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SEARCH FOR NEW DRUGS

PHARMACOLOGICAL ACTIVITY OF 4,5-DIHYDROPYRAZOLE DERIVATIVES (REVIEW)

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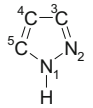
The various types of pharmacological activity of 4,5-dihydropyrazole derivatives are reviewed. Attention is focused on the influence of various substituents in the dihydropyrazole core on the pharmacological effects of these compounds.

Keywords: dihydropyrazole, pyrazoline, anti-inflammatory activity, antitumor activity, antimicrobial activity, pharmacological activity.

A significant proportion of synthetic drugs incorporate a variety of nitrogenous heterocycles. For example, pyrazole derivatives (metamizole sodium, phenylbutazone, etc.) are already non-narcotic analgesics. However, recent research showed that this compound class has other pharmacological effects [1].

Pyrazolines are five-membered heterocyclic azoles with two adjacent N atoms and an endocyclic double bond. They are also called dihydropyrazoles in the literature because they can be viewed as partially reduced pyrazoles.



Pyrazole

2-Pyrazoline

As a rule, 2-pyrazoline derivatives receive special attention because of not only their availability and stability but also their broad spectrum of pharmacological activity [2].

Anti-inflammatory and analgesic activity of dihydropyrazole derivatives

Several pyrazole derivatives were applied clinically as nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., metamizole sodium, phenazone, phenylbutazone, and propiphenazone. Noteworthy selective cyclooxygenase (COX-2) inhibitors containing a pyrazole ring include celecoxib, which is a relatively safe drug with anti-inflammatory, analgesic, and antipyretic activity. It is also indicated for arthrosis and arthritis.

Serious side effects (e.g., suppression of hematopoiesis and kidney and liver disorders) of most currently used pyrazolones seriously limit their use. Therefore, most recent research has been directed toward the discovery of new pyrazole derivatives with adequate efficacy and lower toxicity.

3,5-Diaryl-2-pyrazolines showed promise during research on this topic [3 – 6]. For example, several compounds with a C3 4-methylsulfonylphenyl substituent showed selective COX-2 inhibition [7].

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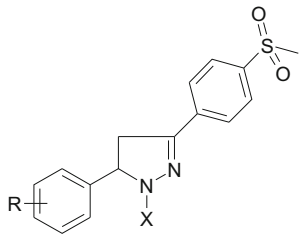
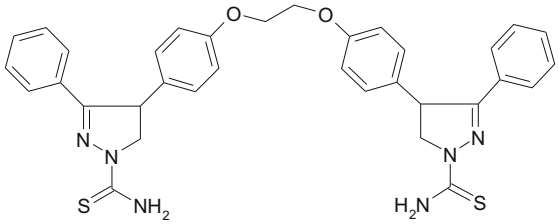


1

R = H, 4-Cl, 4-F, 4-CH_3, 4-CF_3, 4-OCH_3, 2-OCH_2Ph, 3-OCH_2Ph, 4-OCH_2Ph; X = $COCH_3$, $CSNH_2$.

1-Acetyl derivatives of 2-pyrazoline showed better results than thiocarbamoyl analogs in *in vitro* tests [7].

Other heterocyclic groups as substituents were found in a significant number of pyrazoline derivatives with rather high anti-inflammatory [8 – 16] and analgesic [17, 18] activity. *bis*-Pyrazoline derivatives **2** and **3** [3] showed positive results in the *in vivo* carrageenan-induced rat-paw edema model and noticeable inhibitory activity on prostaglandin E2 (PGE2) synthesis. The ulcerogenicity index of these compounds was less than that of indomethacin as a reference.



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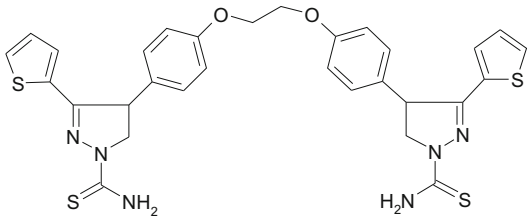
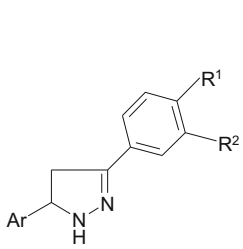


3

One strategy for diminishing the undesirable side effects of NSAIDs on gastrointestinal tract (GIT) membranes is based on the gastroprotective properties of nitric oxide (NO) [19]. The preparation and *in vivo* testing of 2-pyrazoline derivatives with and without NO-releasing groups were reported [20].



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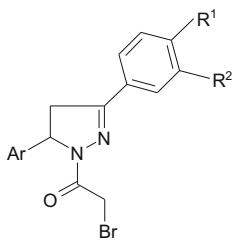

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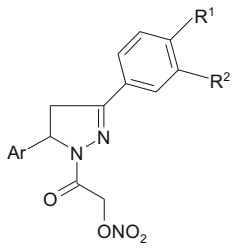

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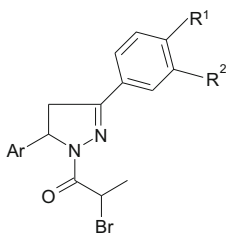

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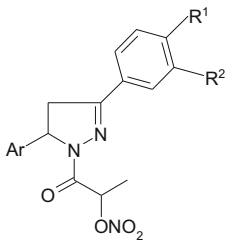

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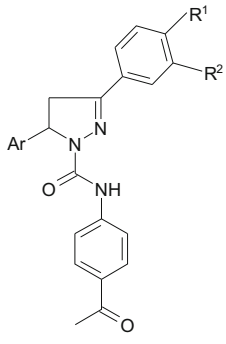

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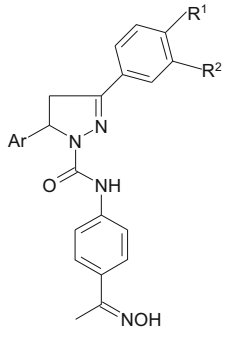


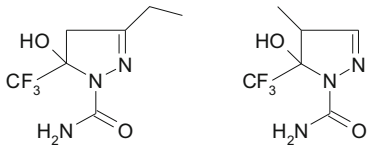
10

R^1 = H, OCH_3; R^2 = H, OCH_3; Ar = furyl, 2,4-$(OCH_3)_2C_6H_3$, 2,6-$(Cl)_2C_6H_3$.

Most of the compounds showed significant anti-inflammatory activity and less toxicity on the GIT at an administered dose of 100 mg/kg than the reference (indomethacin). In summary, it seemed that adding NO-donors diminished slightly the anti-inflammatory activity but reduced markedly gastric ulceration as compared with other pyrazoline derivatives prepared in that work.

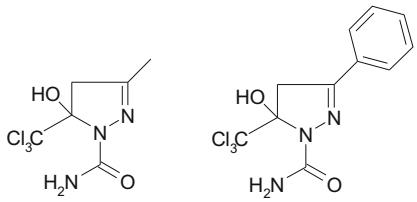
Several groups studied the *in vivo* pharmacological activity and toxicity for single [21] and multiple administrations [22] of pyrazolines without aromatic substituents.

Compounds **11** and **12** had activities analogous to analgin for a single administration and prolonged treatment of animals with arthritis induced by Freund adjuvant. Side effects and signs of toxicity were not observed.



11 **12**

A study of the mechanisms of action of structurally similar **13** and **14** showed a relationship between the analgesic effect and the effect on the spinal noradrenergic or serotoninergic systems. These compounds were not anti-inflammatory agents, in contrast with analgin [23].



