e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:03/Issue:09/September-2021 Impact Factor- 6.752 www.irjmets.com

REVIEW- IMIDAZO[2,1-B][1,3,4]THIADIAZOLE DERIVATIVES: AN INSIGHT TO SYNTHESIS, BIOLOGICAL ACTIVITIES AND STRUCTURE ACTIVITY RELATIONSHIP

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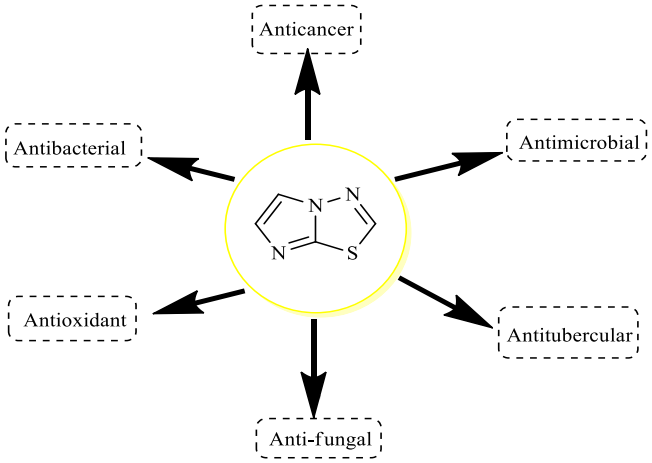
ABSTRACT

During the 1950s, the imidazo[2,1-b][1,3,4]thiadiazole heterocycle become located. On account of that then, many more recent derivatives were superior and tested for his or her natural profiles. The organic capability of imidazo[2,1-b][1,3,4]thiadiazole derivatives is significantly investigated, which incorporates antimicrobial, antifungal, anticancer, anticonvulsant, analgesic, anti-inflammatory, anesthetic, and diuretic homes. The extensive healing variety of imidazo[2,1-b][1,3,4]thiadiazole has caused us to behaviour extra studies on it

Keywords: Imidazo[2,1-B][1,3,4]Thiadiazole, Anticancer Activity, Antimicrobial Activity, Anti-Tubercular Activity, Anti-Fungal Activity.

I. INTRODUCTION

Heterocyclic compounds are very interesting in our daily lives. Heterocyclic compounds have numerous applications. They are primarily employed as pharmaceuticals, agrochemicals, and veterinary products. Thiadiazole is a five-component heterocyclic aromatic compound composed of two nitrogen atoms and one sulfur atom. There are four different types of isomeric compounds found in nature: 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole. Among these isomers, 1,3,4-thiadiazole and their derivatives are particularly active in the evolution of nucleophilic reaction and have a variety of organic activities. Fischer was introduced 1,3,4-thiadiazole in 1882, while Freund and Kuh were described as ring-nature of the compound[1].



Imidazole, with the formula $C_3H_4N_2$, is another heterocyclic aromatic compound which also has significant importance in the field of pharmaceutical chemistry[2]. Imidazo[2,1-b][1,3,4]thiadiazole and its derivatives are among the most commonly utilized heterocyclic compounds in pharmaceutics and therapeutic medicines. There has been a regular growth inside the synthesis and characterization of bioactive compounds including imidazole and 1,3,4-thiadiazole in the latest years[3-7]. Imidazo[2,1-b][1,3,4]thiadiazoles (1) are heterocyclic systems composed of imidazole and 1,3,4-thiadiazole rings linked by a bridgehead nitrogen atom. It was first discovered in the early fifties of the 19th century. Numerous imidazo[2,1-b][1,3,4]thiadiazoles with various substitutions at C-2, C-5, and/or C-6 positions of the general structures (2-4) have been synthesized and their biological activities have been reported extensively in the literature.

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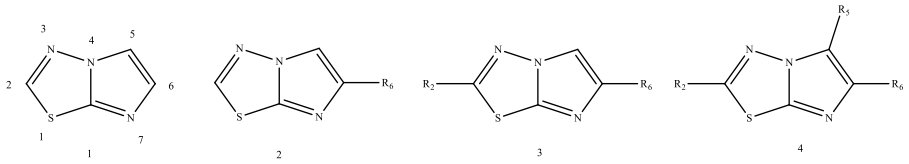

Figure 1: Imidazo[2,1-b][1,3,4]thiadiazoles with various substitutions at C-2, C-5, and/or C-6 positions

