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BIOLOGICAL ACTIVITY OF 5-(2,3,4-PYRIDYL)-1,3,4-OXADIAZOL-2-THIONES AND THEIR DERIVATIVES.

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ABSTRACT

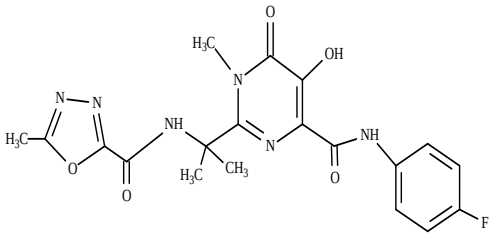
Annotation. Various biologically activity of oxadiazole derivatives, such as antibacterial, antifungal, antiviral, anticonvulsant, anticancer and others, as well as the availability of drags containing 1,2,4-oxadiazole group (**Raltegravir**, **Zibotentan**, **Tiodazosin**, **Furamizole** and **Nesapidil**) attracts much attention of chemists engaged in the search for new therapeutic molecules. In this regard, special attention cause five-membered heterocycles - 1,3,4-oxadiazol group-2-thiones having in its molecule two nitrogen atoms and one oxygen and sulfur atoms. In this review, we have attempted to describe the different kinds of biological, especially the pharmacological activity of unique and interesting representatives of this class – isomeric 5-(2,3,4-pyridyl)-1,3,4-oxadiazol-2-thiones, consisting important pharmacophoric groups – pyridine and oxadiazolthione.

KEYWORDS: 1,3,4-oxadiazoles, isomeric 5- (2,3,4-pyridyl) -1,3,4-oxadiazol-2-thiones, antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, anti-tuberculosis and other activities.

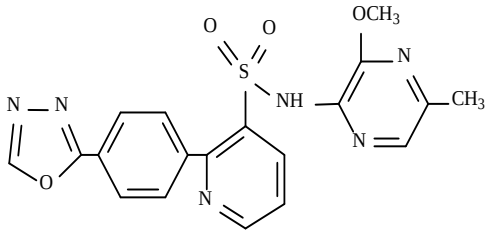
INTRODUCTION

One of the most rapidly developing fields of synthetic organic chemistry is the chemistry of five-membered heterocycles with one or more hetero atoms in the ring. Oxadiazoles, including 5-substituted 1,3,4-oxadiazol-2-thiones one of interesting representatives of this class containing in its molecule of oxygen, sulfur and two nitrogen atoms, which gives many synthetic possibilities, related to the chemical nature of these compounds. Substances containing 1,3,4-oxadiazole core have a wide range of biological activity, including

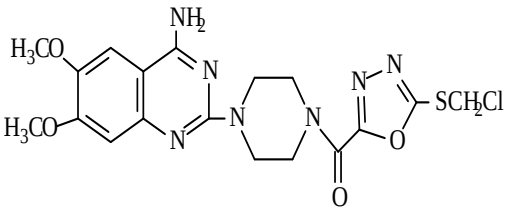
antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, anti-tuberculosis and other activities.[1-9] As an example can be several drugs made on the basis of 1,3,4-oxadiazoles, which are currently used in medical practice or undergoing clinical tests: antiretroviral **Raltegravir**, antitumor **Zibotentan**, antihypertensive **Tiodazosin**, **Nesapidil** and **Furamizole** antibiotic.



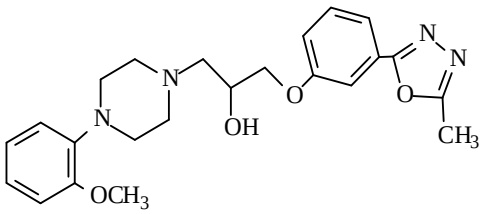
Raltegravir



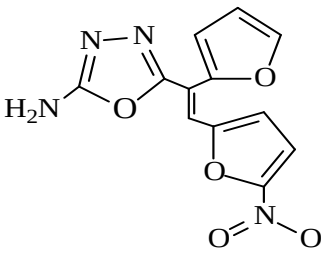
Zibotentan



Tiodazosin



Nesapidil

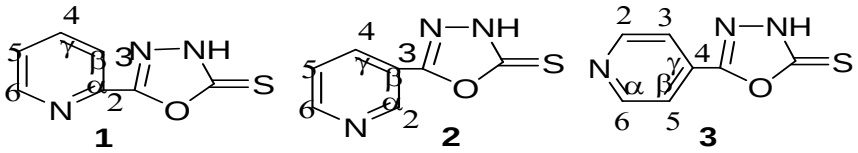


Furamizole

Methods of preparation, chemical transformations, the biological activity of 1,3,4-oxadiazol-2-thiones and their derivatives are described in detail in the works of several authors [10-16] and in particular in our publications.[17-23] To continue previously carried out by us[24-26], systematic studies of the various chemical reactions of the isomeric 5-pyridyl-1,3,4-oxadiazol-2-thiones and their derivatives, we have carefully studied, as possible, works on these compounds, and especially paid attention to the reporting of various kinds of biological activities has been published in international journals between the years 2003-2016. We hope that the collected and generalized data in the form of a small review will be useful to researchers involved in the chemistry of five-membered heterocycles and especially studying

of chemical transformations and biological activity of various derivatives of the isomeric 5-pyridyl-1,3,4-oxadiazol-2-thiones.

This oxadiazolthione drew our attention to the fact that its molecule consists of two interesting heterocycles. One of them is a pyridine, a six membered heterocycle with one heteroatom and another is 1,3,4-oxadiazol-2-thione having in its molecule more heteroatoms (nitrogen, oxygen, sulfur). By location of oxadiazol-2-thione group relative to the nitrogen atom in the pyridine ring differ the three possible isomers which are labeled by numbers or by alphabetic using Greek letters (α, β, γ). Accordingly, in the literature there are variants of naming such as 5-(2-pyridyl) - or 5-(α-pyridyl)-1,3,4-oxadiazol-2-thione **1**, 5-(3-pyridyl) - or 5-(β-pyridyl)-1,3,4-oxadiazol-2-thione **2** and 5-(4-pyridyl) - or 5-(γ-pyridyl)-1,3,4-oxadiazol-2-thione **3**:



1 **2** **3**

1. Biological activity of 5-(2,3,4-pyridyl)-1,3,4-oxadiazol-2-thiones and their derivatives

1.1. 5-(2,3,4-Pyridyl)-1,3,4-oxadiazol-2-thiones

D.Dewangan[27] with co-authors synthesized 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione **3** and studied its antibacterial (Gram-negative bacterium *Escherichia coli*), analgesic (Diclofenac standard in the dose 5 mg/kg), anti-inflammatory (indomethacin standard, 10 mg/kg) and anti-tuberculosis (*Mycobacterium tuberculosis*) activities:

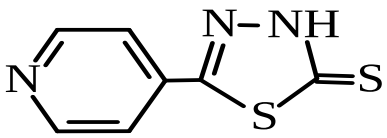
It was found that oxadiazolthione **3** showed moderate or medium activity in all tested types of activities.

Also, M.S.Y.Khan[28] et al. studied the antibacterial activity of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione **3** against microorganisms of *Escherichia coli*, *Staphylococcus aureus*, and found that it makes 29 and 50% activity of the standard Norfloxacin dosed 100 mg/ml, respectively. Besides reported anti-inflammatory activity (45-50%) of the thione **3**, in comparison with indomethacin taken as standard. It should be noted that the indexes of antibacterial and anti-inflammatory activity is consistent with the authors' data[27] on the tion.

