1,3,4-Thiadiazole as Antimicrobial agent: A Review

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ABSTRACT

1,3,4-Thiadiazole nucleus exhibited remarkable pharmacological activities. Literature indicates that compounds having 1,3,4-Thiadiazole nucleus have wide range of pharmacological activities that include antibacterial, antifungal, antitubercular, antiviral, antileishmanial, anti-inflammatory, analgesic, CNS depressant, anticonvulsant, anticancer, antioxidant, antidiabetic, molluscicidal, antihypertensive, diuretic. The present review provides a broad view of the antimicrobial activity possessed by compounds having a 1,3,4-Thiadiazole nucleus.

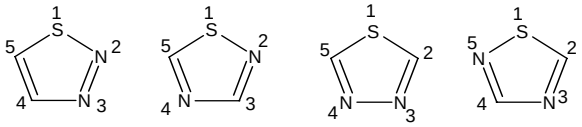
KEY WORDS: Review; 1,3,4-Thiadiazole; Chemistry; Antimicrobial Activity

INTRODUCTION

One of the main objectives of organic and medicinal chemistry is the design, synthesis and production of molecules having value as human therapeutic agents. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures [1], with heterocyclic structures receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry [2]. There are numerous biologically active molecules with five membered rings, containing three hetero atoms. Thiadiazole is an important scaffold known to be associated with several biological activities (Fig.1.).

CHEMISTRY OF 1,3,4-THIADIAZOLE

Thiadiazole is five membered heterocyclic compound. It contains two nitrogen atoms and one sulphur atom as hetero atoms. Thiadiazole may be of 1,2,3- thiadiazoles (a) ; 1,2,4-thiadiazole (b) ; 1,3,4-thiadiazole (c) and 1,3,5-thiadiazole (d).



(a) (b) (c) (d)

Fig.1. Structure of Thiadiazole

ANTIMICROBIAL PROPERTIES

S. Talath and A.K. Gadad synthesized a series of 7-[4-(5-amino-1,3,4-thiadiazole-2-sulfonyl)]-1-piperazinyl fluoroquinolonic derivatives [1]. The compounds were evaluated for their *in vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria. The antibacterial data of the tested *N*-sulfonylfluoroquinolones indicated that all the synthesized compounds showed better activity against Gram-positive bacteria *S. aureus, E.*

faecelis, Bacillus sp. compared to reference drugs. The MIC values of tested derivatives connotes that the sparfloxacin and gatifloxacin derivatives were most active against the tested Gram-positive bacterial strains. All the tested compounds showed poor activity against the Gram-negative bacteria[3].

Lenuta Profire *et al.* synthesized new 1,3,4-thiadiazole (2) compounds containing a *D,L*-methionine moiety. The potential antimicrobial effects of the synthesized compounds were investigated using the *Staphylococcus aureus* ATCC 25923, *Bacillus antracis* ATCC 8705, *Bacillus cereus* ATCC 10987, *Sarcina lutea* ATCC 9341 and *Escherichia coli* ATCC 25922 strains. The newly synthesized compounds exhibited promising activities against *Bacillus anthracis* and *Bacillus cereus* [4].

A. Foroumadi *et al.* synthesized a series of 5-(nitroaryl)-1,3,4-thiadiazoles (3-4) bearing certain sulfur containing alkyl side chain similar to pendent residue in tinidazole molecule and evaluated against *Helicobacter pylori* using disk diffusion method. The synthesized compounds were also evaluated for their antibacterial, antifungal and cytotoxic effects. Study of the structure–activity relationships of this series of compounds indicated that both the structure of the nitroaryl unit and the pendent group on 2-position of 1,3,4-thiadiazole ring dramatically impact the anti-H. pylori activity. While compound containing 2-[2 (ethylsulfonyl)ethylthio]-side chain from nitrothiophene series was the most potent compound tested against clinical isolates of *H. pylori*, however, nitroimidazoles were found to be more promising compounds because of their respectable anti-H. pylori activity besides less cytotoxic effects [5].

A. Foroumadi *et al.* synthesized a series of *N*-(5-benzylthio-1,3,4-thiadiazol-2-yl) and N-(5-benzylsulfonyl-1,3,4-thiadiazol-2-yl) derivatives of piperazinyl quinolones [5] and evaluated for antibacterial activity against Gram-positive and Gram-negative microorganisms. Some of these derivatives exhibit high activity against Gram-positive bacteria; *Staphylococcus aureus* and *Staphylococcus epidermidis*, comparable or more potent than their parent *N*-piperazinyl quinolones norfloxacin and ciprofloxacin as reference drugs. The SAR of this series indicates that both the structure of the benzyl unit and the S or SO_2 linker dramatically impact antibacterial activity [6].

S. Tehranchian *et al.* synthesized a series of 1-[1,3,4-thiadiazol-2-yl]-3-methylthio-6,7-dihydrobenzo[*c*]thiophen-4(5*H*)ones [6] and tested for *in vitro* antimicrobial activity. Some of these compounds exhibited a good activity against *Staphylococcus aureus*, *S. epidermidis* and *Bacillus subtilis* [7].

