

REVIEW

**Biological Activities of the Compounds Bearing
1,3,4-Oxa(thia)diazole Ring**

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Recent literature concerning the antibacterial, antiinflammatory, anti-tuberculosis, anticancer, anticonvulsant, insecticidal, fungicidal, herbicidal and other biological activities of organic compounds containing 1,3,4-oxa(thia)diazole ring has been summarized.

Key Words: 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles, Biological activities.

INTRODUCTION

The compounds containing 1,3,4-oxa- or 1,3,4-thiadiazole ring have been known for about a hundred years. Their synthesis was extensively studied at the beginning of the 20th century by Stoll *et al.*^{1–5} Since that time a vast amount of papers devoted to these compounds has been published. An increase in the number of publications devoted to their biological activities observed recently is worth noting and their brief review is given in this paper. Although 1,3,4-selenadiazoles are also already known^{6–9}, their biological activity has not been reported yet.

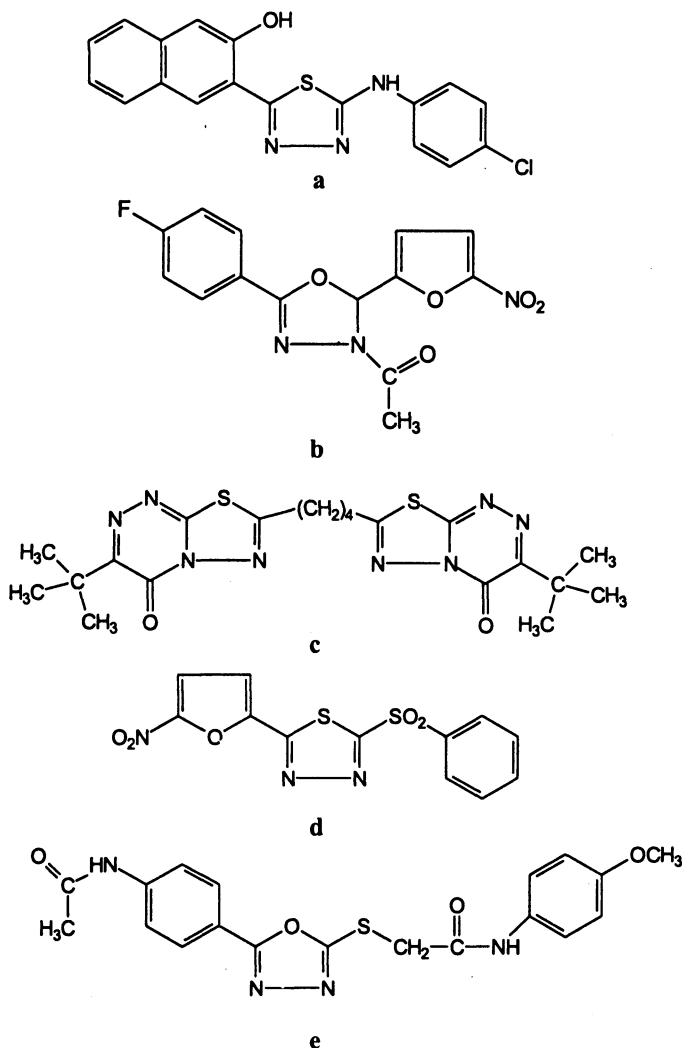
Antimicrobial activities

2-Amino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole derivatives have been screened for their antibacterial (against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*) and antifungal (against *Candida albicans*) activities by Dogan *et al.*^{10,11} The highest antibacterial activity (against *Staphylococcus aureus*) was observed for *p*-chlorophenylamino derivative (**Scheme-1a**). The compounds studied did not show expected antifungal activity. Activities against the above bacteria were studied by Hui *et al.*^{12,13} for some methylisoxazole derivatives of 1,3,4-oxa(thia)diazoles and better results were observed for thiadiazoles. Activities against the above microbes were studied by Mohan and Kataria¹⁴ for two imidazol[1,2-*d*]-s-triazolo[3,4-*b*][1,3,4]thiadiazoles and by Rollas *et al.*¹⁵ for four 3-acetyl-5-(4-fluorophenyl)-2-substituted-2,3-dihydro-1,3,4-oxadiazoles. 3-Acetyl-5-(4-fluorophenyl)-2-(5-nitro-2-furanyl)-2,3-dihydro-1,3,4-oxadiazole showed a reasonable activity against *S. aureus* and *C. albicans* (**Scheme-1b**). Some 5-(1/2-naphthylloxymethyl)-1,3,4-oxadiazole-2(3H)-one