5-(2-Pyridyl)-1,3,4-oxadiazole-2-thione **1** was synthesized by A.A. Othman et al[29] from the corresponding 2-pyridine carboxylic acid and tested in vitro on the following

microorganisms: *Escherichia coli*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, reference standards were cephalosporin and gentamicin antibiotics. Oxadiazoltion showed relatively low inhibition of *S.aureus* and *E.coli*, but against *P. aeruginosa* was more effective.

U.Ghani and authors[30] studied tyrosinase inhibition by oxadiazolthione **1** and its activity compared with the other pyridine containing heterocycles - 5-(4-pyridyl)-1,3,4-thiadiazole-2-thione **4** and 4-amino-5-(4-pyridyl)-2,4-dihydro-1,2,4-triazole-3-thione **5**. The results showed that 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione 3 has a weaker inhibitory activity than heterocycles of **4** and **5**:



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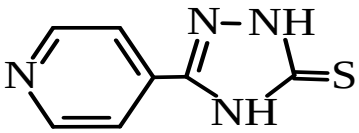


5

Antibacterial activity, as well as the minimum inhibitory concentration (MIC) for 5-(β-pyridyl)-1,3,4-oxadiazol-2-thione **2** studied in vitro by M. Zareef et al [31] in bacteria of *Escherichia coli (ATCC-25922), Staphylococcus aureus (ATCC-25923), Bacillus subtilis (recultured), Pseudomonas picketti (recultured) and Micrococcus luteus (recultured)*. Only in the bacteria of *Escherichia coli* this thione showed moderate activity and MIC value was 12.20mm (0.5mg/ml), for Roxythromycin standard it was 15.00mm (1mg/ml). Activity of oxadiazolthione 2 was not found against the rest of bacteria.

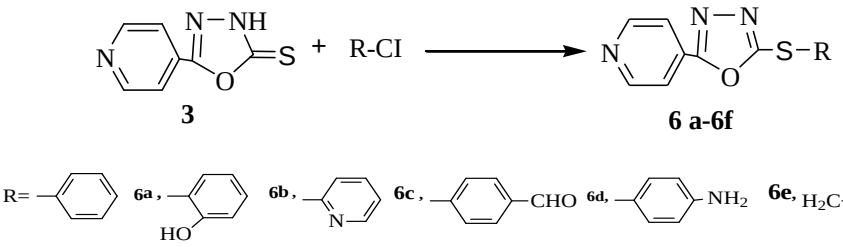
S.A. Shahzad et al.[32] conducted research and found that the 5-(β-pyridyl)-1,3,4-oxadiazol-2-thione 2 has no influence of depressing urease, inhibition standard was thiourea with IC50 21μM.

1.2. The biological activity of the derivatives of 5-(2,3,4-pyridyl)-1,3,4-oxadiazol-2-thiones.

1.2.1. Antibacterial, antiviral, anti-tuberculosis and fungicidal activity

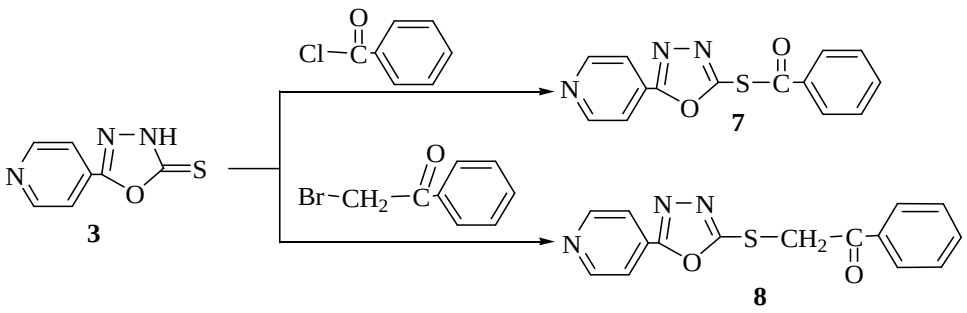
Synthesized by S. Pattan [33] et al. S-substituted-5-(4-pyridyl)-1,3,4-oxadiazoles **6a-f** were tested in vitro for antibacterial activity against microorganisms of *Escherichia coli (NCTC 10418), Staphylococcus aureus (ATCC 29737), Bacillus subtilis (ATCC 6633)* using ciprofloxacin standard and fungicidal activity on the test organisms of *Candida albicans*

(ATCC 10231) and *Aspergillus niger (ATCC 16404)* using Griseofulvin standard. These compounds also were tested for antituberculous activity against *Mycobacterium tuberculosis H37Rv* strain where streptomycin was used as standard:



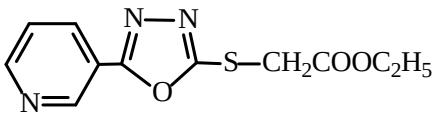
From the tested substances, the authors evaluated the compound **6a** as the most promising substances having antibacterial and antifungal activity, while for the compounds **6f** noted the same perspective on the antituberculous activity.

2-Benzoylthio-5-(4-pyridyl)-1,3,4-oxadiazole **7**, 2- phenacylthio-5-(4-pyridyl)-1,3,4-oxadiazole **8** were obtained by M.S.Y. Khan[28] et al. by reaction of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione **3** with benzoyl chloride and phenacyl bromide respectively:

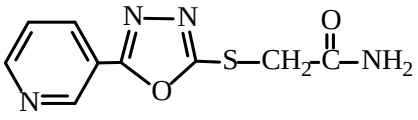


They had a good antimicrobial activity on the example of Staphylococcus aureus - 58% for compound **7** and 60% for compound **8** (Norfloxacin standard - 100%). Activity of both compounds against Escherichia coli were more moderate, 35-36%.

M.Zareef[31] et al., studied in vitro antibacterial activity and minimal inhibitory concentration (MIC) for ethyl ether of [5-(3-pyridyl)-1,3,4-oxadiazol-2-ylthio] acetic acid, **9** and acetamide **10** on bacteria *Escherichia coli (ATCC-25922), Staphylococcus aureus (ATCC-25923), Bacillus subtilis (recultured)* and *Pseudomonas picketti (recultured)*:



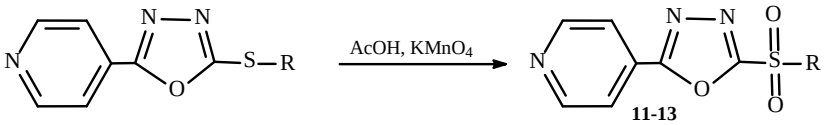
9



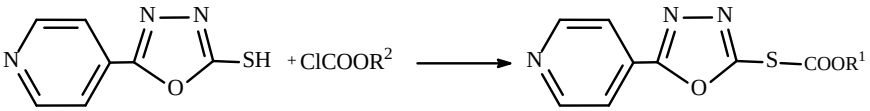
10

Inhibition of compound **9** was 10.30mm (0.6mg/ml) for *E.coli* and 10.35mm (0.8mg/ml) for *P.Picketti*, inhibition of compound **10** for *E.coli* was 11.22mm (0.8mg/ml) and for *S.Aureus* was 13.10mm (0.5 mg/ml). These values on Roxythromycin standard were 15.00mm (1mg/ml) for *E.coli*, 30.60mm (1mg/ml) for *P.Picketti* and 26.45mm (1mg/ml) for *S.Aureus*.