L. M. Thomasco *et al.* reported that Replacement of the morpholine C-ring of linezolid with a 1,3,4-thiadiazolyl ring leads to oxazolidinone analogues (7) having potent antibacterial activity against both gram-positive and gram-negative organisms. Conversion of the C5 acetamide group to a thioacetamide further increases the potency of these compounds [8].

A. A. Kadi *et al.* synthesized 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazole derivatives (8). These compounds were tested for *in vitro* activities against a panel of Gram-positive and Gram-negative bacteria and the yeast-like pathogenic fungus *Candida albicans*. Several derivatives produced good or moderate activities particularly against the

tested Gram-positive bacteria *Bacillus subtilis*. Some compounds displayed marked antifungal activity against *C. albicans* [9].

J. Mirzaei *et al*. synthesized N-[5-(5-nitro-2-heteroaryl)-1,3,4-thiadiazol-2-yl]thiomorpholines and some related compounds (9-13) and evaluated for *in vitro* anti-Helicobacter pylori activity. The anti-H. pylori activity of target compounds along with commercially available antibiotics such as metronidazole and amoxicillin was evaluated by comparing the inhibition zone diameters determined by the paper disc diffusion bioassay. It is evident that most compounds still had strong activity at 4 and 2 mg/ disc (average of inhibition zone >20 mm) while metronidazole had little activity at these doses. Nitrofuran analog containing thiomorpholine S,S-dioxide moiety was the most potent compound tested [10].

A. Foroumadi *et al.* synthesized a series of *N*-[5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole-2-yl] and *N*-[5-(nitrophenyl)-1,3,4-thiadiazole-2-yl] piperazinyl quinolone derivatives (14) and evaluated for *in vitro* antibacterial activity against some Gram-positive and Gram-negative bacteria. The antibacterial data revealed that all nitroimidazole derivatives showed interesting activity against tested Gram-positive bacteria (minimum inhibitory concentration, MIC=0.008-0.03 µg/ml) while they did not show good activity against Gram-negative organisms. Despite the significant activity of nitroimidazole series, all nitrophenyl analogues were inactive against both Gram-positive and Gram-negative bacteria. Among all of the tested compounds, ciprofloxacin derivative in nitroimidazole series exhibited excellent activity against *Staphylococcus aureus* and *Staphylococcus epidermidis* (MIC=0.008 µg/ml) [11].

S. Jazayeri *et al.* synthesized a number of gatifloxacin analogues (15) containing a nitroaryl-1,3,4-thiadiazole moiety attached to the piperazine ring at C-7 position and evaluated as antibacterial agents against a panel of Gram-positive and Gram-negative bacteria. Among synthesized compounds, nitrofuran analog exhibited more potent inhibitory activity against Gram-positive bacteria including *Staphylococcus epidermidis*, *Bacillus subtilis Enterococcus faecalis* and *Micrococcus luteus*, with respect to other synthesized compounds and reference drug gatifloxacin [12].

A. Foroumadi *et al.* synthesized a series of *N*-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-yl]piperazinyl quinolones (16) and evaluated for *in vitro* antibacterial activity against some Gram positive and Gram-negative bacteria. The compounds had strong and better activity against tested Gram-positive organisms than the reference quinolones such as ciprofloxacin, norfloxacin and enoxacin. However, all three compounds were nearly inactive against Gram-negative bacteria. Compound ciprofloxacin analogue was the most active compound against Gram-positive bacteria (MIC=0.008-0.015 µg mL^{-1}) [13].

A.K. Gadad *et al.* synthesized 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide derivatives (17-18). Compounds showed a high degree of antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus* comparable to that of sulfamethoxazole and Norfloxacin. However, they were found to show

moderate activity against *Salmonella typhi, Pseudomonas aeruginosa* and *Pneumococci* [14].

Kalluraya B. *et al.* synthesized a new series of 6/8-substituted-3-(3-substituted anilinomethyl-1,2,4-triazole[3,4-b]-1,3,4-thiadiazol-6-yl)-2-chloroquinolines (19). The newly synthesized compounds were screened for their antibacterial and antifungal activity. Most of the compounds showed activity comparable with that of the standard drug [15].

A. Demirbas *et al.* synthesized 4-Amino-2-[(5-arylamino-4,5-dihydro-1,3,4-thiadiazol-2-yl)methyl]-5-(4-methylphenyl)-2,4-dihydro-3H-1,2,4-triazol-3-ones (20). They were screened for their antimicrobial activities. Some compounds showed good activity against a variety of microorganisms [16].

M. R. Banday and A. Rauf synthesized a series of new 2-benzamide-5-alkenyl/hydroxyalkenyl-1,3,4-thiadiazoles (21) from fatty acid hydrazides. The bioassay results indicate that some compounds have good antibacterial activity [17].

R.S. Lamani *et al.* synthesized Novel methylene bridged benzisoxazolyl imidazo[2,1-b][1,3,4]thiadiazoles (22). All the compounds were screened for their antibacterial and antifungal activities. Some of the compounds displayed very good antibacterial and antifungal activity [18].

A.A. Bekhit *et al.* synthesized thiadiazolyl (23) and thiadiazolinyl derivatives (24) of 1*H*-pyrazole. Antimicrobial activity revealed that some compounds showed comparable antibacterial activity to that of ampicillin against *Escherichia coli*, while some compounds possessed about half the activity of ampicillin against *Staphylococcus aureus* [19].