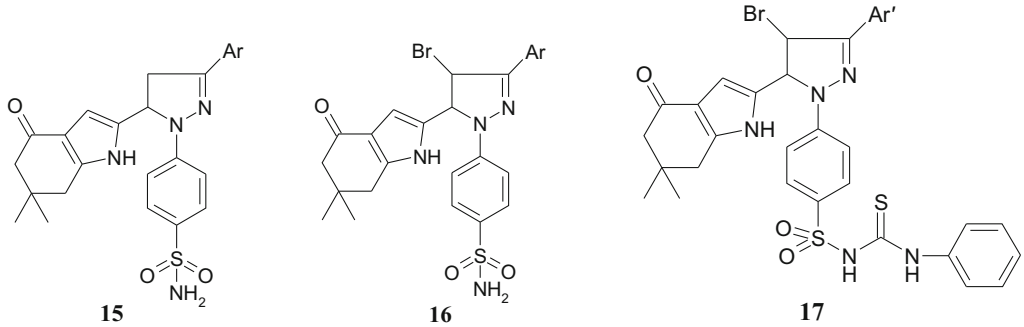
13 **14**

Because replacing the pyrazoline 3-methyl by 3-phenyl did not affect the antinociceptive properties of these compounds, we assume that a common bioactive metabolite acting analogously to α_2-adreno-receptor and 5-HT-receptor antagonists is formed via *in vivo* biotransformation [23].

Antimicrobial activity of dihydropyrazole derivatives

Various dihydropyrazole derivatives exhibit not only antibacterial but also antifungal, antiviral, and antimalarial activity.

Lead compounds are often discovered by creating novel molecules incorporating fragments of already known drugs [24]. In this manner, 2-pyrazolines (**15**, **16**, **17**) with sulfonylamide structures were prepared [25].

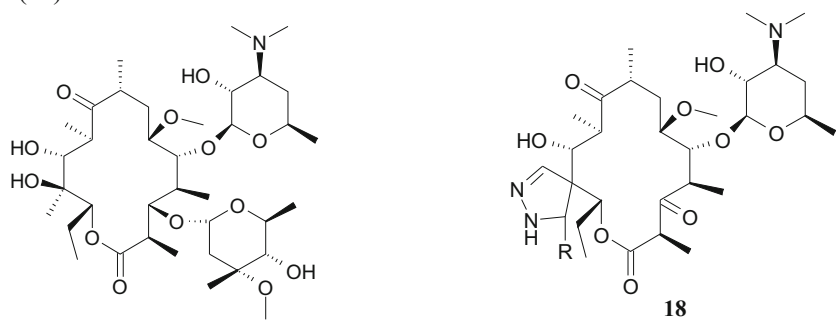


15 **16** **17**

Ar = 4-BrC_6H_4; 4-Cl C_6H_4; 4-$OCH_3C_6H_4$; Ar′ = 4-ClC_6H_4.

The compounds were tested by the agar diffusion method. Several of them exhibited good antibacterial (against *Staphylococcus aureus*) and antifungal (against *Candida albicans*) activity.

Clarithromycin was selected as a platform for another study [26]. It was sequentially modified to produce various C-12 pyrazolinylspiroketolides (**18**).

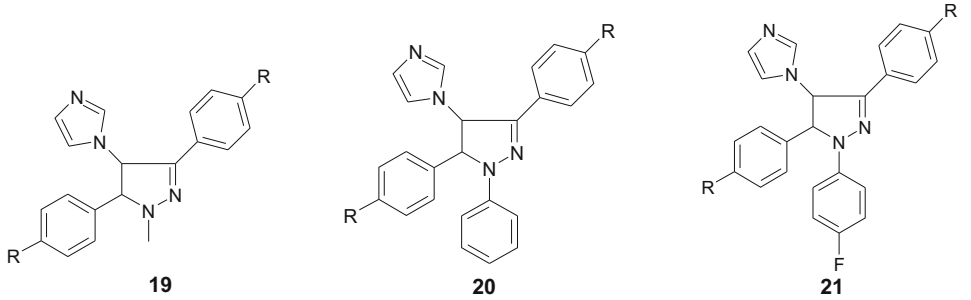


18

Clarithromycin R = H; CH_3; $COOC_2H_5$; $COOCH_3$

All synthesized derivatives showed better antibacterial activity than erythromycin A and clarithromycin against *S. aureus* and similar activity against *S. pneumonia* and *H. influenza*. Compounds with an ester on the pyrazoline ring had the best minimum inhibiting concentrations (MICs).

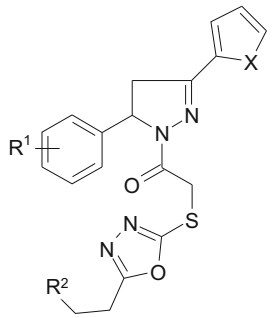
Many studies focused on pyrazoline derivatives containing other azole substituents that are known to be fragments of many antimicrobial agents. Thus, compound **19** with an added pyrazoline 4-imidazole heterocycle had more pronounced fungicidal activity than the reference drugs (miconazole and amphotericin B) [27]. Furthermore, analogs **20** and **21** were moderately active against strain *M. tuberculosis* H_{37}Rv although their MICs were greater than that of the reference isoniazid.



19 **20** **21**

R = Br, Cl; R = Cl, 2,4-$(Cl)_2$, CH_3; R = Br, Cl, CH_3.

Oxadiazole-containing pyrazoline derivatives (**22**) also exhibited antifungal activity [28].



22

X = O, S

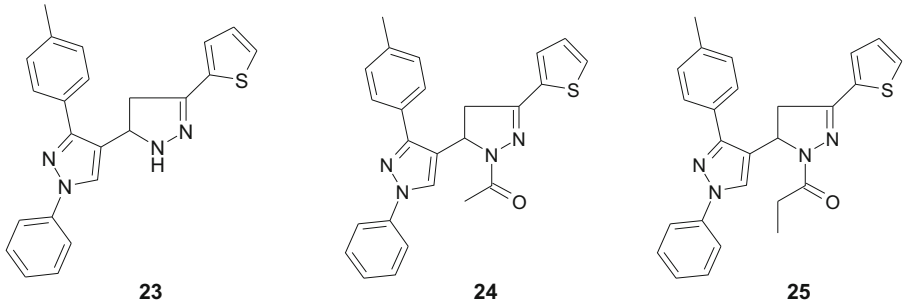
R^1 = H, *n*-CH_3, *n*-$N(CH_3)_2$, 3,4-OCH_2O, *n*-F, *n*-Cl, *n*-Br, *n*-OCH_3, *n*-OH.

R^2 = cyclopentyl, cyclohexyl.

Among similar compounds, a dihydropyrazole with a 3-furan substituent and 5-*p*-BrPh substituent showed the best results. Its MIC was similar to that of ketoconazole against *C. tropicalis*. The compound was reported to have low toxicity against NIH/3T3 cell line.

Compounds combining into one molecule pyrazoline, pyrazole, and thiophene heterocycles may be useful for discovering novel antimalarial drugs according to recent reports [29].

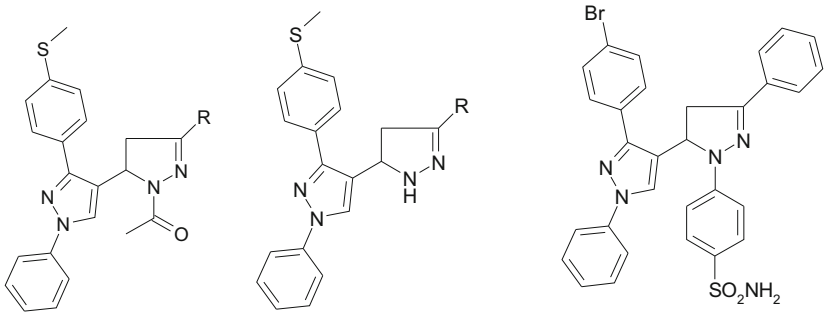
The *in vivo* activity of such compounds was less than that of the standard drug (chloroquine sulfate). Nevertheless, compound **23** showed significant suppression of 63.40%, which indicated that it was promising for further research.