A number of 2-alkyl/aralkyl sulfonyl 5-(4-pyridyl)-1,3,4-oxadiazoles **11-13**, 2-alkyl/benzyloxycarbonylthio-5-(4-pyridyl)-1,3,4-oxadiazoles **14**,**15** were synthesized by Zuhair Muhi-eldeen[34] et al.:



11-13

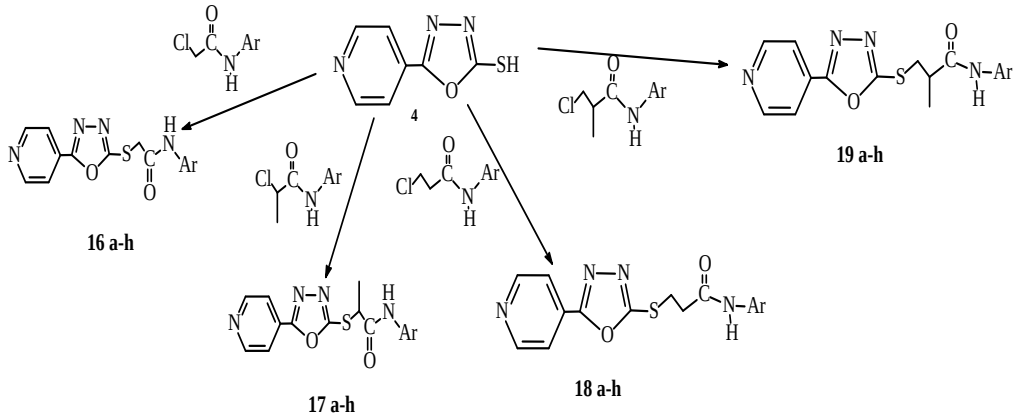


14,15

R= C_2H_5(**11**), i-C_3H_7(**12**), Ph-C_2H_5(**13**); R^1= i-C_4H_9(**14**),$CH_2C_6H_5$(**15**).

The antibacterial activity (minimum inhibiting concentration - MIC) was investigated in tests of *Escherichia coli (ATCC 25922), Staphylococcus aureus (ATCC 29213), Pseudomonas aeruginosa (ATCC 27953)* bacteria and fungicidal activity on the test organisms of *Candida albicans*. Sulfonyl derivative **11** showed poor antimicrobial activity. However carbonylthio derivatives **15** were effective against gram-positive bacteria of *S.aureus* with MIC of 8 mg/ml (Linezolid standard with MIC of 16 mg/ml) and gram-negative bacteria of *E.Coli*, *P.Aeruginosa* with MIC of 8-16 mg/ml (Linezolid standard with MIC 32-64mg/ml), but with lower activity against the fungi *Candida albicans*.

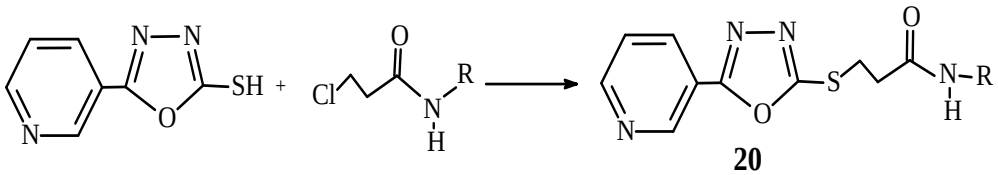
N.S.Mahajan[35] with co-authors reacting 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione with N-aryl-substituted chloroalkylamides involving sodium alkoxide synthesized a series of new derivatives:



Ar = C_6H_5(**16-19a**), $CH_2C_6H_5$(**16-19b**), CH_2-2-ClC_6H_4(**16-19c**), CH_2-4-ClC_6H_4(**16-19d**), 2-ClC_6H_4(**16-19e**), 4-ClC_6H_4(**16-19f**), 2,5-$Cl_2C_6H_3$(**16-19g**), 2,4-$Cl_2C_6H_3$(**16-19h**).

All synthesized compounds were tested for anti-TB activity. Varying the substituents of the aryl group on N-arilacetamide and N-arilpropanamide radicals of synthesized compounds, **18f** has been identified as most active compound. The authors compared the **18f** with isocyanide on susceptibility with 18 kinds of clinical Mycobacterium tuberculosis, of which 16 were generally susceptible and 2 mono-rifampicin-resistant. According to the results of comparisons its activity was almost equivalent to activity of widely used drug isoniazid. In addition, it was estimated potential of **18f** against 9 of multidrug-resistant (MDR) and 2 poly drug-resistant strains of MTB (Mycobacterium tuberculosis), where it has also shown good results. Thus, substance **18f** has promising activity against practically all resistant strains.

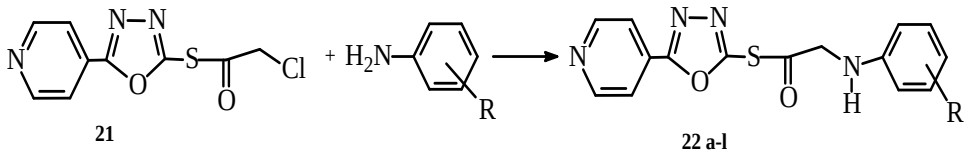
Similarly 2-N-aryl/alkylcarboxyamidomethylthio-5-(3-pyridyl)-1,3,4-oxadiazoles were obtained by Somani R.R[36] et al. by reaction of 5-(3-pyridyl)-1,3,4-oxadiazol-2-thione with an N-aryl /alkyl-β-chloropropionylamides:



R=aryl, alkyl.

In tests on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonelly typhi* studied antibiotic activity in concentrations of 50,100 μg/ml and anti-TB activity in 50 μg/ml, where most of the compounds showed moderate activity.

In the paper of J.P.Raval[37] et al. was reported the reaction of 2-chloroacetylthio-5-(4-pyridyl)-1,3,4-oxadiazole with aryl(hetaryl)amines, where obtained new of 2-aryl(hetaryl)aminoacetylthio-5-(4-pyridyl)-1,3,4-oxadiazoles **22a-l**:



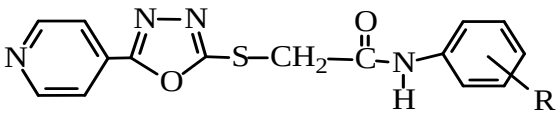
21 **22 a-l**

R= H(**a**), 2-Cl(**b**), 3-Cl(**c**), 4-Cl(d), 2-NO_2(**f**), 4-NO_2(**g**), 2-CH_3(**h**), 3-CH_3(**i**), 4-CH_3(**j**), 2-C_5H_5N(**k**), 2-OH(**l**)

In *in vitro* experiments were investigated the antibacterial activity of the synthesized compounds **22a-l**, depending on the nature of the substituent in phenyl nucleus against gram-positive *Staphylococcus aureus (MTCC 96), Bacillus subtilis (MTCC 121)* and gram-negative *Escherichia coli (MTCC 443), Salomonella paratyphi (MTCC 735)* microorganisms. Thus substances with substituents in the 2-Cl (**22b**) and 2-CH_3 (**22h**) in the phenyl core showed activity moderate to good against gram-negative, and substances of **22c**, **22d** with substituents of 3-Cl and 4-Cl against gram-positive bacteria. Substance **22j** with 4-CH_3 had activity moderate to good against *Staphylococcus aureus (MTCC 96)* and *Salomonella paratyphi (MTCC 735)*. But very good antibacterial activity against all tested organisms possessed compound **22k** with C_2H_5N substituent in the second position of the phenyl nucleus.

