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1, 3, 4-Thiadiazole Scaffold; Its Ancillary Outcomes

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ABSTRACT

1,3,4-Thiadiazole is a heterocyclic compound known for its unique structure, featuring a five-membered aromatic ring with two nitrogen atoms and one sulfur atom. This molecule and its derivatives have been identified for their wide-ranging biological activities including anticancer, anti-inflammatory, anticonvulsant, antidiuretic, etc. Docking study techniques have revealed that 1,3,4- Thiadiazole derivatives offer promising pathways for development of novel therapeutics and these findings underscore the potential of 1,3,4- thiadiazole and its derivatives in bridging chemistry and biology for advancing treatment options. The effectiveness of 1, 3, 4-Thiadiazole in treatment of various ailments can be attributed to their interaction with several molecular targets such as carbonic anhydrase, cyclooxygenase, etc. The insights from structural modifications to the 1,3,4-thiadiazole nucleus demonstrate its potential as a versatile scaffold in medicinal chemistry, offering promising pathways for the development of novel therapeutics aimed at treating a range of diseases.

1. INTRODUCTION

1, 3, 4-Thiadiazole is a five membered heterocyclic ring with two nitrogen atoms and one sulphur atom with lone pair of electrons. [2]

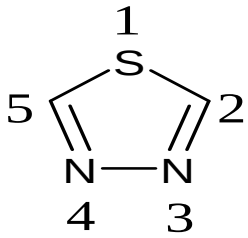


Fig 1: Structure of 1, 3, 4- thiadiazole

Table 1: Physical properties of 1, 3, 4-thiadia

Preferred IUPAC Name	1,3,4 Thiadiazole
Chemical formula	$C_2H_2N_2S$
Molecular weight	86.11568 g/mol
Density	1.648 g/mL at 25 °C (lit.)
Boiling point	121-123 °C (lit.)
Acidity (pKa)	5.1

1.1 PHARMACOLOGICAL ACTIVITIES OF THIADIAZOLE.

Thiadiazole possess various pharmacological activities such as:

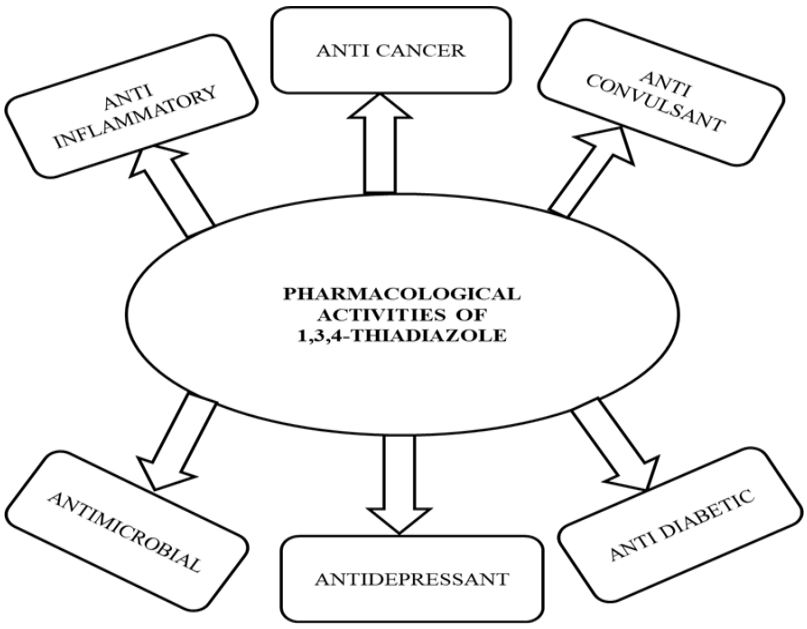


Fig 2: Pharmacological activities of 1, 3, 4-thiadiazole

1.2 DOCKING

The two basic approaches of Computer-aided drug design (CADD) used in modern drug discovery and drug development programme are Structure-based drug design (SBDD) and Ligand-based drug design (LBDD). Molecular docking is a computational tool used extensively in Structure-Based Drug Design (SBDD) for the determination of binding affinity and relative orientation between a protein and a ligand when they are bound to each other. Docking is a preliminary tool of CADD that has gained significance in the field of the pharmaceutical research because it's a productive and cost-effective technology in search for novel molecules of interest. Virtual screening or *in silico* screening plays a significant role in drug discovery program as a complementary tool to high throughput screening (HTS) to identify biologically active compounds. Docking is also used for virtual screening of new ligands on the basis of biological structures for identification of hits and generation of leads or optimization of leads in drug discovery. Hence, docking approach of SBDD plays a prominent role in rational designing of new drug molecule.