23 **24** **25**

It was interesting that compounds of a similar structure but differing from the aforementioned ones mainly by the pyrazoline 3-substituents were reported earlier [30, 31] but were not tested for antimalarial activity. Compounds **26**, and **27** exhibited

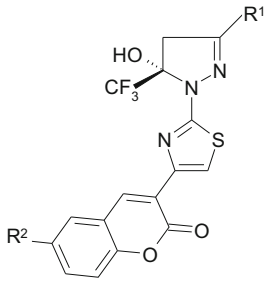
antimicrobial (including antituberculosis) activity. Compound **28** displayed a double pharmacological effect, i.e., antibacterial and anti-inflammatory.



26 **27** **28**

R = C_6H_5, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-SCH_3-C_6H_4, 4-OH-C_6H_4, 2-OH-C_6H_4, 3,5-$(Br)_2$ – 4-OH–C_6H_2, 4-NO_2–C_6H_4, 3-NO_2-C_6H_4, C_5H_4N.

Thiazolyl-derivatives of pyrazolines are especially well studied. According to the literature, they are efficacious antimicrobial agents. It is noteworthy that adding the thiazole substituent to N1 of 4,5-dihydro-1*H*-pyrazole [32 – 37] was more successful than adding it to the 3-position [38]. According to other data, compound **29** with a coumarylthiazole substituent exhibited antibacterial and anti-inflammatory activity [32].



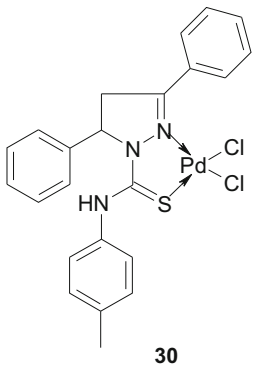
29

R^1 = CF_3, *n*-ClPh, *n*-BrPh, *n*-FPh; R^2 = H, Cl, Br.

Despite the fact that adding an additional azole substituent in most instances obviously enhanced the antimicrobial activity of pyrazoline derivatives, many dihydropyrazoles without other azole heterocycles in their structure were just as efficacious. For example, 3,5-diarylpyrazolines showed good results in *in vitro* tests against *Mycobacterium tuberculosis* [39], *E. coli* [40, 41], *S. aureus* [42], *P. aeruginosa* [41, 43] and moderate inhibitory activity against these and other microorganisms [44 – 46]. Moreover, several structurally similar compounds were more active than the reference drugs [47 – 50].

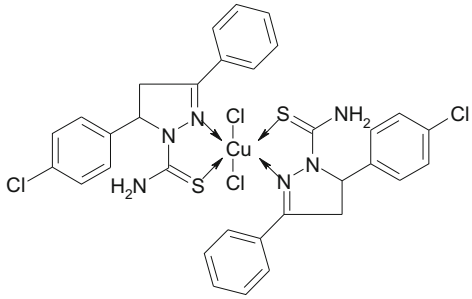
Dihydropyrazole complexes should be discussed separately with respect to biological activity. According to the literature, several pyrazoline coordination compounds with various metal ions exhibited antimicrobial activity [51] greater than that of the ligand itself [52, 53].

Thus, palladium complexes of pyrazoline thiocarbamoyl derivatives were investigated for antiamoebic activity [54]. In general, their effects on *Entamoeba histolytica* were more pronounced that those of the corresponding ligands. The IC_{50} value of **30** was significantly less than that of metronidazole.



30

Coordination compounds of other thiocarbamoyl dihydropyrazoles with copper (**31**) and nickel (**32**) showed good inhibitory activity against several *Candida* strains. The activity decreased in the order CuL > NiL > L for the separate compounds. Co-administration of the coordination compounds and amphotericin B or fluconazole gave the reverse order L > NiL > CuL. In general, the therapeutic effect of such combinations was greater [52].



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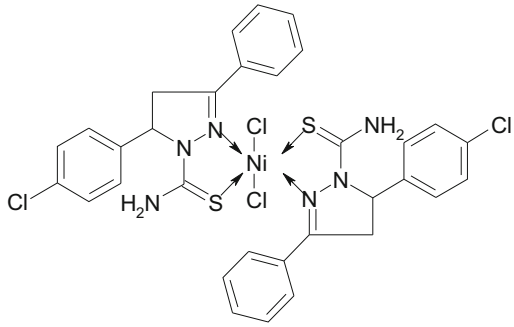
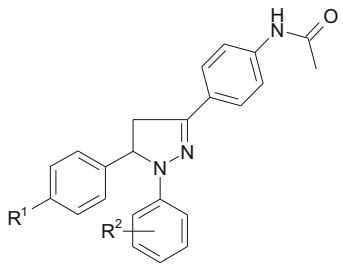


32

Neurotropic activity of dihydropyrazole derivatives

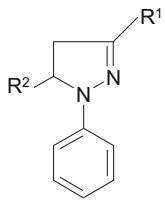
Type A monoamine oxidase (MAO-A) inhibitors are used as antidepressants and anxiolytics whereas MAO-B inhibitors are used to treat Parkinson's disease and may be useful in Alzheimer's disease therapy [55].

Early studies [56, 57] showed that 1,3,5-triaryl-substituted pyrazolines (**33** and **34**) not only inhibited MAO but also exhibited anticonvulsant activity.



33

R^1 = H, Cl, OCH_3; R^2 = H, 2-NO_2, 4-NO_2, 2,4-$(NO_2)_2$.



34

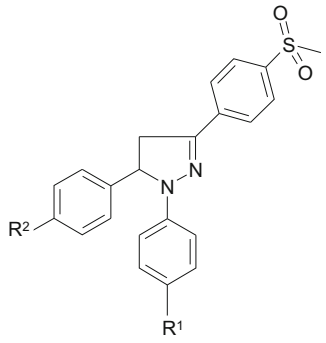
R^1 = 2,3,4-$(OH)_3$Ph, 4-Cl-Bn;R^2 = Ph, 4-Cl-Ph, 4-OCH_3Ph, 3,4-$(OCH_3)_2$Ph, 3-(O-Bn)Ph, CH=CH-Ph, 3-OCH_3,4-(OH)Ph, 4-(OH)Ph, 4-CH_3Ph, furyl.

Recent research [58] confirmed that tri-aryl-substituted pyrazolines (**35**) were highly efficacious as antidepressants in various *in vivo* tests (in mice). The researchers proposed that the pharmacological effect of the compounds was related to an effect on the CNS serotoninergic system. However, the exact mechanism of action requires further study.

Several of these compounds had comparatively low toxicity and showed better results than fluoxetine as a reference drug.

N1-Acylpyrazolines with various, as a rule, 3- and 5-aromatic substituents represent the largest group of CNS-active dihydropyrazole derivatives [59]. Several such compounds exert a double effect, i.e., antidepressant and anticonvulsant [60, 61]. Conversely, others have selective activity.

Anti-epileptic activity was typical of compounds with various groups on the pyrazoline N1 atom such as acetyl (**36**) [62], carbamoyl (**37**) [63], thiocarbamoyl (**38**) [64], and NH-substituted carbamoyl (**39**) [65] and other acyl groups (**40**, **41**) [66, 67].



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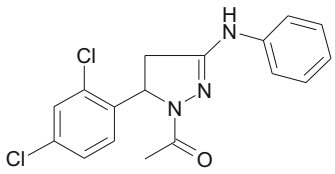
R^1 = F, Cl, Br, OCH_3, CH_3; R^2 = F, Cl, Br.



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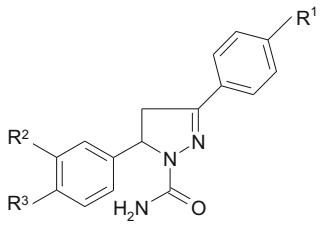

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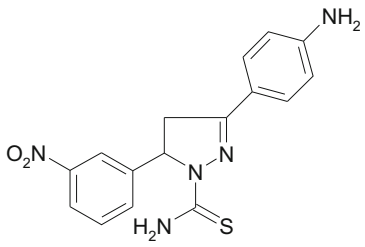
R^1 = H, OCH_3; R^2 = H, Cl; R^3 = H, F, Cl, OCH_3.