(thione) and 2-amino-5-(1/2-naphthylloxymethyl)-1,3,4-oxadiazole have been screened for their activity against the above microbes and for two other fungi (*C. krusei* and *C. parapsilosis*) by Sahin *et al.*¹⁶, the compounds studied showed moderate activities. A series of 5-aryl-2-[(N,N-disubstituted thiocarbamoylthio)acylamino]-1,3,4-oxadiazoles were tested against various microorganisms by Ates *et al.*¹⁷, but only 5-phenyl-2-[(N,N-dimethylthiocarbamoylthio)propionylamino]-1,3,4-oxadiazole showed a reasonable activity against *S. aureus* and *S. epidermidis*. The same group¹⁸ performed analogous study for a series of 2-[[α -(4-substituted benzyloxy)- α -phenylacetyl/ methylacetyl]amino]-5-(4-methoxyphenyl)-1,3,4-oxadiazoles and some of them also showed activity against *S. aureus* and *S. epidermidis*. Holla *et al.*¹⁹ tested antibacterial activities of bis-(6-aryl(aryloxymethyl, anilinomethyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-4-yl)alkanes on *E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis*. Two compounds bis-(6-(4-chlorophenyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-4-yl)butane and bis-(6-(2-chlorophenoxyethyl)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-4-yl)ethane showed good activity against two latter bacteria. The same group²⁰ has studied antibacterial (*E. coli*, *P. aeruginosa*, *S. aureus* and *B. subtilis*) and antifungal (*C. albicans*) activities of bis-(4-oxo-4H-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazin-7-yl)alkanes and bis-thiadiazolotriazines. Most of the compounds studied showed reasonable activities and bis-(4-oxo-4H-3-*t*-butyl-1,3,4-thiadiazolo[2,3-c]-1,2,4-triazin-7-yl)butane showed extremely high anti-fungal activity (**Scheme-1c**).

Activities against the above four bacteria were also studied for 6-aryl-3-(1-*p*-chlorophenyl-5-methyl-1,2,3-triazol-4-yl)-s-triazolo[3,4-b]-1,3,4-thiadiazoles²¹. The highest activity (comparable with chloramphenicol) was observed against *P. aeruginosa* for aryl substituent being phenyl and methylphenyl. Two of the compounds studied (with aryl being *o*-chlorophenyl and *m*-bromophenyl) were tested for their inhibitory effects against a number of plant pathogenic fungi. The activity comparable to that of sulfamethazole or norfloxacin against *E. coli* and *S. aureus* was shown by some of the 5-guanylhydrazone(thiocyanato)-6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamides²². The antifungal activities of 2-phenyl(2-pyridyl-5-(2,4-dihydrobenzene)-1,3,4-thiadiazole against dermatophytes, yeasts and moulds were tested by Banachiewicz *et al.*²³; among them 2-(2-pyridyl)-5-(2,4-dihydrobenzene)-1,3,4-thiadiazole showed good activity against dermatophytes. Foroumadi *et al.*²⁴ have tested the activities of 2-aryl-5-phenylsulfonyl-1,3,4-thiadiazoles against several fungal strain. The most active compound was 2-(5-nitro-2-furyl)-5-phenylsulfonyl-1,3,4-thiadiazole (**Scheme-1d**); against most tested fungal strains its activity was several times higher than that of fluconazole. Tsotinis *et al.*²⁵ have studied antibacterial and antifungal activities of 1-(5-substituted amino-1,3,4-thiadiazole-3-yl)indoles; however, these compounds appeared to be rather inactive. A number of 2-benzylidenylamino-5-(*N*⁹-carbazolylmethyl)-1,3,4-thiadiazoles and 1-(5-(*N*⁹-carbazolylmethyl)-1,3,4-thiadiazol-2-yl)-4-phenyl-3-chloro-2-oxo-azetidines showed antibacterial activities (against *E. coli*, *S. aureus*, *Shigella flurxeni* and *S. dysenteriae*) similar to that

of streptomycin and antifungal activities (against *C. albicans*, *A. niger*, *C. parvum* and *R. oryzae*) similar to that of griseofulvin²⁶. Shah *et al.*²⁷ have studied antibacterial activities (against *E. coli*, *S. aureus* and *S. typhi*) of 2-(N-substituted carboxamidomethylthio)-5-(4-acetylaminophenyl)-1,3,4-oxadiazoles. The N-3-methoxyphenyl derivative (**Scheme-1e**) showed higher activity than that of chloramphenicol. A number of 2-aryl-5-(α -methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles, 2-arylsulfonamido-5-(α -methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles and 2-substituted benzamido-5-(α -methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles showed antimicrobial activities (against *B. subtilis*, *S. pyogenes*, *K. pneumoniae*, *A. niger* and *S. cerevisiae*) comparable to those of chloramphenicol, norfloxacin and griseofulvin²⁸.