Because of their broad range of biological activities, imidazo[2,1-b][1,3,4]thiadiazoles and their derivatives have become widely used compounds in pharmaceutical chemistry such as antimicrobial, antibacterial, antifungal, antiviral, antioxidant, anticonvulsant, antidepressant, anti-inflammatory, antituberculosis, antihypertensive, and antiproliferative activities. Some drugs of this class are displayed in Figure 2[8-11]Imidazothiadiazole is a type of imidazo-fused heterocyclic agent and other imidazothiadiazoles found as TGF-β receptor kinase I inhibitors can be used to treat tumors. The transforming growth factor-β (TGF-β) family consists of more than 30 members involved in various bodily processes such as fetal growth, proliferation, differentiation, apoptosis, and immune responses. TGF-β 1, TGF-β 2, and TGF-β 3 are three mammalian TGF-β isoforms that are genetically engineered but work with the same signature system[12-14]. Interestingly, TGF-plays signaling plays a dual role during tumorigenesis, having both tumor suppression and oncogenic functions[15]. The most important component of imidazothiazole is levamisole, which is widely used in the treatment of cancer. The FDA approved levamisole as a curative treatment of colon cancer in 1990[16]. Before to this, levamisole was used as an antirheumatic therapy in the 1970s and 1980s for patients with rheumatoid arthritis. Due to the immune system's effects, the drug has been studied in the treatment of various immune-mediated diseases, and some studies have shown positive effects. The drug has been used in combination with other drugs to treat various types of cancer [17-18]. In 1982, a clinical trial found that combining levamisole with 6-mercaptopurine and methotrexate led to better cancer remission than chemotherapy alone in patients with acute myeloid leukemia[19].

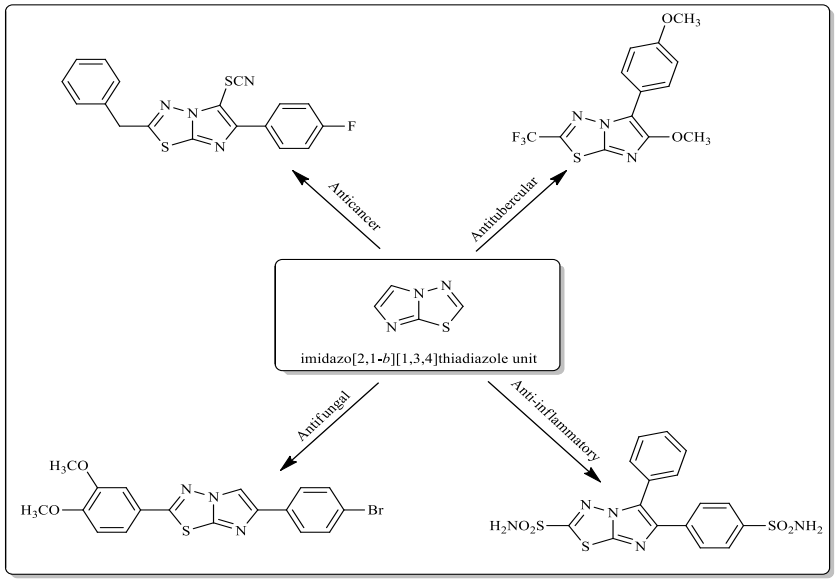

Figure 2: Drugs containing an imidazo[2,1-b][1,3,4]thiadiazole unit.

II. GENERAL METHOD OF SYNTHESIS

Dagli *et al.*,(2020) highlighting the assessment of fashionable techniques of the synthesis of imidazo[2,1-b][1,3,4] thiadiazoles. The compound 2-amino-1,3,4thiadiazole derivative (7) become acquired with the aid of using the response of 5-amino-1,three,4-thiadiazole-2-thiol (5) with 4-fluorobenzylchloride (6) withinside the presence of potassium hydroxide. Further compound 7 reacts with bromoacetophenone derivatives in ethanol offers 2,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazole derivatives (8). The Mannich response entails the response of imidazo[2,1-b][1,3,4]thiadiazole derivatives in methanol with morpholine, piperidine, and pyrrolidine. (9-11)[20].