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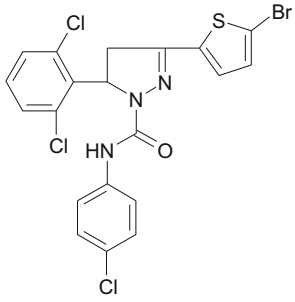

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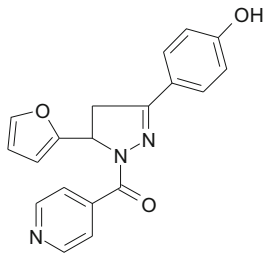

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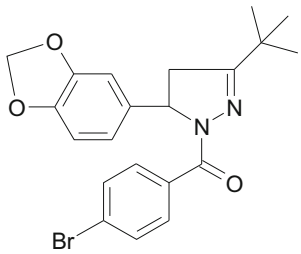

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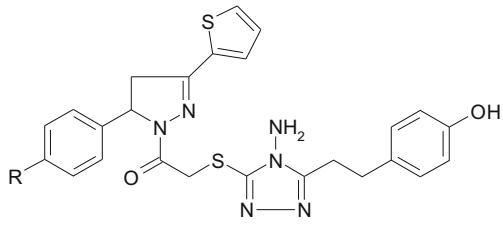
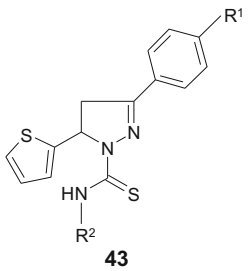
Significant antidepressant action was found in *in vivo* tests of polyheterocyclic structures (**42**) including pyrazoline, triazole, and thiophene fragments [68].



42

R = H, F, Cl.



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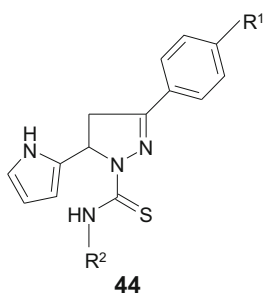

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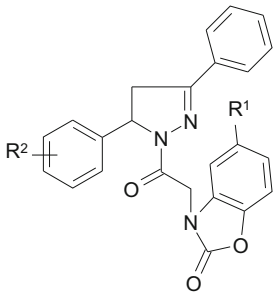
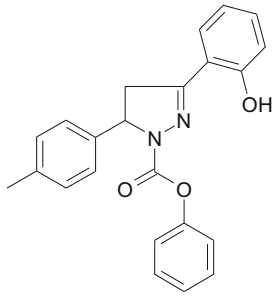
R^1 = CH_3, Cl, OCH_3. R^1 = CH_3, Cl, OCH_3. R^2 = CH_3, C_2H_5, $CH_2CH{=}CH_2$, C_6H_5. R^2 = CH_3, C_2H_5, $CH_2CH{=}CH_2$, C_6H_5.

The selectivity of the action of dihydropyrazole derivatives capable of inhibiting MAO in one of its two isoforms depends on not only the N1 substituent but also the 3- and 5-substituents [69]. Thus, compounds **43** and **44** and others with five-membered heterocycles in the pyrazoline 5-position inhibited selectively MAO-B [70 – 72] whereas phenyl-substituted **45** and **46** and others inhibited MAO-A [72 – 75].



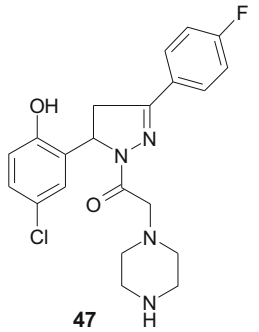
45



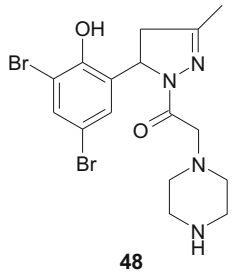
46

R^1 = H, CH_3, Cl; R^2 = H, 2-OCH_3, 4-OCH_3, 3,4,5-$(OCH_3)_3$.

Another recent study [76] showed that compounds **47** and **48** with electron-accepting substituents (F, Cl) on the pyrazoline C3 or C5 phenyl rings had the highest inhibitory activity for MAO-A.



47

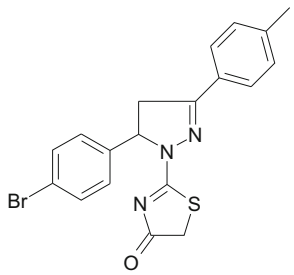


48

Other researchers noted that lengthening the dihydropyrazole N1 radical reduced its inhibitory activity for MAO-B because of the formation of an unstable complex with this isoform [77]. Addition of another aromatic ring to this position increased the binding selectivity to MAO-A [78].

Antitumor activity of dihydropyrazole derivatives

Thiazolylpyrazolines can act as epidermal growth factor receptor (EGFR) kinase inhibitors. Many such compounds exhibited antiproliferative activity against MCF-7, B16-F10, and HCT-116 cell lines. Compound **49** showed the best results [79]. Thiazolylpyrazoline derivatives of similar structures also had antiproliferative activity against MCF-7 and B16-F10 cell lines [80]. Compound **50** was the most efficacious HER-2 receptor inhibitor.



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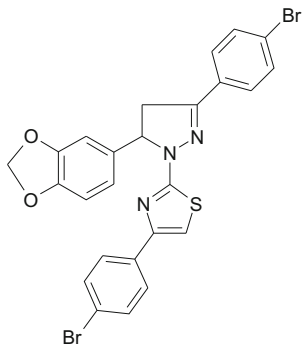
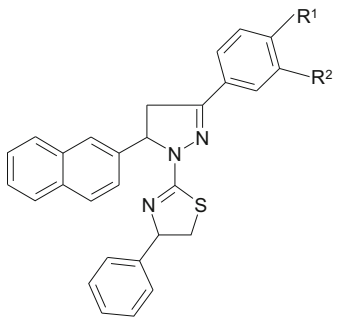
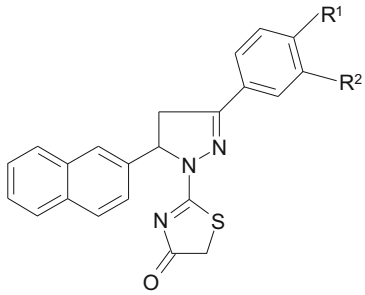


50

Another study showed that addition of a thiazolinone ring was more successful than a thiazoline ring for a series of pyrazolines (**51** and **52**) with the same 3- and 5-substituents [81]. Furthermore, the antiproliferative activity depended on the pyrazoline 3-phenyl substituents (OCH_3 > CH_3 > H > Br > Cl > F).



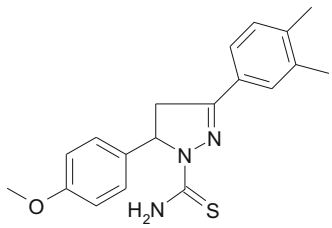
51



52

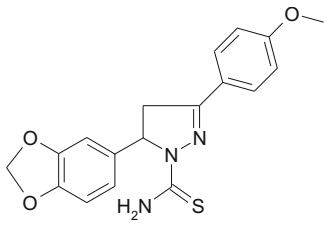
R^1 = H, F, Cl, Br, OCH_3, CH_3; R^2 = H, CH_3.

1-Thiocarbamoylpyrazolines also exhibited inhibitory activity against EGFR receptors [82]. The cytotoxicity of the compounds was checked using MCF-7 cell line. Compound **53** showed the highest activity.