All the newly synthesized derivatives (**22a-l**) were tested for anti-tubercular activity against *Mycobacterium tuberculosis H37Rv (AT CC27294)* using radiometric BAKTEK 460 system, the standard used for comparison was isoniazid. Among the tested compounds **22e, g, k** have shown high efficiency and showed not less than 90% inhibition at concentrations of 0.0077, 0.0052 and 0.0089 1 M, respectively. Cytotoxicity tests have shown that synthesized compounds are non-toxic.

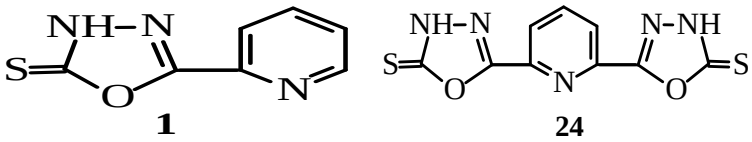
M.E.Bhanoji Rao[38] et al. synthesized a number of N-phenyl-substituted [5-(4-pyridyl)-1,3,4-oxadiazol-2-ylthio]acetamides **23** and examining their established that they possess good antifungal, antibacterial and anti-inflammatory activity.



23

R= halogen, alkyl.

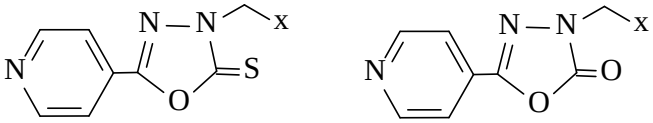
Researchers S.Benhammadi[39] et al. from the corresponding 2-pyridine carboxylic acid (picolinic acid) and 2,5-pyridine dicarboxylic acid were synthesized in traditional technique a 5-(2-pyridyl)-1,3,4-oxadiazol-2-thione **1** and bis-5-(2,6-pyridyl)-1,3,4-oxadiazol-2-thione **24**:



1 **24**

They were tested in vitro against the following microorganisms: *Escherichia coli (ATCC-25924), Pseudomonas aeruginosa (ATCC-27853), Enterococcus faecalis (ATTC-29212), Staphylococcus aureus (ATCC- 25923), Pseudomonas Fluorescens (ATCC-17552)*. Standards for comparison were used known antibiotics of cephalosporin (cefotaxime) and gentamicin. Results showed that oxadiazolthion **1** has smaller result than the compound of bis-5-(2,6-pyridyl)-1,3,4-oxadiazol-2-thione **24** which had the greatest effect on all tested microorganisms in general and especially for gram-negative bacteria of *Pseudomonas Fluorescens* where its effect was higher than effect of cephalosporin standard (cefotaxime).

In order to obtain new antimycobacterial agents M.G.Mamolo [40] et al synthesized a number of derivatives of 5-(4-pyridyl)-(3H)-1,3,4-oxadiazol-2-thione **25a-l** and 5-(4-pyridyl)-(3H)-1,3,4-oxadiazol-2-one **26a-l** in which the nitrogen in position 3 of oxadiazole cycle linked with cyclic amines via a methylene bridge (Mannich bases):



25 a-l **26 a-l**

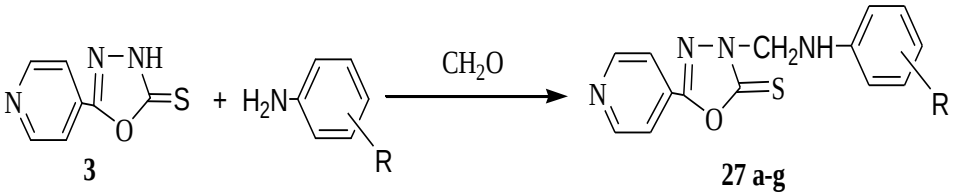
X= 4-acetylpiperidine(**a**), N-benzylpiperidine(**b**), piperidine(**c**), 3-methylpiperidine(**d**), 4-benzylpiperidine(**e**), isoquinoline(**f**), morpholine(**g**), 4-methylpiperidine(**h**), 4-methylpiperazine(**i**), 2-methylpiperidine(**j**), azepane(**k**), thiomorpholine(**l**).

The antimycobacterial activity of derivatives **25a-l** and **26a-l** were tested against strains of mycobacteria *M. tuberculosis H37Rv*, drugs for comparison were isoniazid and ofloxacin. The test results show that the derivatives of 1,3,4-oxadiazol-2-ones **26a-l** possess significant activity against the test strain, reaching MIC (minimum inhibitory concentration) values of 1.25 mg/ml for compounds **26d**, **26f** and 2.5 mg/ml for all other compounds. However

antimycobacterial activity of derivatives 1,3,4-oxadiazol-2-thiones **25a-l** is very low or absent. The presence in the active compounds of **26a-l** a carbonyl functional group apparently responsible for maximum efficiency of these compounds regarding to the corresponding thione derivatives **25a-l**.

Based on the above showed factors of antimycobacterial activity of compounds **25a-l** and **26a-l** M.A.Kale[41] et al. carried out studies on these analogues to create prediction models affecting the activity. According to the authors, the model predictions made by them indicates that four important properties of molecules presented in the form of descriptors, such as thermodynamic (molar refraction), electronic (dipole moment) and the principal moment of inertia, play an important role for the manifestation of antimycobacterial activity.

R. Somani[42] et al., by reaction of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione with various aromatic amines in the presence of formaldehyde received some Mannich bases (**27a-g**) and evaluated and their antitubercular antibacterial action:



3 **27 a-g**

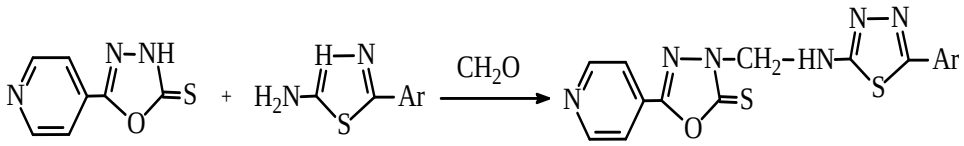
R=3,4-Cl_2(**a**), H(**b**), 2,6-$(CH_3)_2$(**c**), 2,3-Cl_2(**d**), 2-NO_2(**e**), 2,6-Cl_2(**f**), 4-COOH(**g**).

Antituberculous activity was tested against *Mycobacterium tuberculosis H37Rv*, pyrazinamide and streptomycin used as a standard drug at 10 μg/ml. Antibacterial activity (minimum inhibitory concentration MIC) was also performed in laboratory conditions on *Escherichia coli*, *Staphylococcus aureus*, and also in this case streptomycin used as a standard drug (50 μg/ml).