The technique of docking assist in the prediction of the binding free energy as well as interaction geometry of a bound protein-ligand complex. Thereby, Docking predicts the preferred orientation (i.e., 'best fit' or' best match' orientation in 3D space) of a ligand that binds to a particular protein of interest. Molecular docking aims in achieving an energetically favorable or minimized energy conformation between the protein and ligand binding to obtain a stable protein-ligand complex. [3, 4, 5]

1.3 SYNTHESIS

1) A transition-metal-free condensation of semicarbazide or thiosemicarbazide with aldehydes followed by iodine mediated oxidative C-O/C-S bond formation provides 2-amino-substituted 1, 3, 4-thiadiazoles.

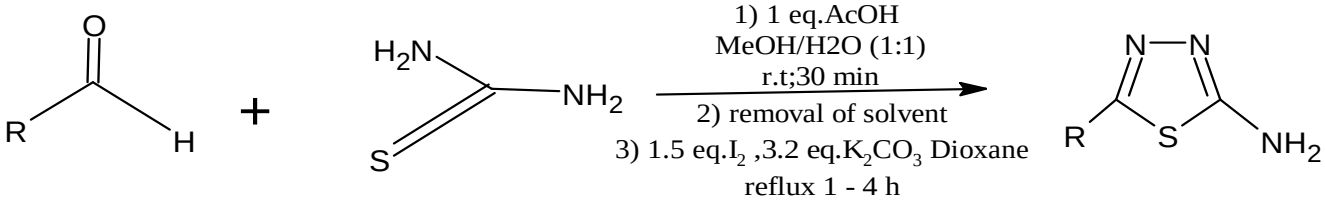


Fig 3: Synthesis of thiadiazole

2) *N*-Tosylhydrazones, reacts with potassium thiocyanate results in formation of substituted 1, 3, 4-Thiadiazole.[6]

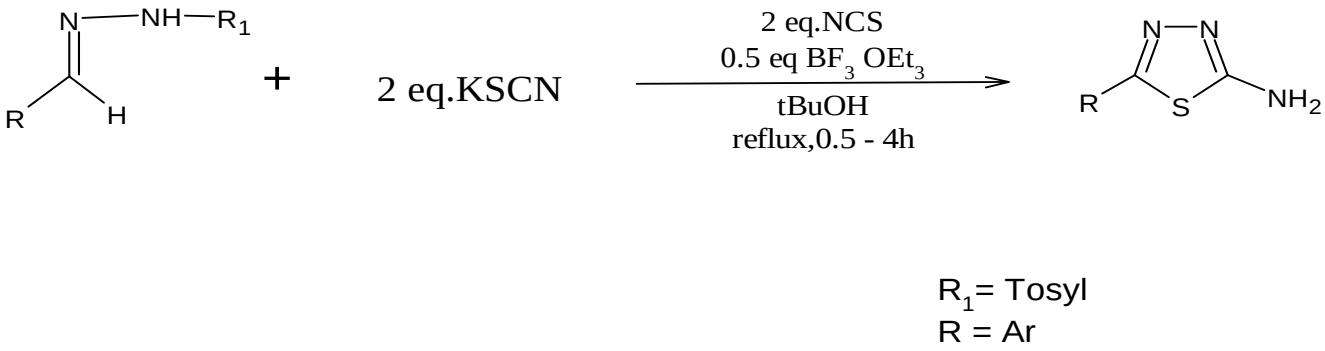


Fig 4: Synthesis of thiadiazole

BIOLOGICAL OUTCOME

Anticancer activity

Dalip Kumar, N. Maruthi Kumar synthesized and studied compound 1,2,3,4 by performing formazan dye (MTT) conversion assay for its anticancer activity using prostate (PC3, DU145 and LnCaP), breast (MCF7 and MDA-MB-231) and pancreatic (PaCa2) cancer cell lines. The structure-activity relationship (SAR) study of 1,3,4-thiadiazole ring shows that the substitution at its C-2 position plays an important role in imparting the cytotoxic activity to the compound. The compound 1 possessing a phenyl ring at C-2 position was found to be selectively cytotoxic against PaCa2 cell line (IC50 41.7 µm). The compound 2 possessing a benzyl moiety at C-2 position instead of phenyl group in compound 1 shows increased cytotoxicity against all cancer cell lines (IC50 values are nearly uniform against LnCaP, MCF7 and PaCa2 cell lines and below 30 µm in PC3, DU 145 and MDA-MB-231 cell lines). The compound 3 with p-chlorophenyl group at C-2 position is moderately active against four cancer cell lines (<100µm)whereas, compound 4 with 4-(dimethylamino)pheny group showed an apparent increase in activity against three cancer cell lines LnCaP (23 µm) DU145 (35.6 µm) and MCF7 (12.3 µm). [7]