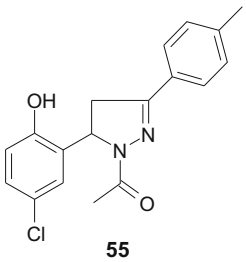
53

Another study [83] did not establish the target of thiocarbamoylpyrazoline action but found significant antitumor activity for **54** against prostate and kidney cancer and leukemia.

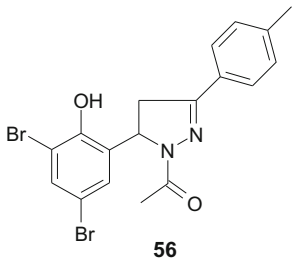


54

B-Raf kinase is yet another potential target for antitumor drugs. Normally, it is involved in mitogenic signal transduction from the cell membrane into the nucleus. However, mutations can begin to stimulate constant activation of this pathway, causing uncontrolled cell proliferation, increased cell survivability, and tumor growth. Molecular docking showed that **55** and **56** could bind to the B-Raf active site and inhibit it [84].



55

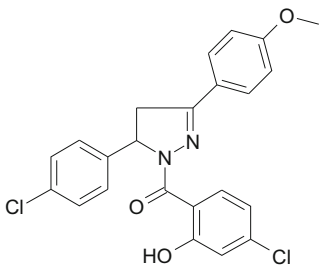


56

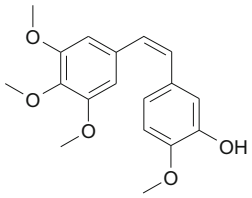
Results of *in vitro* tests confirmed that these compounds possessed potent antiproliferative activity against WM266.4 human melanoma cell line and MCF-7 human breast cancer cell line [84].

Compounds based on salicyloyl-3,5-diarylpyrazoline possessed analogous activity. Compound **57** turned out to be the most promising of a series of synthesized compounds [85].

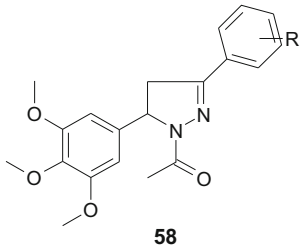
Combretastatin analogs are another group of antitumor pyrazolines. Combretastatin-4 is a strong antiproliferative agent against a broad spectrum of cancer cells, including a line with multi-drug resistance, because of inhibition of mitosis and microtubule assembly. Pyrazolines with a 3,4,5-trimethoxyphenyl fragment also possessed antitumor activity. Compounds **58** and **59** inhibited tubulin polymerization analogously to combretastatin [86].



57

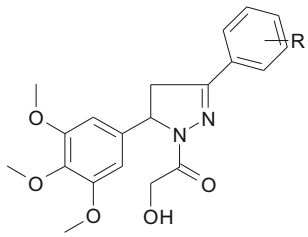


Combretastatin R = 3-Br



58

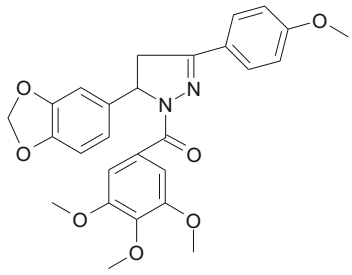
4-$(C_2H_5)_2$N, 3-OCH_3,4-OH.



59

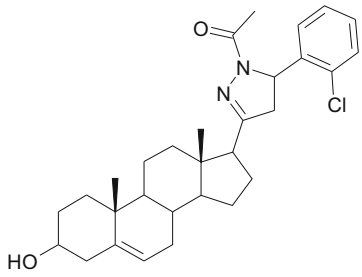
R = 4-CH_3, 4-$(C_2H_5)_2$N.

It is interesting that pyrazoline derivatives prepared with the trimethoxyphenyl fragment in another position acted in the same manner, i.e., inhibited tubulin polymerization. Compound **60** was the most active compound in the series. Furthermore, it was shown to induce apoptosis in cells with HEPG-2 receptor expression [87].



60

Steroids and steroidal glycosides were added to a dihydropyrazole fragment [88]. For example, 17-pyrazolinyl pregnenolone (**61**) exhibited noticeable antitumor activity against HT-29 and HCT-15 cancer cell lines [89].

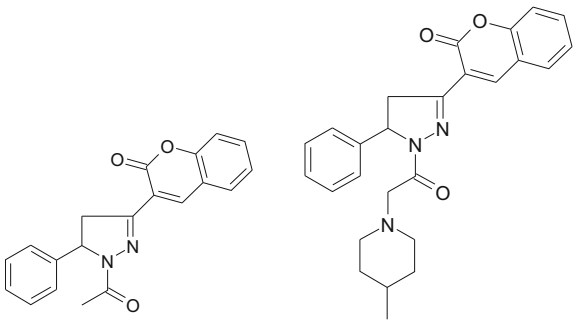


61

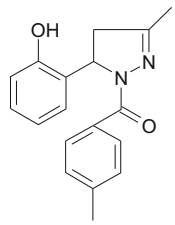
Telomerase inhibitors represent yet another promising platform for discovering antitumor agents. Several studies [90 – 92] showed that such drugs could be designed based on coumarylpyrazolines (**62**, **63**, **64**).

Acylpyrazolines (**65**) can also interact with the active site of telomerase to inhibit it. Compound **65** was active against SGC-7901, Hep-G2, and PC-3 cell lines [93].

Recently, transition-metal complexes with organic ligands have attracted more and more attention in the search for novel antitumor agents. The development of pyrazoline chemistry in this direction is highly promising because the N atoms of this heterocycle can form ligand—metal coordination bonds. The composition, geometry, and stability of coordination complexes with a selected metal can be varied by adding various substituents to the dihydropyrazole ring.

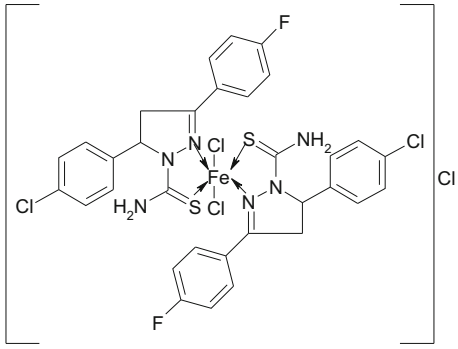


62 **63** **64**



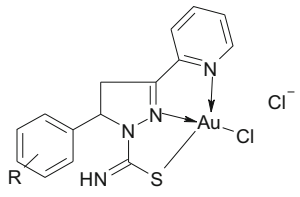
65

Thiocarbamoyldihydropyrazoles are good complexants. Thus, 3,5-diarylsubstituted thiocarbamoyl-2-pyrazolines form stable coordination complexes with Cu(II), Ni(II), and Fe(III) that can bind to DNA [94]. All complexes in that work showed moderate antiproliferative activity against MCF-7 cell line. Compound **66**, the iron complex, gave the best effect.



66

Thiocarbamoylpyrazolines containing a 3-pyridyl fragment can form complexes with gold (**67**). In contrast with the aforementioned coordination complexes, these compounds had a slightly different structure. The ligand-to-metal ratio in them was 1:1.



67

R = 2-Cl, 3-Cl, 4-Cl, 3-NO_2, 4-OCH_3, 3,4-OCH_2O, 4-CH_3, H.

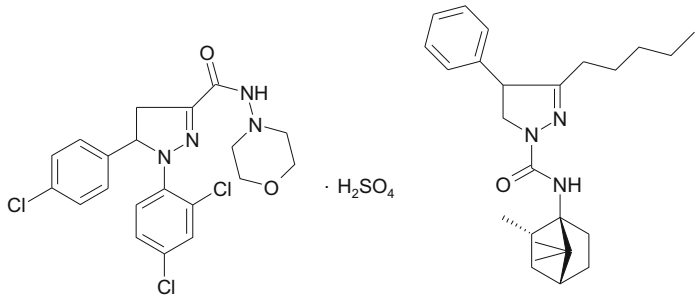
The MTT assay showed that this series of compounds with phenyl, 2-Cl, 3-NO_2, and 4-OCH_3-phenyl substituents possessed greater cytotoxicity than cisplatin against HeLa cell line [95].