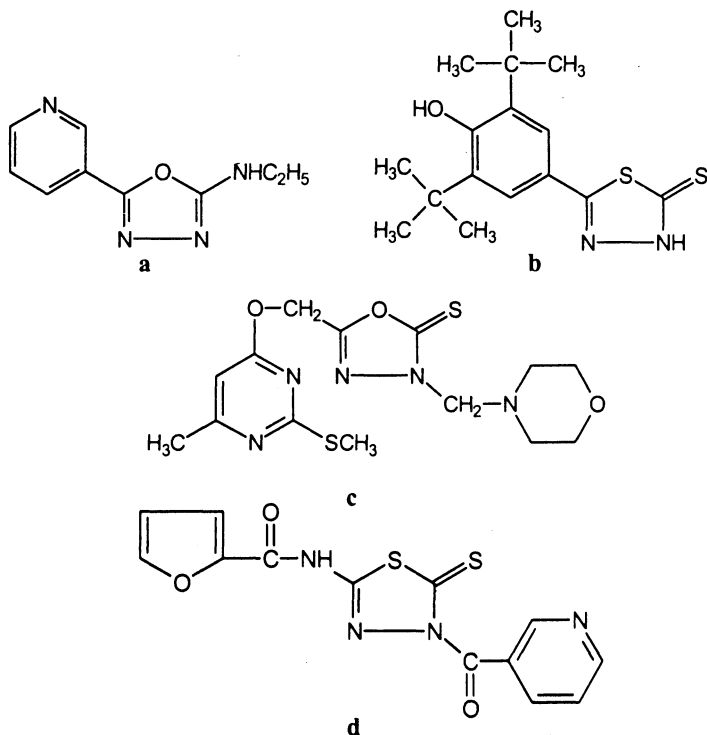


Scheme-1. Exemplary compounds having antimicrobial activities.

Antiinflammatory activities

Palaska and co-workers^{29,30} have tested 2-(2-naphthylloxymethyl)-5-substitutedamino-1,3,4-oxa(thia)diazoles for their antiinflammatory activity. Among the compounds studied, 2-(2-naphthylloxymethyl)-5-methylamino-1,3,4-oxadiazole showed the best inhibition of prostaglandin production and none of the compounds showed significant side effects. Omar *et al.*³¹ have studied antiinflammatory activity of a number of 2,5-disubstituted-1,3,4-oxadiazoles in relation to the standard reference drug, namely ibuprofen. Five compounds were found to have higher antiinflammatory activity than ibuprofen and the highest activity was revealed by 2-(3-pyridyl)-5-ethylamino-1,3,4-oxadiazole (**Scheme-2a**). Activities similar to ibuprofen were also observed for 2-(3-aminophenyl(4-chlorophenoxy)methyl)-5-(α -methyl-4-isobutylbenzyl)-1,3,4-oxadiazole and 2-(4-hydroxy-3-carboxyphenyl)-sulfonamido-5-(α -methyl-4-isobutylbenzyl)-1,3,4-oxadiazole²⁸. Antiinflammatory activities of the series of 2-substituted-5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-oxa(thia)diazoles have been studied by Mullican *et al.*³² and among the compounds studied, the choline salt of 5-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-1,3,4-thiadiazole-2(3H)-thione (**Scheme-2b**) appeared to be non-ulcerogenic, effective orally-active antiinflammatory agent. Jakubkiene *et al.*³³ have studied the antiinflammatory activity of 5-(6-methyl-2-substituted-4-pyrimidinylloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thiones and their 3-morpholinomethyl derivatives, relative to that of acetylsalicylic acid. The highest active compounds appeared to be 5-(6-methyl-2-morpholino-4-pyrimidinylloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione and 5-(6-methyl-2-methylthio-4-pyrimidinylloxymethyl)-3-morpholinomethyl-2,3-dihydro-1,3,4-oxadiazole-2-thione (**Scheme-2c**).