V. Mathew *et al.* synthesized Several 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadizoles (25) by the condensation of 4-amino-3-aryl/aralkyl substituted-5-mercapto-1,2,4-triazoles with various substituted aromatic/hetero aromatic acids through a single step reaction. Synthesized triazolo thiadiazoles investigated for their antibacterial, antifungal, anti-inflammatory and analgesic activities. Some of the tested compounds showed moderate antimicrobial activity against various tested bacterial and fungal strains [20].

V. Mathew *et al.* synthesized several 3,6-disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole and their dihydro analogues (26). Synthesized compounds are studied for their antibacterial, antifungal, anti-inflammatory and analgesic activities. The antimicrobial results showed that some of the compounds are active against both Gram-positive and Gram-negative bacteria. Compounds also showed good inhibition of growth of the yeast-like *Candida albicans* and the fungi *Aspergillus niger* [21].

H. N. Dogan *et al.* synthesized two new series of 2,5-disubstituted-1,3,4-thiadiazoles (27) for their possible anticonvulsant, antibacterial and antifungal activities. Antimicrobial tests showed that the MIC value of one compound against *Pseudomanas aeruginosa* was equal to that of penicillin [22].

T. Karabasanagouda *et al.* synthesized new 6-aryl-3-{(4-substituted phenoxy) methyl}-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles (28). All the title compounds were subjected to *in vitro* antibacterial

testing against four pathogenic strains and antifungal screening against three fungi. Results indicate that some of them exhibited promising activities and they deserve more consideration as potential antimicrobials [23].

S.N. Swamy *et al.* synthesized two series of 4,6-disubstituted 1,2,4-triazolo-1,3,4-thiadiazole derivatives (29). The compounds were checked for their efficacy as antimicrobials *in vitro*. Most of the compounds showed significant inhibition against all the strains tested, when compared to standard drugs [24].

N. Demirbas *et al.* synthesized some new 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4]triazole derivatives (30). Most of the compounds have shown antimicrobial activity against one or more microorganism [25].

P. Mishra *et al.* synthesized a series of novel 2-Methyl-3-(1'3'4'-Thiadiazolyl)-4-(3H) Quinazolinones (31). The designed compounds were screened *in vitro* for antibacterial activity on *Staphylococcus aureus*, *Bacillus subtilis*, and *Escherichia coli*. Antifungal activity was screened against *Candida albicans*, *Aspergillus niger*, and *Curvularia lunata*. Synthesised compounds exhibited both antibacterial and antifungal activity [36].

F. Liu *et al.* synthesized novel sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-thiadiazole moiety (32). The bioassay results showed that title compounds possess high antifungal activities with EC_{50} values ranging from 19.91 to 63.97 µg/mL [27].

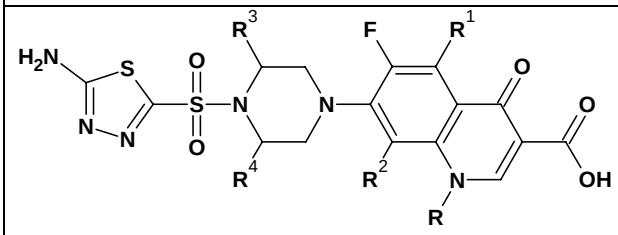
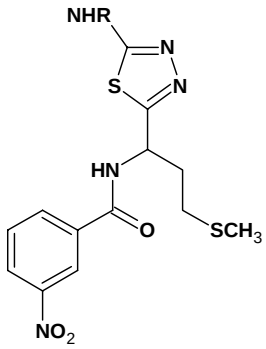
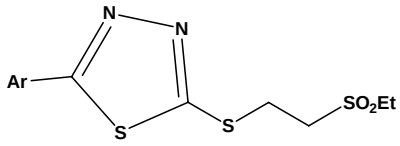
C.J. Chen *et al.* synthesized 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-thiadiazole derivatives (33). The compounds have been shown to be fungicidally active. Title compounds can inhibit mycelia growth by approximately 50% (EC_{50}) at 2.9-93.3 µg/mL in vitro against 10 kinds of fungi [28].

A.R. Jalilian *et al*. synthesized substituted 4,5-dihydronaphtho[1,2-*d*][1,2,3]thiadiazoles (34). Compounds showed significant antifungal activity against *Cryptococcus neoformans* [29].

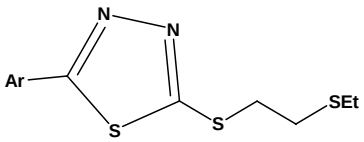
Atul K. Srivastava *et al.* synthesized 2,6-Diaryl-1,3,4-thiadiazolo[3,2-b]-s-triazine-5,7-dithiones (35) and tested *in vitro* for their antifungal activity against two fungal species *Colletorichum falcatum* and *Fusaruium oxysporum* [30].

D. Jagadeesh Prasad *et al.* synthesized a series of substituted triazolothiadiazoles (36-37). The synthesized compounds were screened for their antimicrobial activities. The preliminary results revealed that some of the compounds exhibited promising antimicrobial activities [31].

