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REVIEW ON PYRAZOLINE DERIVATIVES HAVING ANTIDEPRESSANT PROPERTY

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ABSTRACT

Depression is potentially life-threatening disorder which is affecting people worldwide. It is not limited by age and is a curse to the society as it causes severe distress and, if left untreated, can even cause death. There are different chemical moieties showing antidepressant properties such as benzodiazepines, hydrazones, imidazoles, indoles, piperazines, piperidines, pyrazolines, pyrimidines, pyrrolidones, quinazolines, quinolines,

thiadiazoles and triazoles. Among all these chemical moieties, the pyrazolines possess a broad spectrum of pharmacological activities such as analgesic, anti-pyretic, anti-inflammatory, insecticide, uricosuric, anti-epileptic, anti-depressant, anti-microbial, anti-cancer, anti-tubercular, hypotensive, anti-nociceptive, and anti-oxidant activity. Recently synthesized antidepressants having pyrazoline moiety has been the highlight of this present review. It has been found that most of the substitutions are taking place in the 1st, 2nd, 3rdand 5th position to exhibit antidepressant property in the form of MAO inhibition. The substitution in the 4th position has found to decrease the activity, but fused phenyl ring in the 3rd and 4th position exhibited acute potency. Marked response is observed when 3rd and 5th positions encounter substitutes or non substituted six membered aromatic rings attachment along with substituted thioacetamide in the 1st position. These conclusions were drawn on the basis of results obtained from Despair Swim Test.

Keywords: Pyrazolines, Antidepressant property, MAO inhibition

INTRODUCTION

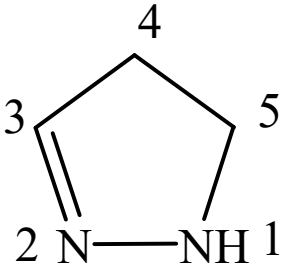
Depression is a major heterogeneous mood disorder **[1]**. Chronic and acute depression interfere severely in one's healthy life, consequently causing a discontinuation in the normal physical, mental, and social well-being of the affected person and the family from which he belongs, drives him even to commit suicide **[2]**. It is a state of low mood **[3]**. Patients suffering from depression may feel sad, anxious, empty, hopeless, worried, helpless, worthless, guilty, irritable, or restless, loss of interest in activities that were once pleasurable, loss of appetite, overreaction, loss of concentration, memory and making in correct decisions **[4]**. Life events that may precipitate depressed mood include personal conflicts or disputes with family members or friends, bereavement, losing a job or income, divorce, stress, retirement, menopause, social isolation, and social rejection **[2]**. Depression can be a consequent result of fluctuating circadian rhythm **[6]**.

Monoamine Oxidase was first discovered seventy years ago. This enzyme naturally exists in two isoforms: MAO-A and MAO-B. MAO-A degrades to 5-hydroxytryptamine (5-HT) and noradrenaline (NA) but MAO-B turns to phenyl ethylamine and secondary amine. Clorgyline and deprenylare well know drugs used as MAO-A and MAO-B inhibitors respectively. Inhibitory activities to these receptors are irreversible **[7]**.

There are different chemical moieties showing anti-depressant properties such as, benzodiazepines **[8]**, hydrazones

[9], imidazoles, indoles, piperazines, piperidines, pyrazolines, pyrimidines, pyrrolidones **[10]**, quinazolines **[11]**, quinolines, thiadiazoles and triazoles. Among them pyrazolines possess a wide range of pharmacological activities such as anticonvulsant, anti-psychotic, anti-arrhythmic, anti-microbial, cytotoxic, anti-oxidant and anti-malarial activity **[12]**.

Chemically pyrazolines can be characterized by a five-membered heterocyclic ring structure containing two nitrogen atoms in it along with a double bond. They are classified as an important class of heterocyclic compounds due to their pronounced biological and pharmacological activities **[13]**.



pyrazoline

The present review is about recently synthesized pyrazolines possessing antidepressant activity.

ANTIDEPRESSANT ACTIVITY OF PYRAZOLINES

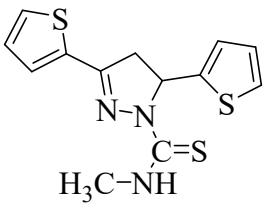
Ozmedir *et al.* designed and synthesized a set of derivatives of 3-(2-Thienyl) pyrazolines, out of which the given compounds were found to be the most potent forms as conclusions received from duration of immobility tests **[14]**. These potent compounds **1a** and **1b** have duration of immobility time of 43±15.3 seconds and 48.±18.9 seconds respectively whereas standard drug Tranylcypromine sulfate showed duration of immobility time of 57±11.6 seconds.

