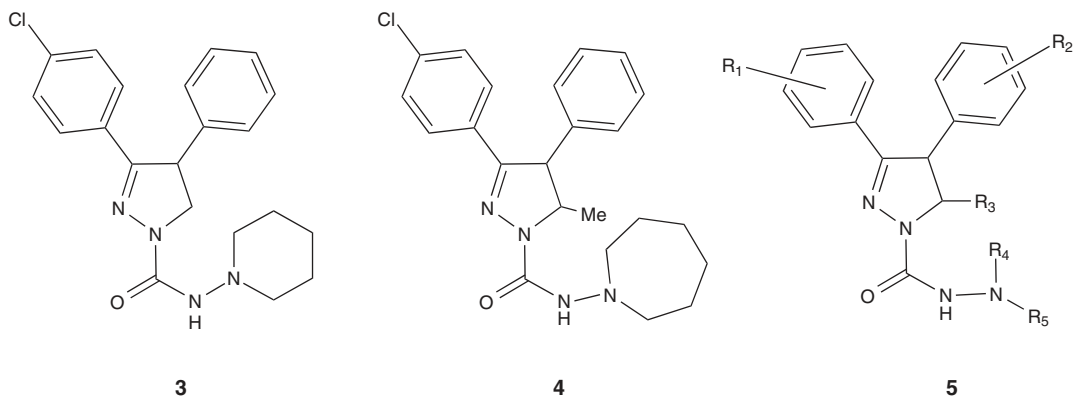
In the same context, Mcelroy and Chorvat have achieved the preparation of substituted *N*-phenyl-5-phenyl-pyrazolin-3-yl amides as cannabinoid receptor antagonists/inverse agonists useful for treating obesity, diabetes, dyslipidemias, cardiovascular disorders and/or hepatic disorders [22].

3,4-Diarylpiprazoline derivatives **7** have been reported by Lange *et al.* as potent CB1 receptor antagonists. Compound **7** showed lower lipophilic characters. The dramatic change was the replacement of the arylsulfonyl group by a dialkylamino-sulfonyl moiety. One of these compounds exhibited the highest CB1 receptor affinity as well as very potent CB1 antagonistic activity and a high CB1/CB2 subtype selectivity [23].

Sulfonamide-containing pyrazoline derivatives of general structure **8** were prepared by Buschmann *et al.* [24] and were used as CB1 modulators. Compounds **9** have been prepared *via* a multistep synthesis starting from 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylic acid. The pyrazoline **9** showed a high affinity to the CB1 receptor and IC_{50} value of 14.1 nM.

A number of analogs of diaryl-2-pyrazoline-3-carboxamides **10** have been prepared by Srivastava *et al.* and were evaluated for appetite suppression and body weight reduction in animal models. Both of the bisulfate salt of (\pm)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide and (-)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylic acid morpholin-4-ylamide (**11**) showed significant body weight reduction *in vivo*. This was attributed to their CB1 antagonistic activity together with favorable pharmacokinetic profiles [25].

Donohue *et al.* used the radio-labeled ligands of (-)-3-(4-chlorophenyl)-*N*-[(4-cyanophenyl)sulfonyl]-4-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (**12**) for imaging of CB1 receptors *in vivo* with positron emission tomography (PET) for understanding their importance in neuropsychiatric disorders [26].



Also, some substituted pyrazoline derivatives 13 have been reported by Fisas-Escasany and Buschmann [27] and were evaluated for preventing weight gain. They reported a multistep synthesis of pyrazoline derivatives 14, starting from 4-chlorobenzaldehyde and ethyl pyruvate. Compounds 14 showed IC_{50} value of 26 nM when tested *in vitro* for the rat CB1 receptor subtype.

In the same consequence, Buschmann *et al.* reported the preparation of 4-substituted pyrazoline derivatives 13 as cannabinoid receptor inhibitors for treating various diseases [34].

Lange *et al.* [30] reported the reaction of (pentylhydrazono) acetic acid ethyl ester, with *N*-chlorosuccinimide (NCS)

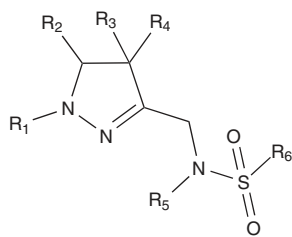
followed by *in situ* treatment with styrene, hydrolysis and amidation with 2-adamantanamine hydrochloride to afford the pyrazoline 16. The latter compound showed high affinity for cannabinoid receptors and agonistic activity on CB1 receptor, which is also useful for the treatment of multiple sclerosis and traumatic brain injury.

4,5-Dihydro-(1*H*)-pyrazole derivatives 17 and 18 have been prepared by Yildirim *et al.* [31]. Compounds containing the pyrazoline structure 17 are used as CB1 receptor modulators. Pyrazoline 18 exhibited pK_i values of 8.1 and 8.4 for CB1 and CB2, respectively, in cannabinoid receptor affinity assays.

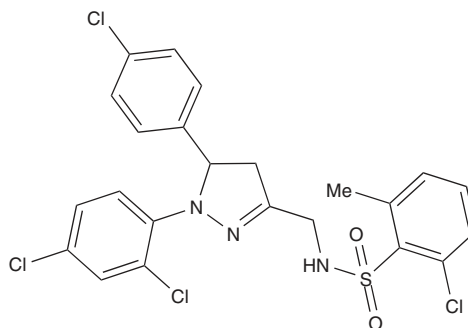
Indoline-substituted pyrazoline derivatives 20 and 21 have been reported as cannabinoid receptor modulators by Torrens-Jover *et al.* [32]. Compounds of the general structure 19 were tested for their cannabinoid activity *in vivo*.

In addition, azepane- or azocane-substituted pyrazoline derivatives 22 have been also prepared by Torrens-Jover *et al.* [33].

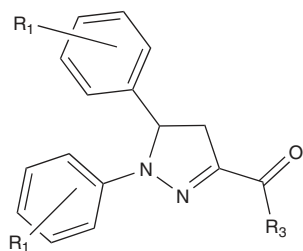
Preparation of octahydropentalene- and cycloalkane-substituted pyrazoline derivatives 23 and 24, respectively have been achieved by Torrens-Jover *et al.* [36,37]. Some of the selected compounds of the general formula 25 were tested for their *in vivo* cannabinoid activity. Also, some prodrugs of pyrazoline compounds 25 have been prepared by Torrens-Jover *et al.* as CB1 receptor antagonists [38].



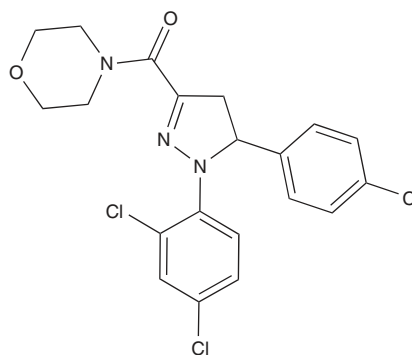
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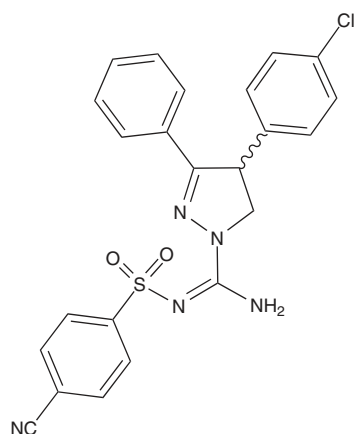
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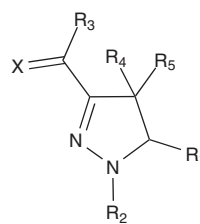
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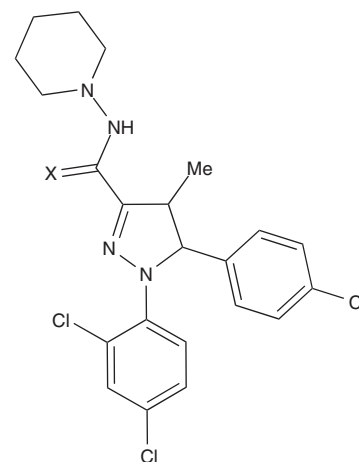
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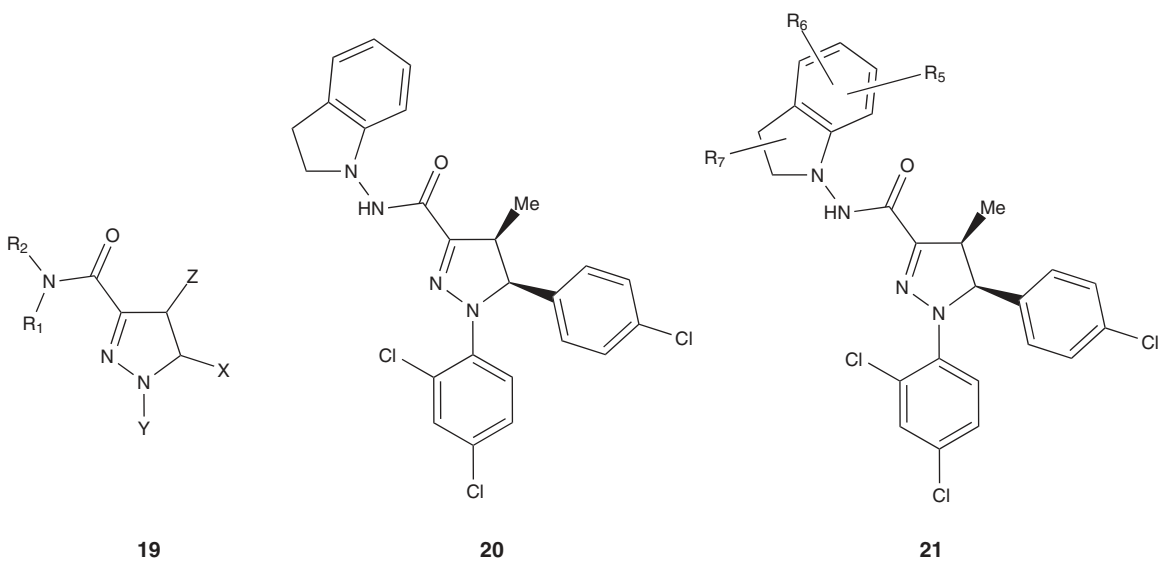
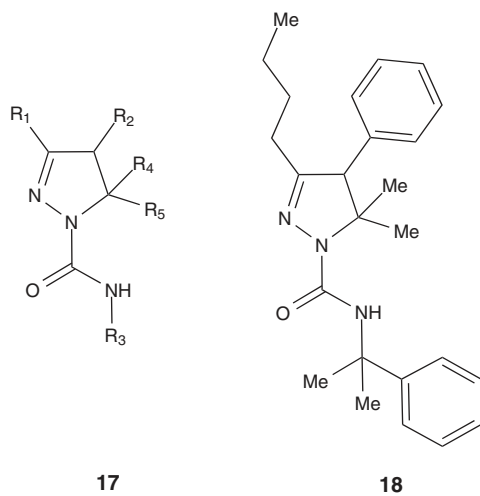
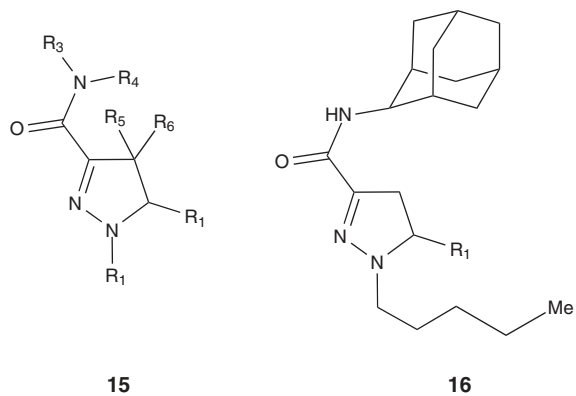


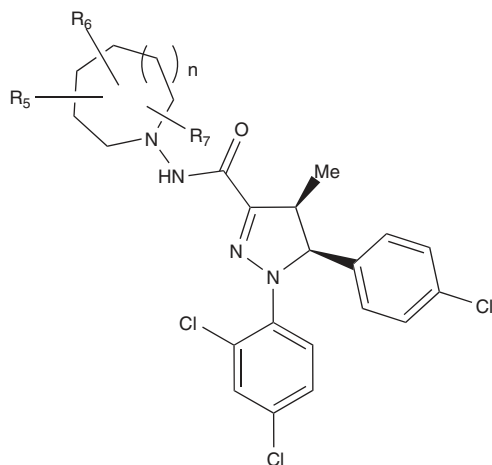
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2.2.2 Anticancer activity

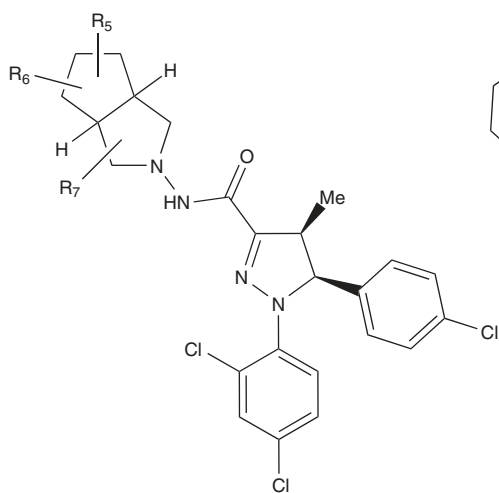
Recently, syntheses of 4-substituted 1*H*-pyrazolines have been achieved by Yenes-Minguez and Torrens-Jover [39]. The synthesized pyrazoline derivatives 26 have been investigated for cancer treatment or prophylaxis. Pyrazolines such as 27 and 28 could be successfully employed in treatment and/or cancers prophylaxis of many types ranging from the brain, bone, mouth, esophagus, stomach, liver, bladder, pancreas, cervix, lung, breast, colon, rectum or prostate cancers.