Table 1- Antimicrobial compounds containing 1,3,4-thiadiazole scaffold

Molecular structure	Activity/Usage	Ref.
 (1)	Antibacterial	3
R=  , C_2H_5- R^1= H, $NHCOCH_3$, NH_2 R^2= H, F, OCH_3 R^3= H, CH_3 R^4= H, CH_3		
 (2)	Antibacterial	4
R= $-CH_3$, $-C_6H_5$, $-C_6H_4-CH_3$, $-C_6H_4$-Br, $-CH_2-CH=CH_2$		
 (3)	Antibacterial	5
Ar = 5-nitrothiophene-2-yl; 5-nitrofuran-2-yl;		

1-methyl-5-nitroimidazol-2-yl; nitrophenyl

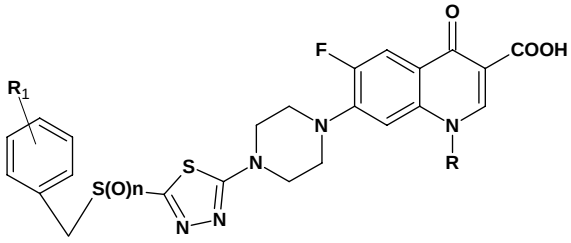


Antibacterial 5

(4)

Ar = 5-nitrothiophene-2-yl; 5-nitrofuran-2-yl;

1-methyl-5-nitroimidazol-2-yl; nitrophenyl



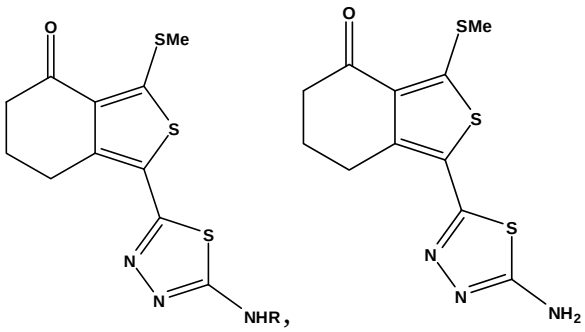
Antibacterial 6

(5)

R= Ethyl, Cyclopropyl

R_1= H, 2, 3, or 4-NO_2

n= 0, 2

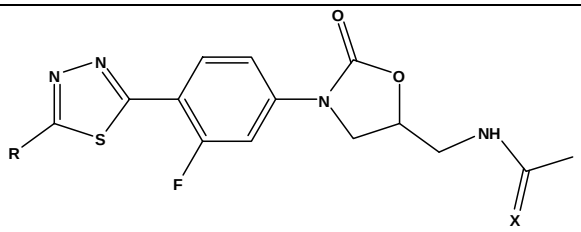


Antibacterial 7

(6)

R= Me, Et, *n*-Bu, cyclohexyl, 4-$NO_2C_6H_4$,

4-$OCH_3C_6H_4$, 4-FC_6H_4



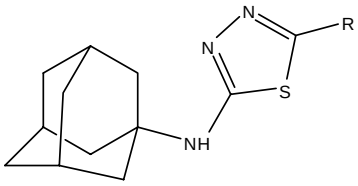
Antibacterial 8

(7)

R= H, OH, CH_3, C_2H_5, FCH_2, CH_3OCH_2,

$AcOCH_2$,-$COOC_2H_5$ etc.

X= O, S



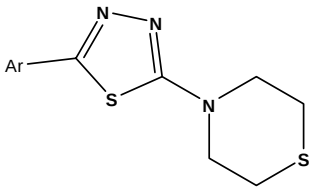
Antibacterial and Antifungal 9

(8)

R= C_6H_5-, 4-FC_6H_4-, 4-ClC_6H_4-, 4-BrC_6H_4-,

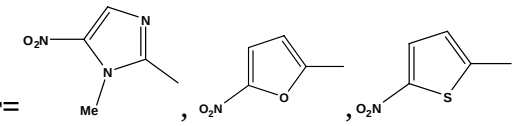
4-$NO_2C_6H_4$-, 3,4-$(OCH_3)_2C_6H_3$-, 3,5-$(NO_2)_2C_6H_3$-,

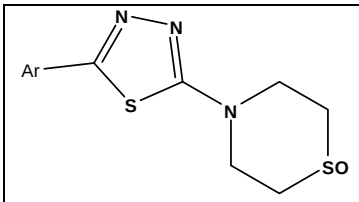
2-Cl,4-$NO_2C_6H_3$-, 2-Thienyl, 1-Adamantyl



Antibacterial 10

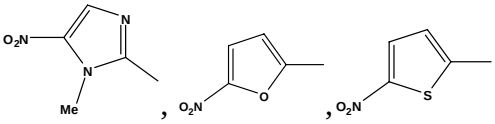
(9)

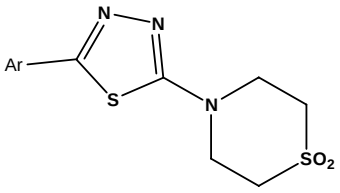
Ar= 



Antibacterial 10

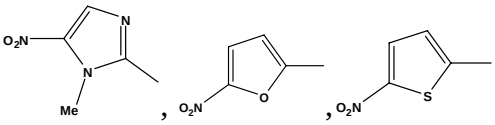
(10)