Kaplancikli *et al* synthesized a set of derivatives of 3-Thiophen-2-yl-4,5-dihydro-pyrazole-1-carbaldehyde **[15]**. Among them, marked response with duration of immobility time of 33.3±3.9 seconds was observed for the derivative **2** and in comparison, the standard drug, Fluoxetine experimentally found to have 67.6±4.1 seconds as duration of immobility time.

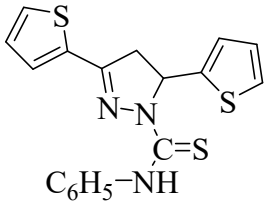
Ruhoglu *et al.* synthesized 1,3,5-Trisubstituted pyrazolines that exhibited antidepressant property **[16]**. Derivatives **3a** and **3b** reported to have duration of immobility time of 4.57±2.92 seconds and 14.78±22.01 seconds respectively whereas standard drug Tranylcypromine sulfate has duration of immobility time of 49.71±2.11 seconds.

Again Iyidogan *et al.* further investigated these1,3,5-Trisubstituted pyrazolines and came across synthesizing another new set of derivatives **[17]**. Most of the derivatives possess low potency but among them thederivatives **4a** and **4b** with duration of immobility time of 7±3.10 seconds and

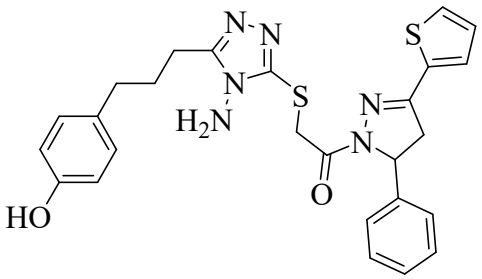
14±8.2 seconds against the standard drug Tranylcypromine sulfate with duration of immobility time of 24±6.6 seconds.



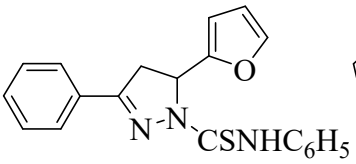
1a



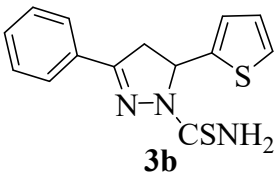
1b



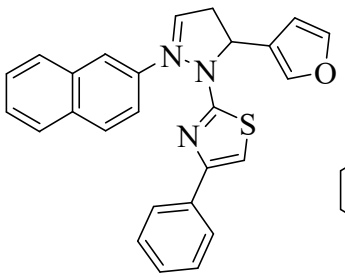
2



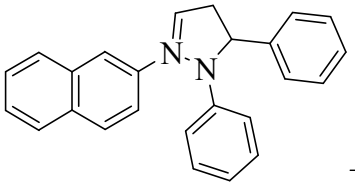
3a



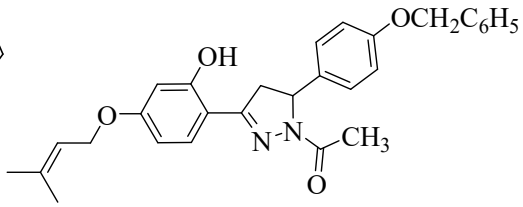
3b



4a



4b



5

Fioravanti *et al* synthesized a set of 1-{3-[2-Hydroxy-4-(3-methyl-but-2-enyloxy)-phenyl]-5-phenyl-4,5-dihydro-pyrazol-1-yl}-ethanone derivativesusing molecular modeling **[18]**. The mentioned compound **5** showed the best potency as hMAO-B inhibitor with K_i value (μM) 6.76 and the standard drug Clorgyline having K_i value (μM) 8.35.

Later molecular modeling became the basic approach for designing anti-depressants and Fioravanti *et al* made a further progress by synthesizing another new set of anti-depressants (*N*1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1*H*)-pyrazoles) **[19]**. Marked response was reported for the mentioned derivatives **6a** and **6b** with IC_{50} (μM) for MAO-A and MAO-B of 6.70 and 6.82 respectively. It was found that the standard drug Moclobemide has given IC_{50} (μM) for MAO-A and MAO-B of 4.94 and 2.00 respectively.