Other types of activity of dihydropyrazole derivatives

A promising direction in pyrazoline medicinal chemistry is the design based on them of ligands for cannabinoid receptors CB_1 and CB_2. Research of the last decades showed that targeted modulation of endocannabinoid activity can produce therapeutic effects for treating psychiatric disorders, various motor disruptions (such as Parkinson's and Huntington's diseases), multiple sclerosis, metabolic syndrome, and several other diseases [96, 97].

CB_1 receptor antagonists affect the demand for food, reduce the body mass, and can be used for obesity. The first drug with this activity was the pyrazole derivative rimonabant [89].

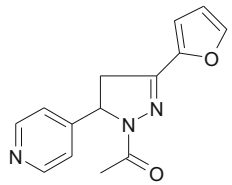
Preparations containing rimonabant are not currently allowed for use in Russia and EU countries because of side effects on the CNS. However, the search for preparations of this pharmacological class with fewer undesired drug reactions is continuing. Pyrazoline rimonabant analogs were shown [98 – 100] to be CB_1 and CB_2 receptor ligands [101]. For example, compound **68** [(–)-enantiomer] acted as a more active CB_1 antagonist than rimonabant reference drug (as rimonabant hydrochloride) in *in vivo* tests [98]. Compound **69** [(–)-enantiomer], in contrast with the aforementioned compound, was a CB_1 receptor agonist.



68 **69**

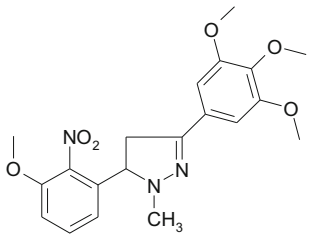
It showed a significant decrease of motor dysfunction in animals after oral administration in *in vivo* studies in a rodent multiple sclerosis model (experimental allergic encephalomyelitis), even when the treatment started on the day following the appearance of the first disease symptoms [102].

Another interesting target for pyrazoline derivatives is xanthine oxidase, inhibitors of which possess antigout activity. The IC_{50} value of **70** among a series of novel tested pyrazoline derivatives was less than that of allopurinol. This indicated that further modifications of this structure were promising [103].

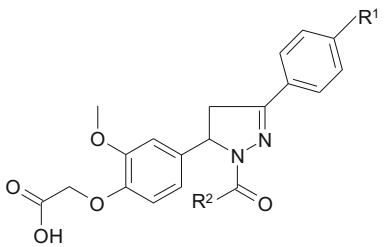


70

Several dihydropyrazole derivatives were active against the renin-angiotensin-aldosterone system (RAAS). Angiotensin converting enzyme (ACE) inhibitors are RAAS drugs that are currently used widely to treat various cardiovascular diseases, diabetic neuropathy, and renal insufficiency. Compound **71**, *N*-methyl-3,5-diarylpyrazoline, showed marked inhibitory activity against ACE [104].



71

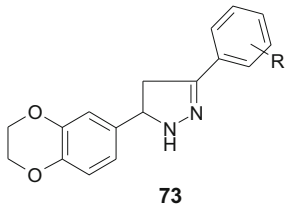


72

R^1 = H, Cl, OCH_3, OH;
R^2 = *p*-ClC_6H_4, *p*-OHC_6H_4, o-OHC_6H_4, *p*-$OCH_3C_6H_4$, C_6H_5-CH_2, *p*-CH_3-C_6H_4-O-CH_2, C_6H_5-O-CH_2.

Pyrazolines (**72**) with a phenoxyacetic acid fragment possessed a diuretic effect. Several of them were stronger in *in vivo* tests than furosemide as the reference drug [105].

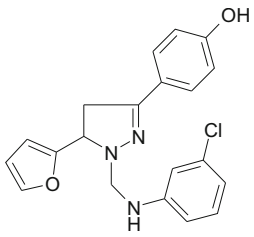
Adding a benzodioxane to the pyrazoline 5-position was thought to produce antihepatotoxic activity in such compounds (**73**) [106]. Several such free-NH pyrazolines showed activity in *in vivo* tests that was comparable with that of the standard silymarin for the CCl_4 toxicity model in rat liver.



73

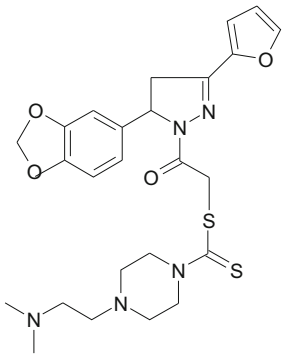
R = H, 2,4-$(OH)_2$, 4-Cl, 3,4-$(OCH_3)_2$, 3-CH_3.

Antioxidant properties were found for several 5-furylpyrazoline derivatives. Compound **74** among others was more active than ascorbic acid and rutin [107].



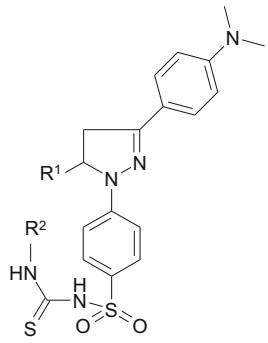
74

A series of 3-furylpyrazoline derivatives with a dithiocarbamate fragment were synthesized. Their anticholinesterase activity and cytotoxicity were evaluated [108]. Compound **75** turned out to be the most active. Its effective concentration was lower than the cytotoxic one.



75

A recent study of novel dihydropyrazole derivatives with a sulfonylurea fragment showed that such compounds could be useful for discovering new preparations to treat diabetes mellitus. It was noted that **76** not only had hypoglycemic activity but also inhibited aldose reductase [109].



76

R^1 = Ph, 4-CH_3-Ph, 2-Cl-Ph, 4-Cl-Ph; R^2 = CH_2-Ph, Ph.

