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Review on Synthetic Strategies for 1,2,4-Thiadiazines and its Biological Activity

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Abstract: *The thiadiazines compound contains one sulphur and two nitrogen atoms at varied positions in six-membered rings. Thiadiazines possess an N-C-S linkage that is believed to be very useful in medicinal and pharmaceutical chemistry. Thiadiazine derivatives shows wide variety of medicinal activities like antibacterial, anti-inflammatory, fungicidal, anticancer, anti-tuberculosis, antiepileptic, antimalarial, antioxidant, antidiabetic. Based on position of nitrogen and sulphur thiadiazine are named as 1,2,3-thiadiazine, 1,2,4-thiadiazine, 1,2,5-thiadiazine, 1,2,6-thiadiazine, 1,3,4-thiadiazine and 1,3,5-thiadiazine. Sulphur containing drugs are known as sulpha drugs. This review aims to summarize recent synthetic strategies and biological activities of 1,2,4-thiadiazines derivatives.*

Keywords: 1,2,4-thiadiazine, Antidiabetic, Anticancer, anti-tuberculosis

I. INTRODUCTION

Based on position of nitrogen and sulphur thiadiazine are named as 1,2,3-thiadiazine, 1,2,4-thiadiazine, 1,2,5-thiadiazine, 1,2,6-thiadiazine, 1,3,4-thiadiazine and 1,3,5-thiadiazine. During the last decades various thiadiazine derivatives have been developed. Most of the work found on 1,3,4- and 1,3,5-thiadiazine derivatives and very less new derivatives of 1,2,4 thiadiazine and 1,2,5-thiadiazine are found due to their ease of formation and less stability. 1,2,4-Thiadiazine derivatives shows wide variety of medicinal activities like antibacterial, AMPA receptor [1], anti-hepatitis[2], anti-HIV [3], anticancer[4], anti-tuberculosis[5], antidiabetic[6], anti-inflammatory, [7] fungicidal, . This review mainly aims to summarize recent synthetic strategies and biological activities of 1,2,4-thiadiazines derivatives.

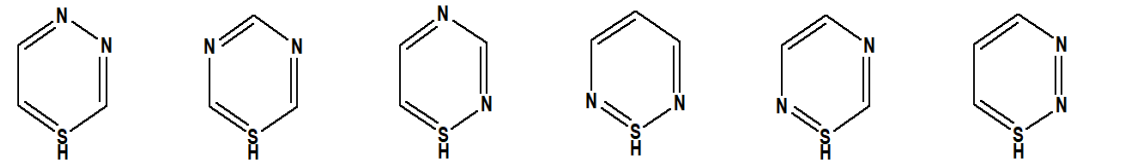

Fig (1) Structures of Thiadiazine derivatives

Synthetic Strategy and Biological Activity:

In 1995 Pascal de Tullio et.al synthesized pyridine analogues of the 1,2,4-benzothiadiazine 1,1-dioxide **(2,3,4,5)** bearing nitrogen at different position from the amino pyridyl sulphonamides **(1)** on treatment with mixed acetic-formic anhydride or with triethyl orthoformate.

The author observed that newly synthesized pyridinyl derivatives of 1,2,4-benzothiadiazine 1,1-dioxide are closely related to potassium channel opener diazoxide.[7]