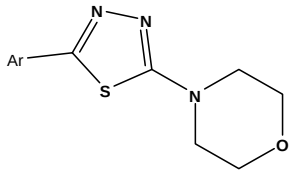
Ar= 



Antibacterial 10

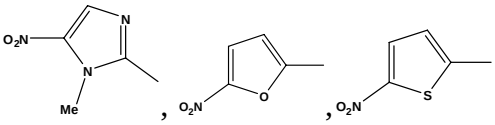
(11)

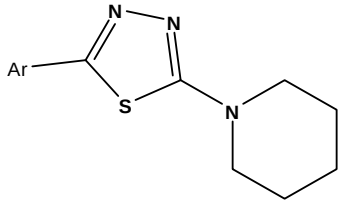
Ar= 



Antibacterial 10

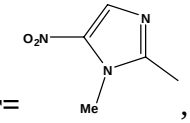
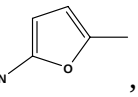
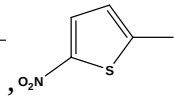
(12)

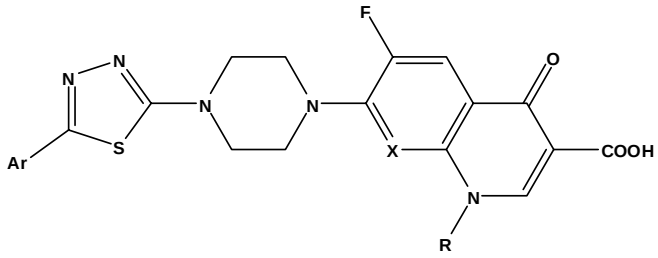
Ar= 



Antibacterial 10

(13)

Ar=  ,  , 



Antibacterial 11

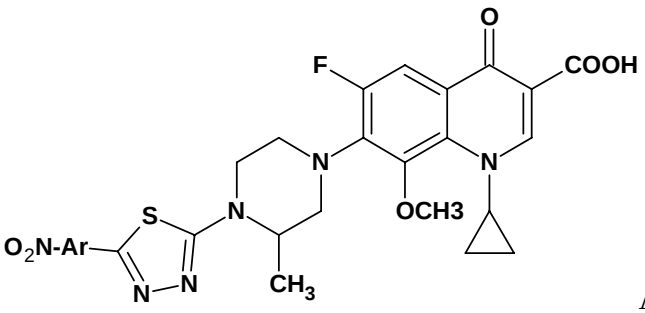
(14)

X= CH, N

R= Cpr, Et

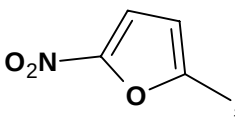
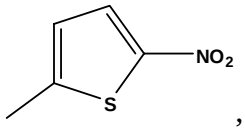
Ar= 1-methyl-5-nitro-2-imidazolyl,

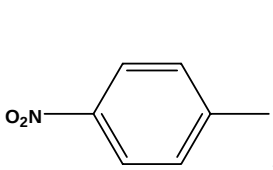
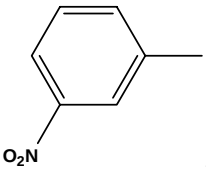
2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl

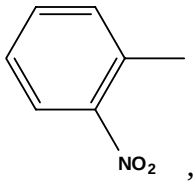
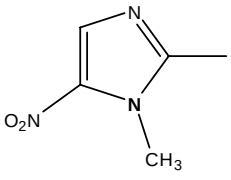


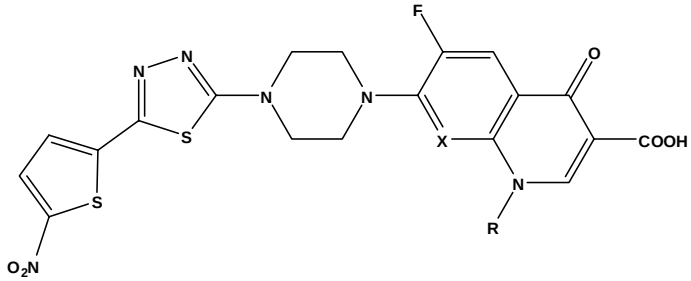
Antibacterial 12

(15)

Ar-NO_2=  ,  ,

 ,  ,

 , 

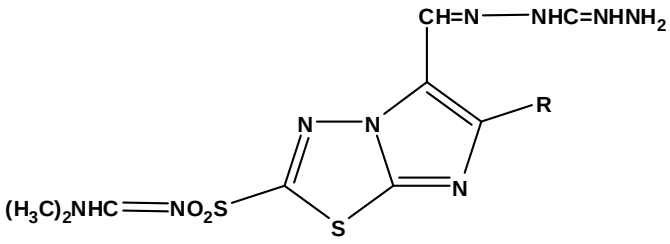


(16)

Antibacterial 13

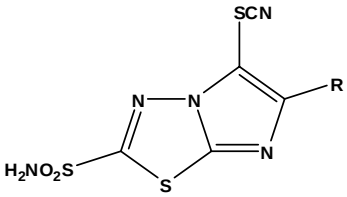
R= Cpr, Et

X= CH, N



(17)