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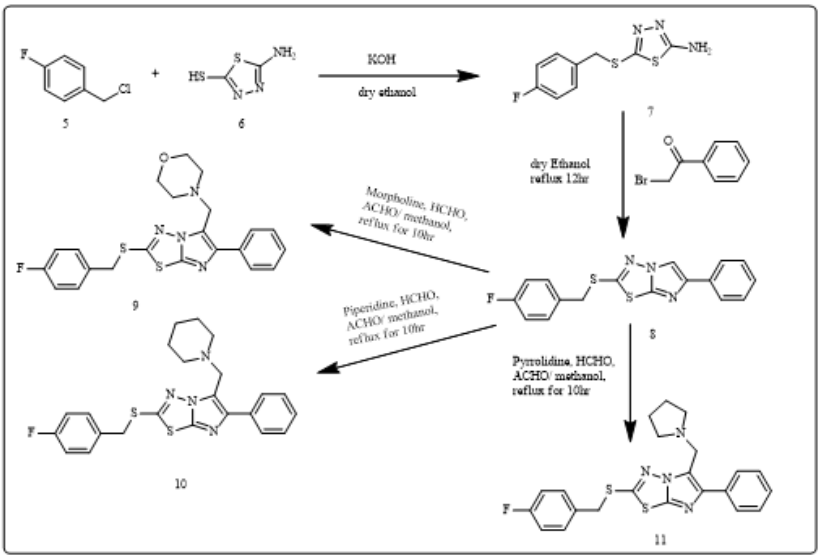
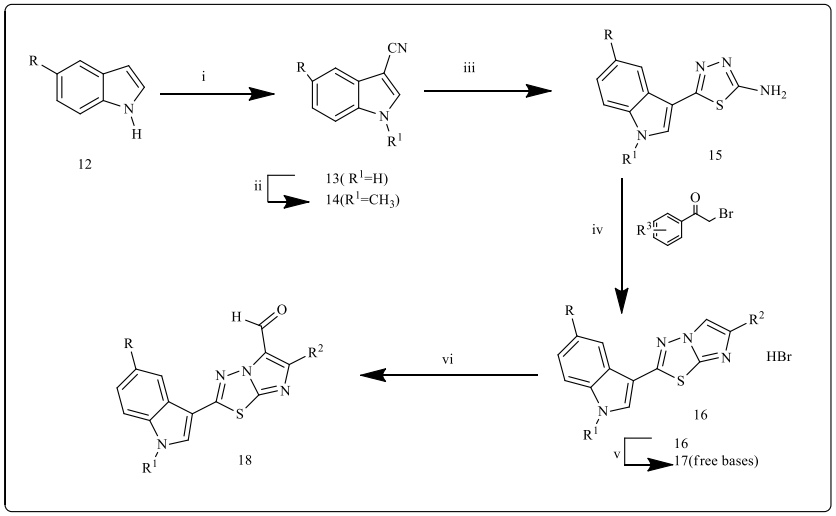


Scheme 1: Synthetic route for the synthesis of 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]thiadiazole derivatives.

Cascioferro S. *et al.*,(2020) highlighting the methods of the synthesis of imidazo[2,1-b][1,3,4] thiadiazoles derivatives. The indole-3-carbonitrile (13) and its derivatives, obtained by reacting the appropriate 1H-indole with chlorosulfonyl isocyanate, were methylated to yield the corresponding 1-methyl-1H-indole-3-carbonitriles 14. By treating the appropriate derivatives 13 or 14 with thiosemicarbazide, the 5-(1H-indol-3-yl)-1,3,4-thiadiazol-2-amines (15) were obtained in high yields. The hydrobromide derivatives (16) were formed by reacting the 1,3,4-thiadiazol-2-amines (15) with the appropriate Bromo acetyl compounds in refluxing ethanol. Instead, hydrobromides (16) was treated with a saturated aqueous NaHCO3 solution, yielding the corresponding free bases (17), which were formylated under standard Vilsmeier conditions to yield the imidazo[2,1-b][1,3,4] thiadiazole derivatives (18)[21].



Scheme 2: Synthesis of 3-(imidazo[2,1-b][1,3,4]thiadiazol-2-yl)-1H-indole derivatives

Chudamani B. *et al.*, (2020) highlighting the synthesis of 4-methoxybenzyl derivatives bearing an imidazo[2,1-b][1,3,4]thiadiazoles. 5-(4-methoxybenzyl)-1,3,4-thiadiazole-2-amine (21) was synthesized by reacting 4-methoxyphenyl acetic acid (19) and thiosemicarbazide (20) for 8hr. in the presence of sulfuric acid and after alkalinizing with ammonia solution. Several 6-aryl substituted 2-(4-methoxybenzyl)-imidazo[2,1-b][1,3,4]thiadiazole (23) was synthesized by refluxing 21 in ethyl alcohol with various 2-Bromo ketones (22) for 12 hours and neutralizing with aqueous sodium carbonate. Electrophilic substitution on imidazo[2,1-b] [1,3,4]thiadiazoles (23) resulted in the expected 5-substituted derivatives (24)[22].