Several novel thiazolone-based compounds containing 5-aryl-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl framework 29a have been reported by Havrylyuk *et al.* [40]. The synthesized compounds were evaluated *in vitro* for their cytotoxic activity. Most of the tested compounds displayed promising anticancer activity versus variety of cancer types including leukemia, melanoma, lung, colon, ovarian, renal, prostate and breast cancer cell lines. Among these series, compound 29b showed the most efficient anticancer potency

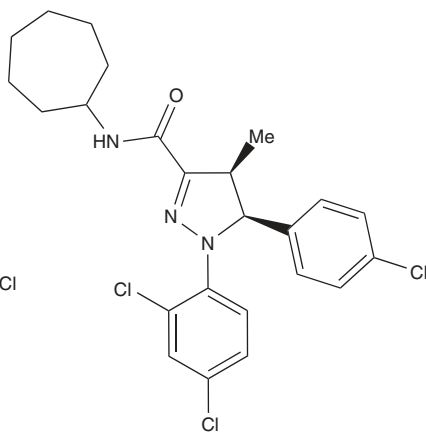




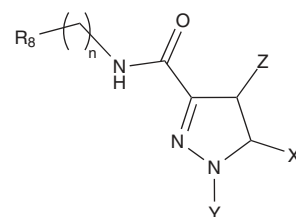
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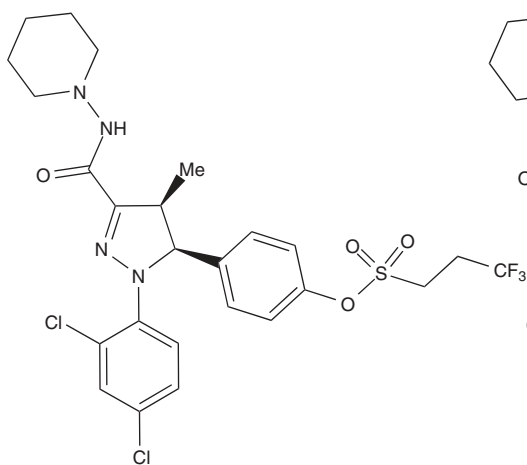
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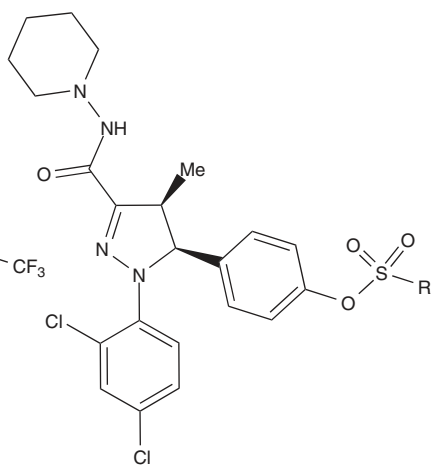
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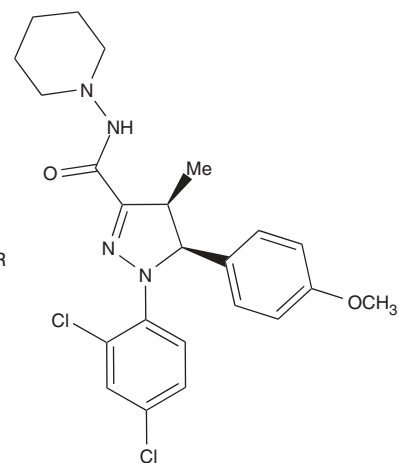
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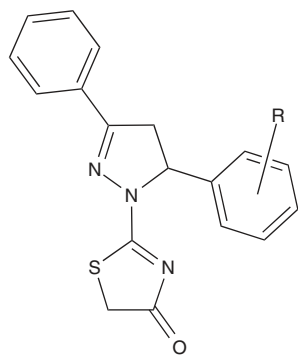
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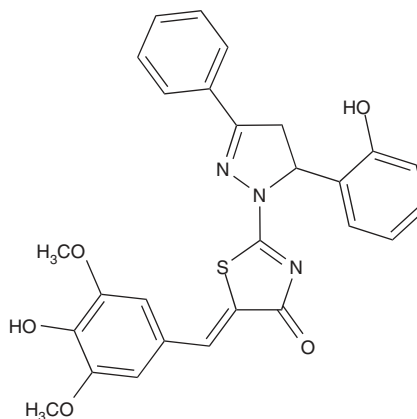
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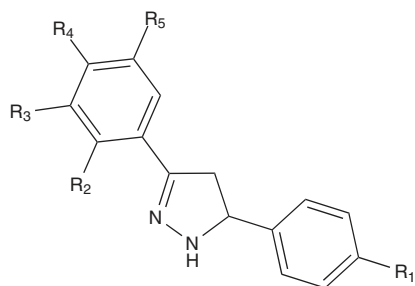
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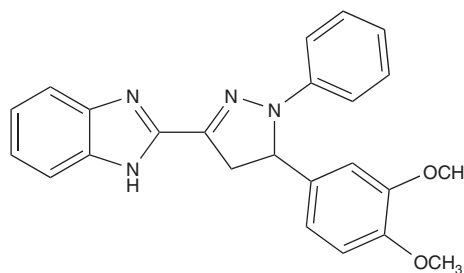
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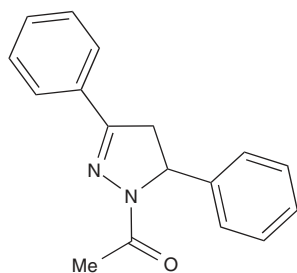
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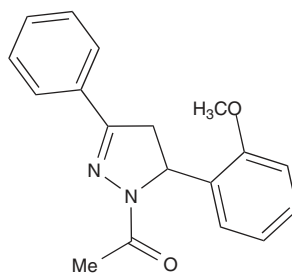
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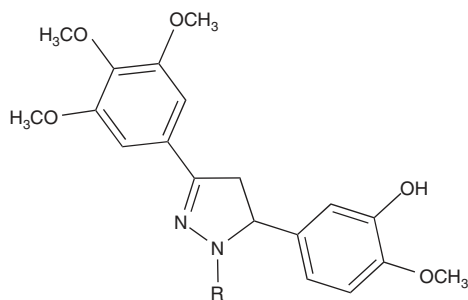
and was found to be active with selective influence on colon cancer cell lines, especially on HT-29 ($\log GI_{50} = -6.37$).

Bhat *et al.* [41] prepared some substituted pyrazoline derivatives **30** and evaluated for their *in vitro* cytotoxic activity against a panel of human cancer cell lines. Only eight compounds showed marked activity out of 93 screened compounds.

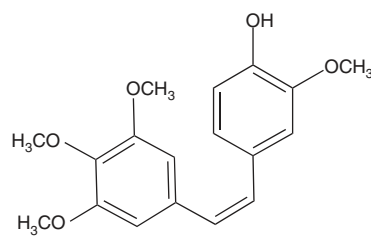
The antineoplastic activities a series of pyrazoline-bearing benzimidazoles versus full NCI 60 cell panel have been reported by Shahrayar *et al.* [42]. Compound **31** demonstrated the best cytotoxic properties. It has high

selectivity against certain cell lines including Leukemia CCRF-CEM and RPMI-8226 cell lines with GI_{50} values of 2.23 and 2.76 μ M, respectively [42].

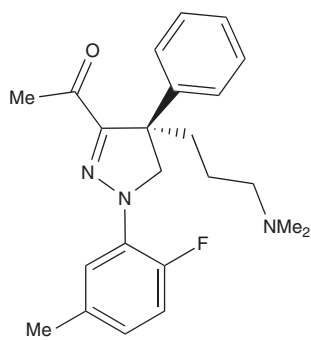
1-Acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives **32** and **33** have been reported by Manna *et al.* [43], evaluated for their antineoplastic activity, and for their inhibitory effect on P-glycoprotein-mediated multidrug resistance protein (MDR1); which confers resistant to tumor cells by decreasing drug accumulation within tumor cells [44]. Both compounds **32** and **33** have been found to be active as MDR1 blockers.



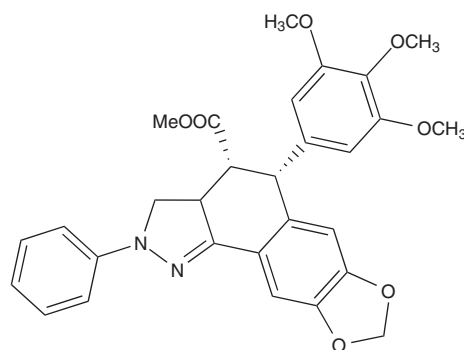
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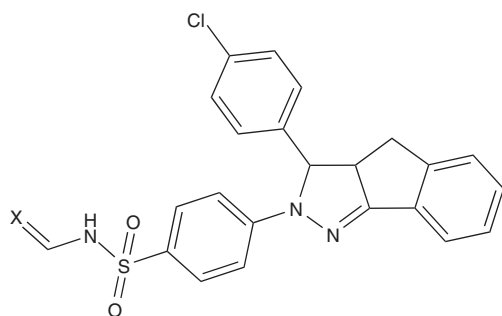
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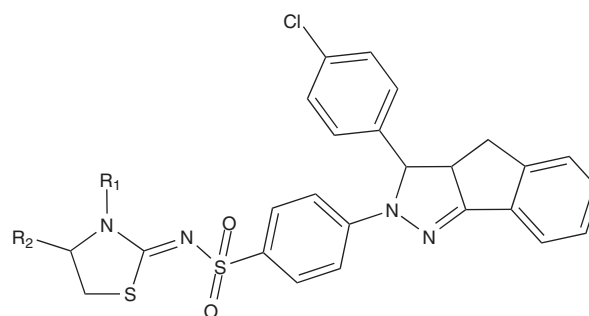
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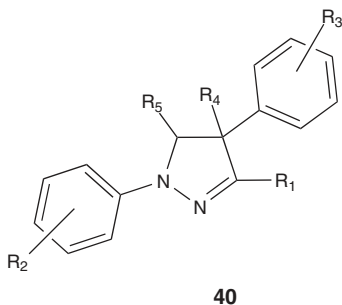


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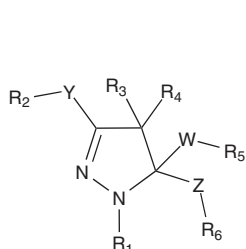
Johnson *et al.* synthesized the pyrazoline derivatives 34 in analogy to the natural *cis*-stilbene derivative combretastatin-A4 35, by replacement the ethylene-bridge with pyrazoline heterocycle, and tested for their anticancer activity [45].

1,4-Diarlyl-4,5-dihydropyrazoles 36 were reported by Roecker *et al.* to be mitotic kinesin spindle protein (KSP) inhibitors [46] with IC_{50} value of 0.2 nM and cell EC_{50} values of 3.2 nM. Some of the fused pyrazoline derivatives of

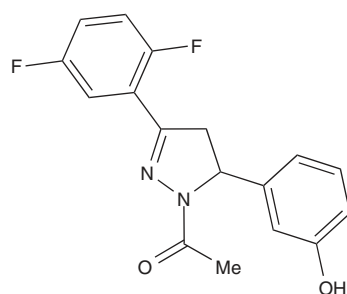
cyclolignans 37 have been reported and evaluated for their cytotoxic activities in culture cells of P-388 murine leukemia, HT-29 colon carcinoma and A-549 lung carcinoma. Indene fused series of 3-(4-chlorophenyl)-[1,2-*c*]pyrazolines substituted with benzene sulfonamides, *N1,N3*-disubstituted sulfonylurea and sulfonylthiourea scaffolds 38,39 and some derived thiazolidinone and thiazoline ring systems have been synthesized by Rostom and evaluated for their antitumor



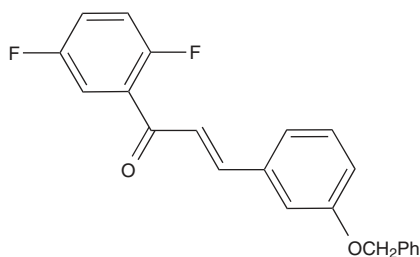
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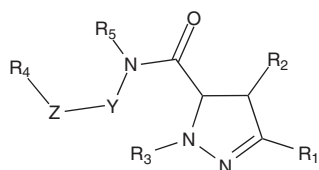
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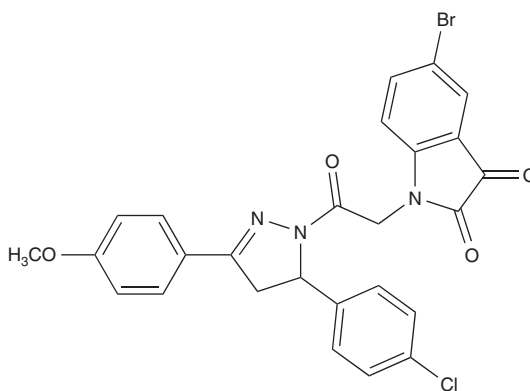
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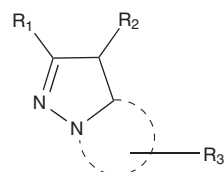
activity. Eight compounds showed promising broad-spectrum antitumor activity against most of the tested sub-panel tumor cell lines [47].

