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REVIEW

The synthesis and biological activities of 3-acyl- 2,3-dihydro-1,3,4-oxadiazole / 3-acyl-1,3,4-oxadiazoline derivatives obtained from hydrazide-hydrazones

Sevim Rollas, Sevgi Karakuş

ABSTRACT: In this review, the synthesis and biological activities of 3-acyl-2,3-dihydro-1,3,4-oxadiazole derivatives are reported. Synthesis of 1,3,4-oxadiazolines via carboxylic acid hydrazide-hydrazones by using acetic anhydride or other cyclization agents establishes the peculiar basis of our work.

KEYWORDS: 2,3-dihydro-1,3,4-oxadiazole, 3-acyl-1,3,4-oxadiazoline, hydrazide hydrazones, biological activities.

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INTRODUCTION

The hydrazide-hydrazones are obtained from the condensation of hydrazides and aldehyde or ketones (1-5). Also, unsubstituted or monosubstituted hydrazones are converted into hydrazide-hydrazones with acylated agents (1). Being one of the most important raw material, hydrazide-hydrazones and hydrazones have been used in the various chemical synthesis (1,6-10). The acyl- and aroylhydrazones are very important as chelating agents (11-14) Compounds containing hydrazide and hydrazone moiety proved to be especially attractive due to their application in biology (4, 15-21) and medicine, isocarboxazide, iproniazide, isoniazid, nifuroxazide, rifampisin as example drugs. Also hydrazones are the most important compounds for prodrug design due to their poor metabolic stability (1, 22-24). The plasma stability of the prodrugs is very important for rapid conversion in plasma (25). The formation of hydrazone is an suitable reaction for prodrug synthesis (26-30). They are easily hydrolyzed to active drugs *in vivo*. Hydrazide-hydrazones have also been employed for the preparation of the heterocyclic compounds such as 4-thiazolidinone (31, 32), azetidinone (33, 34), 1,3,4-oxadiazole and 2,3-dihydro-1,3,4-oxadiazol rings. The substituted 1,3,4-oxadiazole derivatives have been obtained from hydrazide-hydrazones by the oxidative cyclization (35-37). The hydrazone functional group is usually not stable *in vivo* (22, 38) and *in vitro* (23, 39). However the hydrolytic stability of hydrazones are depend on the structure of the substituent (1). 2,3-Dihydro-1,3,4-oxadiazol derivatives are stable structures (40) and obtained from intramoleculer cyclization of hydrazide hydrazones by acid anhydrides or acylchlorides (1, 41-46). In 1953, Yale and co-workers (41) reported the publication of related compounds. In 2002, Rollas and co-workers (45) demonstrated that some hydrazones of 4-fluorobenzoic acid hydrazide and their 1,3,4-oxadiazoline derivatives showed antibacterial and antifungal activities. The monoamine oxidase inhibitory activities of 3-acetyl-1,3,4-oxadiazolines were investigated by Maccioni and co-workers (47). The most detailed researches have been made by Somogyi and co-workers (42, 48-51).

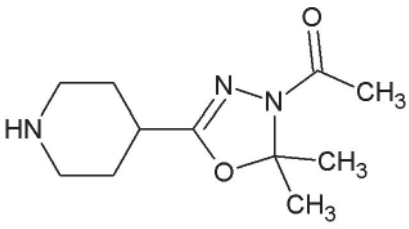
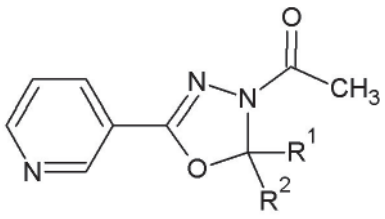
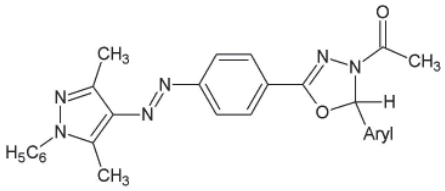
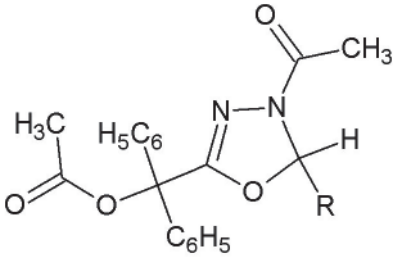
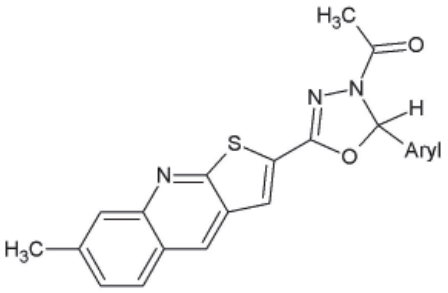
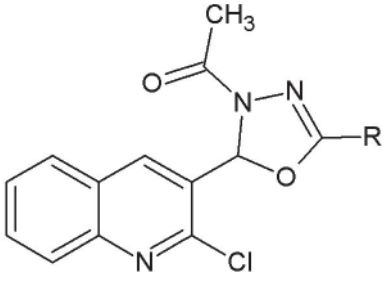
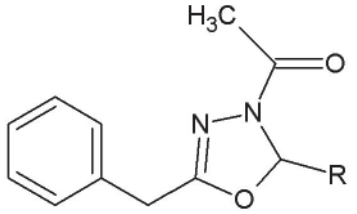
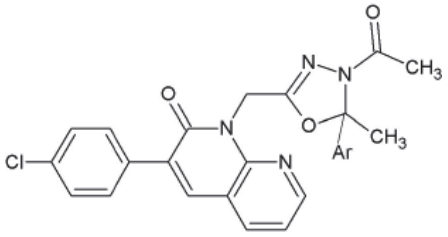
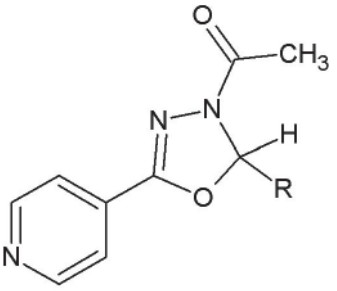
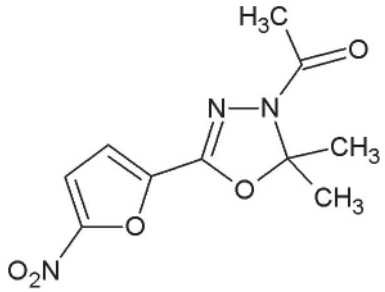
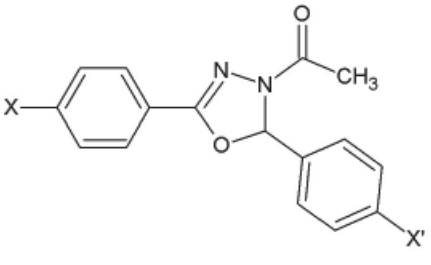
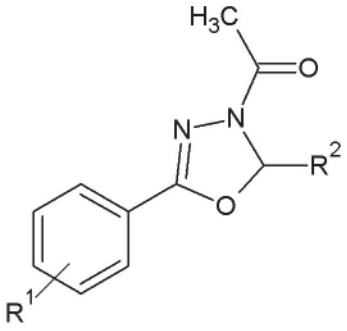
There are only a few reports on 3-acetyl-1,3,4- oxadiazolines which obtained from hydrazide-hydrazones with acetic anhydride and the other cyclization agents. Purpose of this review is to summarize synthetic approaches and report the biological activities of 3-acyl-2,3-dihydro-1,3,4-oxadiazol derivatives. The literature covers through 1953.