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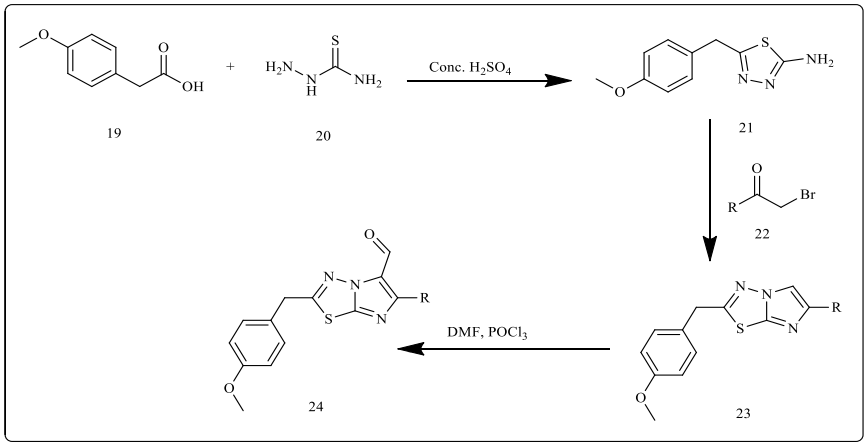
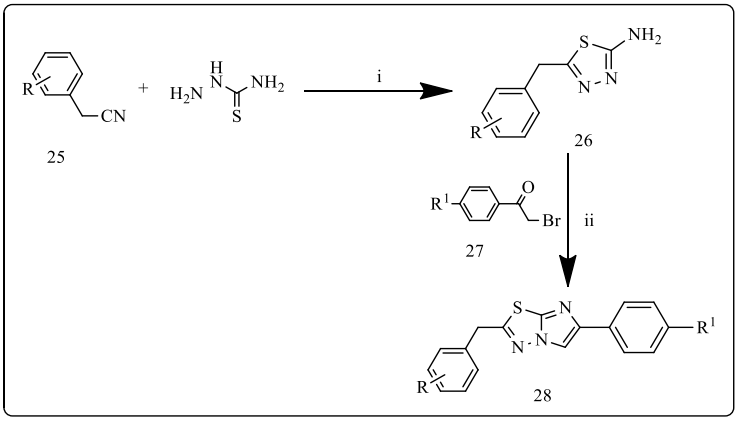


Scheme 3: Synthesis of 2-(4-methoxybenzyl)-6-aryl-imidazo[2,1-b][1,3,4]-thiadiazole.

Mustafa Er. *et al.*, (2019) highlighting the methods of the synthesis of imidazo[2,1-b][1,3,4] thiadiazoles derivatives. High yields of 2-amino-1,3,4-thiadiazole derivatives (26) were obtained by reacting nitrile compounds (25) with thiosemicarbazide in trifluoroacetic acid. 2-amino-1,3,4-thiadiazole derivatives (26) react with 2,4-bromoacetophenone derivatives (27) in absolute ethyl alcohol to give imidazo[2,1-b][1,3,4]thiadiazole (28)[23].



Scheme 4: Synthesis of substituted imidazo[2,1-b][1,3,4]thiadiazole derivatives

III. BIOLOGICAL ACTIVITIES

Anticancer activity:

Reddy A.G., *et al.*, 2020 reported a series of Quinazolinone-imidazo[2,1-b][1,3,4]thiadiazole hybrid derivatives The standard MTT assay method was used to assess the anticancer activities of those derivatives against human cancer cell lines A549 (lung carcinoma), HeLa (cervical), and MDA-MB-231 (breast). The compounds 29c and 29e had in vitro anti-proliferative activity against A549, with GI_{50} values of 0.25μM and 0.54μM, respectively. With GI_{50} values of 0.44μM and 0.23μM, compounds 29c and 29d demonstrated promising anti-proliferative activity against the MDA-MB-231 cell line[24].

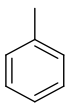
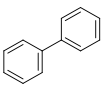
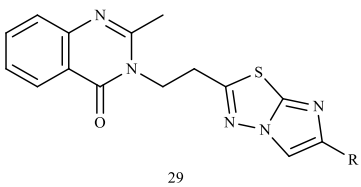
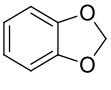
Compound	R	Compound	R	
29a		29b		
29c		29d		

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Figure 3: Structure formulae of Quinazolinone-imidazo[2,1-b][1,3,4]thiadiazole hybrid derivatives

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Sethi *et al*., 2020 reported a series of new 2-cyclopropyl imidazo[2,1-b][1,3,4]thiadiazole derivatives screened in-vitro for PHD2 inhibitory activity and anticancer activity at NCI (National Cancer Institute). Five doses selected compound 2-cyclopropyl-6-(4-methoxyphenyl)-5-phenyl-imidazo[2,1-b][1,3,4]thiadiazole (30) (NSC D-754956/1) was found to be the most active candidate of the series against Leukaemia HL-60 (TB), Colon Cancer HCT-116, Melanoma MALME-3M and Renal cancer A498 with GI50 2.43, 1.82, 2.37 and 2.15 µM respectively with a degree of selectivity toward Leukemic Cancer cell line based on MG MID ratio (3.36)[25].