Preparation of some pyrazole derivatives of related structure to the targeted pyrazolines 40 have been achieved by Coleman *et al.* [48]. The dihydropyrazole compounds of formula 40 are useful for treating cellular proliferative diseases, for treating disorders associated with KSP kinesin activity, and for inhibiting KSP kinesin.

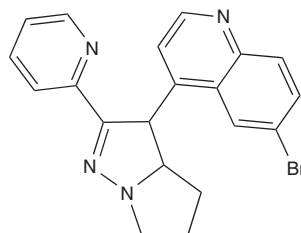
Breslin *et al.* [49] reported the preparation of 4,5-dihydro-1*H*-pyrazole derivatives 41 as potent mitotic kinesin

inhibitors. The antineoplastic activities of compounds 41 have been evaluated by kinesin ATPase *in vitro* assay using human KSP motor domain, and it revealed potent binding affinity. Compound 42 was prepared from the starting precursor 43, and demonstrated IC₅₀ value ≤ 50 μM.

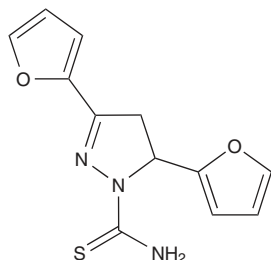
GLI proteins play pivotal roles in both cell proliferations and apoptosis [50]. It is also reported that blocking GLI genes is important in the initiation of DNA damage in early S-phase, leading to cell death in some human carcinomas [51]. He *et al.* [52,53] reported the synthesis of dihydropyrazole carboxamides 44 that were used as kits for



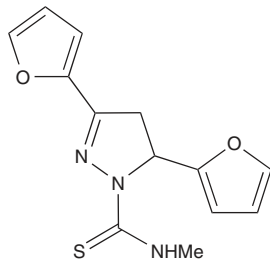
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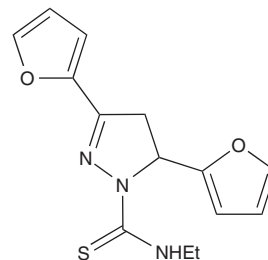
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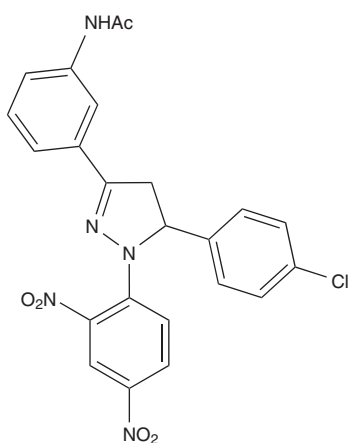
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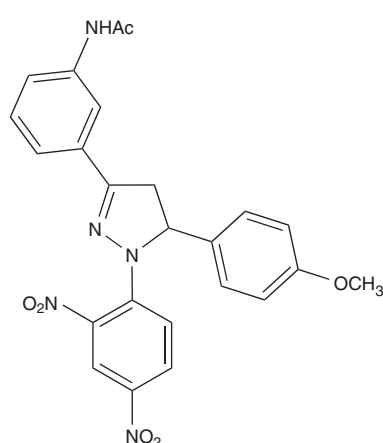
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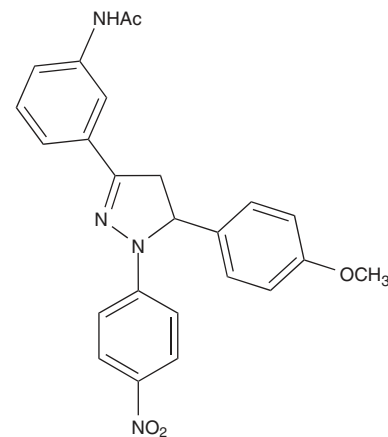
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53

the diagnosis and treatment of cancers expressing a GLI polypeptide; in particular a GLI1, GLI2 or GLI3 polypeptide. All compounds were evaluated for their GLI polypeptide inhibitory activity.

4,5-Dihydropyrazolyl-indole-2,3-dione 45 was identified as an active antitumor candidate by Havrylyuk *et al.* with selective influence on leukemia subpanel tumor cell lines ($GI_{50} = 0.69 - 3.35 \mu\text{M}$) [54].

TGF- β is another cancer attractive target, since it is directly involved in apoptosis induction process [55-58]. The preparation of fused dihydropyrazoles 46 as TGF- β signal transduction inhibitors have been synthesized by Sawyer *et al.* [59]. For instance, 1-[[2-(6-bromoquinolin-4-yl)-1-(pyridin-2-yl)ethylidene]amino]pyrrolidin-2-one was

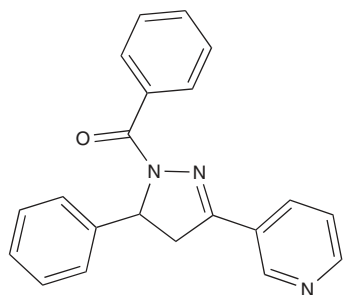
treated with sodium hydride (NaH) in dimethylformamide (DMF) at 80 – 85°C for 18 h to afford the product 47 in 54% yield. The selected pyrazolines had IC_{50} value below 20 μM for the TGF- β type I receptor.

2.2.3 CNS effects

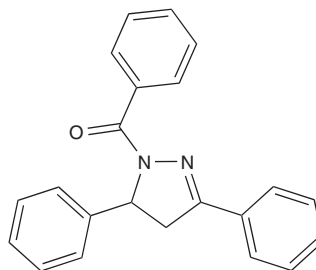
The reported central nervous system (CNS) pharmacological actions of pyrazoline derivatives include antiepileptic and antidepressant effects; in addition to neurodegenerative disorders.

2.2.3.1 Antiepileptic activity

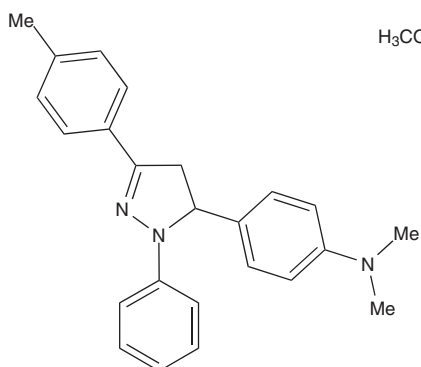
Ozdemir *et al.* [60] prepared 1-phenyl-1-thiocarbamoyl- and 1-*N*-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/



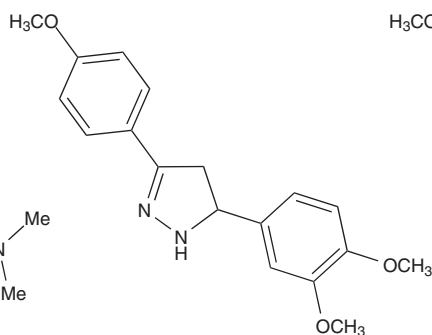
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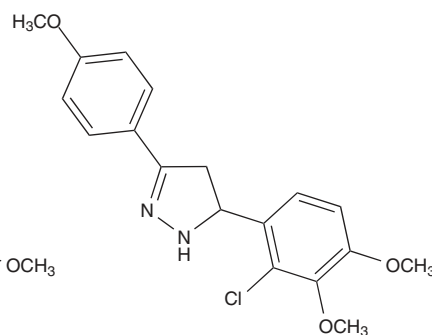
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58

(2-furyl)-2-pyrazoline derivatives 48 – 50 and studied their antiepileptic action by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole tests. Compounds 48 – 50 were found to be protective against MES and subcutaneous metrazole (scMet) at 30 – 300 mg/kg dose levels.

Several 3-(3-acetoamino)phenyl-1,5-substituted phenyl-2-pyrazolines 51 – 53 were synthesized by Singh *et al.* [61] and evaluated for their anticonvulsant activity. The synthesized pyrazolines 51 – 53 exhibited anticonvulsant activity, which was reflected by 60 – 80% protection observed versus PTZ-induced seizures. Those compounds exhibit their anticonvulsant potentials via inhibiting oxidation of certain nicotinamide–adenine–dinucleotide substrates.

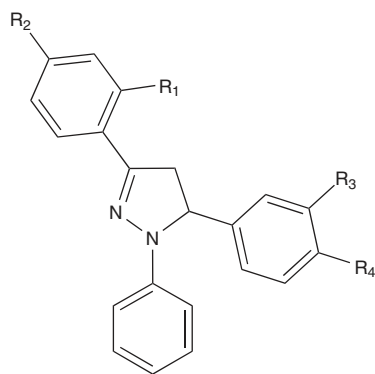
A set of pyrazoline derivatives have been prepared by Shishikura *et al.* [62] and were used as kainic acid neurocytotoxicity inhibitors. The synthesized derivatives showed non-competitive antagonism versus the non-*N*-methyl-D-aspartate (NMDA)-type ionotropic transmembrane receptor for glutamate AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and are useful as nerve cell protectors, or in antiepileptic therapy. Particularly, the pyrazoline derivative; 1-benzoyl-4,5-dihydro-3,5-diphenyl-1*H*-pyrazole 54 and (+)-3-(1-benzoyl-5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)pyridine 55 showed IC_{50} of 2.6 and 1.3 μ M versus AMPA receptors, respectively.

Some quaternary ammonium salts of substituted pyrazoline compounds have been prepared by Torrens-Jover *et al.* [63] and evaluated for their use as medicaments for the treatment of humans and animals neurocytotoxicity. The pyrazoline derivative 1 was prepared by methylation of *N*-piperidinyl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4,5-dihydropyrazole-3-carboxamide with methyl iodide. All of the synthesized pyrazolines were evaluated for their neurocytotoxicity inhibitory effect.

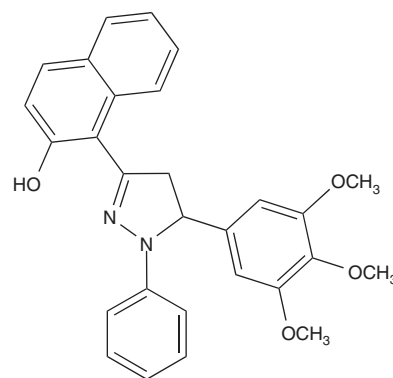
2.2.3.2 Antidepressant activity

3,5-Diphenyl-2-pyrazoline derivatives 56 – 58 showed decent antidepressant activities [64]. 3-(4-Methoxyphenyl)-5-(3,4-dimethoxyphenyl)-2-pyrazoline (56), 3-(4-methoxyphenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline (57) and 3-(4-chlorophenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline (58) reduced 41.9 – 48.6% immobility times at 100 mg/kg dose level. From the structure–activity relationship (SAR) point of view, 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. Replacement of these groups by bromo and methyl substituents has negative impacts on the antidepressant properties.

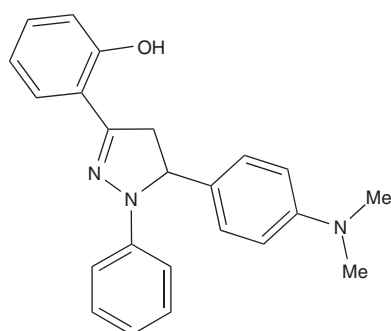
Prasad *et al.* [65] synthesized some 1,3,5-triphenyl-2-pyrazolines having the general formula 59, and



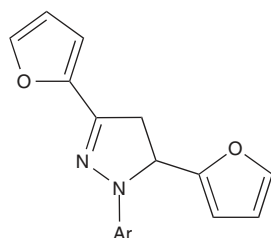
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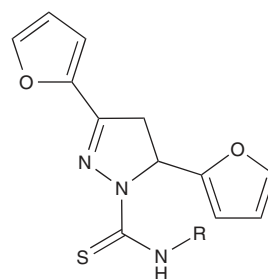
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61



62



63

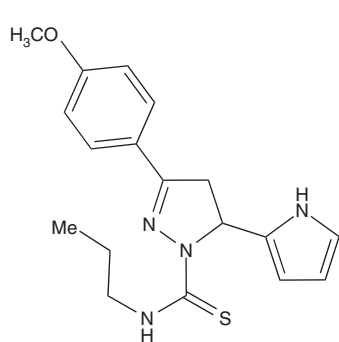
3-(2''-hydroxynaphthalen-1''-yl)-1,5-diphenyl-2-pyrazolines **60** and evaluated their antidepressant activity.

The pyrazoline derivative **61** was found to reduce the immobility times by 25 – 59% at 100 mg/kg dose level. It was found that compounds having electron-releasing groups on both aromatic rings at pyrazoline positions 3 and 5 dramatically enhanced the antidepressant activity when compared with the pyrazolines having no substituents on the aromatic rings [65].

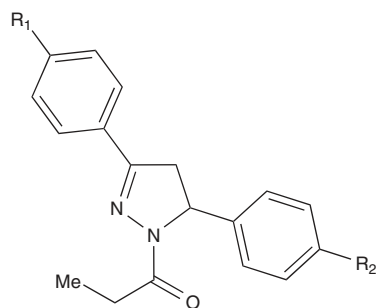
Similarly, some 1-phenyl-, 1-thiocarbonyl- and 1-*N*-substituted thiocarbonyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivatives **62** and **63** were synthesized and

investigated for their antidepressant activity by the Porsolt test (forced swimming test) in albino mice [66].