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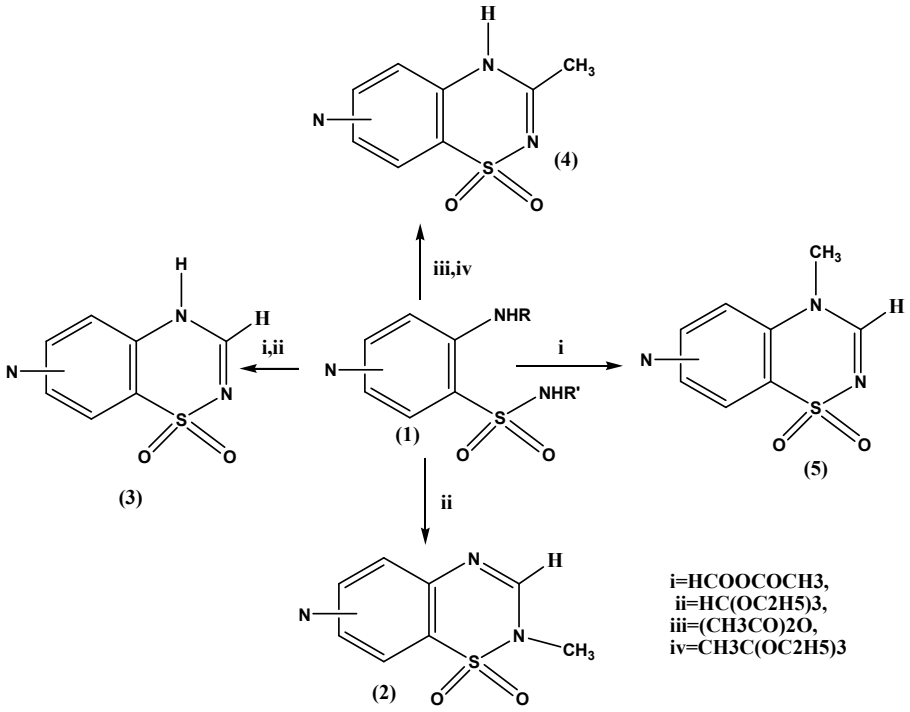

Scheme 1. Pyridinyl derivatives of 1,2,4-benzothiadiazine

In1998 Esther Arranz et.al synthesized a new series of 1,1,3-Trioxo 2H,4H-thieno [3,4-e] thiadiazine derivatives **(10)** which shows non-nucleoside transcriptase inhibitors selectively block HIV type I replication. The derivatives are synthesized by cyclization of the sulfamoyl hetero carboxylic derivatives (**6)** through a Curtius reaction followed by alkylation of the intermediate *N*-2 substituted thiadiazines to give the target *N*-2, *N*-4 di-alkyl hetero [1,2,4]-thiadiazines.

The author observed that introduction of halogenated benzyl substituents at N_2 position increase ability of inhibition of HIV-1 reverse transcriptase with 10 folds. [8]

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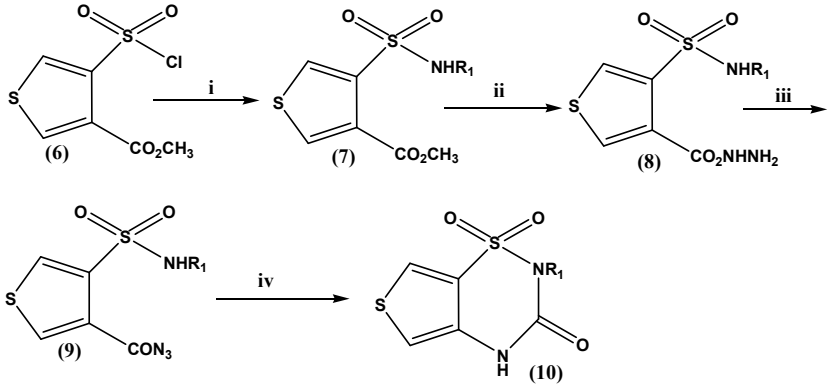
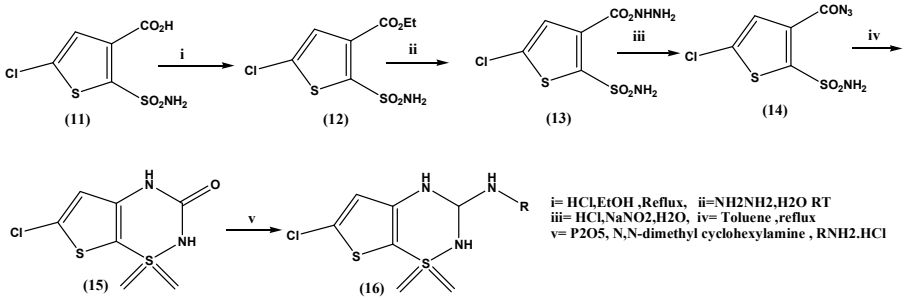