Screening for antituberculosis activity has shown that at a concentration of 100 μg/ml all compounds were active against mycobacteria. At a concentration of 25 μg/ml compound **27c**, **27d** and **27e** were active, and at concentration of 50 μg/ml the compound **27b** has such activity. Tests for antimicrobial activity on all synthesized compounds showed that they have moderate activity against staphylococcus (*S.aureus*). Compounds **27c** and **27e** of these, had MIC value (100 μg/ml) against staphylococcus, whereas in respect of *Escherichia coli* they

have shown activity from weak to moderate levels (150-250 μg/ml). The authors suggest that future structural modifications are promising, leading to an increase in activity.

New Mannich bases obtained by S.Trupti[43] et al reacting 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione with another heterocycle - 5-aryl/substituted-1,3,4-thiadiazol-2-amine used as the amine:

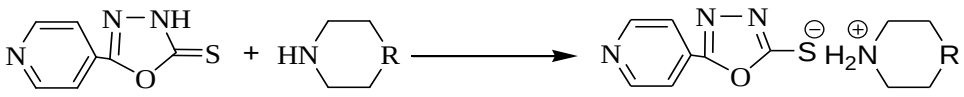


28 a-f

Ar = 4-OCH_3-Ph(**a**), 2-NO_2-Ph(**b**), 4-F-Ph(**c**), 3,4,5-$(OCH_3)_3$-Ph(**d**), 3-NO_2-Ph(**e**), -CH_2-CH=CH-Ph(**f**).

From synthesized substances compounds **28a** and **28c** show good activity against *M. tuberculosis H37Rv (ATCC 27294)*. The results show that the nature of the substituents on the aromatic ring thiadiazole significantly influence the antituberculous activity of the test compounds. Compound **28c** with a electronegative atom such as fluorine, showed better activity than **28e** and **28b** in which on the ortho- and meta- positions respectively situated nitro group. Despite the nature of the electron-withdrawing nitro group, they did not show a significant biological activity that clearly shows the importance of the nature of the substituents. Also showed good activity substance **28a** with a methoxy group. According to the authors complete loss of activity of compounds **28d** and **28f** may be associated with bulky substituents and the steric factors.

A. Rutavičius[44] and co-authors synthesizing piperidine and morpholine salts of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione **28a,d** studied their antituberculous activity:

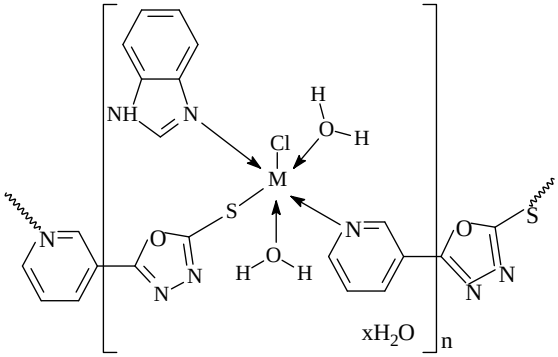


3 **29 a, b**

R=CH_2 (**a**), O (**b**)

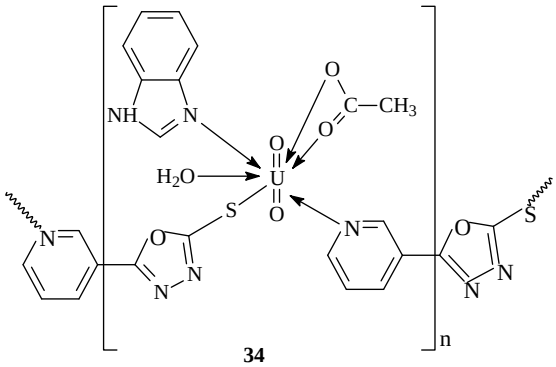
It has been found that they at a concentration of 6.25 mg/ml show a inhibitory activity more then 90% against *M.tuberculosis H37Rv* strain *(ATCC 27294)*.

A new series of coordination polymers of Co(II), Ni(II), Cu(II), Cd(II), UO_2(II) with 5-(3-pyridyl)-1,3,4-oxadiazol-2-thione and benzimidazole was synthesized and characterized by Aref A. Aly[45] et al.:



30-33

M = Co^{+2}(**30**), Ni^{+2}(**31**), Cu^{+2}(**32**), Cd^{+2}(**33**)

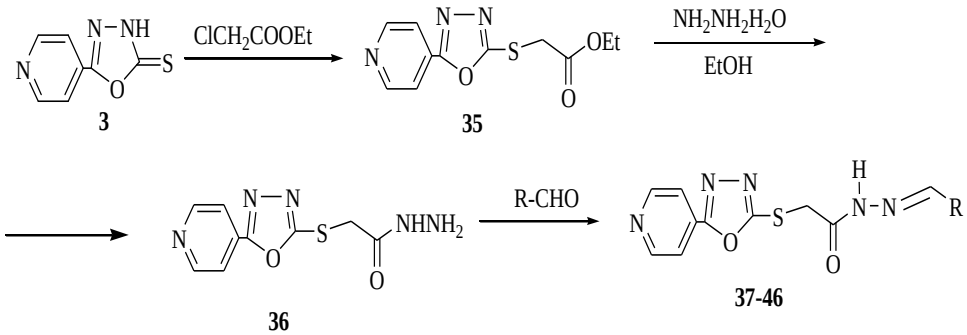


34

U= [UO_2(POZT)(BIMZ) (H_2O)]n(**34**)

Antibacterial and antifungal activity of the synthesized compounds was tested against fungal *(Aspergillus flavus, Candida albicans, Fusarium oxysporum, Geotrichum candidum, Scopulariopsis brevicaulis)* and bacterial strains *(Bacillus cereus, Staphylococcus aureus, Serratia marcescens, Escherichia coli, Pseudomonas Aeruginosa)*. These tests showed that ligands of **33**, **34** have higher potency against *A.flavus* and *T.rudrum*, than the comparison standards - chloramphenicol and clotrimazole. Activity of complexes **30**, **32** for *B.cereus, S.Aureus* and *G.candidum* were closer to the values of standards.

N-substituted-[5-(4-pyridyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazides **37-46** were synthesized by R.R.Somani[46] et al:



3 **35** **36** **37-46**

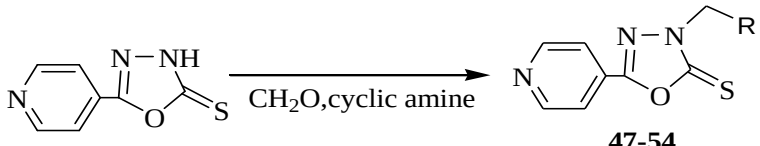
R= Ph(**37**), 2-Cl-Ph(**38**), 4-OCH_3-Ph(**39**), 4-Cl-Ph(**40**), 3-NO_2-Ph(**41**), D-glucose-[1,2,3,4,5-pentahydroxypenta-1-yl](**42**), D-Galactose-[1,2,3,4,5-pentahydroxypenta-1-yl](**43**), D-Arabinose-[1,2,3,4-tetrahydroxybuta-1-yl](**44**), D-Ribose-[1,2,3,4-tetrahydroxybuta-1-yl](**45**), D-Xylose-[1,2,3,4-tetrahydroxybuta-1-yl](**46**).

From the obtained compounds **37,38,41,42,46** showed good antimicrobial activity against *Staphylococcus aureus*, compounds **39,41,42,43** were effective against *Escherichia coli* at 100 and 200 mg/ml dose. Compound **38** with chlorophenyl group showed good activity against staphylococcus, but did not show any activity against *E. coli*, that shows its selective nature of the activity. Sufficiently high activity in both tests has the compound **42**.