Jayaprakash *et al.* took an initiative to synthesize pyrazoline based mycobactin analogues **[20]**. Maximum MAO-Ainhibitory activity was found for derivative **7** with IC_{50} (μM) of 2.84±0.19

which may have therapeutic utility in Alzheimer disease. The standard drug Clorgyline produced IC_{50} (μM) for MAO-A, of 2.05±0.19.

Karuppasamy *et al.* synthesized 3,4-Diaryl pyrazolines analogues and evaluated for their MAO inhibitory activity **[21]**. The compounds were found reversible and selective towards MAO-A with selectivity index in magnitude of 10^3 -10^5. The mentioned derivative **8** with K_i value (μM) 150.10±10.05 (MAO-A) was found to have the maximum potency against the standard drug Moclobemide showing K_i value (μM) of 5.53±0.27.

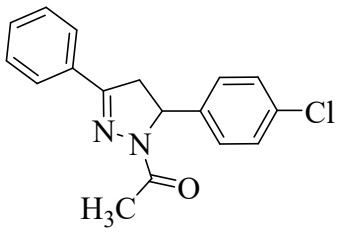
A novel series of 2-thiocarbamoyl-2,3,4,5,6,7-hexahydro-1*H*-indazole and 2-substituted thiocarbamoyl-3,3a,4,5,6,7-hexahydro-2*H*-indazole were synthesized by Kelekci *et al.* and investigated their MAO-A & B inhibitory activity **[22]**. The mentioned derivatives **9a** and **9b** with K_i values (μM) 0.96±0.01 and 0.90±0.01 both showing MAO-B inhibitory activity, were found to have the optimized potency whereas the standard drug Selegeline produced K_i value (μM) of 1.35±0.12.

Rahman *et al.* have synthesized 2-pyrazoline derivatives possessing selective MAO-B inhibition property **[23]**. The compound **10** was found to be the most potent with IC_{50} (μM) for MAO-B of 40.78±3.66 while that of Selegeline is 2.01±0.15.

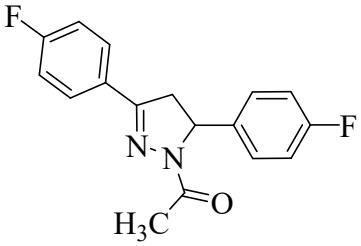
Anti-depressant property of a new series of synthesized pyrazoline derivatives attached to quinazolinone ring was evaluated. Kelekci *et al* prepared this series of pyrazolines derivatives **[24]**. According to the experiments performed, it was found that the derivative **11**have K_i value (μM) 0.9±0.07 (MAO-A) whereas the standard drug Clorgyline was found to have 1.20±0.09 and 5.60±0.44 for MAO-A and B respectively.

Ten new 3,5-diphenyl-2-pyrazoline derivatives were synthesized by reacting 1,3-diphenyl-2-propen-1-one with hydrazine hydrate by Palaska *et al.* and for the evaluation of the anti-depressant property, these compounds were subjected to the 'Porsolt Behavioral Despair Test' on Swiss–Webster mice **[25]**. 3-(4-Methoxyphenyl)-5-(3,4-dimethoxyphenyl)-2-pyrazoline; 3-(4-methoxyphenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline and 3-(4-chlorophenyl)-5-(2-chloro-3,4-dimethoxyphenyl)-2-pyrazoline reduced 41.94–48.62% immobility times at 100 mg/kg dose level. Along with that, it was found that 4-methoxy and 4-chloro substituents on the phenyl ring at position 3 of the pyrazoline ring maximized the anti-depressant activity; the replacement of these groups by bromo and methyl substituents

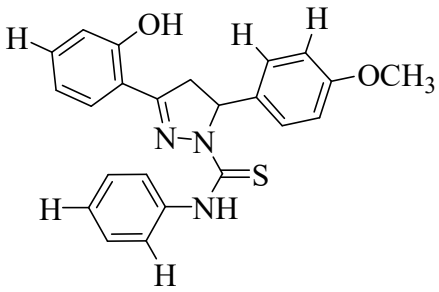
decreased activity in mice. The most potent was derivative **12** with duration of immobility time of 22.3±6.0 seconds whereas the standard drug Tranylcypromine sulfate (20mg/kg) has duration of immobility time of 9.6±2.6 seconds.