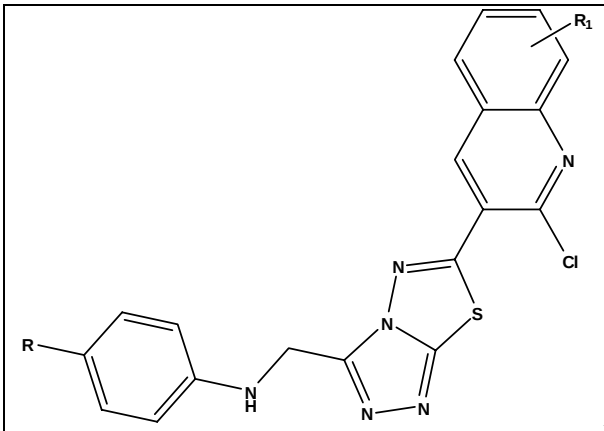
Antibacterial 14



(18)

Antibacterial 14

Where R= C_6H_5-, p-BrC_6H_4-, p-ClC_6H_4-, p-$CH_3C_6H_4$-, p-$NO_2C_6H_4$-, 3-coumarinyl

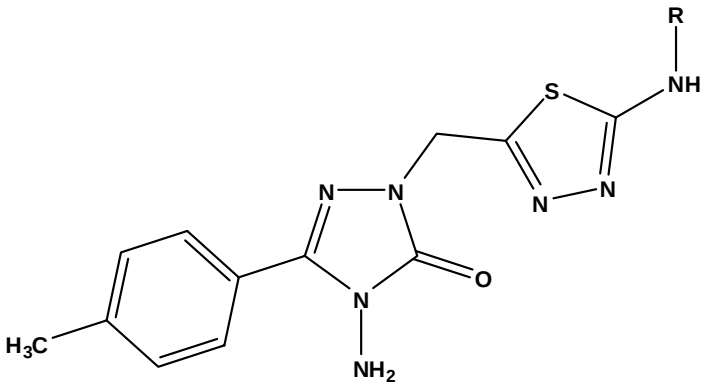


Antibacterial and Antifungal 15

(19)

R= H, Cl, CH_3, OCH_3

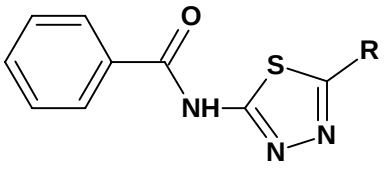
R_1= H, 6-Methyl, 8-Methyl, 6-Methoxy



Antibacterial 16

(20)

R=C_6H_5, *p*-FC_6H_4, *p*-$OCH_3C_6H_4$



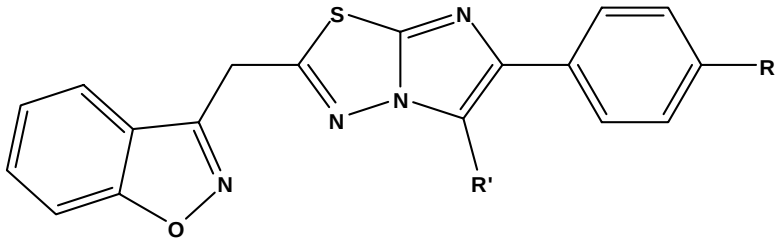
Antibacterial 17

(21)

R= CH_2=$CH(CH_2)_8$, $CH_3(CH_2)_7CH$=$CH(CH_2)_7$,

$CH_3(CH_2)_5CH(OH)CH_2CH$=$CH(CH_2)_7$,

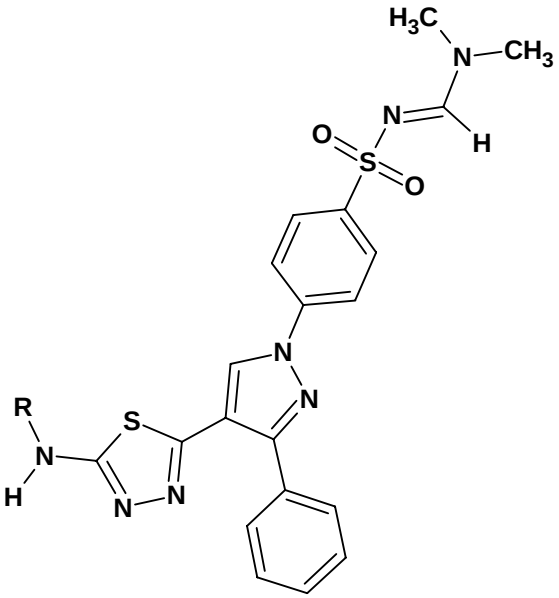
$CH_3(CH_2)_4CH$=$CH(CH_2)_2CH(OH)(CH_2)_7$