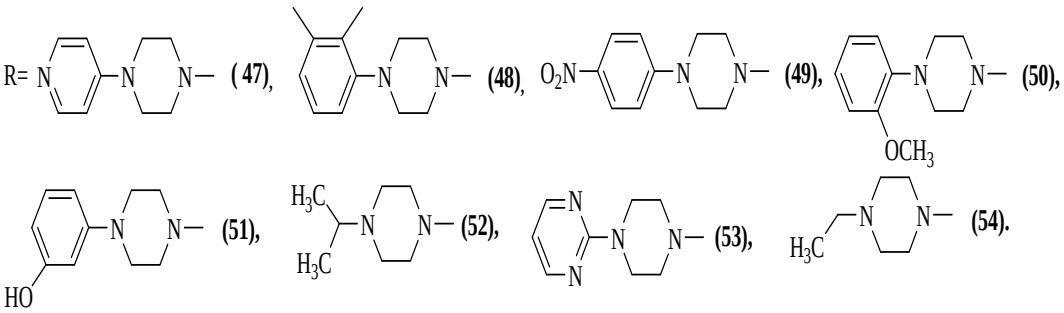
Compounds **37,38,43-45** show antifungal activity against *Candida albicans*, while compounds **40,41,42,45** were active against *Aspergillus niger*. Compounds containing a sugar in the molecule do not show any significant anti-fungal actions. The authors believe this may be due to their low penetration ability into the cell wall due to the hydrophilic nature.

Compound **42** showed high activity against HIV-2 strain, while other compounds were not active against this virus. Results of antiviral activity against some other viruses such as *Para-influenza-3 virus, Reovirus-1, Sindbis virus, Coxsackie B4 virus, Punta Toro virus* shows that the compounds **37,38,39** have good antiviral activity.

Piperazine derivatives of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione as a Mannich base obtained by K.K.Oza[47] et al.:



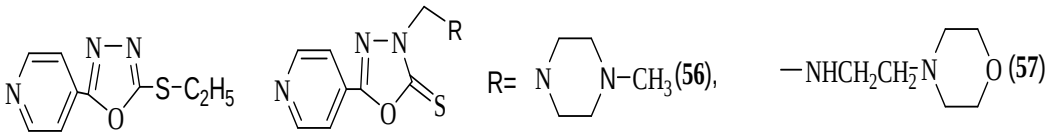
3 **47-54**



The antibacterial activity of the compounds was studied in respect of gram-positive (*Staphylococcus aureus, Bacillus subtilis*) and gram-negative (*Escherichia coli, Salmonelly typhi*) bacteria at a concentration of 50 μg /ml with tetracycline standard. Compounds **50** and **51** were more active against microbes above-mentioned (inhibition of compounds **50** and **51** are 41-46mm, standard 39-41mm) while the other compounds showed moderate or less activity, than tetracycline.

When the antifungal activity tests of compound **50** and **51** also showed a greater activity than the rest of the synthesized compounds on the pathogenic organisms such as *Nigrospora Sp.*, *Aspergillus niger*, *Rhizopus nigricum*, *Botrydepladia thiorbomine* and *Penicillium expansum*.

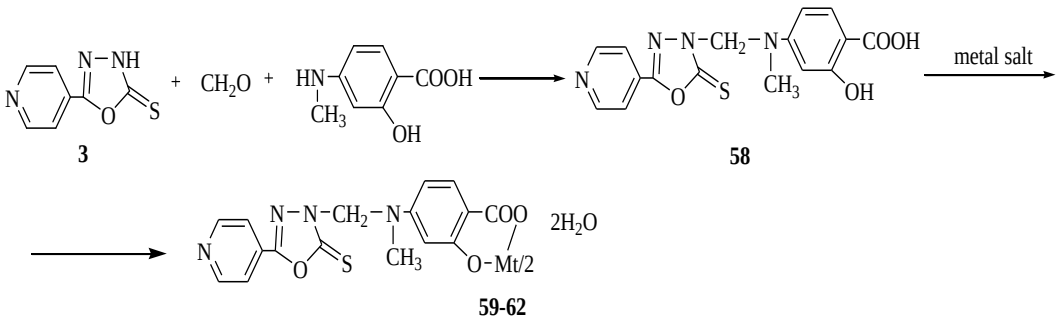
Researchers H.Bayrak[48] et al. investigated the antimicrobial activity of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione and its some S- and N- derivatives **52-54** against test microorganisms of *Escherichia coli (ATCC 25922), Yersinia pseudotuberculosis (ATCC 911), Pseudomonas aeruginosa (ATCC 27853), Enterococcus faecalis (ATCC 29212), Staphylococcus aureus (ATCC 25923), Bacillus cereus (709 ROMA), Candida tropicalis (ATCC 13803)* and *Candida albicans (ATCC 60193*:



55 **56,57**

Among the test compounds 2-ethylthio-5-(4-pyridyl)-1,3,4-oxadiazole **55** showed good antimicrobial activity against all the test organisms, besides *Candida tropicalis (ATCC 13803)* and *Candida albicans (ATCC 60193)*. Relevant Mannich bases **56,57** showed moderate activity against all organisms except *Candida tropicalis (ATCC 13803)* and *Candida albicans (ATCC 60193)* against which they have not shown any activity. Contrary to this derivative itself 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione **3** opposite active against *Candida tropicalis (ATCC 13803)* and *Candida albicans (ATCC 60193)* at level of Fluconazol standard, whereas on the other tests he was quite not active.

By D.K.Solanki [49] et al. were obtained metal complexes of 3-(4-carboxy-3-hydroxyphenyl-(N-methyl) aminomethyl-5-(4-pyridynil)-1,3,4-oxadiazole-2-thione **58-61** and tested their fungicidal activity against fungi *Botrydepladia thiobromine*, *Nigrospora Sp*, *Rhizopus Nigricans*, *Aeperginus niger*, *Amdida Albicans*, *Amdida Kruseigos candida glabrata 405*:



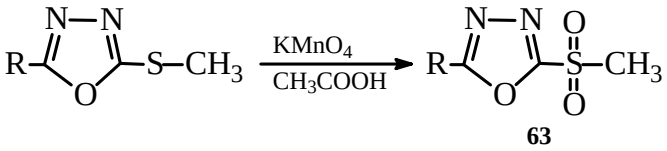
3 **58**

59-62

Mt = Cu^{2+}(**59**), Ni^{2+}(**60**), Zn^{2+}(**61**), Fe^{2+}(**62**).

The most active were copper complexes **59** which had 82% inhibition.

Researchers Weiming Xu[50] et al. synthesized a series of 2-methylsulfonyl-5-aryl-1,3,4-oxadiazoles, including 2-methylsulfonyl-5-(4-pyridyl)-1,3,4-oxadiazole **62** and studied their fungicidal activity:

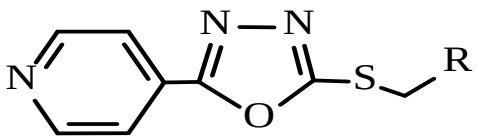


63

R = Ar(hal), alkyl; 4-C_5H_5N(**63**).

