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A Review On 1, 3, 4-Thiadiazole & It's Pharmacological Activities

Nisha Prajapati [*1], Vivek Pal[1], Jitendra Chaudhary[1], Kuldeep Savita[1], Manish Pathak[2]

[1]Smt. Vidyawati College of Pharmacy, Goramachhiya, Jhansi-284121 (U.P), INDIA
[2]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Swami Vivekanand Subharti University, Meerut (U.P)- 250005 INDIA
**Corresponding author:*
Ms. Nisha Prajapati
Research Scholar
Smt. Vidyawati College of Pharmacy, Jhansi
nishprajapati234@gmail.com

Thiadiazole is a heterocyclic molecule made up of one sulphur atom, two nitrogen atoms, and two double-bonded 5- membered ring systems. The 1, 3, 4-thiadiazole nucleus is one of the most important and well-known heterocyclic nuclei, which is a common and integral feature of a variety of natural products and medicinal agents. Thiadiazole nucleus is present as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, and antitubercular agents. In the present study, novel different Schiff bases of 2, 5-disubstituted-1, 3, 4-thiadiazole were synthesized. The chemical structures were confirmed by IR, 1 H NMR and elemental analysis. All the new compounds were tested In-vivo for their analgesic and anti-inflammatory activities.

Keywords: 1, 3, 4-Thiadiazole derivatives, heterocyclic compounds, microbial, anti-inflammatory activity.

INTRODUCTION

A heterocyclic compound is that which contain more than one kind of atoms if ring are only made up of the carbon atoms than that are called the homocyclic compounds but the heterocyclic ring contain more than one compounds as nitrogen, oxygen or sulfur for example, pyrole, furon, thiophene[1]. The identification of compounds able to treat both acute and chronic pain is challengingin pharmaceutical research[2,3,4], pain is in fact a very important problem present in 90% of diseases, from the simple back pain to pain associated with different forms of cancer. The classical therapies for pain treatment are mainly the non-steroidal anti-inflammatory drugs (NSAIDs) and opiates, whose lead compounds, acetylsalicylic acid and morphine, respectively, were isolated in 19th century[5]. NSAIDs show side effects such as gastrointestinal irritation and lesions, renal toxicity and inhibition of platelet aggregation, while the use of opoids is limited to severe pain because of adverse secondary reactions as respiratory depression, dependence, sedation, and constipation[6].

THIADIAZOLE

Over the past decade, drug resistance has become a growing problem in the treatment of infectious disease caused by bacteria, fungi and viruses. In particular, resistance of bacterial pathogens to current antibiotic has emerged as a measure health problem[7]. This is especially true in case of infectious diseases such as pneumonia, meningitis and tuberculosis, which would once have been easily treated with antibiotics, is no longer so readily treated. At present, all widely used antibiotic, including some of the agent such as streptogramins and new generation flouroquinolones are subjected to bacterial resistance[8]. The search for new antimicrobial agent is one of the most challenging tasks to the medicinal chemist. A recent literature survey revealed that the 1, 3, 4- thiadiazole moiety have been widely used by the medicinal chemist in the past to explore its biological activities[9]. The Development of 1, 3, and 4- Thiadiazole Chemistry is linked to the discovery of Phenylhydrazines and hydrazine in the late nineteenth century. The first 1, 3, 4-Thiadiazole was described by Fischer in 1882 but thetrue nature of the ring system was demonstrated first in 1890 by Freund and Kuh[10]. There are several isomers of thiadiazole, that is 1, 2, 3 Thiadiazole, 1, 2, 5 Thiadiazole, 1, 2, 4 Thiadiazole and 1, 3, 4 Thiadiazole (fig.1) .

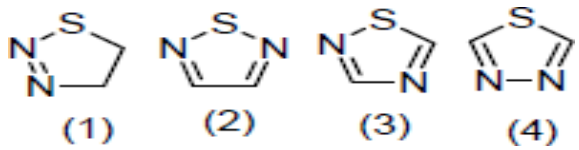


Fig 1. Different type of thiadiazole

1, 3, 4-Thiadiazole is the isomer of thiadiazole series. A glance at the standard reference works shows that more studies have been carried out on the 1, 3, 4 Thiadiazole than all the other isomers combined[11]. Members of this ring system have found their way in to such diverse applications as pharmaceuticals, oxidation inhibitors, cyanide dyes, metal complexing agents[12]. The ending - azole designates a five membered ring system with two or more heteroatoms, one of which is Nitrogen. The ending –ole is used for other five membered heterocyclic ring without Nitrogen. The numbering of monocyclic azole system begins with the heteroatom that is in the highest group in the periodic table and with the element of lowest atomic weight in that group. Hence the numbering of 1, 3, 4-Thiadiazole (4) is done in following manner. This designates that one sulphur group is present in the ring[13].

1, 3, 4 THIADIAZOLE

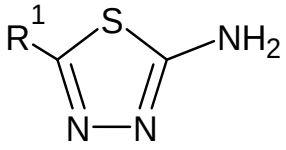
During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial, antituberculosis, anti-inflammatory, anticonvulsants, antihypertensive, antioxidant, anticancer, and antifungal activity[14].

(I) RECENT STRATEGIES ON THE SYNTHESIS OF 1, 3, 4-THIADIAZOLES:-

Recent strategies on the synthesis of 1, 3, 4-Thiadiazole derivatives can be summarized in to following points:-

1. From Thiosemicarbazides:

Many synthesis of the 1, 3, 4-Thiadiazole proceed from thiosemicarbazide or substituted Thiosemicarbazide[15].