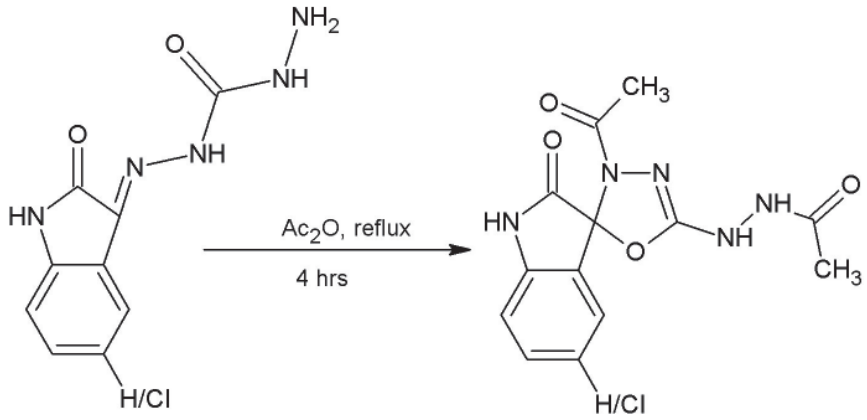
SYNTHESIS OF 3-ACYL-2,3-DIHYDRO-1,3,4-OXADIAZOLE DERIVATIVES

Cyclizaton of hydrazide-hydrazones

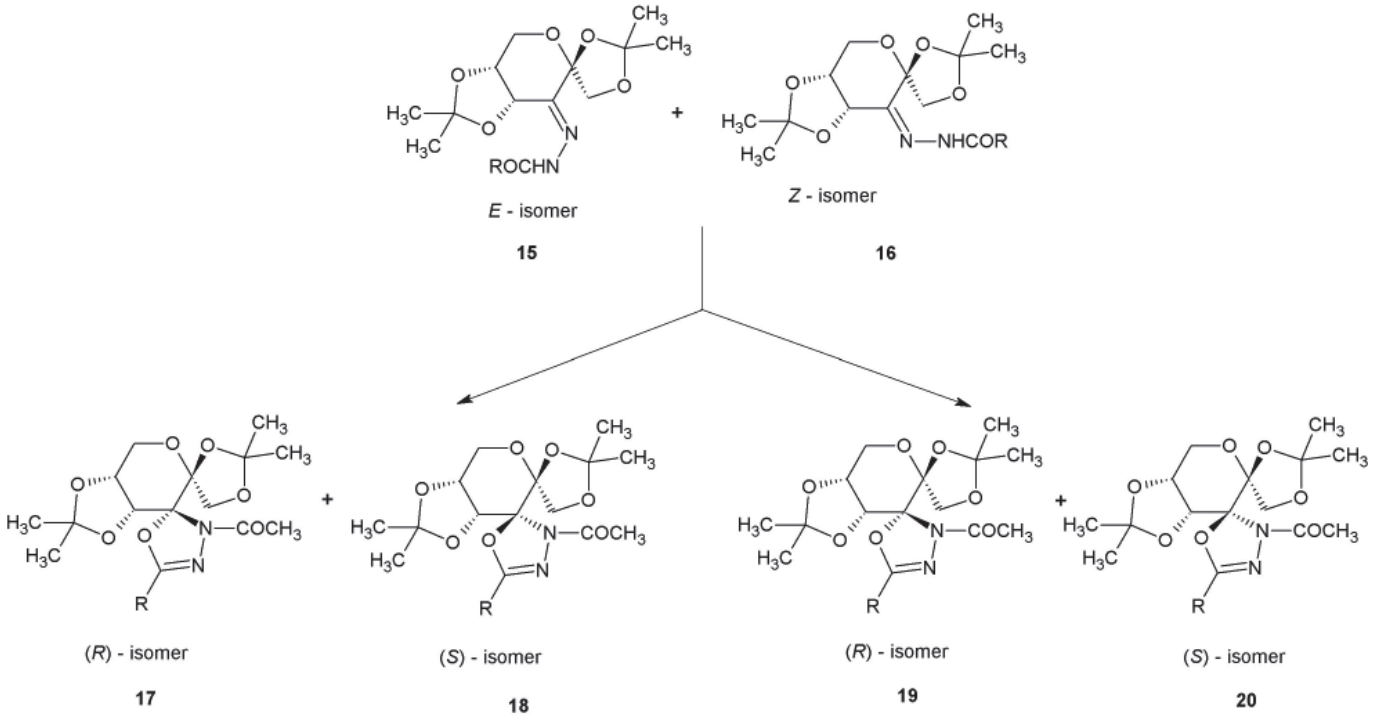
Acetyl derivatives

The 3-acetyl-2,3-dihydro-1,3,4-oxadiazole derivatives have been obtained via acetylation and intramolecular cyclation of hydrazide-hydrazones using acetic anhydride. The 3-acetyl-1,3,4-oxadiazolines **1** (41), **2** (43), **3** (44, 52), **4** (53), **5** (54), **6** (55), **7** (56), **8** (57) and **9** (58), **10** (59), **11** (60) and **12** (61) were synthesized by the cylization of the corresponding hydrazide-hydrazone derivatives in acetic anhydride. The reaction time, temperature, and yields have been shown slightly different.