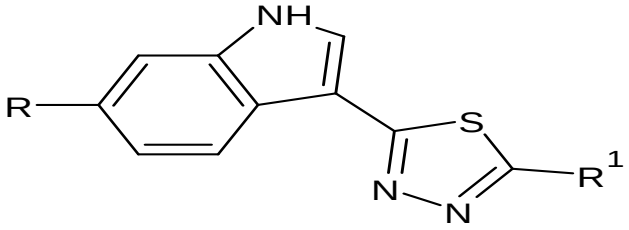


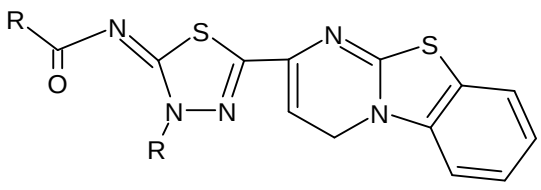
Fig 5: 5-(3-indolyl)-2-substituted-1, 3, 4-thiadiazoles

Table 2: Derivatives of 5-(3-indolyl)-2-substituted-1, 3, 4-thiadiazoles with anticancer activity

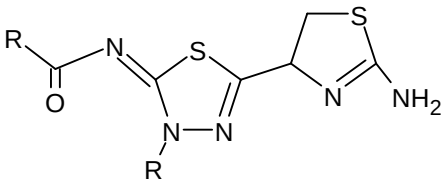
Compound	R	R_1
1	C6H5	H
2	CH2C6H5	H
3	4-Cl C6H4	H
4	4-N,N'(CH3)2C6H4	H

Anti-inflammatory activity

Sobhi M. Gomh 2-Bromoacetyl-3-phenyl-1, 3, 4-thiadiazole derivative was synthesized by reacted with a number of heterocyclic amines to give a series of fused imidazole derivatives. Also, reaction of 2-bromoacetyl-3- phenyl-1, 3, 4-thiadiazole with o-phenylene diamine and 2-aminothiophenol yielded the respective products. Moreover, reaction of 2-bromoacetyl-3-phenyl-1, 3, 4-thiadiazole with thiourea, thiosemicarbazide, thiocarbahydrazide gave the respective thiazoles. Experiment was carried out by carrageenan induced rat paw edema for evaluating the anti-inflammatory properties of the different compounds. The anti-inflammatory effect of the synthesized compounds was studied and observed that they exhibit a more pronounced effect than that of their standard drug (Indomethacin). Also, their intensity persisted along the 4 h after administration. Among them the following Compounds 5 and 6 showed the highest anti-inflammatory effect in relation with different tested chemical compounds. [8]



Compound 5



Compound 6

Fig 6: Thiadiazole derivatives with anti-inflammatory activity

Anticonvulsant activity

Vinit Raj, Amit Rai, Mahendra Singh, Arvind Kumar studied demonstrated to compile the medicinal chemistry, anticonvulsant screening and their structural activity relationship as well as pharmacophoric pattern of various synthesized 1,3,4-thiadiazole derivatives. In this study substituent in the 2-position of the aromatic ring produced compounds (i.e., 7-11) shown desirable anticonvulsant activity with significantly reduced neurotoxicity in comparison to the 2-CH3 compound 7 and replacement of the 2-phenyl group (9) by a 4-phenyl (11) shown a complete loss of activity. [9, 10, 11, 12]

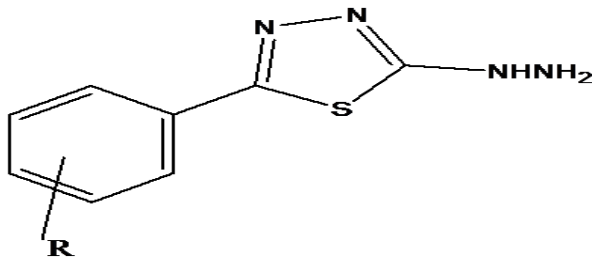


Fig 7: 2-aryl-5-hydrazino-l, 3, 4-thiadiazole

Table 3: 2-aryl-5-hydrazino-l, 3, 4-thiadiazole Derivatives with anti-convulsant activity

Compounds	R
7	-2-CH3
8	2-Cl
9	2-Ph
10	2-C6H13O
11	4-Ph

Antidepressant activity

Francesca Clerici and Donato Pocar in this study focuses on the synthesis of novel derivatives of 2-amino-5-sulfanyl-1, 3, 4-thiadiazole and their subsequent evaluation for antidepressant

activities. The synthesis involved a series of reactions starting from readily available starting materials, with careful consideration of structural modifications to enhance pharmacological properties. The structures of synthesized compounds were confirmed through various spectroscopic techniques, including NMR and mass spectrometry.