6a



6b



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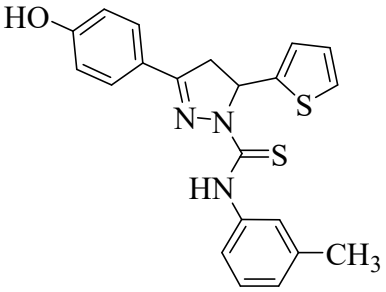

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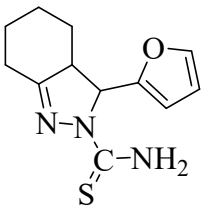
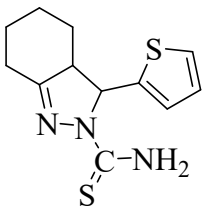
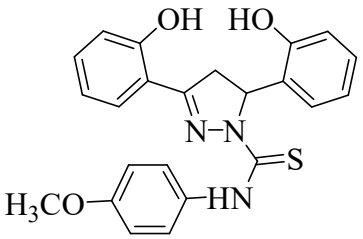


9a



9b



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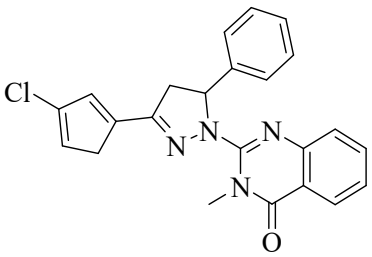
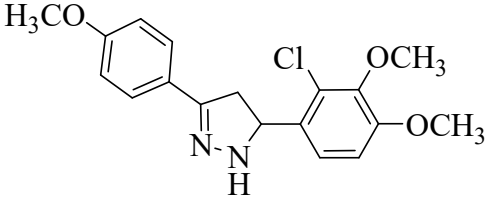


11



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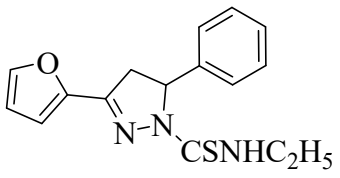


13

Ozdemir *et al* synthesized twelve 1-phenyl-, 1-thiocarbamoyl- and 1-N-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivatives **[26]**. The nonselective MAO inhibitory activity of the compounds were investigated by Porsolt behavioral despair (forced swimming) test on albino mice and the potent compound with duration of immobility time of 139±12 seconds found was **13** and the standard drug Tranylcypromine sulfate (10mg/kg, *ip*) with duration of immobility time of 57±11.6 seconds**.**

Five new 1, 3, 5-triphenyl-2-pyrazolines were synthesized by reacting 1, 3-diphenyl-2-propene-1-one with phenyl hydrazine hydrochloride and another five new 3-(2"-hydroxynaphthalen-1"-yl)-1,5-diphenyl-2-pyrazolines were synthesized by reacting 1-(2'-hydroxynaphthyl)-3-phenyl-2-propene-1-one with phenyl hydrazine hydrochloride. Prasad *et al p*erformed this experiment **[27]**. The anti-depressant activity (MAO inhibition) of these compounds was evaluated by the Porsolt behavioral despair test on Swiss-Webster mice. 1-Phenyl-3-(2"-hydroxyphenyl)-5-(4'-dimethylaminophenyl)-2 pyrazolines; 5-(4'-dimethylaminophenyl)-1,3-diphenyl-2-pyrazoline, 1-phenyl-3-(2'-hydroxynaphthalen-1"-yl)-5-3',4',5'-trimethoxyphenyl)-2-pyrazoline; 1-phenyl-3-(4"-methylphenyl)-5-(4'-dimethylaminophenyl)-2-pyrazoline and 1-phenyl-3-(4"-bromophenyl)-5-(4'-dimethylaminophenyl)-2-pyrazoline reduced time of immobility by 25.63–59.25% at 100 mg/kg dose level. The most potent derivative **14** has duration of immobility time of 22.95±4.21 seconds against the standard drug Clomipramine (20mg/kg) has immobility time of 18.68±2.25 seconds.

Twelve 1-*N*-substituted thiocarbamoyl-3-phenyl-5-thienyl-2-pyrazoline derivatives were synthesized by Ucar *et al.* which were presented as selective and irreversible MAO-B inhibitors **[28]**. The experimental data suggested that newly synthesized *N*-substituted pyrazoline derivatives can be evaluated as both MAO-B and cholinesterase inhibitors which may have promising activity in the treatment of Alzheimer's and Parkinson's diseases. The main derivative **15** hasIC_{50} (μM) 22.0±0.91 and the standard drug Pargyline has IC_{50} (μM) of 2.8±0.80.

3,5-Diaryl pyrazolines analogs were synthesized and evaluated by Mishra *et al.* for their MAO inhibitory activity **[29]**. The compounds were found to have reversible and selective inhibitory effect towards MAO-B with selectivity index of 10^3 - 10^5. The main derivative **16** with K_i value (μM) 0.33proved to be the most potent form.