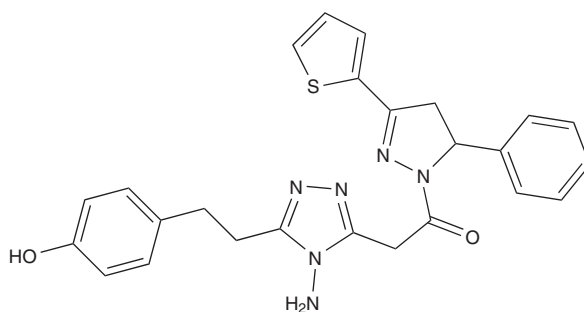
Monoamine oxidase (MAO) inhibitors are well-established antidepressant agents [67-77]. Gokhan-Kelekci *et al.* [78,79] synthesized several pyrazoline derivatives such as **64a** and evaluated their antidepressant potentials via measuring their MAO inhibitory activities. In addition, the anxiolytic and monoamine oxidase-A (MAO-A) and monoamine oxidase-B (MAO-B) inhibitory activities have been also evaluated by *in vivo* and/or *in vitro* tests. The synthesized compounds showed high activity against both MAO-A and MAO-B isoforms.



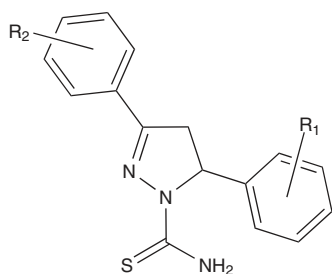
64a



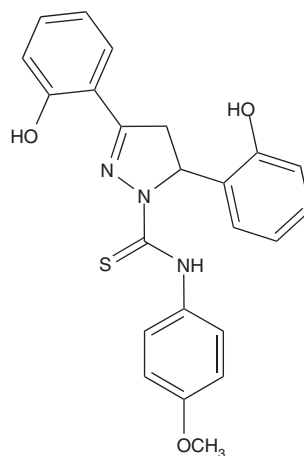
64b



65



66

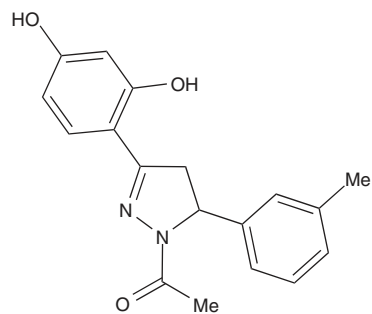


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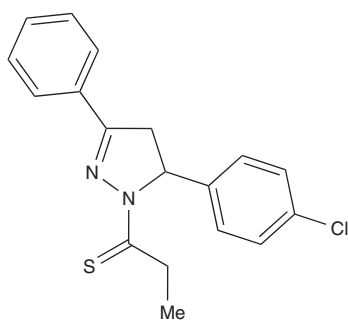
Chimenti *et al.* [66] reported the synthesis of series of *N*1-propanoyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives **64b** and tested their pharmacological activities as MAO inhibitors. Most of the tested compounds showed inhibitory activity within the micromolar range and high selectivity versus the more clinically important isozyme, that is, MAO-A [80].

The antidepressant-like activities of compound X analogs were found to be favorably comparable with the clinically used fluoxetine [81]. This action was suggested to be mediated by modulating the CNS serotonin pathway [81].

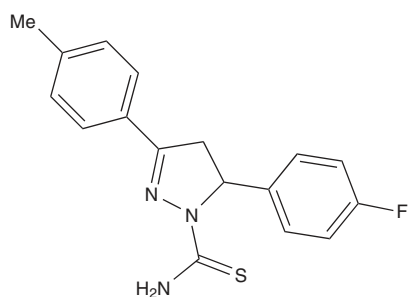
Jayaprakash *et al.* [82] synthesized a series of 3,5-diaryl carbothioamide pyrazoline derivatives **66** designed as mycobactin analogs (mycobacterial siderophore), and



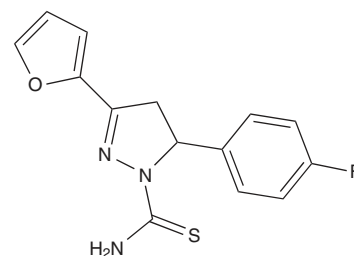
68



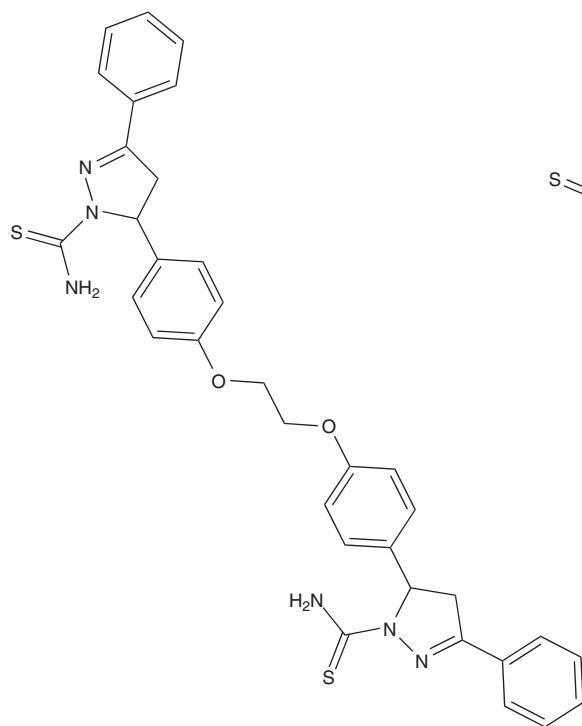
69a



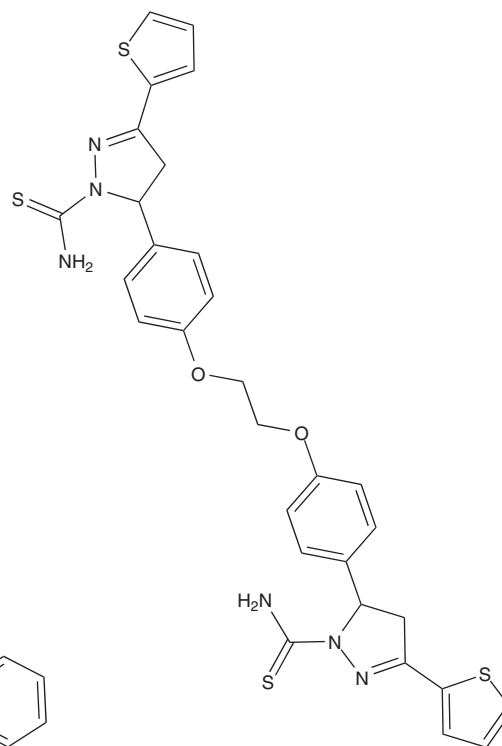
69b



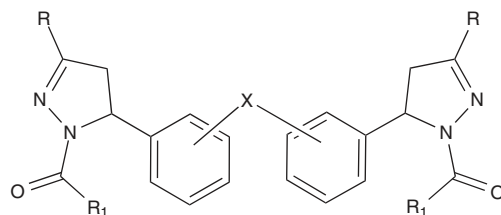
69c



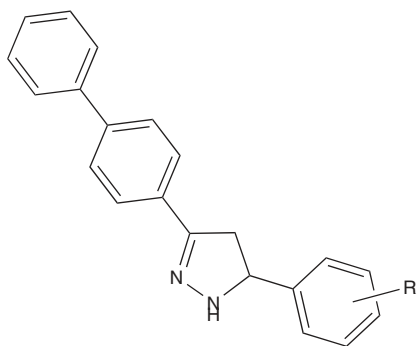
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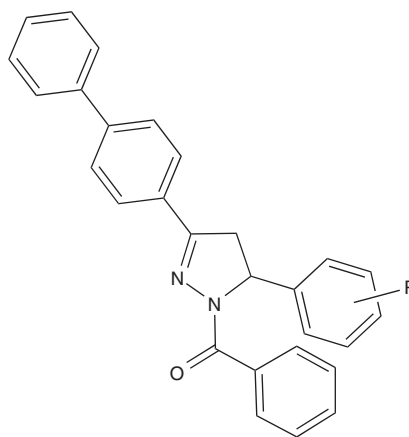
71



72



73a



73b

evaluated their antidepressant and MAO inhibitory activities. Interestingly, it was found that compound 67, which has antitubercular potential, acts also as a selective inhibitor of rat liver MAO-B.

The substituted 1-thiocarbamoyl-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazole derivatives 66 was found to selectively inhibit MAO-A and MAO-B isoforms [83].

Manna *et al.* [43] synthesized a novel series of 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives and studied their ability to selectively inhibit MAOs, swine kidney oxidase and bovine serum amine oxidase. The pyrazoline 68 showed a potent MAO inhibitor with a K_i value of about 10 – 8 nM.

2.2.3.3 Antineurodegenerative effects

A series of pyrazoles 69 were synthesized by Chimenti *et al.* [66,84] and assayed as MAO inhibitors. Compound 69a showed inhibitory activity in micromolar range and high selectivity toward MAO-A isozyme. In addition, it was found to be useful as adjuvant therapy in the treatment of neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease.

2.2.4 Anti-inflammatory, antipyretic and analgesic activities

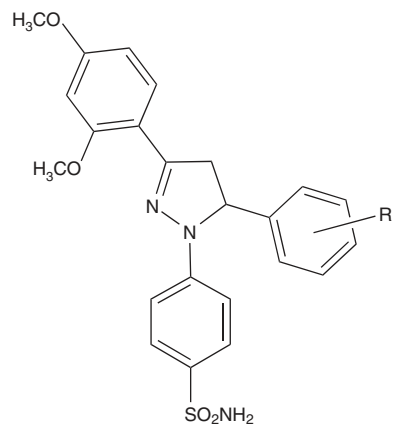
The *bis*(3-aryl-4,5-dihydro-1*H*-pyrazole-1-carboxamide) derivatives 70 – 71 were synthesized and screened for their

anti-inflammatory properties utilizing *in vivo* acute carrageenan-induced paw edema standard method in rats [85]. This set of pyrazolines also demonstrated a decent inhibitory activity versus prostaglandin E2 (PGE2) that is responsible for fever [86-88], at a dose level of 50 mg/kg [85]. The *bis*-pyrazoline derivative 70 exhibited considerable anti-inflammatory properties [85]. Compounds 70 and 71 showed remarkable anti-inflammatory activities relative to indomethacin, as a standard reference, with a lower ulcer index values [85].

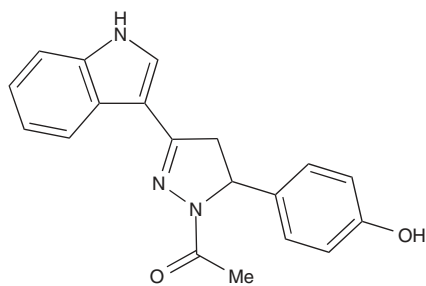
Also, some novel *bis*(1-acyl-2-pyrazolines) derivatives 72 were synthesized by the same research group and screened for their anti-inflammatory and ulcerogenic activities as well. Some of the synthesized compounds showed advanced anti-inflammatory properties with lower ulcerogenic liability than the standard used drug [89].

A series of 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines 73a and 1-benzoyl-3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines 73b have been reported by Amir *et al.* and were screened for their anti-inflammatory and analgesic activities [90].

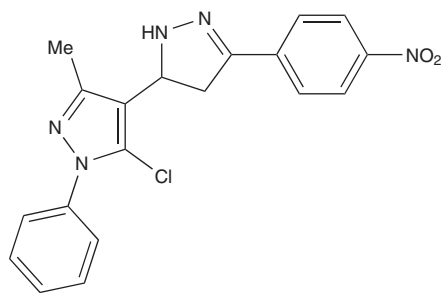
2-Pyrazoline-bearing benzenesulfonamide derivatives 74 have been synthesized by Rathish *et al.* [91] and screened for their anti-inflammatory activity. Pyrazoline derivatives 74 were found to be more active than celecoxib throughout their study.