(22) Antibacterial and Antifungal 18

R'= Br, NO, SCN

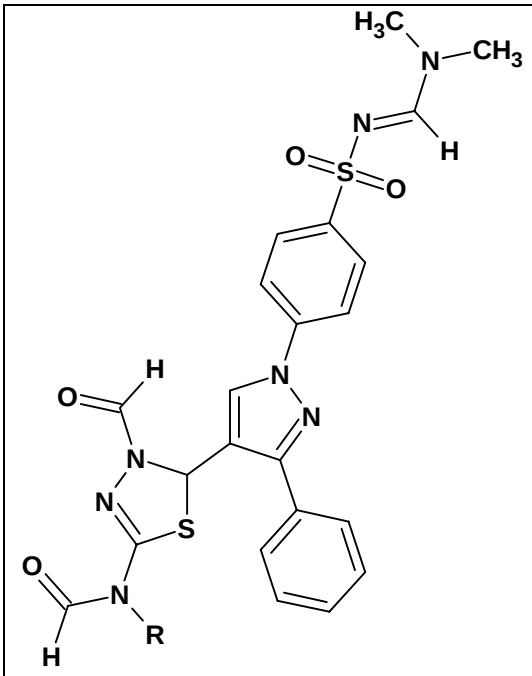
R= H,-Cl, NO_2, Br, OMe, 3-Coumarinyl



Antibacterial 19

(23)

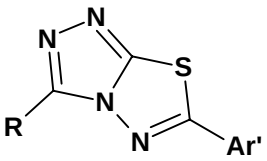
Where R= C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4



Antibacterial 19

(24)

Where R= C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4



Antibacterial and Antifungal 20

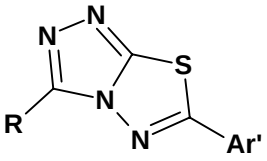
(25)

R= aryl/alkyl

Ar'= 2-Phenyl-4-quinolinyl, 2-Methyl-4-quinolinyl,

4-Quinolinyl, 6-Dihydroxy-4-pyridinyl,

2-Chloro-4-pyridinyl, 2-Flouro-4-pyridinyl



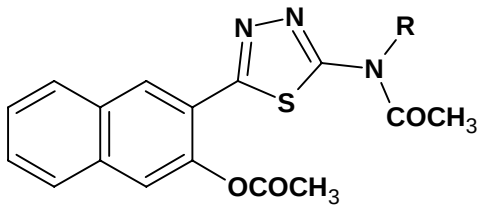
Antibacterial and Antifungal 21

(26)

R= 2-Chloro-5-methoxy phenyl, 3,4-Dimethoxy benzyl,

2-Methyl-3-furanyl

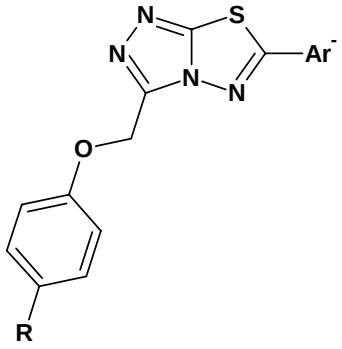
Ar'= 2-Phenyl-4-quinolinyl, 2-Methyl-4-quinolinyl,
4-Quinolinyl, 6-Dihydroxy-4-pyridinyl, 2-Chloro-4-pyridinyl,
2-Flouro-4-pyridinyl, 5-Methoxy-3-indolyl methyl,
5-Methoxy-2-methyl-3-indolyl methyl, 3-Indolyl methyl



Antibacterial and Antifungal 22

(27)

R= ethyl, phenethyl, phenyl, p-bromophenyl,
p-chlorophenyl, p-fluorophenyl, m-fluorophenyl,
p-methoxyphenyl, p-methylphenyl,
m-trifluoromethylphenyl.

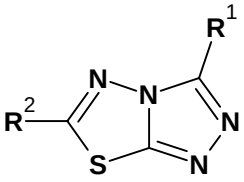


Antibacterial and Antifungal 23

(28)

R= SCH_3, SC_2H_5, SO_2CH_3

Ar= C_6H_5, 2-ClC_6H_4, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-$NH_2C_6H_4$ etc.

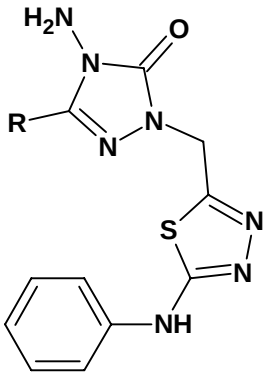


Antibacterial and Antifungal 24

(29)

R^1= CH_3, C_2H_5, C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4

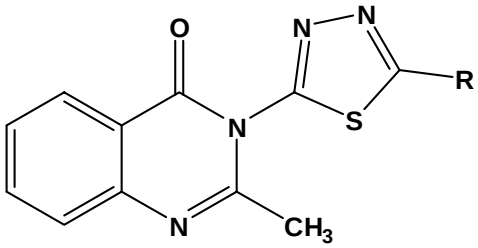
R^2= 2-ClC_6H_4 , (**C_3H_7)(C_2H_5)CH-**



Antibacterial and Antifungal 25

(30)

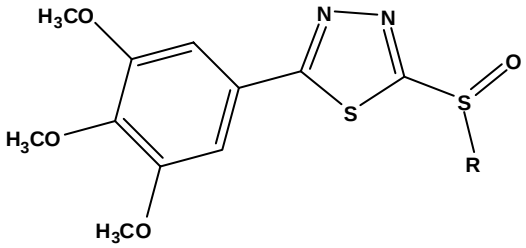
R= -CH_3, -C_2H_5, -C_6H_5, -$CH_2C_6H_5$, -C_3H_7, -$CH_2C_6H_4Cl$