Linezolid, due its MAO inhibitory activity, was subjected to synthesis of its derivatives and evaluation for their MAO-

inhibitory activity. Thirty-two compounds analyzed by Jayaprakash *et al.*showed selective to nonselective, competitive, reversible to non-competitive, irreversible inhibitory activity against two isoforms of rat liver MAO-A and MAO-B **[30]**. The potent derivative **17** hasIC_{50} for MAO-A (μM) 2.84±0.19 and the standard drug Clorgyline has IC_{50} for MAO-A (μM) 2.05±0.19.

Ten novel 3,5-diaryl pyrazolines were synthesized and investigated by Sahoo *et al.* for their MAO inhibitory property **[31]**. All the molecules were found to be reversible and selective inhibitor for either one of the isoform (MAO-A or MAO-B) but the derivatives **18a** and **18b** having K_i value(μM) 0.16(MAO-A) and 0.54(MAO-B) were found to be most potent derivatives.

Jagrat *et al* synthesized and analyzed twenty-two pyrazoline derivatives for their human MAO-A inhibitory activity **[32]**. The derivative **19** provedto have maximum potency with $K_i$value (μM) 0.1±0.01 whereas the standard drug Selegeline has $K_i$value (μM) 9.060±4.40.

Some differently substituted 3-aryl-4,5-dihydropyrazoles-1-carbothioamides have been synthesized by Maccioni *et al* with the aim to investigate their MAO inhibitory activity **[33]**. The potent derivatives **20a** and **20b** have IC_{50} 13.70±0.95 and 15.47±0.61and the standard drug Clorgyline has IC_{50}(μM) of 61.35±13.

A novel series of 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazole derivatives have been synthesized by Manna *et al* through the process of condensation and investigated for the ability to inhibit selectivity monoamine oxidase and found that the most potent derivative **21** had K_i value of $8.0 * 10^{-4}$± 0.09 where 0.09 is standard deviation **[34]**.

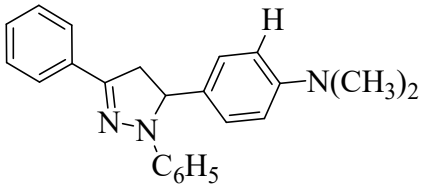
Kelekci *et al* synthesized a novel series of 1-thiocarbamoyl-3-substituted phenyl-5-(2-pyrrolyl)-4,5-dihydro-(1*H*)-pyrazole derivatives and came to the conclusion that the derivative **22** was the most potent form as promising MAO-A inhibitor with $IC_{50}$of 11.23±1.06 μM with respect to the standard drug Clorgyline IC_{50} of 2.72±0.98 μM **[35]**.

New substituted pyrazole derivatives were designed and synthesized by Aziz *et al* and evaluated its anti-depressant property and found that the derivative **23** was most potent with duration of immobility time of 198.70±6.80 seconds with respect to the standard drug imipramine having duration of immobility time of 132.00±2.60 seconds **[36]**.

A novel series of crude 1-acetyl-3-(4-hydroxy- and 2,4-dihydrophenyl)-5-phenyl-4,5-dihydro-(1*H*) pyrazole derivatives have been synthesized by Chimenti *et al* from chalcones and

investigated for their MAO (monoamine oxidase) inhibitory activity and they were found to have both MAO-A and B inhibitory activity. The most potent derivatives **24a** and **24b** had IC_{50} of 1.0 * 10^{-8} ± 0.01 µM and 1.0 * 10^{-4} ± 0.06 µM for MAO-A and MAO-B respectively **[37]**.

A new series of *N*1-thiocarbamoyl-3,5-di(hetero)aryl-4,5-dihydro-(1*H*)-pyrazole derivatives has been synthesized by Chimenti *et al* by Claisen-Schimdt condensation at reflux between substituted aryl or heteroaryl ketones and appropriate substituted aryl or heteroaryl aldehydes and subjected them for the evaluation of their antidepressant property **[38]**. The conclusion thus obtained revealed that the derivative **25** proved be most potent with IC_{50}(MAO-B) value of 2.75±0.81 µM with respect to the standard drug Iproniazide having IC_{50} value of 7.54±0.36 µM.