		
1 1h, reflux, 95%	**2** 1h, reflux, 56-87%	**3** 30 min, 130-140 oC reflux, 47-75%; 30 min, reflux, 140-200 oC
		
4 60 min, 130 oC reflux, 32-63%.	**5** 3h, reflux, 85-90%	**6** 1h, reflux, 60-70%
		
7 1h, reflux	**8** 3.5-5.5 min, microwave oven, 400W, 84-88%	**9** 4h, reflux, 16-67%
		
10 1h, reflux, 60.5%	**11** 30 min-2 h, reflux, 44-85%	**12** 3h, reflux, 25-84%



13 **14**

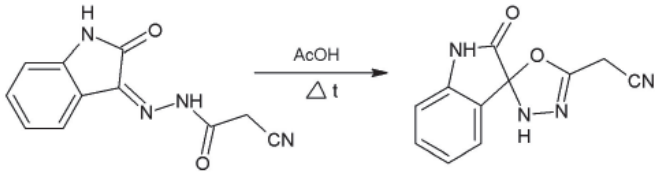


In the other variations of this method, anhydrous sodium acetate (62) has been added in the reaction medium besides acetic anhydride. Also, the 1,3,4-oxadiazolines were synthesized from the corresponding hydrazide-hydrazones in acetyl chloride (48, 63, 64).

On the other hand, the spiro 1,3,4-oxadiazolines were obtained from the reaction acetic anhydride **14** (65) **17, 18, 19, 20** (66) or acetic acid **22** (67) on cyclic ketone–hydrazone derivatives.

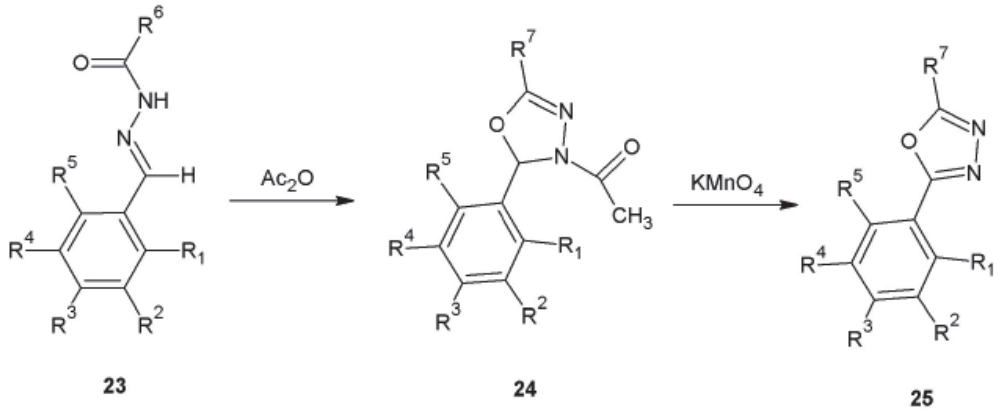
The compounds were obtained with (R)- and (S)- configurations at C-3 (66). Wang and co-workers (67) isolated also the E and Z isomer of some hydrazide hydrazones and from these isomers synthesized the S and R isomers of spiro1,3,4-oxadiazoline derivatives.

The cyclization of **21** was carried out in acetic acid by Allam and co-workers (68) and obtained nonacetylated spiro1,3,4-oxadiazoline derivative **22**.



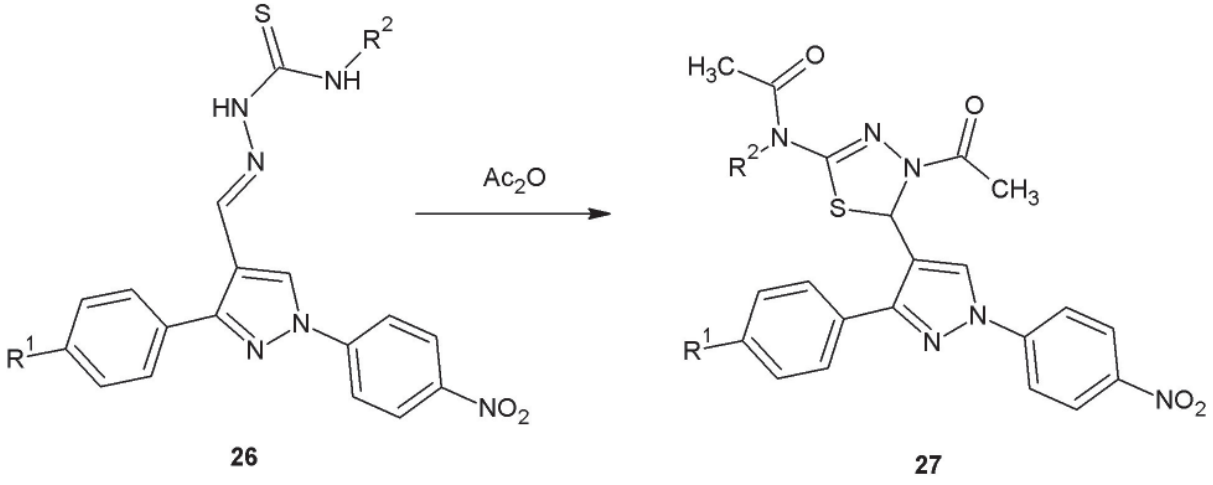
21 **22**

The dehydrogenation of 3-acetyl-2,3-dihydro-1,3,4-oxadiazoles **24** with potassium permanganate has been given substituted 1,3,4-oxadiazoles **25** (51)