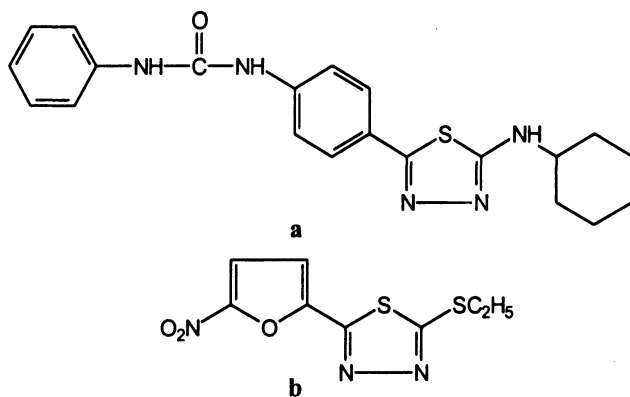
Other 1,3,4-oxa(thia)diazole-2(3H)-thiones having good antiinflammatory activity were 5-[2-[[3-(trifluoromethyl)phenyl]amino]phenyl]-1,3,4-oxa- and -thiadiazole-2(3H)-thione³⁴. Schenone *et al.*³⁵ have screened antiinflammatory activity of a series of 5-arylamino-3-nicotinoyl/isonicotinoyl-1,3,4-thiadiazol-2(3H)-ones. The most active were two compounds, namely 5-furoylamino-3-nicotinoyl-1,3,4-thiadiazol-2(3H)-one (**Scheme-2d**) and its isonicotinoyl correspondent. The authors also tested the compounds studied for their antipyretic activity but they did not have such properties. Dodd *et al.*³⁶ observed moderate antiinflammatory effect of 2-(4-methoxy-3,5-dimethyl-2-pyridyl)methylsulfine-5-methyl-1,3,4-oxadiazole and its derivatives in mouse dermatitis model but only in a local administration. A series of 2-benzylidenylamino-5-(*N*⁹-carbazolylmethyl)-1,3,4-thiadiazoles and 1-(5-(*N*⁹-carbazolylmethyl)-1,3,4-thiadiazol-2-yl)-4-phenyl-3-chloro-2-oxo-azetidines have been tested for their antiinflammatory activities; however, none of the compounds studied showed higher activity than that of phenylbutazone²⁶.



Scheme-2. Exemplary compounds having antiinflammatory activities.

Antituberculosis activity

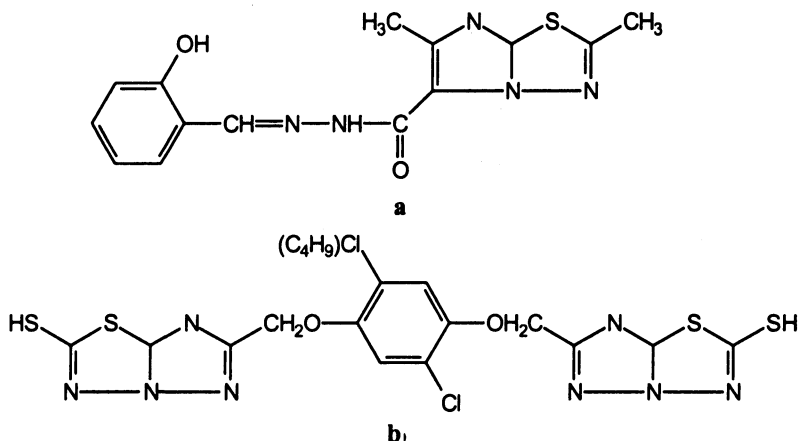
Karakus and Rollas³⁷ have studied antituberculosis activity (against *Mycobacterium tuberculosis*) of a series of N-phenyl-N'-[4-(5-alkyl/aryl/amino-1,3,4-thiadiazole-2-yl)phenyl]thioureas. The highest activity was observed for N-phenyl-N'-[4-(5-cyclohexylamino-1,3,4-thiadiazole-2-yl)phenyl]thiourea (**Scheme-3a**). Similar studies have been performed by Küçükgülzel *et al.*³⁸, for three 2-[4-(4-methoxybenzylamino)phenyl]-5-(substituted phenyl)amino-1,3,4-oxadiazoles (phenylamino-, 4-methylphenylamino- and 4-methoxyphenylamino-) but these compounds did not reveal any activity against *Mycobacterium tuberculosis*. Antituberculosis activity of some 2-(5-nitro-2-furyl)- and 2-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2-sulfides, sulfoxides and sulfones has been studied by Foroumadi *et al.*^{39, 40} and the most active compound was 2-ethylthio-(5-nitro-2-furyl)-1,3,4-thiadiazole (**Scheme-3b**). Mamolo *et al.*⁴¹ have screened thirty four [5-(pyridin-2-yl)-1,3,4-thiadiazol-2-ylthio]acetic acid benzylidenehydrazides for their antimycobacterial activity against *Mycobacterium tuberculosis* and *Mycobacterium avium*. Five compounds showed moderate activity against *Mycobacterium tuberculosis*, 4-chloro-, 2-bromo-, 4-bromo-, 3-fluoro- and 2,6-dichlorobenzylidene derivatives. The compounds studied had rather low activity against *Mycobacterium avium*. Some of the 2-(N-substituted-carboxamidomethylthio)-5-(4-acetylaminophenyl)-1,3,4-oxadiazoles also showed antituberculosis activity²⁷.