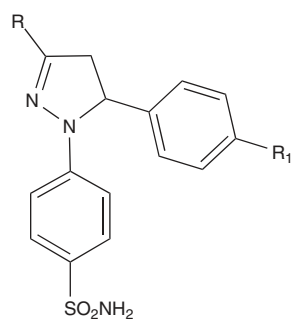
74



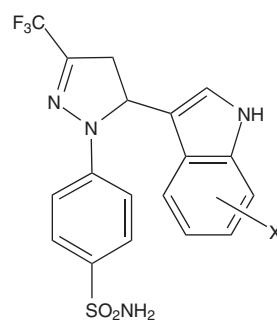
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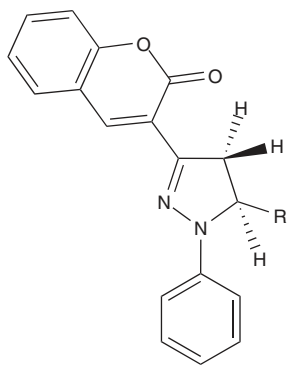
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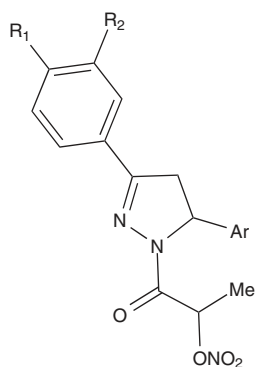
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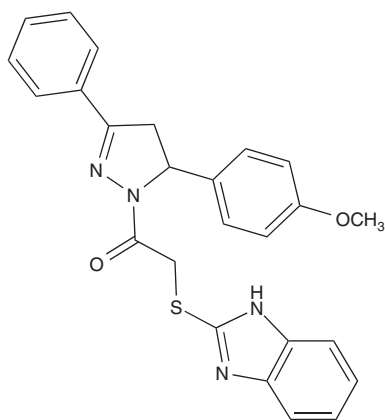
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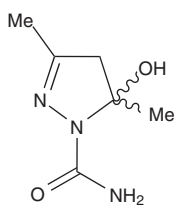
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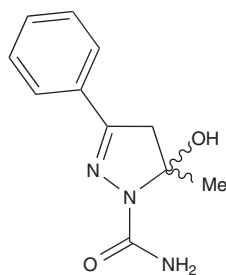
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81



82



83

Rani *et al.* [92] synthesized a series of pyrazoline derivatives pendant to an indole moiety and reported their evaluation for their anti-inflammatory activity against carrageenan-induced edema in albino rats at an oral dosage regimen of 50 mg/kg. All of the synthesized pyrazolines showed promising anti-inflammatory activity. 3-[1-Acetyl-5-(*p*-hydroxyphenyl)-2-pyrazolin-3-yl]indole (75) was found to be the most potent derivative in this series. It showed higher percentile of edema inhibition, along with lower ulcerogenic liability and acute toxicity than phenylbutazone as a standard drug [92].

Compound 76 that bears an electron withdrawing nitro group in the aryl moiety showed good activity comparable with that of standard drugs pentazocin and diclofenac sodium [93].

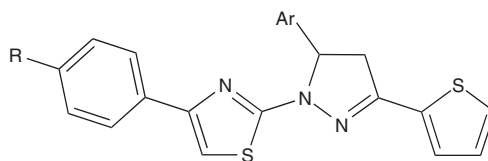
Rathish *et al.* synthesized a series of 1,3,5-trisubstituted pyrazolines-bearing benzene sulfonamides 77 and evaluated their anti-inflammatory activity. Among the tested compounds, several showed promising anti-inflammatory activity [91]. Some 1-(4-sulfamylphenyl)-3-trifluoromethyl-5-indolylpyrazoline derivatives 78 were prepared and screened for cyclooxygenase-2 (COX-2) and lipoxygenase (LOX) inhibitory activities [94].

Phenyl-5-(2-pyrrolyl)-4,5-dihydro-(1*H*)-pyrazole derivatives containing a thiocarbamoyl group such as 64 have been reported by Gokhan-Kelekci *et al.* [79]. The synthesized series of pyrazolines were tested for their *in vivo* anti-inflammatory activity by two different bio-assays namely, carrageenan-induced edema and acetic acid-induced increase in capillary permeability in mice. Moreover, analgesic and ulcerogenic activities were also investigated.

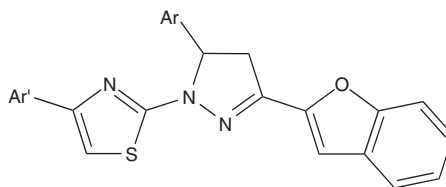
A series of 5-(substituted) aryl-3-(3-coumarinyl)-1-phenyl-2-pyrazolines 79 have been synthesized by Khode *et al.* [95] and screened for *in vivo* anti-inflammatory and analgesic activities. Among the 12 prepared compounds, the pyrazoline derivatives 79 exhibited significant anti-inflammatory activity in a model of acute inflammation.

Shoman *et al.* [96] synthesized a group of NO-donating 2-pyrazoline derivatives 80 and evaluated for their anti-inflammatory activity using carrageenan-induced rat paw edema and compared with indomethacin as a known standard. The ability of the prepared derivatives to induce gastric toxicity was also evaluated. Most of the prepared series showed significant anti-inflammatory activity, with higher safety margins than indomethacin in regard to gastric toxicity. When NO-donating group was incorporated into the parent pyrazoline derivatives, they caused a non-significant reduction in the anti-inflammatory activity and a marked decrease in gastric ulcerations induced by pyrazolines that lack the same group.

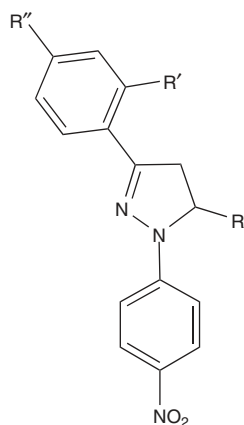
Pyrazoline derivatives containing benzoxazole and benzimidazole moiety 81 have been reported by Kaplancikli *et al.* [97]. The synthesized compounds were evaluated for antinociceptive activities. Compounds 81 exhibited significant antinociceptive activities in both hot plate- and acetic acid-induced writhing tests.



84

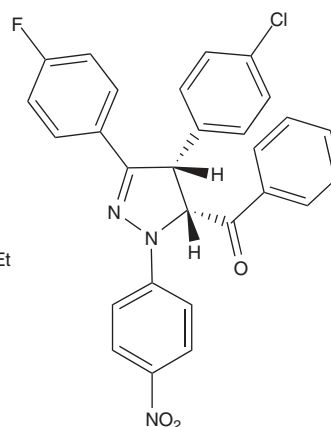


85



R = CN, CONH₂, COOEt
 R' = H, Cl
 R'' = F, Cl

86



87

The pyrazolines **82** and **83** were synthesized by Godoy *et al.* [98] and tested for their antinociceptive activity [98]. Moreover, Godoy *et al.* has also investigated whether the pain relief effect is mediated by spinal noradrenergic or serotonergic systems. The results showed that, unlike the standard dipyrrone, both spinal serotonin receptors and α 2-adrenoceptors are involved in the antinociception induced by **82** and **83** [98].

2.2.5 Antimicrobial activities

Pyrazoline ring represents a central scaffold for diverse antimicrobials that include antibacterials, antifungals, antivirals and antiamoebics. However, antitubercular could be considered a sub-class from antibacterials, we opted here to separate it under a specific subtitle, because of its clinical importance.

2.2.5.1 Antibacterial and antifungal activities

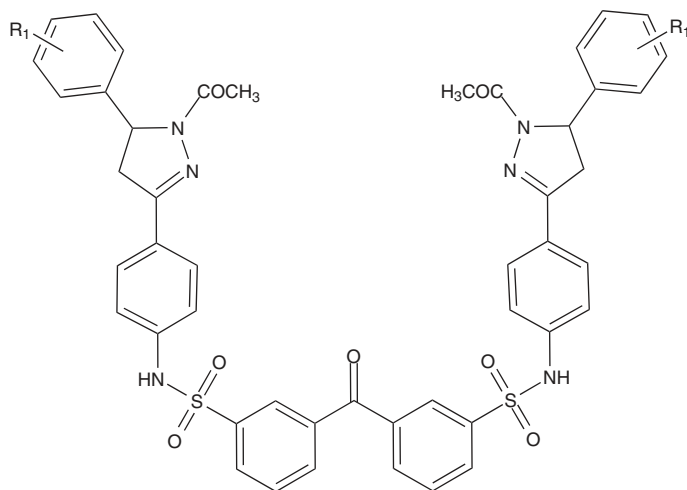
Several 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives **84** have been synthesized by Ozdemir *et al.*

[99] and were evaluated for their antimicrobial activities against *Escherichia coli*, *Bacillus cereus*, *Salmonella typhimurium*, *Streptococcus faecalis*, *Staphylococcus aureus*, *Aeromonas hydrophila*, *Candida glabrata* and *Candida albicans*. A significant level of activity was observed.

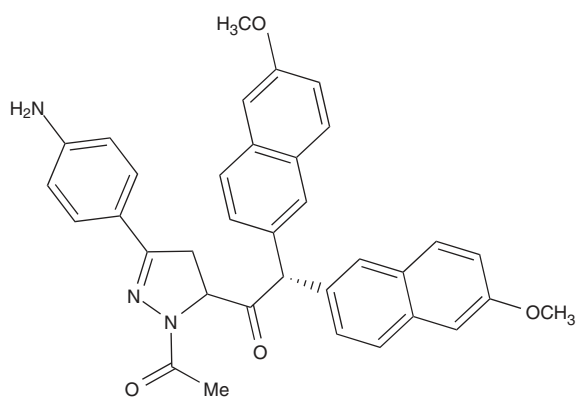
In the same context, Abdel-Wahab *et al.* [100] reported the synthesis of several 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles **85** and evaluated their antibacterial and antifungal activities. Some of the synthesized compounds showed enhanced antimicrobial activities than control drugs.

1,3-Diaryl-5-(cyano-, aminocarbonyl- and ethoxycarbonyl)-2-pyrazoline **86** and 1,3,4,5-tetra-aryl-2-pyrazoline derivatives **87** have been prepared by Abunada *et al.* [101] and screened for their antimicrobial activities against *E. coli*, *S. aureus*, *Aspergillus flavus* and *C. albicans*.

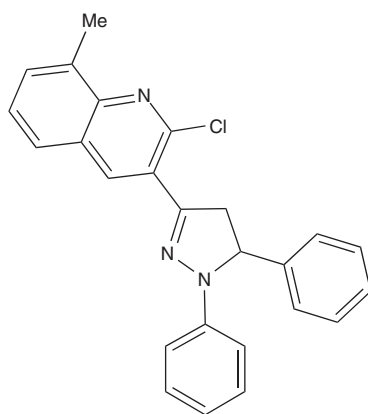
Bhatt *et al.* [102] synthesized several substituted pyrazolines **88** as potential antimicrobial agents. The synthesized



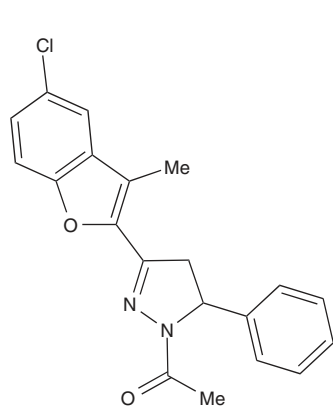
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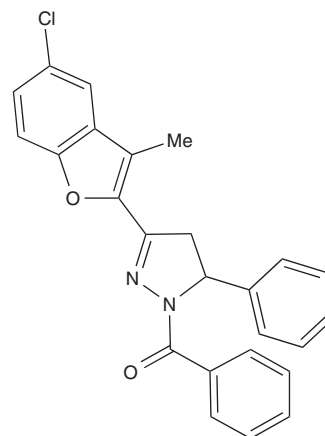
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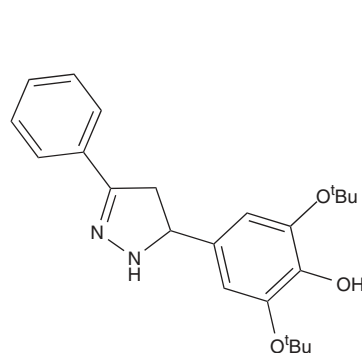
90



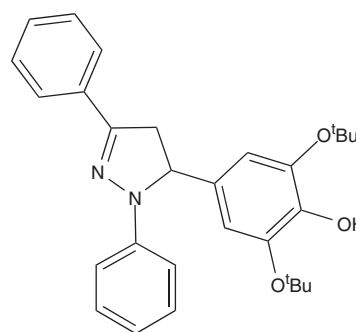
91a



91b



92a



92b

compounds were found to have remarkable activity against *Bacillus megaterium*, *Bacillus subtilis*, *E. coli* and *Mycobacterium tuberculosis* H37Rv.

The synthesis of pyrazoline derivatives of naproxen, as represented by compound 89, have been achieved by Udupi *et al.* [103]. The biological evaluation showed that some compounds of the series showed significant dual antimicrobial and anti-inflammatory activities.

Bharmal *et al.* [104] synthesized the pyrazoline derivative 90 with antimicrobial activity against *Salmonella typhosa* and *Aspergillus niger*.

Basawaraj *et al.* [105] reported the synthesis of some 1*H*-pyrazolines pendent to benzofuran 91a and 91b and tested their antimicrobial activity against both Gram-positive and Gram-negative bacteria represented by *S. aureus* and *E. coli*. Compounds 91a and 91b revealed potent antibacterial effect versus Gram-positive bacteria. By contrast, their antimicrobial effect has been significantly reduced in case of Gram-negative strains.