Scheme 2

In 2002 Flemming E. Nielsen et.al synthesized 6-Chloro-3-alkylamino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide derivatives (16) from 2-(*tert*-butyl amino) sulfonyl-5-chlorothiophene-3-carboxylic acid **(11)** which is converted into ester **(12)** and hydrazide **(13)** followed by Curtius reaction gives target compound **(16).**

The author observed that 6-Chloro-3-(1-methylcyclobutyl) amino-4H-thieno[3,2-e]-1,2,4-thiadiazine 1,1-dioxide is 1000 times more potent than reference compound diazoxide against inhibition of insulin in rat cells. The synthesised derivatives show anti-diabetic activity in vitro.[9]



Scheme 3

In 2005 Salvador Vaga synthesizes series of Synthesis of Oxazolo [3,2-b] hetero [1,2,4] thiadiazine 1,1-Dioxides.Compound **(17)** on treatment with allyl bromide in presence sodium hydride and N,N-dimethyl formamide gives allyl derivatives**(18)** which on further strategic reaction with N-bromo succinimide following Baldwins rule form Oxazolo [3,2-b] hetero [1,2,4] thiadiazine 1,1-dioxides **(20).[10]**

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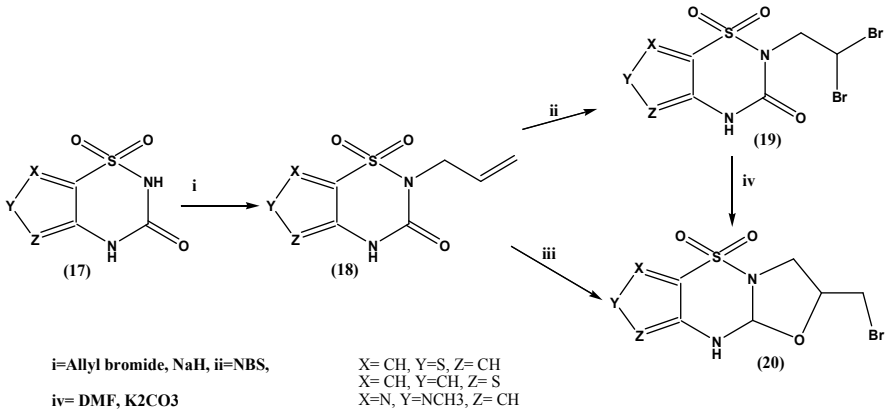
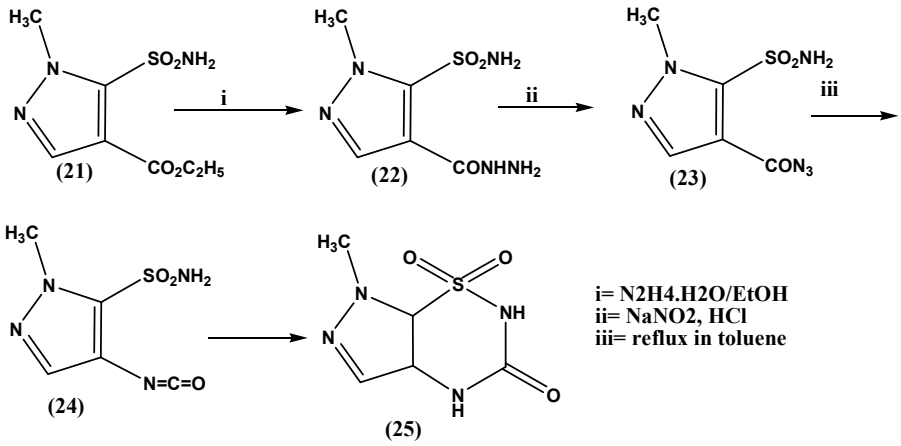