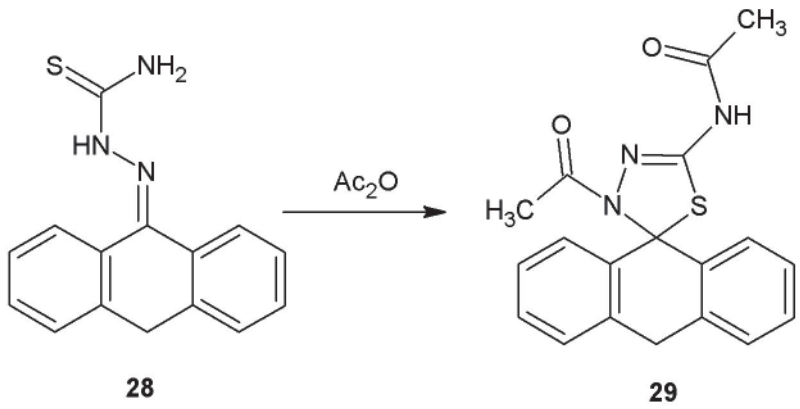


23 24 25

Similarly, the 3-acetyl-2,3-dihydro-1,3,4-thiadiazole derivatives **27** (69) are obtained from thiosemicarbazones. When the cylic ketone is used, the spiro 1,3,4-thiadiazolines **29** have been formed (70).



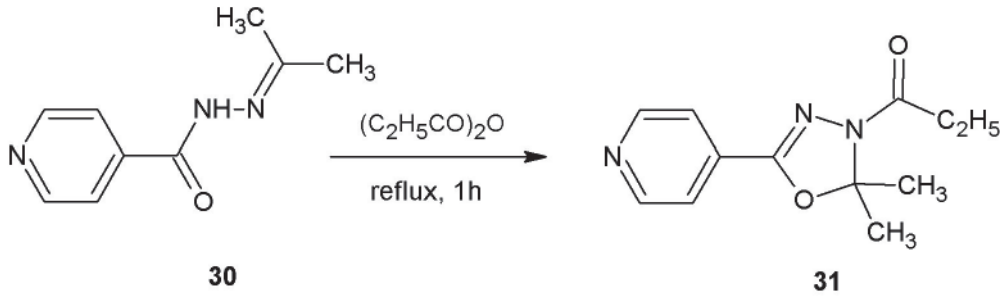
26 27



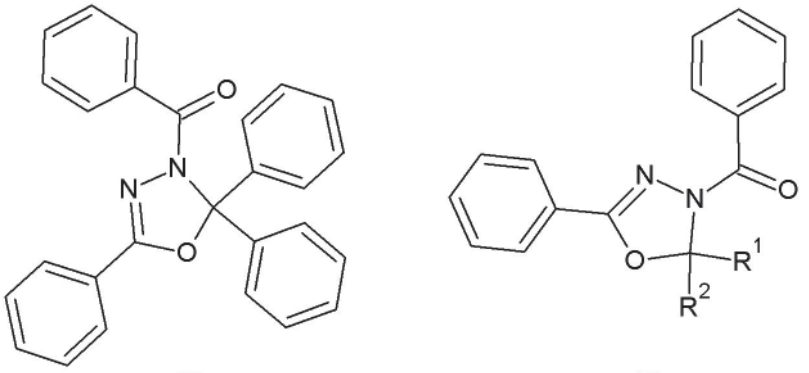
28 29

Other acyl derivatives

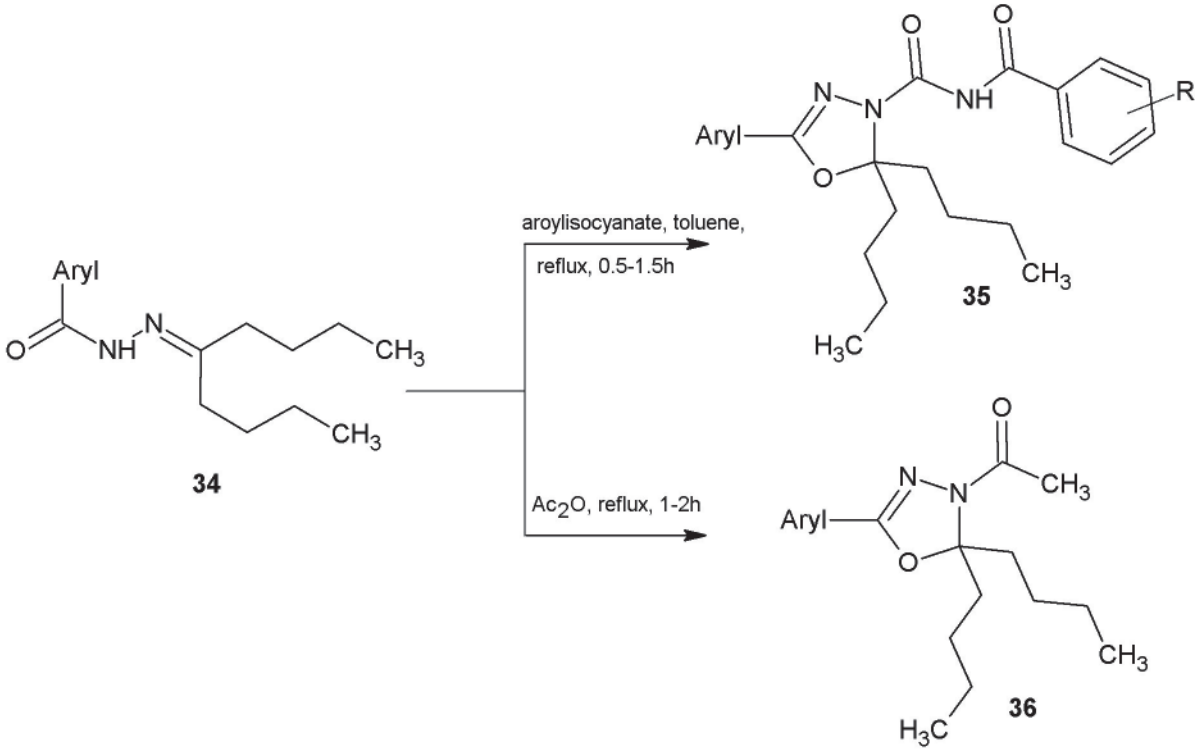
The intramoleculer cyclization of hydrazide hydrazones have also been carried out with propionic anhydride **31** (40), benzoyl chloride **32** (48), **33** (63) and substituted isocyanates **35, 36** (71, 72).