All the compounds tested at a concentration of 50 μg/ml have a good inhibitory effect on *Fusarium oxysporum, C. mandshurica* and they all showed superiority over the commercial fungicide preparation hymexazol. The activity of 2-methylsulfonyl-5-(4-pyridyl)-1,3,4-oxadiazole **63** was 72.6 and 78.2% (standard hymexazol 58.4 and 57.3%) respectively.

Patent of Chinese researchers[51] provides data on the compounds on the basis of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione, wherein R is 2-chlorophenyl, 3-cyanophenyl, 4-tert-butylphenyl, 4- methoxyphenyl, 2-substituted pyrazole or ethoxy group, and others.



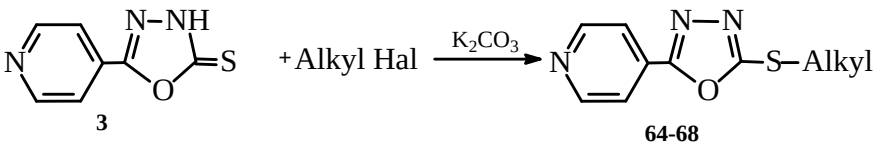
R= 2-ClPh, 3-CNPh, 4-t-(C_4H_9)Ph, 4-OCH_3Ph and others.

These compounds are the basis of the fungicidal drug for prevention and treatment of diseases of bacterial speck in tomatoes, late blight and gray mold in cucumbers.

1.2.2. Anti-inflammatory, analgesic and antioxidant activity

S.J.Gilani[52] et al. studied antiinflammatory and analgesic activity of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione **3**. It was found that it shows a moderate anti-inflammatory (62.88%) and analgesic (54.28%) activity compared to a standard ibuprofen (82.69% and 73.52%), respectively.

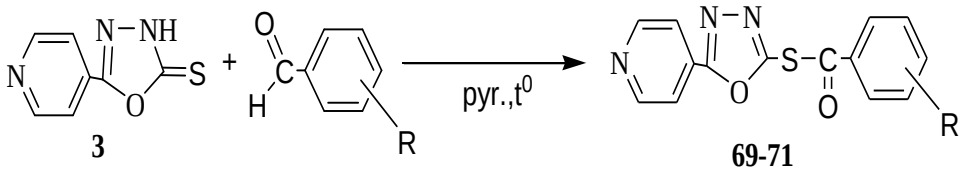
2-Alkylthio-5-(4-pyridyl)-1,3,4-oxadiazoles (alkyl = methyl, ethyl, propyl, amyl, iso-amyl) were synthesized by A.Toma[53] et al.:



Alkyl = CH_3(**64**), C_2H_5(**65**), C_3H_7(**66**), C_5H_{11}(**67**), i-C_5H_{11}(**68**). Hal.= Cl, Br, J.

According to the anti-inflammatory activity the 2-methylthio-5-(4-pyridyl)-1,3,4-oxadiazole **64** was more effective (40.17, 55.06, 37.50%) than standard diclofenac (36.75, 15.82, 16.87%) inhibition of carrageenan-induced rat paw edema after 2, 3 and 4 hours, respectively, while the remaining compounds **65-68** showed moderate anti-inflammatory action. The authors believe further research is promising in this regard.

Using conventional techniques and microwave C.R.Biju[54] and co-authors have synthesized various analogs of 2-benzoylthio-5-(4-pyridyl)-1,3,4-oxadiazole:

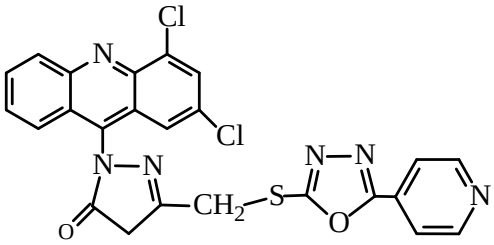


R= H(**69**), 4-Cl(**70**),4-NO_2(**71**).

From synthesized compounds substances 2-(4-nitrobenzoyl)thio-5-(4-pyridyl)-1,3,4-oxadiazole **71** showed good analgesic and anti-inflammatory activity with low toxicity.

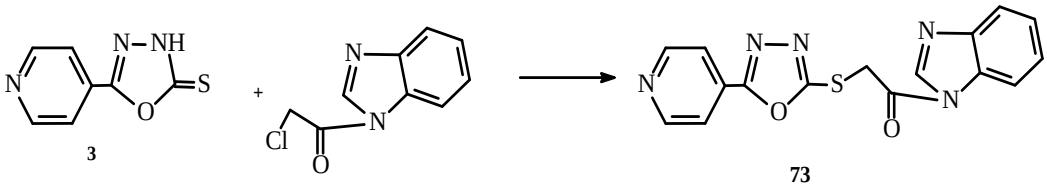
One of these compounds previously synthesized by authors[28] 2-benzoylthio-5-(4-pyridyl)-1,3,4-oxadiazol **7** as well as 2-phenacylthio-5-(4-pyridyl)-1,3,4-oxadiazol **8** showed 39 and 43% anti-inflammatory activity at 65% of the activity of indomethacin standard.

In order to detect and study the anti-inflammatory properties T.Chandra[55] with other authors received several acridinyl pyrazoline derivatives. All the synthesized substances were tested in different dosages and among the compounds 1-(2',4'-chloroacridin-9'-yl)-3-(5'-pyridin-4-yl)-(1,3,4-oxadiazol-2-yl-thiomethyl)-pyrazole-5-one **72** showed higher anti-inflammatory and analgesic activity than others in doses of 25, 50 and 100 mg/kg.



72

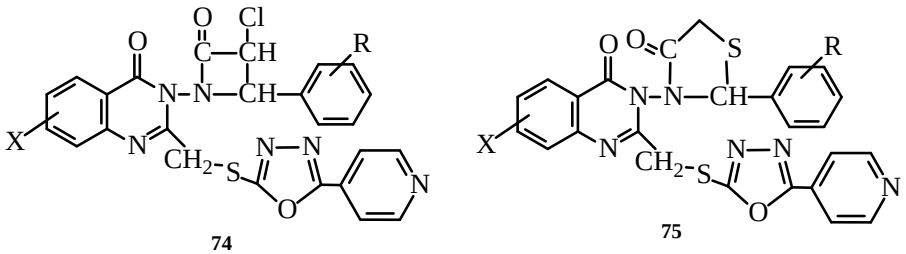
Benzimidazoles are known to be an important class of compounds with a broad spectrum of biological activity. S. Rajasekaran[56] et al synthesized their derivative with interesting heterocycle, 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione, bonded via thioacetamide bond:



3 **73**

Antiinflammatory (diclofenac standard) and antioxidant (ascorbic acid standard) property studies of the compound **73** under conditions in vitro showed that it shows good activity for both prospect.