Some new pyrazolines and *N*-phenylpyrazolines, 92a and 92b have been prepared by Desai *et al.* [106] and evaluated

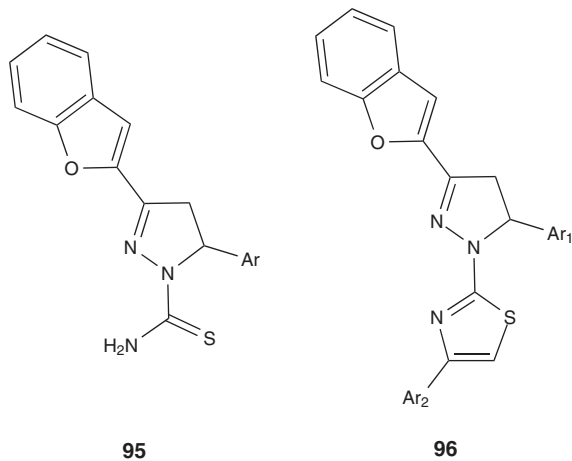
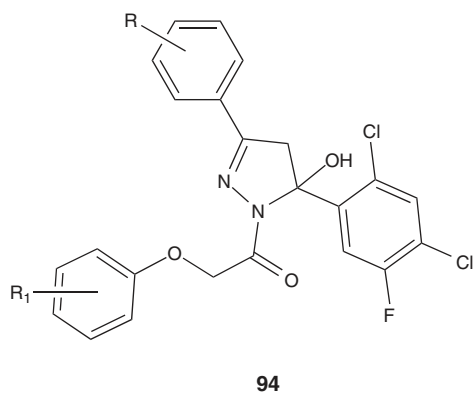
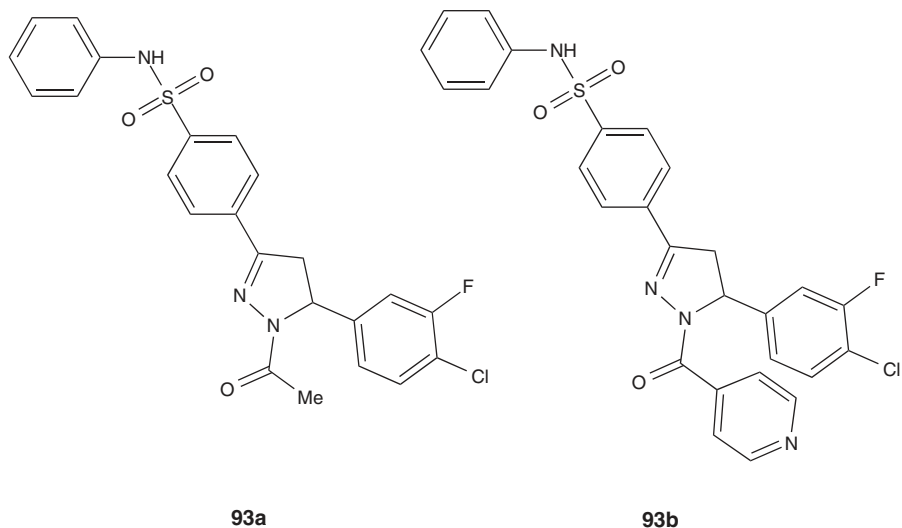
for their antimicrobial activities. The synthesized compounds exhibited activity against Gram-positive bacteria.

Jamode *et al.* [107] reported the synthesis of the 1-isonicotinoyl/carboxamido-2-pyrazolines 93a and 93b and evaluated their antimicrobial properties against *S. aureus*, *E. coli*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Most of the pyrazoline derivatives were found to have moderate antibacterial activity.

A series of chlorofluoropyrazolines 94 were prepared by Karthikeyan *et al.* [108]. Some of such pyrazolines showed significant antibacterial and antifungal activity.

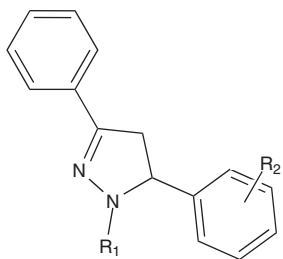
Treatment of the chalcones with nitromethane under Michael addition condition, followed by subsequent cyclization with thiosemicarbazide under basic reflux conditions gave 3-(benzofuran-2-yl)-5-(4-aryl)-4,5-dihydropyrazole-1-carbothioamides 95. These pyrazolines were further reacted with phenacyl bromides to afford thiazole-substituted pyrazolines 96. Some of the compounds showed a significant antimicrobial activity against *E. coli* and *A. niger* [100].

Some *N*1-substituted 3,5-diphenylpyrazoline derivatives 97 have been synthesized by Chimenti *et al.* [83] and evaluated for

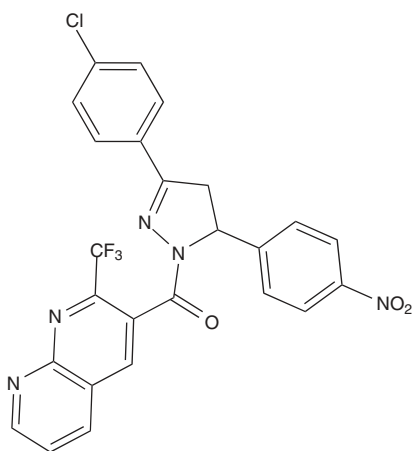


their *in vitro* antibacterial activity against *Helicobacter pylori*. Pyrazolines with an *N*1-acetyl group and 4-methoxy substituent in the 5-phenyl ring showed the highest activity against *H. pylori* metronidazole-resistant strains with minimum inhibitory concentration (MIC) value of 1 – 4 µg/ml [83].

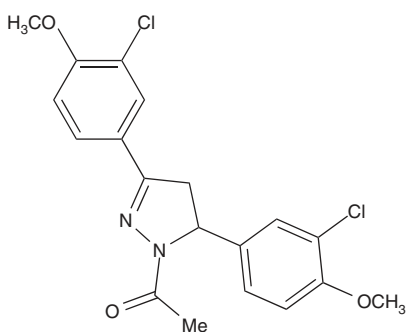
Mogilaiah *et al.* [109] evaluated the antibacterial activities of the pyrazoline derivatives containing 1,8-naphthyridine moiety as represented by compound 98. The prepared compounds showed less activity than the standard aminoglycoside gentamycin.



97



98



99

Vijayvergiya *et al.* [110] synthesized some 3,5-diaryl-1-phenyl/isonicotinoyl-2-pyrazoline derivatives **99** and evaluated their antibacterial activity. The new pyrazolines showed remarkable antibacterial activity against Gram-positive bacteria *S. aureus*, *Staphylococcus albus*, *Streptococcus pyogenes*, *Streptococcus viridans* and Gram-negative bacteria *E. coli* and *S. typhosa* [110].

Waheed and Khan [111] synthesized some derived substituted 1,2-pyrazolines **100** from nalidixic acid as antibacterial and analgesic agents. These pyrazolines were found to

have a significant antibacterial activity against Gram-negative bacteria and possessed appreciable analgesic activity.

2.2.5.2 Antimycobacterial activity

Stirrett *et al.* [112] synthesized some pyrazolines represented by compound **101** with structural similarities to siderophores and evaluated their ability as novel antimicrobials against *M. tuberculosis* and *Yersinia pestis*.

1,3,5-Trisubstituted-2-pyrazolines **102** were reported by Shenoy *et al.* [113] and were tested for their antimicrobial activity. Some of the compounds exhibited potential antitubercular activity.

Zampieri *et al.* [118] reported the synthesis of 1-(3,5-diaryl-4,5-dihydro-1H-pyrazol-4-yl)-1H-imidazole derivatives **103** and tested them against strains of *C. albicans* and a strain of *M. tuberculosis* H37Rv.

Shaharyar *et al.* presented a series of *N*1-nicotinoyl-3-(4-hydroxy-3-methylphenyl)-5-(substituted phenyl)-2-pyrazolines **104** and tested them *in vitro* for their antimycobacterial activity. Some of these pyrazolines were found to be an active agent against different strains of TB, with MIC value of 0.26 μ M [114].

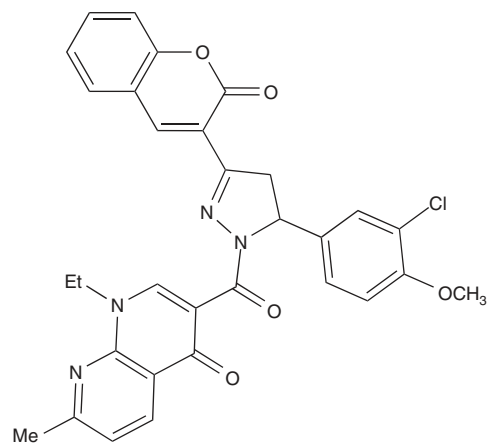
5-Aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole derivatives **105** have been synthesized by Mamolo *et al.* [115] and tested for their *in vitro* antimycobacterial activity. The latter pyrazoline derivative showed an interesting activity against different strains of *M. tuberculosis*.

Several 1-[(*N,N*-disubstituted thiocarbamoylthio)acetyl]-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives **106** were synthesized by Ozdemir *et al.* [116] and Shaharyar *et al.* [114] and evaluated for their *in vitro* antimycobacterial activity against H37Rv strain.

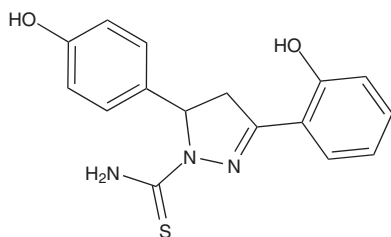
The potential benefits of medicaments endowed with both antimycobacterial and antifungal characters represent a valuable goal, since the association between TB and mycotic infections often occurs in immunocompromised patients [117]. So far, some 1,3,5-triaryl-4,5-dihydro-1H-pyrazoles, as represented by structure **107**, pendent to 1H-imidazole ring have been reported by Zampieri *et al.* [118] and tested for their *in vitro* antifungal and antimycobacterial activities. These imidazole-substituted pyrazole derivatives showed significant antifungal activity against a clinical strain of *C. albicans* and remarkable antitubercular activity against *M. tuberculosis* H37Rv.

A series of heterocyclic-substituted diphenyl ether derivatives of pyrazoles **108** have been synthesized and evaluated for their activity against H37Rv strain of Mycobacterium. Ten compounds inhibited the growth at concentrations as low as 1 μ g/ml. This level of activity was found comparable with the reference drugs rifampicin and isoniazid at the same concentration [119].

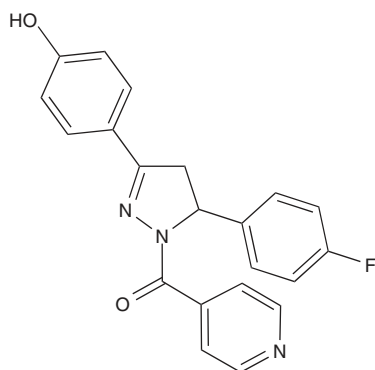
Another series of 5-(4-(substituted)phenyl)-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-toluidinome-thanethione and 5-(substituted)phenyl-3-(4-hydroxy-3-methylphenyl)-4,5-dihydro-1H-1-pyrazolyl-2-methoxyanilino



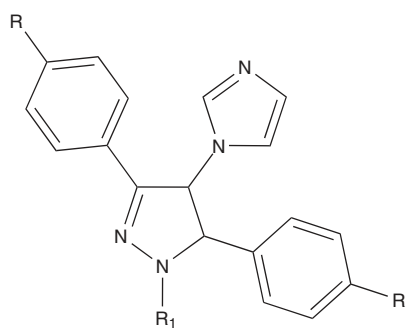
100



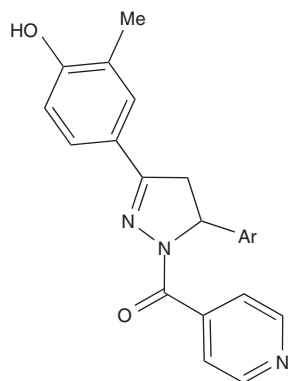
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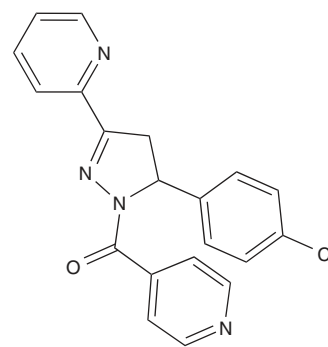
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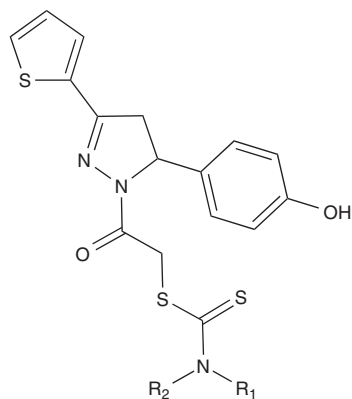
103



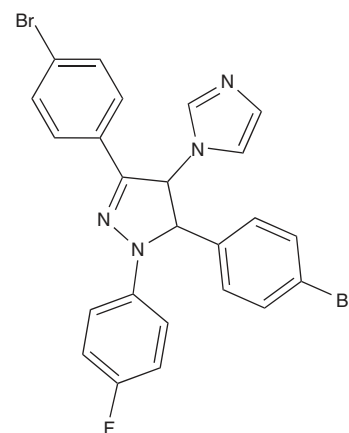
104



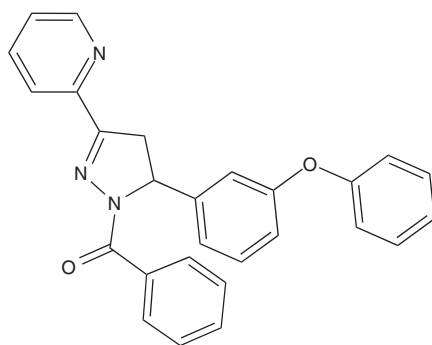
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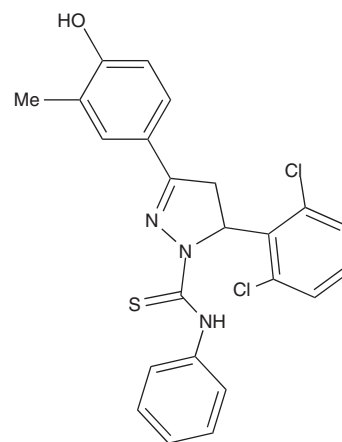
106