30 **31**

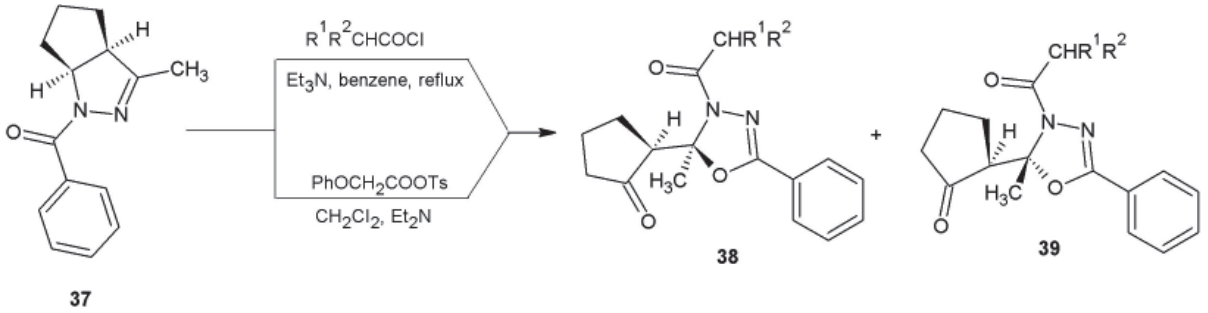


32 **33**



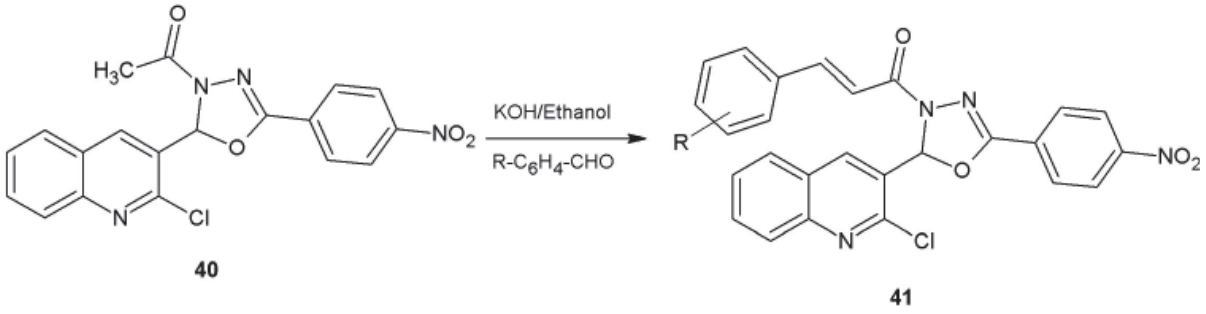
34 **35** **36**

The isomer compounds **38** and **39** were synthesized with the different method by Tsoleridis and co-workers (73).



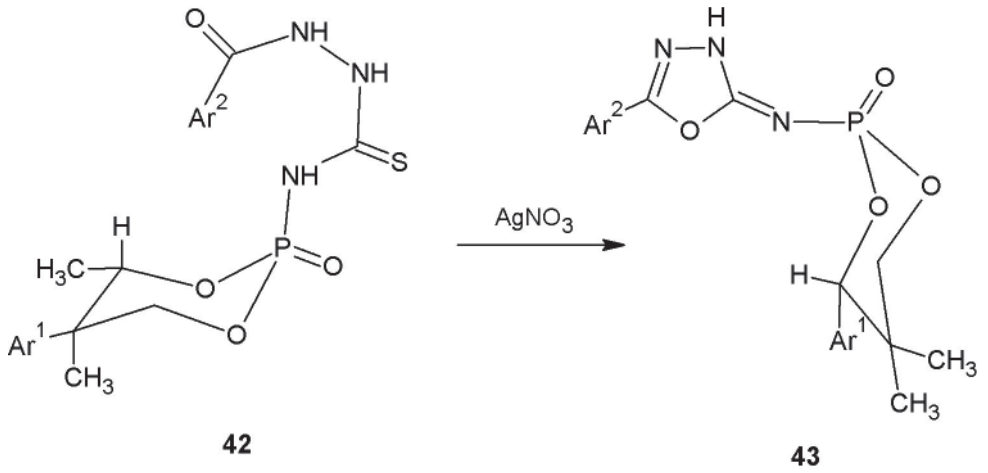
	R¹	**R²**
38a, 39a:	Cl	Cl
38b, 39b:	Cl	H

Desai and co-workers (74) synthesized 3-(substituted-phenylpropenoil)-1,3,4-oxadiazoline derivatives **41** from 3-acetyl-2-(2-chloroquinolin-3-yl)-5-(4-nitrophenyl)-1,3,4-oxadiazoline **40**.

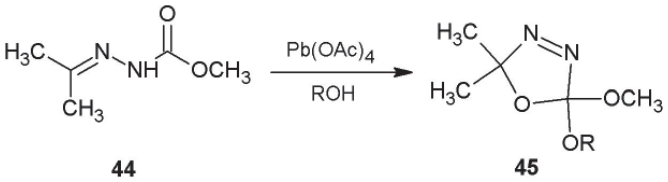


Different methods for the synthesis of 1,3,4-oxadiazolines

The regioselective cyclization of 1,4-disubstituted thiosemicarbazides has been shown to be a good method for the synthesis of substituted 1,2,4-triazoles (75, 76) and 1,3,4-thiadiazoles (77, 78) in alkaline and acidic media respectively. Feng and co-workers (79) published the first report on the regioselective cyclization of 1,3,4-oxadiazolines from 1,4-disubstituted thiosemicarbazides using silver nitrate as an oxidant. The products have isolated as the *trans*-isomer.

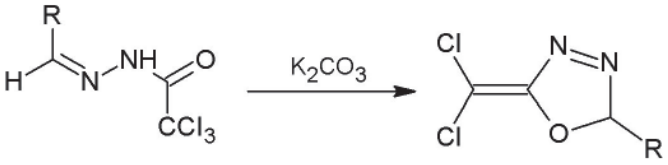


El-Saidi and co-workers (80) prepared the Δ^3-1,3,4-oxadizoline derivatives **45** by oxidative cylization of compound **44** using the different starting compound with lead tetraacetate in alcohol.