Antibacterial 26

(31)

R=-CH_3, -C_3H_7, -C_6H_5, -C_4H_9, -C_6H_4(*p*-Cl), -C_6H_4(*p*-CH_3)

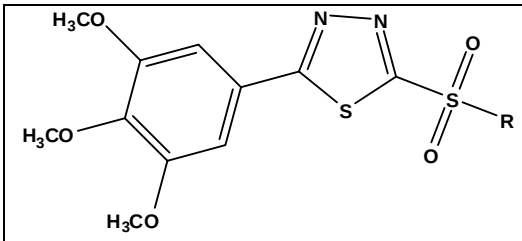


Antibacterial and Antifungal 27

(32)

R= $C_6H_5CH_2$-, $CH_3CH_2COOCH_2$-, $OCH_3C_6H_4CH_2$-,

$NO_2C_6H_4CH_2$-, $FC_6H_4CH_2$-, -$CH_2CH_2OCH_2CH_3$



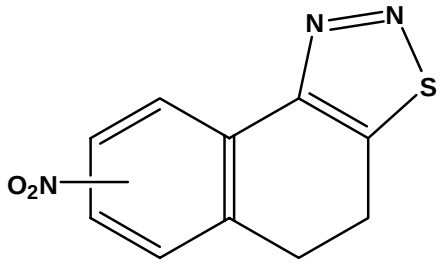
Antibacterial and Antifungal 28

(33)

R= CH_2=CH-CH_2-, 4-$NO_2C_6H_4CH_2$-, $ClC_5H_3NCH_2$-,

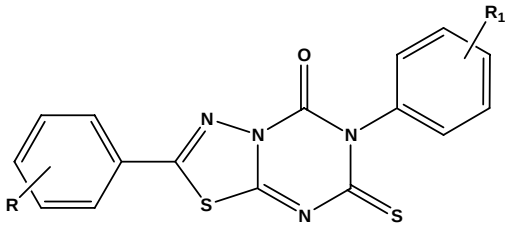
$C_6H_5CH_2$-, $CH_3CH_2CH_2$-, 4-$ClC_6H_4CH_2$-,

$CH_3CH_2COOCH_2$-,3-$OCH_3C_6H_4CH_2$- etc.



Antibacterial and Antifungal 29

(34)

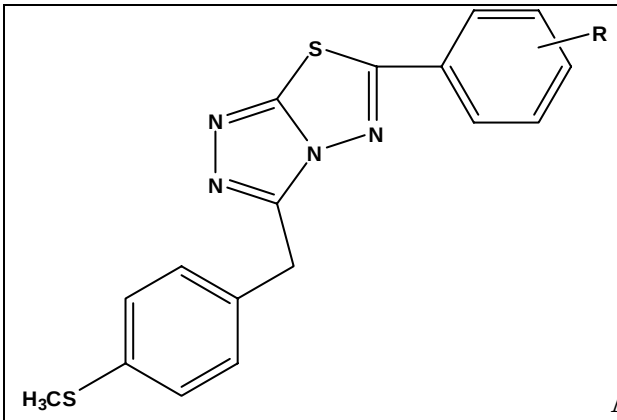


Antibacterial and Antifungal 30

(35)

R= 2-Cl, 4-Cl, 4-CH_3, 4-OCH_3, 4-NO_2

R_1= H, 2- CH_3, 4-CH_3

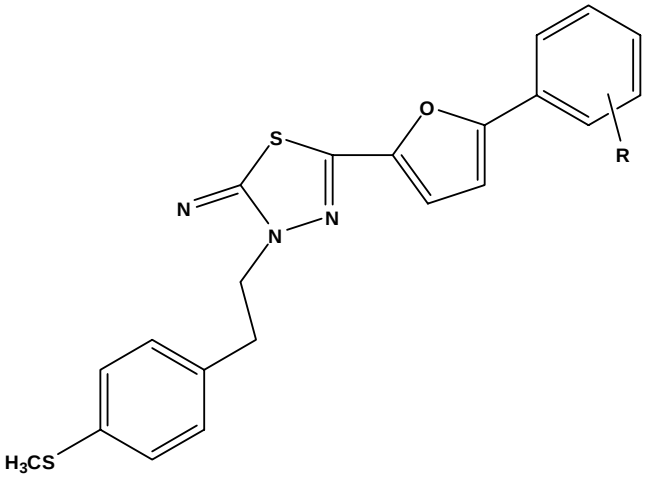


Antibacterial and Antifungal 31

(36)

R=2,3,4-Cl_3-C_6H_2-, 4-OH-C_6H_4, 4-Br-C_6H_4,

4-F-C_6H_4, 4-NO_2-C_6H_4, C_6H_4-CH_2- etc.



Antibacterial and Antifungal 31

(37)

R=2,3,4-Cl_3-C_6H_2-, 4-OH-C_6H_4, 4-Br-C_6H_4,

4-F-C_6H_4, 4-NO_2-C_6H_4, C_6H_4-CH_2- etc.

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