Scheme 4

In 2006 Xin Yong Liu et. al. synthesized series of 2- and 4-substituted pyrazolo [4,5] [1,2,4] thiadiazines **(25)** from hydrazinolysis of the ethyl-1-methyl-5-sulfamoyl pyrazole-4-carboxylate **(21)** which on refluxing with hydrazine in ethanol form hydrazide **(22).** This on further reaction with sodium nitrate and hydrochloric acid at 10^0 C form azide **(23)** which on Curtius reaction gives isocyanate **(24)** followed by refluxing with Toluene gives final product **(25).**

The author seen some of the derivative's form shows inhibition of HIV-1.[11]



Scheme 5

In 2007 Jozef Zienkiewicz et.al. synthesized a novel 4-H benzo 1,2,4-thiadiazine from condensation of aniline and benzonitrile followed by oxidative cyclization.[12]

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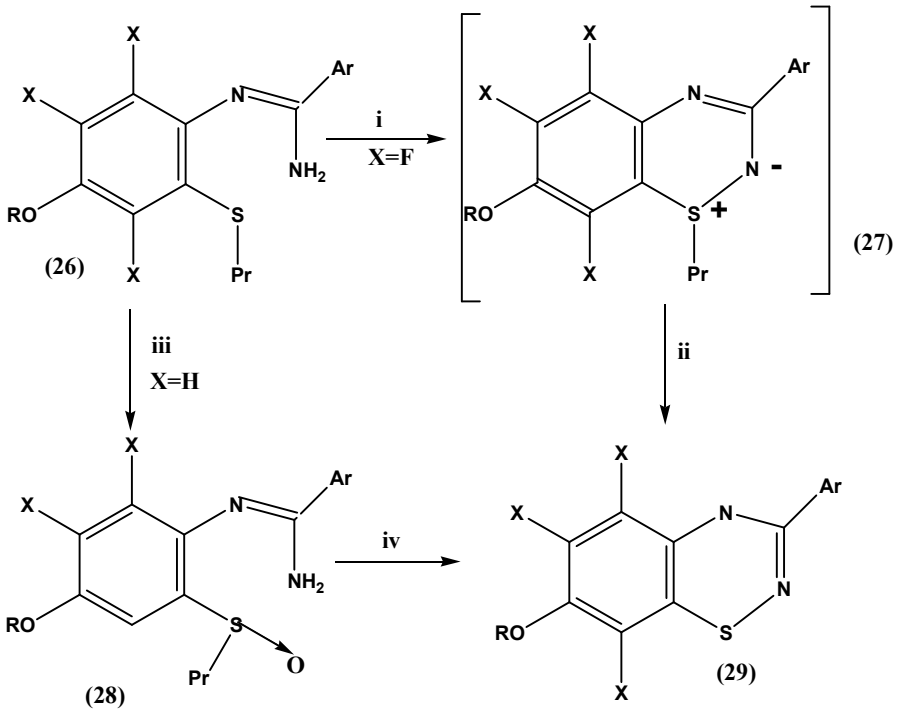

i=NCS, 5%NaOH, ii=Toluene reflux,
iii= NaIO4, iv= PhCl reflux 12%

Scheme 6

In 2011, Artem Cherepakha synthesized 1,2,4-benzothiadiazine-1,1-dioxides (33) in one pot reaction without catalyst, by the condensation of o-halo-substituted benzene sulfonyl chlorides (30) with 2-aminopyridines and amidines (31).[13]