44 **45**

Also, El-Kaim and co-workers (81) synthesized the Δ^3-1,3,4-oxadiazolines **47** from trichloroacetic acid hydrazones **46**.

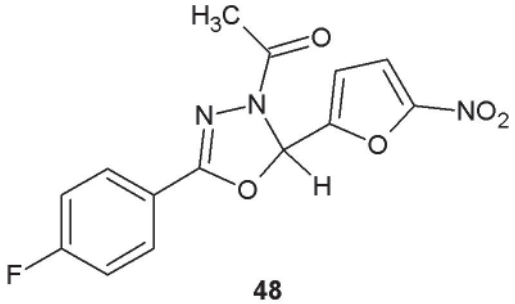


46 **47**

Biological Activity

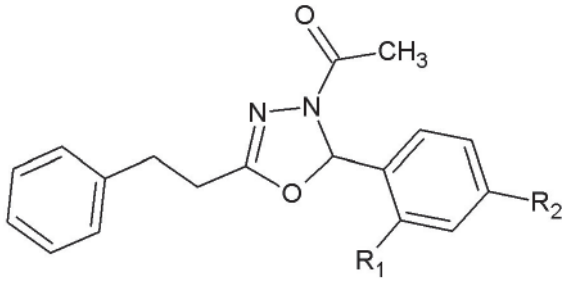
The investigation of the biological activities of 3-acyl-2,3-dihydro-1,3,4-oxadiazole derivatives has been focused on antibacterial, antitumor, antioxidant, monoamine oxidase inhibitory and anticonvulsant activity.

Rollas and co-workers (45) synthesized 4-fluorobenzoic acid[(4-nitrophenyl/5-nitro-2-furanyl)methylene]hydrazide derivatives and tested against various bacteria and fungus. Compound **48** showed equal activity with ceftriaxone against *S.aureus.*



48

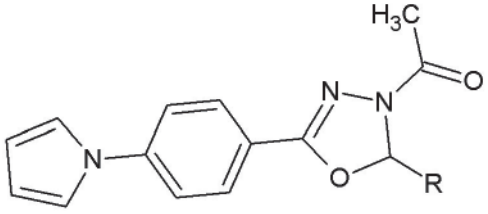
Also, Fuloria and co-workers (82) screened the compounds **49a-e** for their antibacterial and antifungal activity against *S. aureus, P. aeruginosa, C. albicans* and *A. flavus*. Compounds were found to be active against tested microorganism.



49

a	R_1: H	R_2: $(CH_3)_2$
b	R_1: H	R_2: Cl
c	R_1: OH	R_2: OH
d	R_1: H	R_2: H
e	R_1: H	R_2: OH

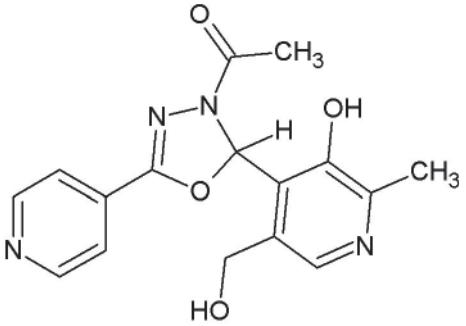
50a and **50b** were tested for their antitubercular activity against *M. tuberculosis* H37Rv strain. Compounds showed moderate activity (MIC: 31.25, Isoniazid: 0.25 μg/mL) (83).



50

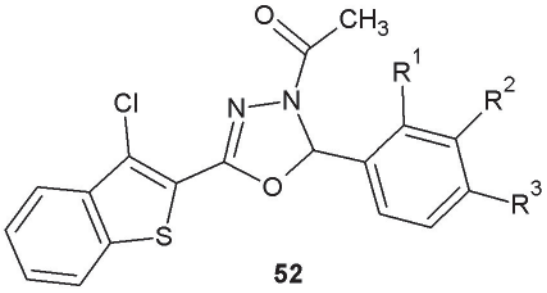
R:	a	$-C_6H_5$
	b	$2,6\text{-}Cl_2C_6H_3$

The cylization of the pyridoxalisonicotinoyl hydrazone with acetic anhydride gave **51**. Compound **51** exhibited inhibitory activity against *M. tuberculosis* H37Rv (MIC, 6.09 μM) (84).



51

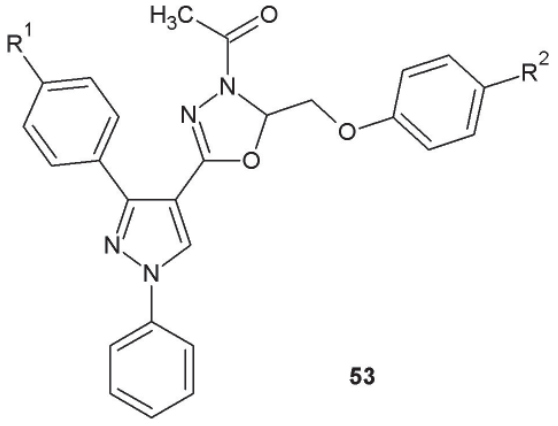
Chawla and co-workers (85) synthesized a series of 3-acetyl-5-(3-chloro-1-benzo[b]thiophen-2-yl)-2-substitutedphenyl-2,3-dihydro-1,3,4-oxadiazoles. Among the tested compounds **52a** and **52b** were found to be most active compounds compare to standart drug ciprofloxacin against *S. aureus and B. subtilis.*



52

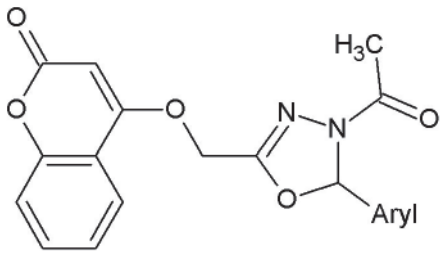
a:	R^1: H	R^2: OCH_3	R^3: H
b:	R^1: H	R^2: H	R^3: OCH_3

Yang and co-workers (86) synthesized 3-(substituted)aryl-4-(acetyl-2-aroyloxymethylene-1,3,4-oxadiazoline-5-yl)-1-phenyl-2-pyrazoline derivatives **53**. Their antibacterial activities were found higher than the initial hydrazide-hydrazones against tested microorganisms.