Scheme-3. Exemplary compounds having antituberculosis activities.

Anticancer activities

Terzioglu and Gürsoy⁴² have evaluated the anticancer properties of 2,6-dimethyl-*N'*-substituted phenylmethylene-imidazo[2,1-*b*]-1,3,4-thiadiazole-5-carbohydrazide hydrazones, 2,6-dimethyl-*N'*-(2-hydroxyphenylmethylidene)imidazo[2,1-*b*]-1,3,4-thiadiazole-5-carbohydrazide (**Scheme-4a**) had the most favourable cytotoxicity, being more active than chlorambucil, 5-fluorouracil and melfalan. Holla *et al.*⁴³ have tested 1,4-bis-(1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-3-ylmethoxy)phenylenes and 1,4-bis-(6-aryl(mercapto)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-3-ylmethoxy)phenylenes for their anticancer properties. The experiments were performed on 60 cell lines; three of the tested 1,4-bis-(6-aryl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-3-ylmethoxy)phenylenes and two of the 1,4-bis-(6-mercapto)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-3-ylmethoxy)phenylenes (**Scheme-4b**) showed good activity against a number of cell lines. A number of imidazo(2,1-*b*)-1,3,4-thiadiazoles were tested for their antitumor activity by Gadad *et al.*⁴⁴ 5-Formyl and 5-bromo derivatives showed high antitumor properties in most cell lines; substitution at 6-position produced different selective

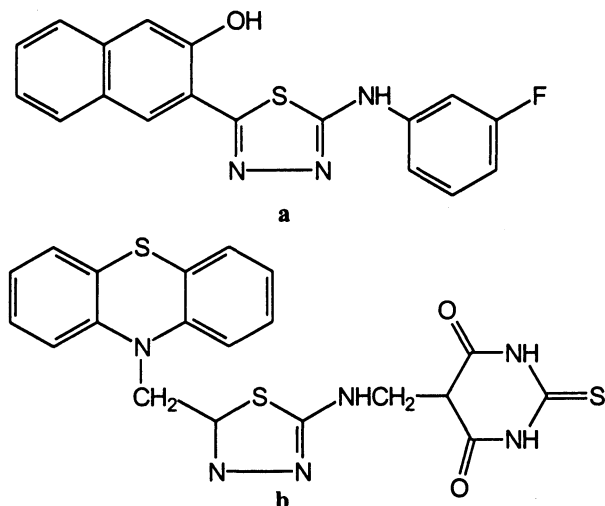


Scheme-4. Exemplary compounds having anticancer activities.

cytotoxicity. Some of the 2-(N-substituted-carboxamidomethylthio)-5-(4-acetylamino-phenyl)-1,3,4-oxadiazoles showed anticancer activities against a number of human cancers²⁷. Rai and Linganna⁴⁵ have screened five 2-N,N-di(3'-bromopropyl)amino-5-aryl-1,3,4-oxadiazoles together with their non-bromopropylated correspondents for their antimitotic activity; the most active appeared to be 2-N,N-di(3'-bromopropyl)amino-5-thienyl-1,3,4-oxadiazole.

Anticonvulsant activity

Dogan *et al.*¹¹ have studied anticonvulsant activities of a series of 2-amino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole derivatives. Their anticonvulsant properties were determined against pentylenetetrazole-induced convulsions in mice. 2-Ethylamino-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole and 2-(*m*-fluorophenylamino)-5-(3-hydroxy-2-naphthyl)-1,3,4-thiadiazole (**Scheme-5a**) showed similar protection to that of sodium valproate. Similar studies have been performed by Srivastava *et al.*²⁶ for 2-benzylidenylamino-5-(N⁹-carbazolylmethyl)-1,3,4-thiadiazoles and 1-(5-(N⁹-carbazolylmethyl)-1,3,4-thia-diazol-2-yl)-4-phenyl-3-chloro-2-oxoazetidines; some of the compounds showed promising protection. Ladva *et al.*²⁸ have tested antiinflammatory activities of 2-aryl-5-(α -methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles, 2-arylsulfonamido-5-(α -methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles and 2-substituted benzamido-5-(α -methyl-4-isobutylbenzyl)-1,3,4-oxadiazoles, however, none of the compounds studied showed better protection than phenobarbital. Archana *et al.*⁴⁶ have screened a series of 5-(2'-indoyl(phenothiazinyl)methylene-5'-aminomethylene-1',3',4'-oxa(thia)-diazol-2'-yl)-2-oxo(thio)barbituric acids for their anticonvulsant properties. The most active appeared to be 5-(2'-phenothiazinylmethylene-5'-aminomethylene-1',3',4'-thiadiazol-2'-yl)-2-thiobarbituric acid (**Scheme-5b**), being more active than the standard drug phenytoin sodium. In general, the exchange of indoyl moiety into phenothiazinyl, oxadiazole ring into thiadiazole or oxobarbituric acid into thiobarbituric acid produced better anticonvulsant properties.