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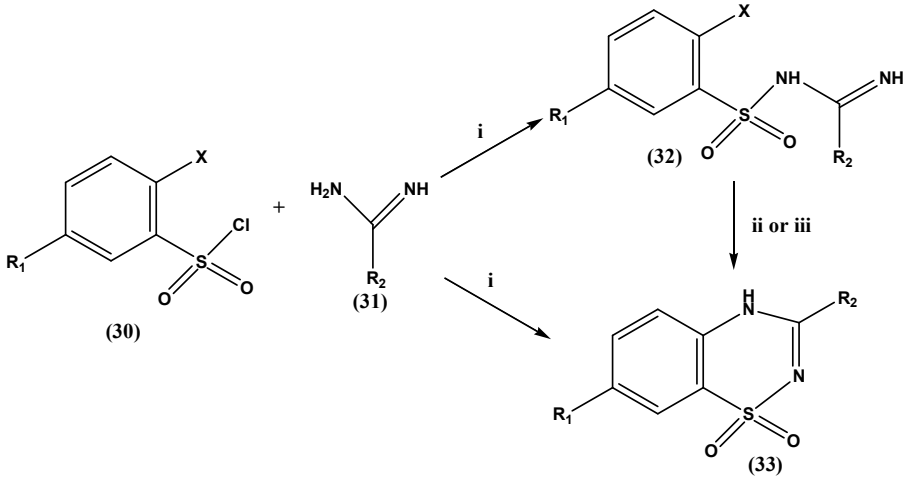
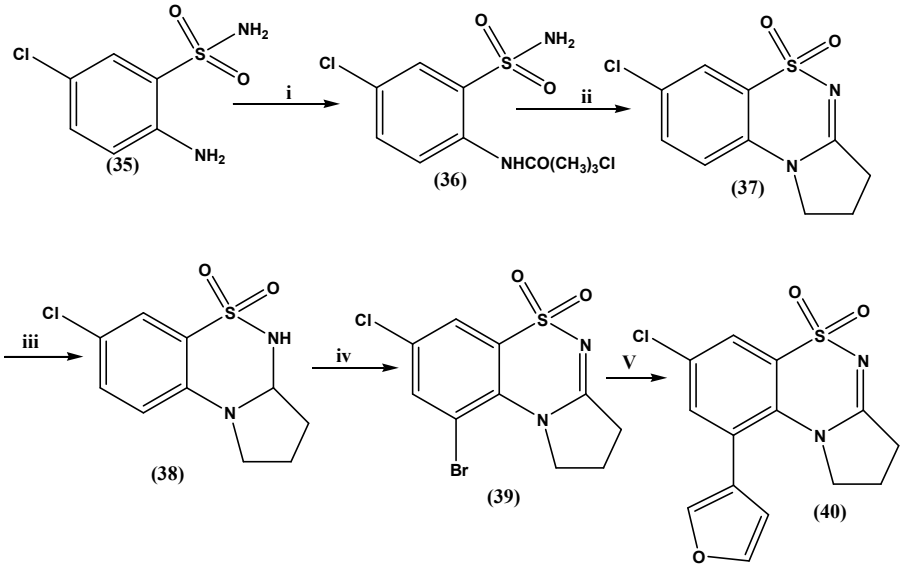


Scheme 7

In 2014 Marina Maria Carrozzo et.al. stereo selectively synthesized 7-chloro-9-(furan-3-yl)-2,3,3a-4-tetrahydro1-H-benzo [e] pyrrolo[2,1-c] [1,2,4] thiadiazine 5,5-dioxide **(40)** to get single enantiomer. [14]



i= Chlorobutyl chloride , N,N,dimethyl acetamide, ii= NaOH ,110^{0}C, iii= LiAlH4, Diethyl ether, iv= NBS, acetic acid, Acetonitrile, Rt, v= Na2CO3, 3-furanyl borornic acid, tetrakis palldium , dioxane