Evaluation of the synthesized compounds for antidepressant activities was carried out using established animal models. Preliminary results indicate promising pharmacological profiles for select derivatives, with significant improvements in behavioral responses compared to standard drugs. Structure-activity relationship (SAR) studies provided insights into the key structural features essential for antidepressant effects.

The simple methyl compound (entry 12) was substantially less active than compound 13, and further lengthening of the alkyl chain did not have a significant effect although substitution with a bulky iso-propyl group (entry 13) did result in a slight increase in activity. Compounds 14, 15, and 16 were selected on the basis of both their potency and their broad window of activity. These were then screened in the rat using the despair test and the social interaction test. [13]

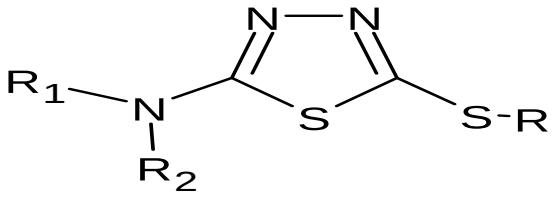


Fig 8: 2-amino-5-sulfanyl-1, 3, 4-thiadiazole derivatives

Table 4: 2-amino-5-sulfanyl-1, 3, 4-thiadiazole derivatives with anti-depressant activity

Compound	R	R_1	R_2
12	Me	H	H
13	i-Pr	H	H
14	4-Cl benzyl	H	H
15	3-Me benzyl	H	H
16	Benzyl	MeCO	H

Diuretic activity

Asrat Ergena,Yerra Rajeshwar and Gebremedhin Solomon studied the diuretic activity of substituted 1,3,4,thiadiazoles and in this study, six 5- and 2-thioate derivatives of 1, 3, 4-thiadiazoles were synthesized by substitution reaction utilizing acetone as solvent and potassium carbonate(K_2CO_3)as base. The compounds were estimated and characterized by using IR and NMR spectroscopy. The diuretic activity was evaluated on Swiss albino mice. Substitutions at 2^{nd} and 5^{th} positions of 1, 3, 4-thiadiazole ring exhibit diuretic activity. 5-methyl-substituted compounds showed significant diuretic activity when they were compared to both the negative control group and 5-amino-substituted compounds. The low electron density of methyl group compared to the amino group at 5^{th} position might be the factor that resulted in increased diuretic activity of the 5-methyl-substituted 1, 3, 4-thiadiazoles. By 3D-QSAR analysis, the steric bulk and the high electron density of substituent at 5^{th} position of 1, 3, 4-thiadiazoles decrease diuretic activity of the compounds. In another study, the presence of additional substituent on the benzene ring at 5^{th} position decreases the diuretic activity of 1, 3, 4-thiadiazole derivatives. The highest diuretic activity was recorded for Para-nitro-substituted benzene ring at 2-thioate group of 5-methyl-1, 3, 4-thiadiazole and the least activity was recorded for propanethioate group at 2^{nd} position and amine group at 5^{th} position of 1, 3, 4-thiadiazole. [14, 15]

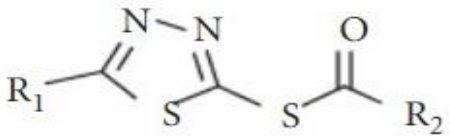
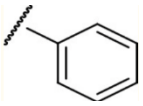
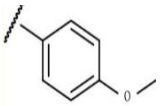
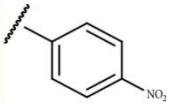
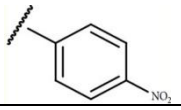
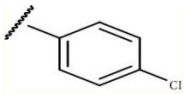


Fig 9:2-Thioacyl substituted 1, 3, 4-thiadiazole

Table 5: Derivatives of Thioacyl substituted 1, 3, 4-thiadiazole with diuretic activity

Compounds	R_1	R_2
17	CH_3-	
18	NH_2-	
19	CH_3-	
20	CH_3-	
21	NH_2-	CH_3CH_2-
22	NH_2-	

CONCLUSION

Thiadiazoles are a class of heterocyclic compounds displayed a wide range of biological activities. Therefore, this nucleus was involved in the drug discovery and drug development processes. Thiadiazoles derivatives showed good biological activities such as anti-convulsant, anti-cancer, anti-inflammatory, anti-depressant, anti-diabetics etc. The present review is about the physical properties, synthesis of thiadiazole derivatives and focused on its biological outcomes such as anti-cancer, ant-inflammatory, anti-depressant, anti-convulsant and diuretic activity.

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