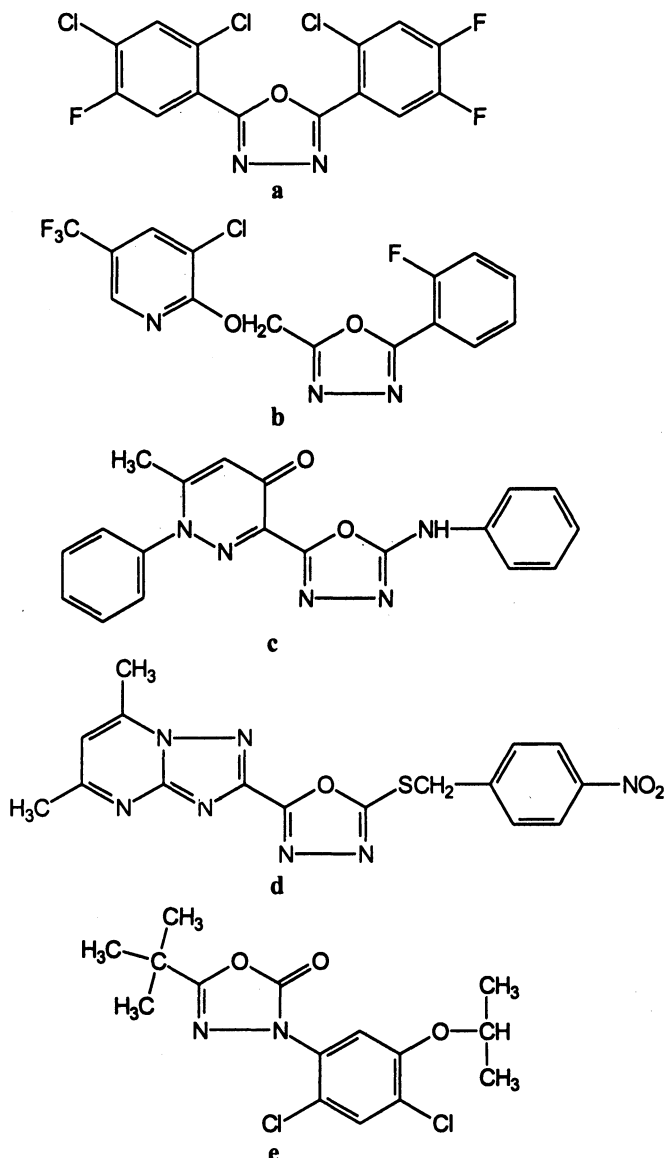
Scheme-5. Exemplary compounds having anticonvulsant activities.

1,3,4-Oxa(thia)diazole conjugates as pesticides

A lot of 1,3,4-oxa(thia)diazoles have insecticidal activities, which allow considering them as insecticides. Zheng *et al.*⁴⁷ have screened a series of 2,5-chloro(fluoro)aryl-disubstituted-1,3,4-oxadiazoles for their insecticidal activities against *Leucania separata*. The highest activity was shown by 2-(2,4-dichloro-5-fluorophenyl)-5-(2-chloro-4,5-difluorophenyl)-1,3,4-oxadiazole (**Scheme-6a**). Huang *et al.*⁴⁸ have shown that many of 2-(4-chloro-3-one-2-*t*-butyl-2H-pyridazinoxylthio)methyl)-5-aryl-1,3,4-oxadiazoles exhibit anti-feedant activities and were effective insect growth regulators. The same group⁴⁹ has studied the insecticidal activity of 2-(3-chloro-5-trifluoromethyl-pyridoxymethyl)-5-aryl-1,3,4-oxadiazoles against *Leucania separata*. The highest activity was observed for 2-(3-chloro-5-trifluoromethyl-pyridoxymethyl)-5-(2(4)-fluorophenyl)-1,3,4-oxadiazoles (**Scheme-6b**). Insecticidal activity (against *Pseudaletia separata*) of a number of miscellaneously 2,5-disubstituted 1,3,4-oxadiazoles has been studied by Shi *et al.*^{50,51} Some of the compounds studied had 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropyl moiety. The highest activity was observed for 2-(2,4-dichloro-5-fluorophenyl)-5-(2-chlorophenoxymethyl)-1,3,4-oxadiazole, 2-(2,4-dichloro-phenyl)-5-(4-chlorophenoxymethyl)-1,3,4-oxadiazole and 2-(2,4-dichloro-5-fluorophenyl)-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole. The authors have performed an excellent discussion on the correlation between the activities of the compounds and their physicochemical properties. Qian and Zhang⁵² have screened insecticidal activities of different 2,5-disubstituted-1,3,4-oxadiazoles against *Dropsophila melanogaster*. The asymmetrical compounds, namely 5-substituted-2-(2,4-dichlorophenyl)-1,3,4-oxadiazoles showed higher activity and the most active was 5-*t*-butyl derivative. However, symmetrical 2,5-bis(2,4-dichlorophenyl)-1,3,4-oxadiazole was also a very active compound. The authors suggested that electronic effects might be of key importance for the insecticidal activities of the compounds studied.