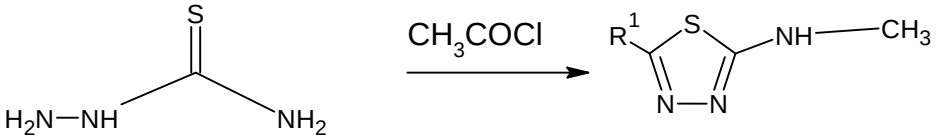


2. From Frund and Meinecke

This method have shown that thiosemicarbazide (6) cyclizes directly to 2-amino-5- methyl-1, 3, 4-thiadiazole (7) with acetyl chloride (5). This simple route to 2- amino 5-substituted-1, 3, 4-thiadiazole seems to be quite general[16]. In the example shown R may bemethy1, norhydnocarpyl, benzyl, cyclopropyl and many others.

3. From Pulvermacher method

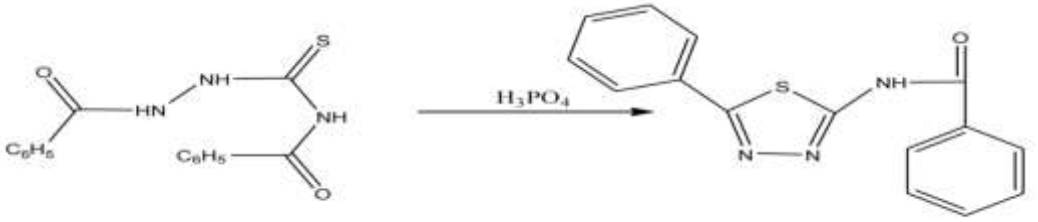
Pulvermacher had earlier shown that acetyl chloride (5) could bring about the cyclization of alkyl – or arylsubstituted thiosemicarbazide[17]. For example, the action of acetyl chloride on 4-methylthiosemicarbazide (8) produces 5-methyl-2-methylamino-1, 3, 4-thiadiazole (9)



(8)
(9)

4. From Hoggarth method

Hoggarth has prepared a number of 2-amino-5-aryl-1, 3, 4-thiadiazole using phosphoric acid as the dehydrating agents[18]. An example of smooth cyclization in high yield by phosphoric



(10) (11)

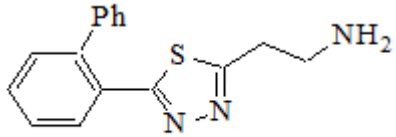
acid is the formation of 2- benzamido-5-phenyl-1, 3, 4-thiadiazole (11) from 1, 4-dibenzoylthiosemicarbazide (10).

BIOLOGICAL ACTIVITIES ASSOCIATED WITH 1, 3, 4-THIADIZOLE RING SYSTEM

There are several reports in the literature discussing the 1, 3, 4-thiadiazole derivatives for their diverse biological activities and the most relevant and recent studies have revealed that 1, 3, 4-thiadiazole derivatives have a broad spectrum of pharmacological activities that can be classified into the following categories[19,20].

Anticonvulsant activity

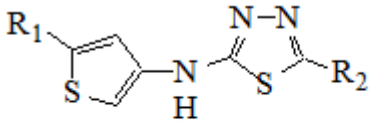
Stillings et al. described the anticonvulsants properties of a number of substituted 2-hydrazino-1,3,4-thiadiazole. Further they found that, 2-(amino methyl)-5-(2-biphenylyl)-1, 3, 4-thiadiazole **(32)** possess potent anticonvulsants properties in rat and mice and compared favorably with the standard anticonvulsants drug phenytoin, Phenobarbital and carbamazepine in a number of test situations[21-24].



(32)

Anticancer activity

Revelant et al. synthesized a series of 5-aryl-2-(3-thienylamino)-1,3,4-thiadiazoles starting from thiophen-3-isothiocyanates. Those compounds as well as the thiosemicarbazide intermediates were screened for their antiproliferative activity against a panel of six cancer cell lines. Among them, two 5-aryl-2-(3-thienylamino)-1,3,4-thiadiazoles (**34a** and **34b)** have shown very interesting results with IC50 < 10μM on three cell lines[25-26]

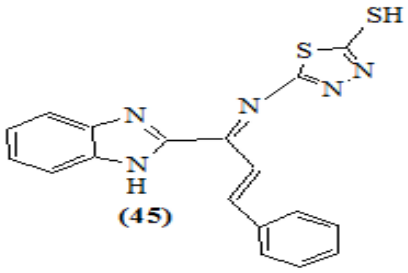


34a, $R_1=C_6H_5$, R_2 = 4-$OMeC_6H_4$

34b, $R_1=C_6H_5$, R_2 = 4-OHC_6H_4

Mucomembranous protector

Mathew et al. discoverd some novel imines of 2-amino, 5-thio, 1,3,4-thiadiazole as mucomembranous protector. A series of some novel imines of 2-amino, 5-thio 1, 3, 4-thiadiazole connected to benzimidazole chalcones were prepared. All the newly synthesized compounds were screened for their antiulcer activity in the pylorus-ligated rats. Free radical scavenging activity of all final derivatives was determined by DPPH Diphenyl picryl hydrazide) method. Compound (**45)** showed the best result[27,28,29].



(45)

CONCLUSION

The review article shows that 1, 3, and 4 thiadiazole heterocyclic has resulted in some therapeutically potential analogs. Some compounds have shown more pharmacological action than standard. Thus it is of need for the researchers to do some more work on thiadiazole derivatives which serves as a core structural component in an array of drug categories such as antimicrobial, anti-inflammatory, analgesic, antiepileptic, antiviral, antineoplastic, and ant tubercular agents. The broad and potent activity of thiadiazole and their derivatives has established them as pharmacologically significant scaffolds. In this study, an attempt has been made with recent research findings on this nucleus, to review the structural modifications on different thiadiazole derivatives for various pharmacological activities.

FUNDING

None

CONFLICT OF INTEREST

Authors have no conflict interest.

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