REFERENCES

1. P. Alam, G. Raj, and B. Kumar, *Ally J. Pharm. Sci.*, **2**(1), 137 – 175 (2014).
2. V. Avupati and R. P. Yejella, *World J. Pharm. Res.*, **3**(8), 1181 – 1215 (2014).
3. F. F. Barsoum and A. S. Girgis, *Eur. J. Med. Chem.*, **44**(5), 2172 – 2177 (2009).
4. I. G. Rathish, K. Javed, S. Ahmad, et al., *Bioorg. Med. Chem. Lett.*, **19**(1), 255 – 258 (2009).
5. F. F. Barsoum, H. M. Hosni, and A. S. Girgis, *Bioorg. Med. Chem.*, **14**(11), 3929 – 3937 (2006).
6. M. Amir, H. Kumar, and S. A. Khan, *Bioorg. Med. Chem. Lett.*, **18**(3), 918 – 922 (2008).
7. R. Fioravanti, A. Bolasco, F. Manna, et al., *Eur. J. Med. Chem.*, **45**(12), 6135 – 6138 (2010).
8. A. A. Bekhit, H. M. A. Ashour, Y. S. Abdel Ghany, et al., *Eur. J. Med. Chem.*, **43**(3), 456 – 463 (2008).
9. P. Rani, V. K. Srivastava, and A. Kumar, *Eur. J. Med. Chem.*, **39**(5), 449 – 452 (2004).
10. K. S. Girisha, B. Kalluraya, V. Narayana, et al., *Eur. J. Med. Chem.*, **45**(10), 4640 – 4644 (2010).
11. M. V. R. Reddy, V. K. Billa, V. R. Pallela, et al., *Bioorg. Med. Chem.*, **16**(7), 3907 – 3916 (2008).
12. S. Khode, V. Maddi, P. Aragade, et al., *Eur. J. Med. Chem.*, **44**(4), 1682 – 1688 (2009).
13. O. M. Khalil, *Med Chem. Res.*, **21**(10), 3240 – 3245 (2012).
14. P. K. Patra, C. N. Patra, and S. Pattnaik, *World J. Pharm. Pharm. Sci.*, **3**(3), 1504 – 1518 (2014).
15. C. Kharbanda, M. S. Alam, H. Hamid, et al., *Bioorg. Med. Chem.*, **22**(21), 5804 – 5812 (2014).
16. K. R. A. Abdellatif, E. K. A. Abdelall, and A. A. F. Wael, *Med. Chem. Res.*, **24**(6), 2632 – 2644 (2015).
17. A. Gursoy, S. Demirayak, G. Capan, et al., *Eur. J. Med. Chem.*, **35**(3), 359 – 364 (2000).
18. Z. A. Kaplancikli, G. Turan-Zitouni, A. Ozdemir, et al., *Eur. J. Med. Chem.*, **44**(6), 2606 – 2610 (2009).
19. N. Borhade, R. Pathan, S. Halder, et al., *Chem. Pharm. Bull.*, **60**(4), 465 – 481 (2012).
20. M. E. Shoman, M. Abdel-Aziz, O. M. Aly, et al., *Eur. J. Med. Chem.*, **44**(7), 3068 – 3076 (2009).
21. P. D. Sauzem, P. Machado, M. A. Rubin, et al., *Eur. J. Med. Chem.*, **43**(6), 1237 – 1247 (2008).
22. P. D. Sauzem, G. D. S. Sant'Anna, P. Machado, et al., *Eur. J. Pharmacol.*, **616**(1), 91 – 100 (2009).
23. M. C. M. Godoy, M. R. Fighera, F. R. Souza, et al., *Eur. J. Pharmacol.*, **496**(1), 93 – 97 (2004).
24. WHO, *Antimicrobial Resistance: Global Report on Surveillance 2014*, World Health Organization, Geneva, Switzerland (2014).
25. S. Y. Hassan, *Molecules*, **18**(3), 2683 – 2711 (2013).
26. L. Hu, P. Lan, Q. L. Song, et al., *Eur. J. Med. Chem.*, **45**(12), 5943 – 5949 (2010).
27. D. Zampieri, M. G. Mamolo, E. Laurini, et al., *Bioorg. Med. Chem.*, **16**(8), 4516 – 4522 (2008).
28. A. Ozdemir, M. D. Altintop, Z. A. Kaplancikli, et al., *Pharm. Chem. J.*, **48**(9), 603 – 612 (2014).
29. A. Tuha, A. A. Bekhit, and Y. Seid, *Thai J. Pharm. Sci.*, **38**(3), 121 – 129 (2014).
30. P. T. Chovatia, J. D. Akabari, P. K. Kachhadia, et al., *J. Serb. Chem. Soc.*, **71**(7), 713 – 720 (2007).
31. P. K. Sharma, S. Kumar, P. Kumar, et al., *Eur. J. Med. Chem.*, **45**(6), 2650 – 2655 (2010).
32. R. Aggarwal, S. Kumar, P. Kaushik, et al., *Eur. J. Med. Chem.*, **62**, 508 – 514 (2013).
33. B. Sharifzadeh, N. O. Mahmoodi, M. Mamaghani, et al., *Bioorg. Med. Chem. Lett.*, **23**(2), 548 – 551 (2013).
34. B. S. Dawane, S. G. Konda, B. M. Shaikh, et al., *Int. J. Pharm. Sci. Rev. Res.*, **1**(2), 44 – 48 (2010).
35. O. I. El-Sabbagh, M. M. Baraka, S. M. Ibrahim, et al., *Eur. J. Med. Chem.*, **44**(9), 3746 – 3753 (2009).
36. B. F. Abdel-Wahab, H. A. Abdel-Aziz, and E. M. Ahmed, *Eur. J. Med. Chem.*, **44**(6), 2632 – 2635 (2009).
37. A. Ozdemir, G. Turan-Zitouni, Z. A. Kaplancikli, et al., *Eur. J. Med. Chem.*, **42**(3), 403 – 409 (2007).
38. S. Bondock, T. Naser, and Y. A. Ammar, *Eur. J. Med. Chem.*, **62**, 270 – 279 (2013).
39. M. A. Ali, M. Shaharyar, and A. A. Siddiqui, *Eur. J. Med. Chem.*, **42**, 268 – 275 (2007).
40. P. M. Sivakumar, S. P. Seenivasan, V. Kumar, et al., *Bioorg. Med. Chem. Lett.*, **20**(10), 3169 – 3172 (2010).
41. V. G. Patel and T. K. Goswami, *J. Chem., Biol. Phys. Sci.*, **4**(4), 3064 – 3069 (2014).
42. P. Wang, H. Qiu, J. Ma, et al., *RSC Adv.*, **5**, 24997 – 25005 (2015).
43. B. K. Sarkar, R. Patel, and U. Bhadoriya, *J. Adv. Pharm. Educ. Res.*, **1**(5), 243 – 250 (2011).
44. I. B. K and J. Pj, *Asian J. Pharm. Clin. Res.*, **7**(4), 237 – 239 (2014).
45. V. N. Bhadani, P. A. Patel, P. V. Bhatt, et al., *Res. J. Pharm., Biol. Chem. Sci.*, **5**(4), 207 – 216 (2014).
46. G. Wanare, R. Aher, N. Kawathekar, et al., *Bioorg. Med. Chem. Lett.*, **20**(15), 4675 – 4678 (2010).
47. R. Chawla, U. Sahoo, A. Arora, et al., *Acta Pol. Pharm. Drug Res.*, **67**(1), 55 – 61 (2010).
48. R. Sasikala, K. Thirumurthy, P. Mayavel, et al., *Org. Med. Chem. Lett.*, **2**(20), 1 – 13 (2012).
49. A. Ahmad, A. Husain, and S. A. Khan, *J. Saudi Chem. Soc.*, doi: 10.1016 / j.jscs.2014.12.004 (2014).
50. N. R. Rao, M. V. B. Rao, and K. Lakshmi, *PharmaChem.*, **7**(2), 112 – 116 (2015).
51. M. N. Al-jibori, S. Al-Bayatiand, and A. Rasheed, *Chem. Mater. Res.*, **3**(12), 1 – 11 (2013).
52. I. Ali, W. A. Wani, A. Khan, et al., *Microb. Pathog.*, **53**(2), 66 – 73 (2012).
53. A. S. Elgazwy, N. S. Ismail, S. R. Atta-Allah, et al., *Curr. Med. Chem.*, **19**(23), 3967 – 3981 (2012).
54. A. Budakoti, M. Abid, and A. Azam, *Eur. J. Med. Chem.*, **42**(4), 544 – 551 (2007).
55. V. Filip and E. Kolibas, *J. Psychiatry Neurosci.*, **24**(3), 234 – 243 (1999).
56. S. P. Singh, A. Chaudhari, J. P. Barthwal, et al., *J. Pharm. Sci.*, **63**(12), 1948 – 1950 (1974).
57. S. S. Parmar, B. R. Pandey, C. Dwivedi, et al., *J. Pharm. Sci.*, **63**(7), 1152 – 1155 (1974).
58. A. Ozdemir, M. Altintop, Z. Kaplancikli, et al., *Molecules*, **20**(2), 2668 – 2684 (2015).
59. D. Secci, A. Bolasco, P. Chimenti, et al., *Curr. Med. Chem.*, **18**(33), 5114 – 5144 (2011).
60. Z. Ozdemir, H. B. Kandilci, B. Gumusel, et al., *Eur. J. Med. Chem.*, **42**(3), 373 – 379 (2007).
61. N. Siddiqui, P. Alam, and W. Ahsan, *Arch. Pharm. (Weinheim)*, **342**(3), 173 – 181 (2009).