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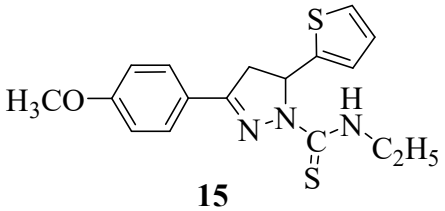

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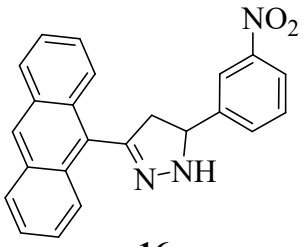

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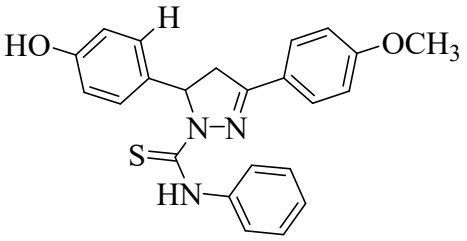
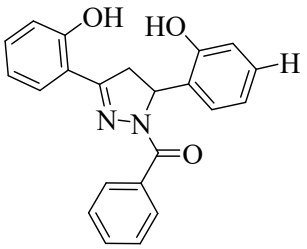
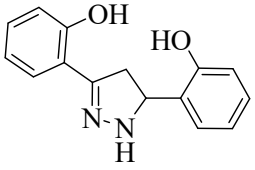


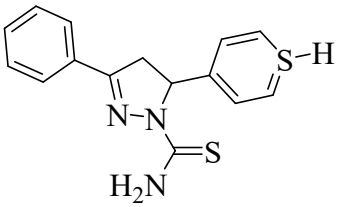
17



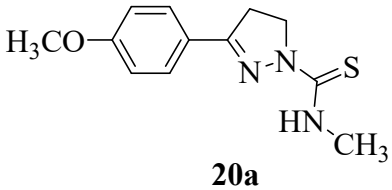
18a



18b



19



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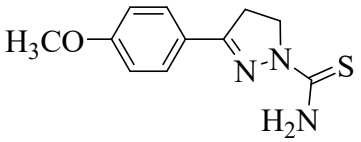

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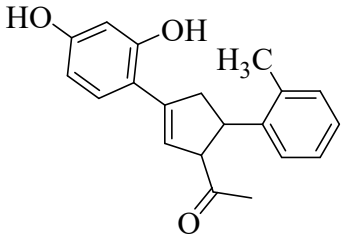

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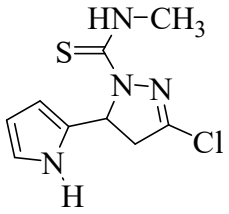

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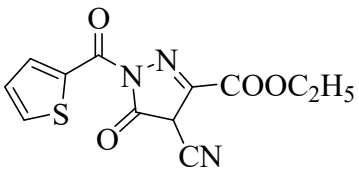

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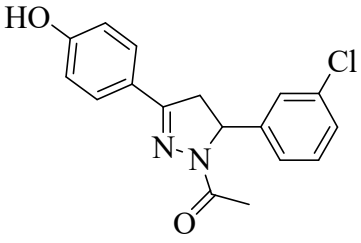
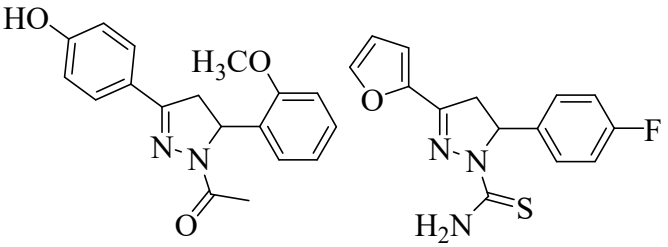


24a



24b **25**

CONCLUSION

It has been found that the potency of the pyrazoline derivatives depend on the type of substitutions in the 3rd and 5th positions. Further the activity is boosted up by either thioacetamide or ketone substituents in the 1st position. The substitutions in the 3rd and 5th position should be aromatic rings, substituted or non-substituted, but the potency has been observed to decrease if 5-membered aromatic rings such as thiophene of furan are placed instead of 6-membered substituted phenyl group. If 1st position has thioacetamide and benzene & 1 λ^4-Thiopyran in the 3rd and 5th position respectively, the derivative was found to be the most potent drug as MAO-A inhibitor. Again the 1st position no substitution and fused phenyl ring in the 3rd and 4th position and furan in the 5th position, potent activity is observed. Now, if thioacetamide in the 1st position be substituted further with alkyl chain or phenyl group along with substituted phenyl groups in the 3rd and 5th position activity slightly decreases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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