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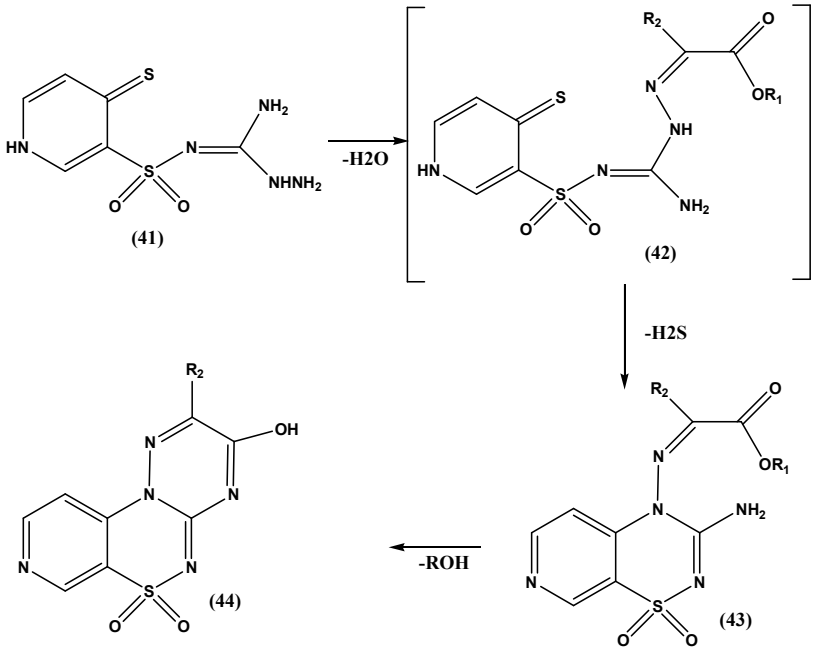
In 2015 Jaroslaw Slawinski et.al synthesized a novel series of substituted pyrido[4,3-e][1,2,4] triazino [3,2-c] [1,2,4] thiadiazine 6,6-dioxides (44) by one pot reaction from 3-amino-2-(4-thioxo-1,4-dihydropyridin-3-yl-sulfonyl) guanidine (41) with either 2-oxoalkanoic acids and its esters, or phenyl glyoxylic hydrates in glacial acetic acid.

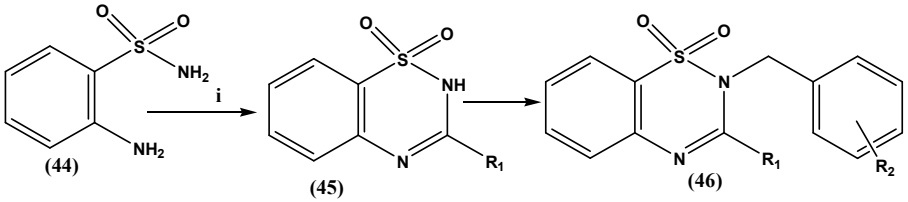
The author evaluated the derivatives of pyrido[4,3-e][1,2,4] tri-azino [3,2-c] [1,2,4] thiadiazine 6,6-dioxides in vitro for three human cancer cell lines HCT-116 (colon cancer), HeLa (cervical cancer), and MCF-7 (breast cancer), It is observed that some the derivatives shows reasonable to moderate anticancer activity against these cancer cell. [15]



Scheme 8

In 2021 Daisy K. Mangwegape, et.al synthesized a novel benzothiadiazine-1,1-dioxide derivatives (46) from the condensation of 2-amino benzene sulphonamide (44) with triethyl orthoacetate/benzoate acts as both reagent and solvent and form Schiff bases. which on ring closure form intermediate benzothiaziadine-1,1-dioxide(45). This intermediate on reaction with potassium carbonate followed by alkylation with alkyl halide form target compound 2,3-substituted benzothiadiazine-1,1-dioxide.

The author assessed the antileishmanial activity against promastigotes of Leishmania strains of L.donovani (1S and 9515) and L. major IR 173 and found selective activity against L. parasite. [16]



Scheme 9

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II. CONCLUSION

1,2,4-Thiadiazines derivatives plays important role in medicinal chemistry as anti-hepatitis, anti-HIV, anticancer, anti-tuberculosis, antidiabetic, anti-inflammatory, fungicidal drug. But very less study is found on this structure due to ease of formation. This mini review will provide information about synthesis and biological activity of 1,2,4-thiadiazine.

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