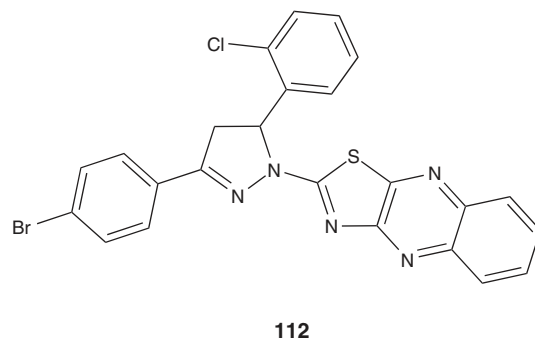
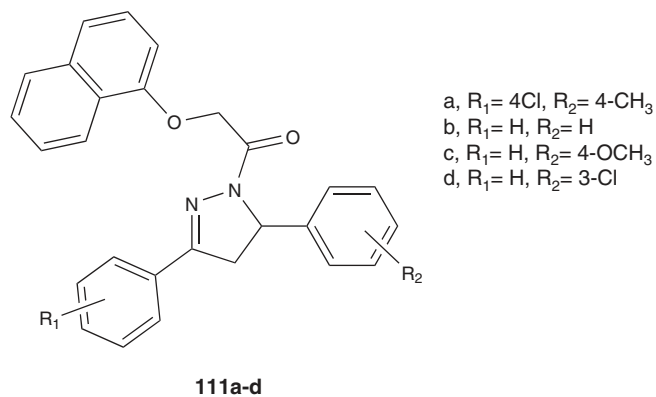
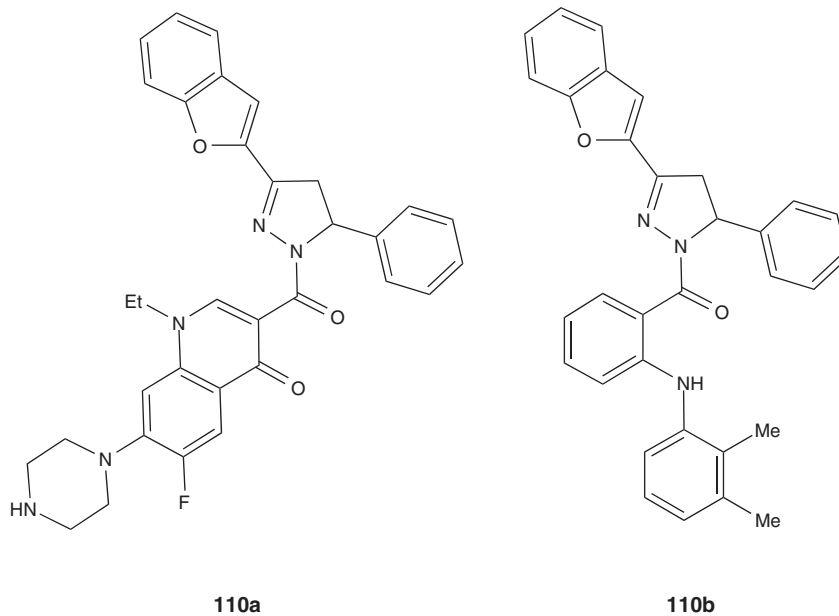
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108

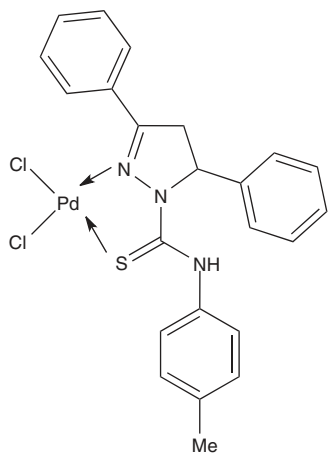


109

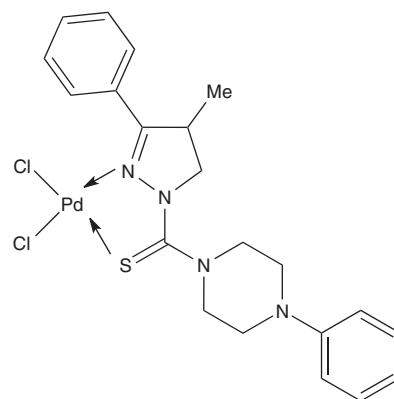


methanethione derivatives were synthesized by Ali *et al.* [120] and tested for their *in vitro* antitubercular activity against *M. tuberculosis* H37Rv. Compound 109 was found to be the most active with MIC value of 0.0034 μ M [120].

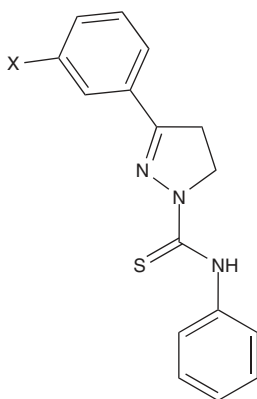
Babu *et al.* [121] evaluated the biological activity of 1,3,5-tri-substituted pyrazolines-bearing benzofuran moiety 110a and 110b. These compounds have been found to have some antitubercular effect.



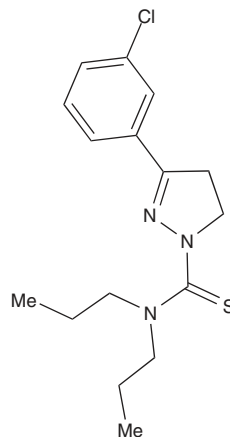
113a



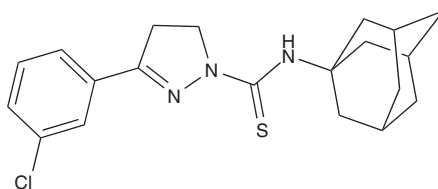
113b



114



115



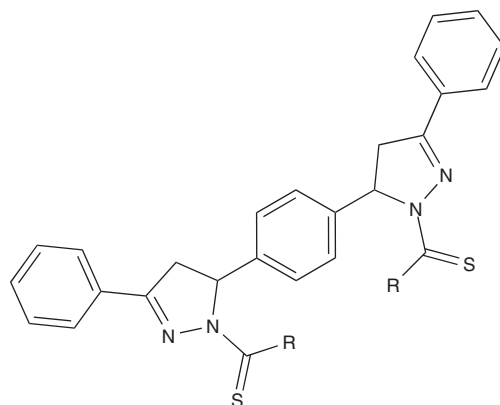
116

2.2.5.3 Antiamoebic activity

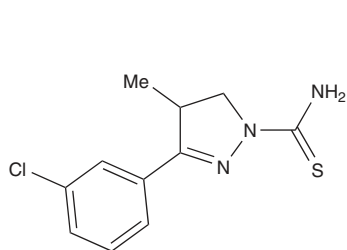
Compounds 111 have been synthesized by Hayat *et al.* and tested *in vitro* for their antiamoebic activity versus HM1:IMSS strain of *Entamoeba histolytica* [122]. The results showed that these compounds exhibited promising

antiamoebic activity ($IC_{50} = 0.05, 0.31, 0.06$ and $0.29 \mu M$, respectively) [122].

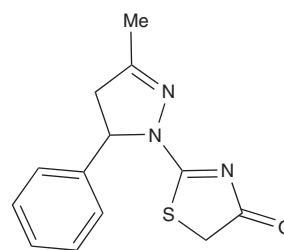
A variety of 3-(3-bromophenyl)-5-phenyl-1-(thiazolo[4,5-*b*]quinoxaline-2-yl)-2-pyrazoline derivative, as represented by compound 112, have been achieved by Budakoti *et al.* [123],



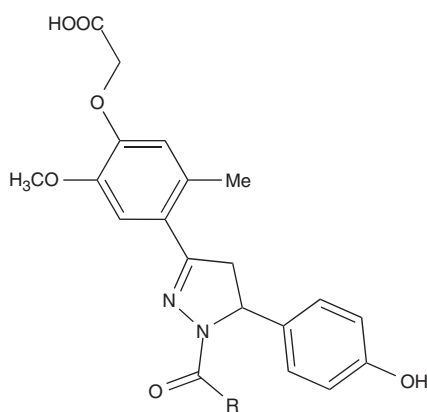
117



118



119

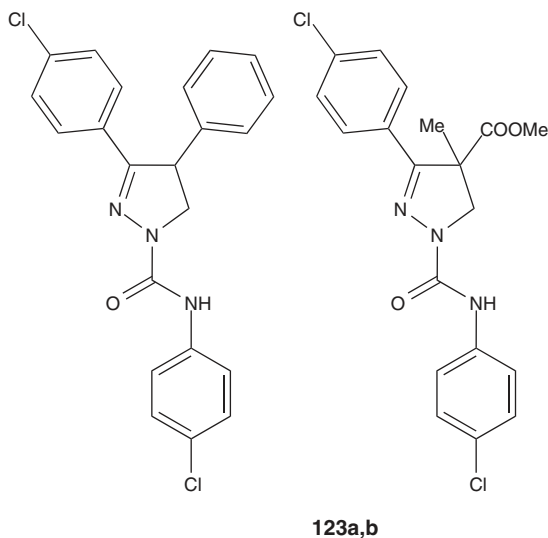
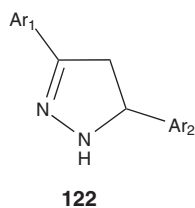
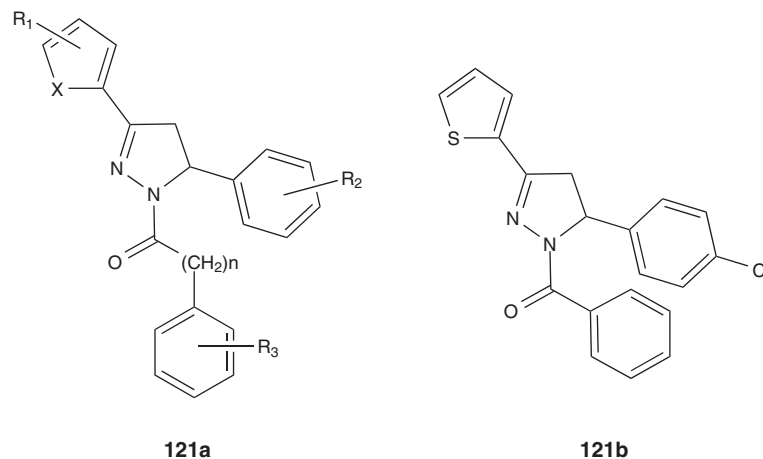


120

and screened for their antiamoebic activity against HMI: IMSS strain of *E. histolytica* by micro-dilution method which compared the IC₅₀ values with the standard drug metronidazole [123].

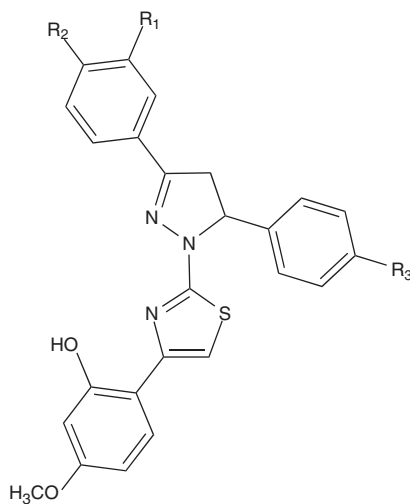
Also, the same authors have synthesized a novel Pd (II) complexes with 1-*N*-substituted thiocarbamoyl-3,5-

diphenyl-2-pyrazoline (Budakoti *et al.* [124]) and evaluated their antiamoebic activity by micro-dilution method against HM1:IMSS strain of *E. histolytica* and compared the results with the standard drug metronidazole. These palladium complexes showed better activity than their corresponding ligands. The pyrazoline 113a showed better inhibitory

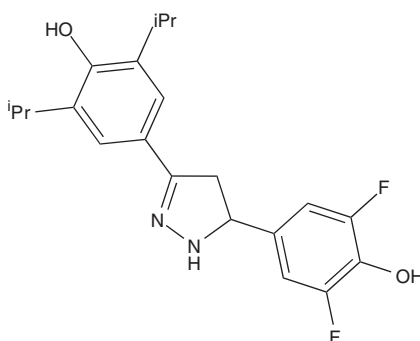


activity as indicated by their lower IC_{50} values ($IC_{50} = 0.05 \mu\text{M}$) as compared with metronidazole ($IC_{50} = 1.82 \mu\text{M}$) [124]. Similarly, Husain *et al.* reported another series of Pd(II) complexes, represented below by the most active compound 113b [125]. But this series of compounds were less active than 113a in terms of IC_{50} values; however, complex 113b ($IC_{50} = 0.37 \mu\text{M}$) is more active than metronidazole [125].

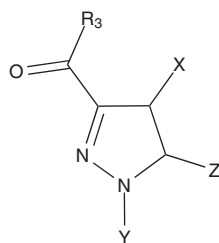
Abid *et al.* [126,127] synthesized a series of 1-*N*-substituted thiocarbamoyl-3-phenyl-2-pyrazoline derivatives 114 by cyclization of Mannich bases with thiosemicarbazide and evaluated their *in vitro* antiamoebic activities against *E. histolytica* in comparison with metronidazole as reference drug. The preliminary SARs indicated that the substitution of 3-chloro or 3-bromo on the phenyl ring at pyrazoline position-3 markedly enhanced the antiamoebic activity.