53

In a recent publication, Hamdi and co-workers (87) have investigated 1,3,4-oxadiazoline derivatives for their antibacterial and antioxidant activities.

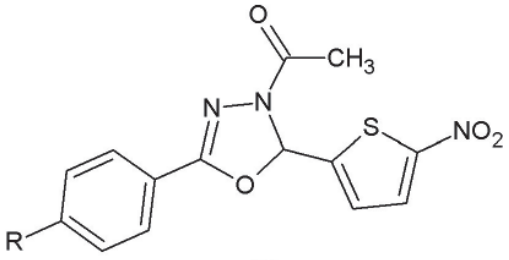


54

Aryl:	$-C_6H_5-$	$4-FC_6H_4-$	$4-OCH_3C_6H_4-$	$4-NO_2C_6H_4-$	$3,4,5-(OCH_3)_3C_6H_2-$

Generally, the antibacterial activities of 1,3,4-oxadiazoline derivatives screened against *S. aureus*. Indeed, all of the researchs showed that 1,3,4-oxadiazolines were active compounds.

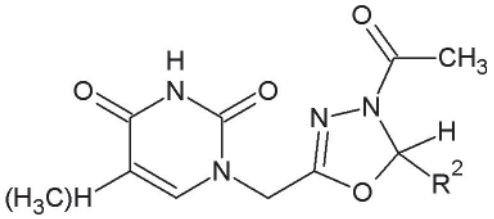
Also, Ishii and co-workers (88) synthesized the 1,3,4-oxadiazolines and tested for their antimicrobial activities against various strains. The most active compounds were **55a-c**. Compound **55b** showed good activity against *S. aureus* (MIC=1.95-1.25 μg/mL) and **55a** against *C. albicans* (MIC=3.28-2.62 μg/mL).



55

R:	a	$-CF_3$
	b	$-OC_4H_9$
	c	$-OCOCH_3$

Omar M. Ali and co-workers (89) synthesized 1,3,4-oxadiazoline derivatives **56** from sugar uracil-1-ylmethylhydrazones by heating in acetic anhydride. Compounds were tested for antiviral activity against hepatitis B virus and showed moderate viral replication inhibition.



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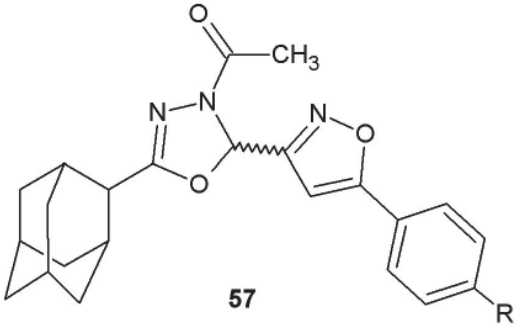
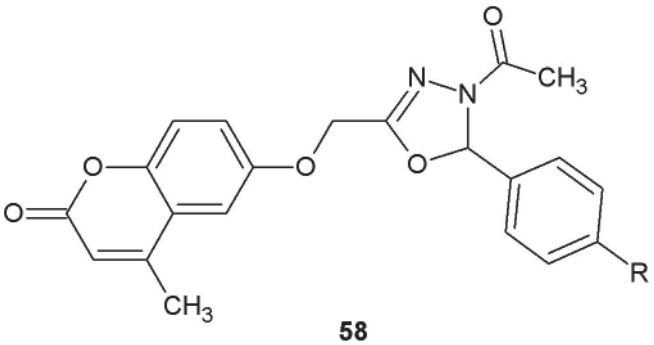
Compounds **57a-c** were tested for antimicrobial activities various strains. The compounds did not show remarkable activity (90).



57

R:	a	$4-Cl-C_6H_4-$
	b	$4-CH_3-C_6H_4-$
	c	$4-OCH_3-C_6H_4-$

Manojkumar and co-workers (91) prepared 3-acetyl-1,3,4-oxadiazolines **58a-c** using starting material 4-methoxycoumarinyl-7-oxyacetic acid hydrazide hydrazones.

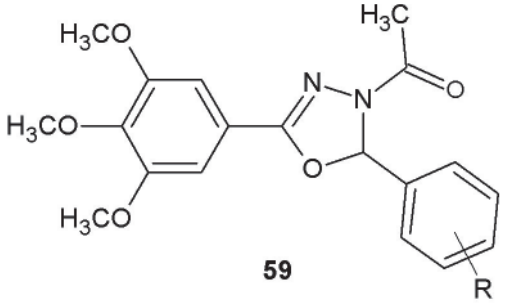


58

	a	CH_3
R:	b	H
	c	F

The compounds **58a-c** have tested for their *in vitro* cytotoxic activity against DLH and EAC cells. 5-Fluorouracil was used as standart cytotoxic agent. In addition, their antioxidant activities have studied by diphenylpicryl hydrazyl (DPPH) assay method.

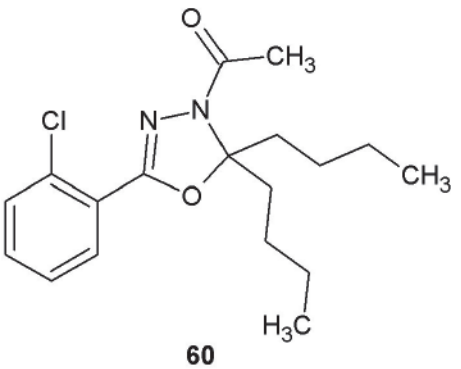
Also Jin and co-workers (92) reported that compound **59** was active against PC3 cells in vitro by MTT method at 0.3 μM.