The fungicidal activities of 1,3,4-oxa(thia)diazoles allow these compounds to be regarded as fungicides. Zou *et al.*⁵³ have tested 5-[1-aryl-1,4-dihydro-6-methylpyridazin-4-one-3-yl]-2-arylamino-1,3,4-oxa(thia)diazoles (**Scheme-6c**) for their fungicidal activity against *Puccinia recondite*. Each of the compounds studied contained at least one chlorine or fluorine atom (at aryl moieties). Two thiadiazoles and four oxadiazoles showed 90% inhibition. Chen *et al.*⁵⁴ have studied fungicidal activity of 2-alkyl(alkylthio)-5-pyrazolyl-1,3,4-oxa(thia)diazoles against *Rhizoctonia solani* many of the compounds studied showed 90% inhibition. Mishra and Singh⁵⁵ have tested a number of fused 1,3,4-oxadiazoles with s-triazine nuclei (2-aryl-6-(4-fluorophenyl)-1,3,4-oxadiazolo[3,2-*a*]-s-triazine-5,7-diones and their 5-thio correspondents) for their antifungal activities against *Aspergillus niger* and *Fusarium oxysporum*. Higher activities were observed for compounds containing both carbonyl and thiocarbonyl groups than for those bearing two carbonyl groups. The former showed antifungal properties comparable to that of dithane M-45, however, only at higher concentrations. Fungicidal activities similar to dithane M-45 against *A. niger*, *F. oxysporum* and

Cephalosporium sacchar were also shown by 2-(3-fluorophenyl)-1,2,4-triazolo[3,2-*b*]-1,3,4-oxadiazole-6-thione, 2-(2(3)-fluorophenyl)-6-(4-chlorophenyl-imino)-1,2,4-thiadiazolo[3,2-*b*]-1,3,4-oxadiazoles and 2-(4-fluorophenyl)-6-(4-methylphenylimino)-1,2,4-thiadiazolo[3,2-*b*]-1,3,4-oxadiazole⁵⁶. Liu *et al.*⁵⁷ have tested fungicidal activities of the compounds containing 1,2,4-triazolo[1,5-*a*]pyrimidine and 1,3,4-oxadiazole ring, namely thio-substituted 5,7-dimethyl-2-(5-



Scheme-6. Exemplary compounds having insecticidal (a, b), fungicidal (c, d) and herbicidal (e) activities.

mercapto-1,3,4-oxadiazole-2-yl)methylenethio-1,2,4-triazolo[1,5-a]pyrimidines. The *p*-nitrobenzyl derivative (**Scheme-6d**) showed better activity against *R. solani* than carbendazim and validamycin A. The activity against *A. niger* and *Penicillium citrinum* comparable to that of carbendazim was also observed for 3-(4-chlorophenyl)-9-phenyl(2-chlorophenyl, 4-methoxyphenyl)-2-thiothiazolo[4,5-d][1,3,4-oxadiazolo[2,3-b]pyrimidines and 3-(4-chlorophenyl)-9-phenyl(2-chlorophenyl)-2-thiothiazolo[4,5-d][1,3,4-oxadiazolo[2,3-b]pyrimidines⁵⁸. Rao *et al.*⁵⁹ have screened a series of 3-(5-arylamino-1,3,4-oxa(thia)diazol-2-yl)-2-phenyl-1,8-naphthyridines for their activities against *F. oxysporum* and *D. rostrata*, however; their antifungal properties were lower than that of carbendazim.