124



125

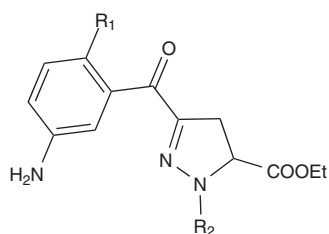


126

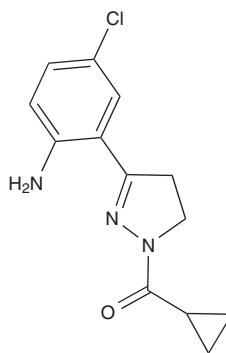
Moreover, compound 115 showed the most promising antiamebic activity with an IC₅₀ value of 0.6 versus 1.8 μM of metronidazole.

Another new series of pyrazoline derivatives were synthesized by cyclization of Mannich bases with thiosemicarbazides being substituted by different cyclic and aromatic amines and

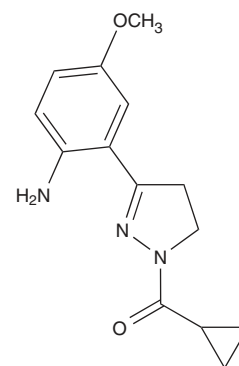
screened for *in vitro* antiamebic activity against *E. histolytica*. The pyrazoline 116 was found to be the most active compound in this series [126]. The Pd(II) complexes of these derivatives have been also prepared and evaluated for their antiamebic activity [128]. As observed previously, the Pd(II) complexes exhibited stronger antiamebic activity [128].



127



128



129

Bhat *et al.* reported some interesting *bis*-pyrazolines 117 prepared by cyclization of chalcones with *N*-4-substituted thiosemicarbazides under basic conditions. Investigation of the antiameobic activity showed that compounds with aromatic substituents at the thiocarbonyl group were more active than those with the cyclic groups [129].

2.2.5.4 Antitrypanosomal activity

Semicarbazone-based pyrazoline derivatives, represented by compound 118, have been designed as drug candidates for Chagas' disease (American trypanosomiasis) [130]. Compound 118 showed inhibitory activity versus *Trypanosoma cruzi* as low as 80 nM. Compound 118 and its analogs exhibited their antitrypanosomal activities by targeting cysteine protease cruzain, interestingly, with low cellular toxicity [130].

Compound 119 was prepared by Seebacher *et al.* in 2003 together with few others. Compound 119 showed moderate activity against *T. cruzi* [131].

2.2.5.5 Antiviral activity

Some new *N*-acetyl and *N*-thiocarbonyl derivatives of 4,5-dihydropyrazoles were synthesized by El-Sabbagh *et al.* and were tested against a broad panel of viruses in different cell cultures [132]. *N*-Acetyl-4,5-dihydropyrazole was the only active compound at sub-toxic concentrations against vaccinia virus (Lederle strain) in HEL cell cultures with an EC₅₀ value of 7 µg/ml [132].

Yar *et al.* reported the synthesis of new pyrazolines derived from phenoxyacetic acid. The synthesized derivatives were tested for their *in vitro* cytotoxicity and antiviral activity. In addition to the antiviral activity of 2-{4-[3-(2,4-dihydroxyphenyl)-1-(2-hydroxybenzoyl-4,5-dihydro-1*H*-5-pyrazolyl)]-2-methoxyphenoxy}acetic acid (120), it showed the maximum cytotoxicity of the series [133-135].

A series of trisubstituted pyrazolines 121a and 121b showed an inhibition for flavivirus infection in cell culture and was identified through high-throughput screening of a compound library using a luciferase-expressing West Nile virus (WNV) infection assay [136]. The aryl-rings in such pyrazolines are essential for the activity against WNV. The pyrazolines

inhibitors of RNA synthesis that were investigated pointed the viral RNA polymerase, RNA helicase or other viral replication enzymes as potential targets [137].

Liang *et al.* [138] reported the synthesis of the 3,5-diaryl-4,5-dihydropyrazole derivatives 122, which inhibits the activity of picornavirus and coronavirus simultaneously. These compounds could be used for preventing and treating diseases caused by pecorino virus and coronavirus, such as influenza, foot-and-mouth disease, epidemic keratoconjunctivitis, aseptic meningitis, myocarditis, hepatitis A and severe acute respiratory syndrome (SARS).

2.2.6 Insecticidal activity

Silver and Soderlund [139] synthesized some insecticides that are related to the pyrazolines 123a and 123b and examined their mechanism of action based on electrophysiological, pharmacological and toxicological information. Eventually, it was found that these compounds exert their insecticidal activity via neuronal targets [139].

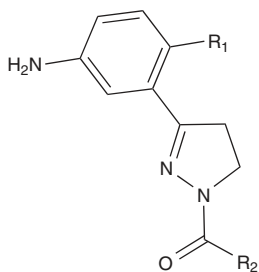
2.2.7 Hypotensive activity

Turan-Zitouni *et al.* [140] synthesized several 1-(4-arylthiazol-2-yl)-3,5-diaryl-2-pyrazolines 124 and studied their hypotensive activity by the tail-cuff method. All the synthesized pyrazolines showed appreciable hypotensive activities comparable with clonidine as a reference drug.

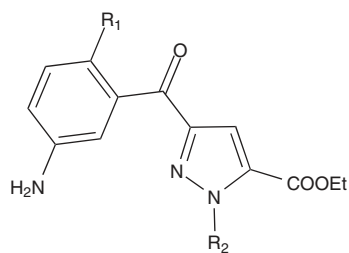
2.2.8 Cholesterol metabolism modulators (ACAT inhibition activity)

A series of 3-(3,5-dialkyl-4-hydroxyphenyl)-5-(multi-substituted-4-hydroxyphenyl)-2-pyrazolines were prepared and evaluated their inhibitory action on acyl-coenzyme A cholesterol acyltransferase (ACAT), which is responsible for formation of cholesterol precursor acetoacetyl CoA in the mevalonate pathway [141]. The pyrazoline 125 as an example of this series showed *in vitro* inhibitory activity on hACAT-1 and -2 [142].

Substituted pyrazoline derivatives of the general formula 126 with ACAT inhibition activity were prepared and their pharmaceutical compositions and uses in the treatment

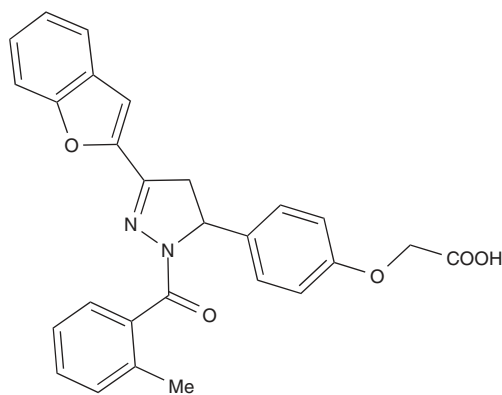


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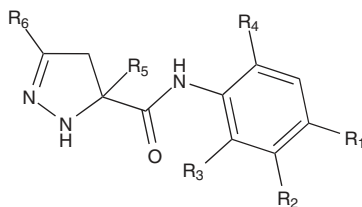


131

R₁ = H, Cl, OMe
R₂ = Me, Et, Bu, Bn



132



133

of dyslipidemia have been reported by Yenes-Minguez and Torrens-Jover [134,143].

2.2.9 Nitric oxide synthase inhibitors

Camacho *et al.* synthesized a new series of neural nitric oxide synthase (nNOS) inhibitors with 4,5-dihydro-1*H*-pyrazole structure 127 in an attempt to find new compounds with neuroprotective activity. The pyrazolines 128 and 129 showed the highest activities with inhibition percentages of 70 and 62%, respectively [144].

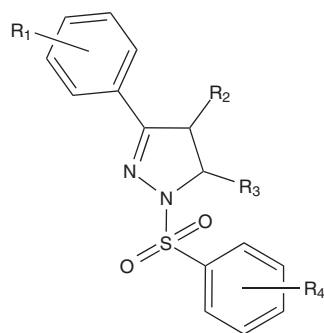
Also, Carrión *et al.* synthesized and evaluated a series of 1-alkyl-3-benzoyl-4,5-dihydro-1*H*-pyrazole derivatives 130 and 1-alkyl-3-benzoyl-1*H*-pyrazoles 131 as potential inhibitors of both neuronal and inducible nitric oxide synthases (nNOS and iNOS) [145].

2.2.10 Antioxidant activity

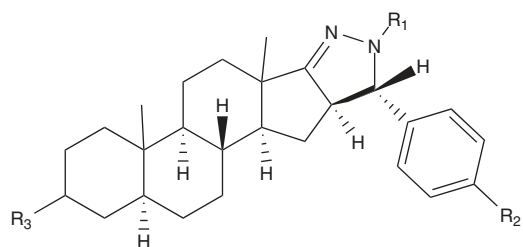
A novel series of pyrazoline derivatives have been synthesized by Babu *et al.* [146] and evaluated for their antioxidant activity at various concentrations against standard ascorbic acid. The pyrazoline 132 among the series of the synthesized compounds showed excellent antioxidant activity as compared with ascorbic acid.

2.2.11 Steroidal hormones modulators

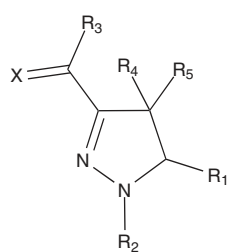
Zhang *et al.* designed several pyrazolines of the general formula 133 and evaluated them by *in vivo* screening as tissue selective androgen receptor modulators (SARMs). SARs were investigated at the R₁ to R₆ positions as well as the core pyrazoline ring and the anilide linker. It was found that, strong electron-withdrawing groups at the R₁ and R₂



134



135



136

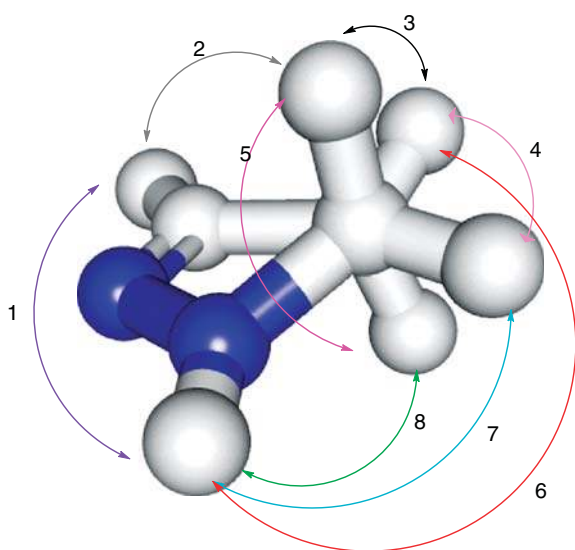


Figure 3. Possible patterns of two substituents in pyrazoline ring.

positions and small groups at the R_5 and R_6 positions were optimal for androgen receptor agonist activity [147].

Jones *et al.* achieved the synthesis of 4-substituted pyrazoline derivatives 134 and studied their docking into a protein receptor homology model. The results of the study revealed that the synthesized compounds exhibited functional antagonism of protein receptor [148].

A series of interesting androstano[17,16-*c*]pyrazolines and their oxidized derivatives 135 have been synthesized and evaluated for their anti-androgenic activity compared with that of cyproterone as a positive control. Some of these compounds showed better anti-androgenic activity than the reference drug [149].

2.2.12 Antidiabetic agents

Fisas-Escasany *et al.* [150,151] achieved preparation of substituted pyrazolines 136 in order to be used in combination therapy with other antidiabetic agents.

2.2.13 Urotensin II and somatostatin-5 receptors modulators

The human urotensin II receptor (*b*-UTR) is a member of the family of rhodopsin-like G-protein-coupled receptors (GPCRs) involved in the modulation of the functionality of many tissues and organs. A combinatorial scaffold approach has been reported by Olsson [152] to build a library of compounds having four diversity points. The synthesized compounds provide the mapping of urotensin II and somatostatin-5 receptors by differential binding of the receptors.

3. Expert opinion

From the aforementioned examples, pyrazoline heterocyclic ring was mainly used as a structural core for building huge variety of biologically active compounds. The versatile pyrazoline structure with semi-saturated status provides a unique spatial configuration which allows various substitution patterns. Figure 3 shows eight possible patterns of only two substitutions. One can imagine the diversity in cases of three or more substituents.

Among the reported activities, there are some important notes; pyrazoline-containing cytotoxic compounds are not only useful in treatment of various cancer types, but also some of them act as cancer chemopreventive agents. Concerning the reported antimycobacterium activity of pyrazoline-containing compounds, all reports have been assayed utilizing the vaccine-strain H37Rv and not the infectious strains, which make the biological impacts doubtful. Evaluating those compounds versus multidrug-resistant (MR-TB) or extreme drug-resistant (XDR-TB) mycobacterium strains will add huge value to the present work.

The reported articles are hampered by lacking molecular target identification. Most of the reported biological activities

for pyrazoline-containing compounds were based on cell-based assays, and the authors have not reported anything about the possible molecular target. So far, these kinds of drug development protocols do not allow conducting structure-based drug design approaches. From our point of view, more attention has to be given for the molecular basis of mode of actions. Hence, rational drug design methods

could be applied and more drug-like candidates will likely be obtained.

Declaration on interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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