A.Kumar[57] with co-authors synthesized and evaluated the anti-inflammatory activity of the compounds containing in their molecule 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione with the general formula of 3-(3-chloro-2-oxo-4-substituted-aryl-azetidin-1-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanyl-methyl)-substituted-3H-quinazolin-4-ones (**74**) and 3-(4-oxo-2-substituted-aryl-thiazolidin-3-yl)-2-(5-pyridin-4-yl-[1,3,4]-oxadiazol-2-yl-sulfanylmethyl)-substituted-3H-quinazolin-4-ones (75):



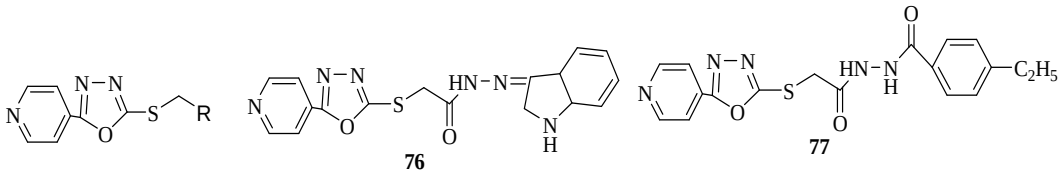
74 **75**

All substances in a dose of 50 mg/kg had varying degrees of anti-inflammatory activity from 16.3 to 36.3% inhibition of edema. Some of the compounds showed similar activity in a standard doses of 25, 50 and 100 mg/kg.

1.2.3. Cytotoxic activity

Small and simple five-membered heterocycle 1,3,4-oxadiazol has its unique position in the medicinal chemistry and plays an important role in finding various compounds which have interesting pharmacological properties, including anti-tumor activity. This activity of the compounds based on 1,3,4-oxadiazoles considered S.Baja[58] et al. related to its unique mechanism of inhibition of various growth factors, enzymes, kinases, including the telomerase enzyme histone deacetylase (hdac), methionine aminopeptidase (meta foam), thymidylate synthetase (TS), glycogen synthase kinase-3 (GSK), epidermal growth factor (EGF), vascular endothelial growth factor (vegf) and focal adhesion kinase (FAK). Targeted search and evaluation of the "structure-activity" of various derivatives of 1,3,4-oxadiazoles is an important criterion for the creation of potential anticancer agents.

A large number of new derivatives of 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione were synthesized by N.A.Khalil[59] et al to study the antitumor activity containing at exocyclic atom S- in the 2-position of the heterocycle different pharmacophore substituents such as alkyl, hydrazine, hydrazide, various heterocycles, etc.:

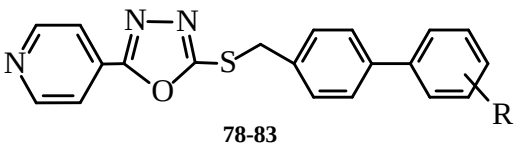


76 **77**

R=alkyl, hydrazide, hydrazone, various heterocycles (triazole, oxadiazole, substituted piperazines, indole) etc.:

Cytotoxic activity of newly synthesized compounds were tested for antitumor activity against breast MCF-7 cancer cell line, using as a reference erlotinib drug. Most of the compounds tested showed good cytotoxic activity, of these substances **76** and **77** were more active than the reference drug with inhibiting value of cell viability (IC50) of 0.010 and 0.012 μM, respectively.

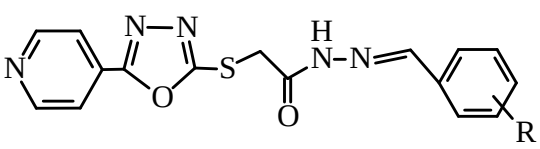
Fabio Lo Monte[60] et al. studied the inhibition of glycogen synthase kinase-3 (GSK-3) which induces neuroprotective effects, for example, associated with Alzheimer's disease. In GSK-3 inhibitor study (there are two isoforms, GSK-3b and 3c-GCS), the authors carried out on the compounds having various heterocyclic skeleton, including 5-(4-γ-pyridyl 88)-1,3,4-oxadiazol-2-thione **78-83**. It was found that one of the pyridylthion containing compounds **82** has selectivity for inhibiting GSK-3b:



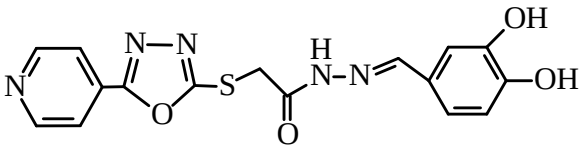
78-83

R= 2-NO_2(**78**),3-CN(**79**),4-CN(**80**),4-OCH_3(**81**), 2-CN,4-F(**82**), H(**83**).

F.Zhang[61] et al synthesized a series of new N-benzylidene-2-[(5-pyridin-4-yl)-1,3,4-oxadiazol-2-ylthio] acetohydrazide with general formula **84** as potential telomerase inhibitors:



84

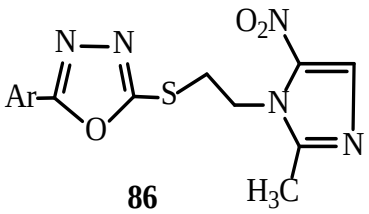


85

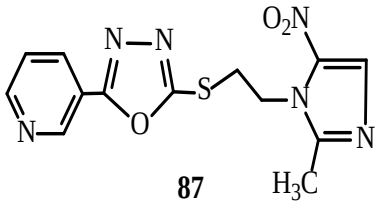
R= Alkyl, Hal., OH.

Bioassay tests showed that most of the compounds have a wide spectrum of antitumor activity with IC50 ranging from 0.76 to 9,59 μM against four cancer cell lines (HEPG2, MCF7, SW1116 and BGC823). In addition, these compounds were tested for inhibition of telomerase using TRAP-PCR-ELISA trap of immunoassay. Compound **85** showed the highest anticancer activity with IC50 0.76-1.54μM on proven cancer cell lines and the most powerful inhibiting telomerase activity with IC50 1.18 ± 0.14μM.

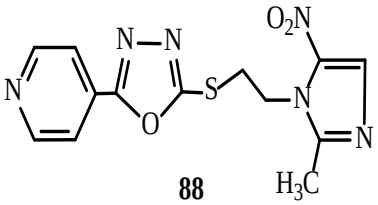
In invention of Chinese authors[62] reported preparations based 2-ethylenthio-(2-methyl-5-nitroimidazole)-5-aryl-1,3,4-oxadiazoles **86** having antitumor activity, including the inhibition of human liver cancer cells (Hep-G2):



86



87



88

Ar = phenyl, substituted phenyl, 3-pyridyl (**87**) 4-pyridyl, and (**88**), and others.

IC50 (μM) values (concentration inhibiting 50% of the cancer cells) for a pyridyl-containing compound **87** are 9.6 ± 0.8μM and for compound containing □-pyridyl **88** is 14.8 ± 0.4μM (IC50 for the standard 5-FU 22.8 ± 1.2).

CONCLUSION

Thus, the materials discussed above for biological activity of isomeric 5-(2,3,4-pyridyl)-1,3,4-oxadiazol-2-thiones and their derivatives has been published in international journals between the years of 2003-2016 in most or generally refer to the 5-(4-pyridyl)-1,3,4-oxadiazol-2-thione and its various derivatives. In our opinion, interest in pyridiloxadiazolthion γ-isomer can be explained by the fact that most of the compounds on its basis, as many researchers believe are isoniazid derivatives widely used in chemotherapy. Therefore, the majority of the synthesized compounds from this class are tested for pharmacological (antibiotic, anti-tuberculosis, anti-tumor, and others.) activity. At the same time works[31,45,62] show that also among compounds of pyridyl thiones other than γ-isomer exist derivatives with high activities. These results for all isomers of (α, β, γ-pyridyl)-oxadiazolthiones and their derivatives generally show perspectivity of the research in this interesting field of heterocyclic compounds.

ACKNOWLEDGMENTS

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