The thio-substituted 5,7-dimethyl-2-(5-mercapto-1,3,4-oxadiazole-2-yl)methylenethio-1,2,4-triazolo[1,5-a]pyrimidines were also tested for their herbicidal activities⁵⁷. Some of the compounds (methyl, ethyl and *sec*-butyl derivatives) studied showed high inhibitory effect (> 90%) against *Brassica campestris* and *Echinochloa crusgalli*. 5-*t*-Butyl-3-(2,4-dichloro-5-isopropoxyphenyl)-1,3,4-oxadiazol-2(3H)-one oxadiazon (**Scheme-6e**) is a common selective contact herbicide used in the cultivation of a number of plants^{60, 61}. This and related compounds have a broad-spectrum of post- and pre-emergence activity against both dicotyledonous and monocotyledonous weeds. It is worth noting that the exchange of oxygen into sulfur (thiadiazon) did not essentially affect its activity⁶².

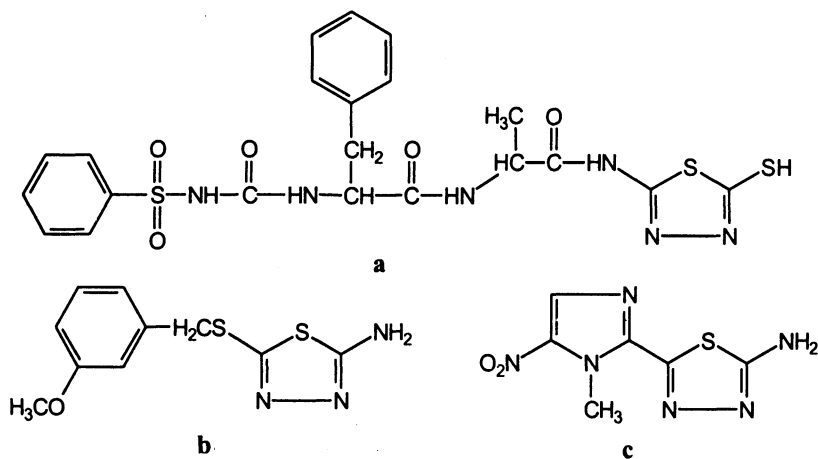
Other activities of 1,3,4-oxa(thia)diazole conjugates

Supuran and co-workers⁶³⁻⁶⁶ have shown that a number of 5-amino-1,3,4-thiadiazole-2-sulfonamides as well as their complexes with Zn(II) or Cu(II), have strong carbonic anhydrase inhibitory properties. Several of the most active inhibitors have a lower intraocular pressure, thus can be considered as potentially effective antiglaucoma drugs. Scozzafava and Supuran⁶⁷ have also shown that arylsulfonyl(ureido)-phenylalanyl-alanyl-5-amino-2-mercapto-1,3,4-thiadiazoles (**Scheme-7a**) are effective metalloprotease inhibitors.

Clerici and Pocar⁶⁸ have found that a number of 2-amino-5-sulfanyl-1,3,4-thiadiazoles are characterized by antidepressant and anxiolytic properties comparable to imipramine or diazepam. The most promising compound, with very low side effects, was 2-amino-5-(3-methoxybenzylsulfanyl)-1,3,4-thiadiazole (**Scheme-7b**). Promising antidepressant activity was also observed for N-{5-[(2-methyl-1H-3-indolyl)methyl]-1,3,4-thiadiazol-2-yl}-N-phenylamine⁶⁹.

Megazol (2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**Scheme-7c**) and a number of its derivatives were found to be effective against *Trypanosoma brucei*, microbials which cause sleeping sickness in Africa⁷⁰⁻⁷². It is worth noting that the activity was lost when the thiadiazole ring was exchanged for oxadiazole; also the activity loss was observed in the case of amino group substitution, unless substitution by acetyl group.

Kritsanida *et al.*⁷³ have tested antiviral activities of 6-substituted 3-(1-adamantyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles, however, the compounds studied did not reveal anti-HIV-1 or anti-HIV-2 properties. Moderate anti-HIV-1 proper-



Scheme-7. Metalloprotease inhibitor (a), exemplary compound having antidepressant properties (b), megazol (c).

ties showed 2-(N-substituted-carboxamidomethylthio)-5-(4-acetylamino-phenyl)-1,3,4-oxadiazoles²⁷. Yadav and Singh⁷⁴ have tested antiviral properties of C-nucleosides incorporating thiazolo-1,3,4-oxa(thia)diazole structure as nucleobase against *Chenopodium amaranticolor*. However, their activities were lower than the respective 1,2,4-triazoles; the latter possessed antiviral properties similar to virazole.

Schelenz *et al.*⁷⁵ have found good correlations between hydrophobicity and algistatic activity of 5-aryl-3H-1,3,4-oxadiazole-2-thiones tested on *Chlorella vulgaris*. The highest activity was observed for 5-(4-bromophenyl)-3H-1,3,4-oxadiazole-2-thione.

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