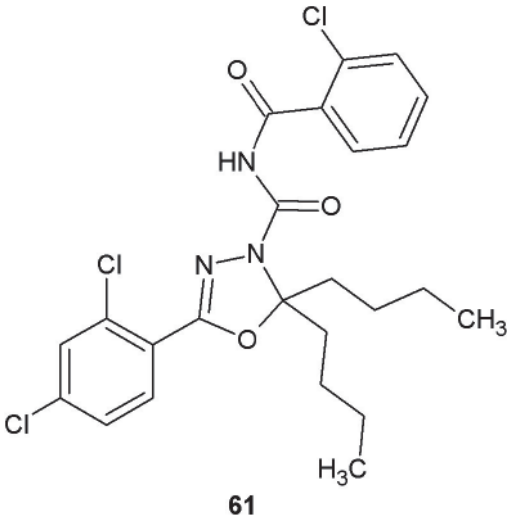
59

Lee and co-workers (93) prepared 2,5-diaryl-1,3,4-oxadiazoline analogs **59** of combretastatin A4 and tested antiproliferative activities against multiple cancer cell lines and reported that it was the major efficient antioxidant bearing 3,4,5-trimethoxysubstituent in the phenyl ring. Other compounds have also exhibited higher antioxidant activity than Trolox.

Ke and co-workers (72) designed and synthesized a series of oxadiazoline derivatives. All synthesized compounds have inhibited chitin biosynthesis in yeast. Compounds **60** and **61** have showed the highest inhibitory activity at lower concentrations.



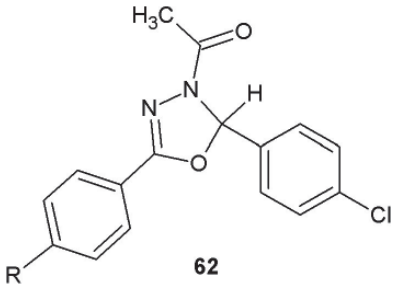
60



61

In 2005, Chimenti and co-workers (94) reported the synthesis of 1-acetyl-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazole derivatives and their human monoamine oxidase activity against (MAO) A and B isoforms.

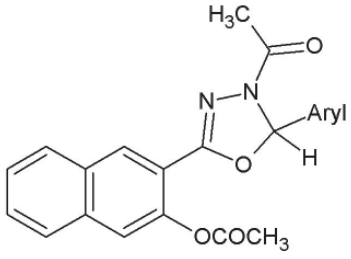
Recently, Maccioni and co-workers (47) designed and synthesized 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazole derivatives as isosteres of 1-acetyl-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazoles to investigate for their inhibitors activity against MAO-A and MAO-B. Some of the compounds **62** exhibited inhibitory activities against the B isoform of the enzyme at nanomolar values. The authors isolated R and S enantiomers of **62b** and **62c**. The R enantiomers were found more active than the racemic mixture. These lead compounds may be used for the design of MAO-B selective inhibitors.



62

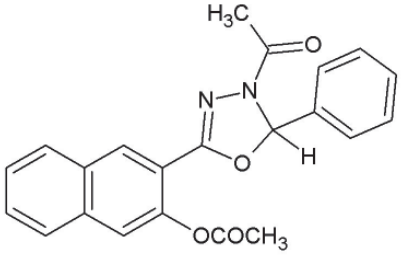
	a	-NO_2
R:	b	-Cl
	c	-Br

The hydrazones derivatived 3-hydroxy-2-naphthoic acid hydrazide gave compounds **63**. Their anticonvulsant activity were investigated against pentylenetetrazole (PTZ) induced convulsions in mice by Doğan and co-workers (95).



63

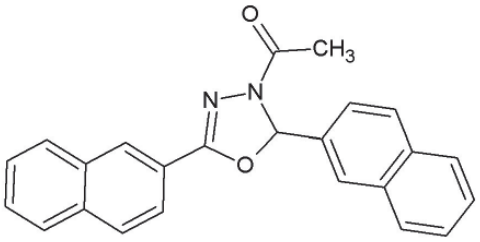
The protection of these compounds was ranged from 0 to 60%. Further research was made on the compound **64** by Şener and co-workers (96).



64

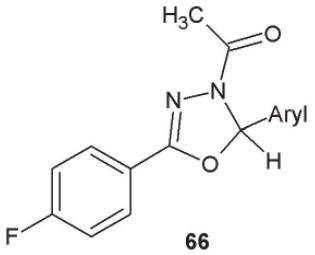
The antioxidant effect of compound **64** was tested in mice brain and liver, compared the antioxidant and anticonvulsive effect with that of valproat (VPA), an antiepileptic drug. Compound **64** and VPA significantly decreased lipid peroxidation levels in brain and liver which were elevated after PTZ administration. Compound **64** and VPA showed a protection on brain and liver tissue against oxidative damage seen at during the seizures.

On the other hand, nonsubstituted analogs of **63, 64** were evaluated for biological activities as tubulin polymerization inhibitors by Hu and co-workers (97).



65

Among these compounds **65** showed the most potent antiproliferative activitiy against HepG2, MFC-7 and B16-F10 cells. Docking simulation study revealed that compounds bearing the naphthyl moiety are promising tubulin inhibitors.



66

Aryl:	4-OH-C_6H_4-	3-OH-4-OCH_3-C_6H_4-	Furan-2-yl

The 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoles were prepared from aryl substituted hydrazones of 4-fluoro benzoic acid hydrazide by Koçyiğit-Kaymakçıoğlu and coworkers (98). **66** can be interesting source for lead compounds for anti-inflammatory research.

CONCLUSION

The number of publications on the 3-acyl-2,3-dihydro-1,3,4-oxadiazole derivatives have increased in the recent years. There are several reports about the synthesis and biological activity of 3-acyl-2,3-dihydro-1,3,4-oxadiazoles. In this manuscript the related articles of 1,3,4-oxadiazolines are reviewed. The future researches may be focused on the 1,3,4-oxadiazolines for the synthesis of active new drugs.

Hidrazid-hidrazonlardan elde edilen 3-açil- 2,3-dihidro-1,3,4-oksadiazol / 3-açil-1,3,4-oksadiazolin türevlerinin sentezi ve biyolojik aktiviteleri

ÖZET: Bu derlemede, 3-açil- 2,3-dihidro-1,3,4-oksadiazol türevlerinin sentezi ve biyolojik aktiviteleri sunulmuştur. 1,3,4-Oksadiazolinler'in karboksilik asit hidrazid-hidrazonlarından hareketle asetik anhidrit veya diğer siklizasyon ajanları kullanılarak yapılan sentez çalışmaları derlememizin temelini oluşturmaktadır.

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