62. A. Singh, A. C. Rana, and R. Magra, *J. Chem. Pharm. Res.*, **2**(1), 505 – 511 (2010).
63. A. A. Siddiqui, A. Rahman, and R. Mishra, *Chem. Sci. J.*, **8**, 1 – 10 (2010).
64. S. Vinayaditya, A. Ameeta, and M. Vikash, *Int. J. Res. Pharm. Sci. (Madurai, India)*, **1**(3), 125 – 146 (2011).
65. N. Beyhan, B. Kocyigit-Kaymakcioglu, S. Gumru, et al., *Arabian J. Chem.*, doi: 10.1016 / j.arabjc.2013.07.037 (2013).
66. B. M. Rao, S. Ramseh, D. Bardalai, et al., *Sch. J. Appl. Med. Sci.*, **1**(1), 20 – 27 (2013).
67. M. N. Aboul-Enein, A. A. El-Azzouny, M. I. Attia, et al., *Eur. J. Med. Chem.*, **47**(1), 360 – 369 (2012).
68. Z. A. Kaplancikli, A. Ozdemir, G. Turan-Zitouni, et al., *Eur. J. Med. Chem.*, **45**(9), 4383 – 4387 (2010).
69. B. Mathew, J. Suresh, S. Anbazhagan, et al., *Cent. Nerv. Syst. Agents Med. Chem.*, **13**(3), 195 – 206 (2013).
70. G. Ucar, N. Gokhan, A. Yesilada, et al., *Neurosci. Lett.*, **382**(3), 327 – 331 (2005).
71. N. Gokhan-Kelekci, S. Yabanoglu, E. Kupeli, et al., *Bioorg. Med. Chem.*, **15**(17), 5775 – 5786 (2007).
72. N. Gokhan-Kelekci, S. Koyunoglu, S. Yabanoglu, et al., *Bioorg. Med. Chem.*, **17**(2), 675 – 689 (2009).
73. U. Salgin-Goksen, S. Yabanoglu-Ciftci, A. Ercan, et al., *J. Neural Transm.*, **120**(6), 863 – 873 (2013).
74. B. V. Nayak, S. Ciftci-Yabanoglu, S. S. Jadav, et al., *Eur. J. Med. Chem.*, **69**, 762 – 767 (2013).
75. B. Evranos-Aksoz, S. Yabanoglu-Ciftci, G. Ucar, et al., *Bioorg. Med. Chem. Lett.*, **24**(15), 3278 – 3284 (2014).
76. X. Tong, R. Chen, T.-T. Zhang, et al., *Bioorg. Med. Chem.*, **23**(3), 515 – 525 (2014).
77. F. Chimenti, R. Fioravanti, A. Bolasco, et al., *Eur. J. Med. Chem.*, **43**(10), 2262 – 2267 (2008).
78. M. Jagrat, J. Behera, S. Yabanoglu, et al., *Bioorg. Med. Chem. Lett.*, **21**, No. 14, 4296 – 4300 (2011).
79. K. M. Qiu, H. H. Wang, L. M. Wang, et al., *Bioorg. Med. Chem.*, **20**, No. 6, 2010 – 2018 (2012).
80. H. H. Wang, K. M. Qiu, H. E. Cui, et al., *Bioorg. Med. Chem.*, **21**(2), 448 – 455 (2013).
81. J. W. Yuan, S. F. Wang, Z. L. Luo, et al., *Bioorg. Med. Chem. Lett.*, **24**(10), 2324 – 2328 (2014).
82. P. C. Lv, H. Q. Li, J. Sun, et al., *Bioorg. Med. Chem.*, **18**(3), 4606 – 4614 (2010).
83. B. Insuasty, L. Chamizo, J. Munoz, et al., *Arch. Pharm. (Weinheim)*, **345**(4), 275 – 286 (2012).
84. J. J. Liu, H. Zhang, J. Sun, et al., *Bioorg. Med. Chem.*, **20**(20), 6089 – 6096 (2012).
85. Q. S. Li, X. H. Lv, Y. B. Zhang, et al., *Bioorg. Med. Chem. Lett.*, **22**(21), 6596 – 6601 (2012).
86. C. Congiu, V. Onnis, L. Vesci, et al., *Bioorg. Med. Chem.*, **18**(17), 6238 – 6248 (2010).
87. Y. J. Qin, Y. Li, A. Q. Jiang, et al., *Eur. J. Med. Chem.*, doi: 10.1016 / j.ejmech.2015.02.058 (2015).
88. S. Kankala, R. K. Kankala, and D. R. Kommidi, *RSC Adv.*, **4**(76), 40305 – 40311 (2014).
89. A. H. Banday, B. P. Mir, I. H. Lone, et al., *Steroids*, **75**(12), 805 – 809 (2010).
90. X. H. Liu, H. F. Liu, J. Chen, et al., **20**(19), 5705 – 5708 (2010).
91. X. H. Liu, J. Li, J. B. Shi, et al., *Eur. J. Med. Chem.*, **51**, 294 – 299 (2012).
92. X. Q. Wu, C. Huang, Y. M. Jia, et al., *Eur. J. Med. Chem.*, **74**, 717 – 725 (2014).
93. X. H. Liu, B. F. Ruan, J. X. Liu, et al., *Bioorg. Med. Chem. Lett.*, **21**(10), 2916 – 2920 (2011).
94. K. Saleem, W. A. Wani, A. Haque, et al., *Future Med. Chem.*, **5**(2), 135 – 146 (2013).
95. S. Wang, W. Shao, H. Li, et al., *Eur. J. Med. Chem.*, **46**(5), 1914 – 1918 (2011).
96. G. G. Muccioli and D. M. Lambert, *Curr. Med. Chem.*, **12**(12), 1361 – 1394 (2005).
97. L. Pacher and N. Ba, *Pharmacol. Rev.*, **58**(3), 389 – 462 (2006).
98. B. K. Srivastava, A. Joharapurkar, S. Raval, et al., *J. Med. Chem.*, **50**(24), 5951 – 5966 (2007).
99. S. R. Donohue, V. W. Pike, S. J. Finnema, et al., *J. Med. Chem.*, **51**(18), 5608 – 5616 (2008).
100. J. H. Lange, M. A. van der Neut, A. P. den Hartog, et al., *Bioorg. Med. Chem. Lett.*, **20**(5), 1752 – 1757 (2010).
101. V. Gembus, C. Furman, R. Millet, et al., *Eur. J. Med. Chem.*, **58**, 396 – 404 (2012).
102. J. H. Lange, A. Attali, M. A. van der Neut, et al., *Bioorg. Med. Chem. Lett.*, **20**(17), 4992 – 4998 (2010).
103. K. Nepali, G. Singh, A. Turan, et al., *Bioorg. Med. Chem.*, **19**(6), 1950 – 1958 (2011).
104. M. Bonesi, M. R. Loizzo, G. A. Statti, et al., *Bioorg. Med. Chem. Lett.*, **20**(6), 1990 – 1993 (2010).
105. M. A. Bakht, M. S. Yar, A. A. Siddiqui, et al, *Med. Chem. Res.*, **22**(2), 916 – 926 (2013).
106. B. Ahmed, Habibullah, and S. Khan, *J. Enzyme Inhib. Med. Chem.*, **26**(2), 216 – 221 (2011).
107. P. C. Jagadish, N. Soni, and A. Verma, *J. Chem.*, **2013**, 1 – 6 (2013).
108. M. D. Altintop, A. Ozdemir, Z. A. Kaplancikli, et al., *Arch. Pharm. (Weinheim*), **346**(3), 189 – 199 (2013).
109. S. Ovais, H. Pushpalatha, G. B. Reedy, et al., *Eur. J. Med. Chem.*, **80**, 209 – 217 (2014).