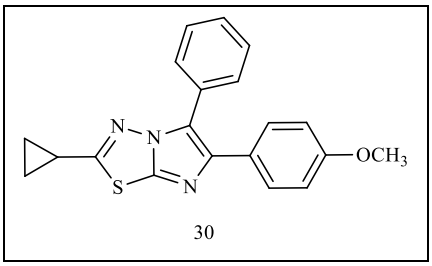

Figure 4: Structure formulae of 2-cyclopropyl imidazo[2,1-b][1,3,4]thiadiazole derivative

Petri *et al*., 2020 reported evaluation of a new class of imidazo[2,1-b][1,3,4]thiadiazole compounds as inhibitors of phosphorylation of focal adhesion kinase (FAK) in pancreatic cancer. The effect of ten imidazo[2,1-b][1,3,4]thiadiazole compounds was evaluated on MesoII and STO cells, by the SRB assay. Only four out of the ten compounds showed more than 50% inhibition of growth at 10µM. Compounds 31a and 31b demonstrated promising antitumor activity in both cell lines grown as monolayers, with IC_{50} values ranging from 0.59 to 2.81µM. Their antiproliferative and anti-migratory activity was associated with inhibition of phospho-FAK, as detected by a specific ELISA assay in STO cells[26].

Compound	R	R1
31a	H	H
31b	H	CH3
31c	Br	H
31d	F	H

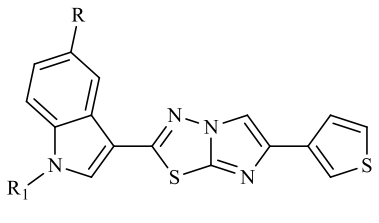

Figure 5: Structure formulae of imidazo[2,1-b][1,3,4]thiadiazole derivative

Chakrapani B. *et al*., 2018 reported 1,2,4-oxadiazole linked imidazothiadiazole derivatives for evaluation for anticancer activity against three human cancer cell lines. The MTT assay was used to assess their anticancer activity in vitro against a panel of three human cancer cell lines, A375 (melanoma), MCF-7 (breast), and ACHN (Renal). The drug doxorubicin was used as a control. The compound 32a exhibited the strongest anticancer activity, outperforming the positive control doxorubicin. The compound 32b has excellent activity against the melanoma cancer cell line (A375) as well as potent activity against MCF-7 and ACHN[27].

Compound	R
32a	3,4,5-OCH_3
32b	4-CF_3

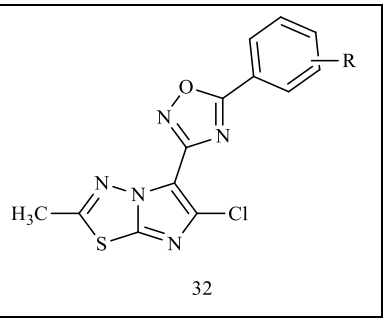

Figure 6: Structure formulae of 1,2,4-oxadiazole linked imidazothiadiazole derivatives

Rao M.P.N. *et al*., 2018 published antiproliferative activity of compounds containing indolinone-linked imidazo[2,1-b][1,3,4]thiadiazole nucleus against human cancer cell lines. Among all the compounds synthesized, 33a, 33b, and 33c were found to be the most potent, with GI_{50} values ranging from 0.13 to 3.8µM

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against HeLa, MIAPACA, and MCF-7 cell lines. The antiproliferative activity was demonstrated by disrupting the microtubule network, as well as apoptosis in HeLa cell lines[28].

Compound	R	R_1	R_2	R_3
33a		OCH_3	H	H
33b		Cl	OCH_3	H
33c		Cl	Cl	H

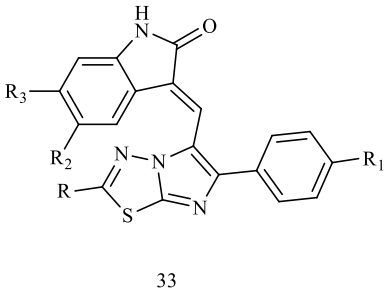

Figure 7: Structure formulae of indolinone linked imidazo[2,1-b][1,3,4]thiadiazole derivatives

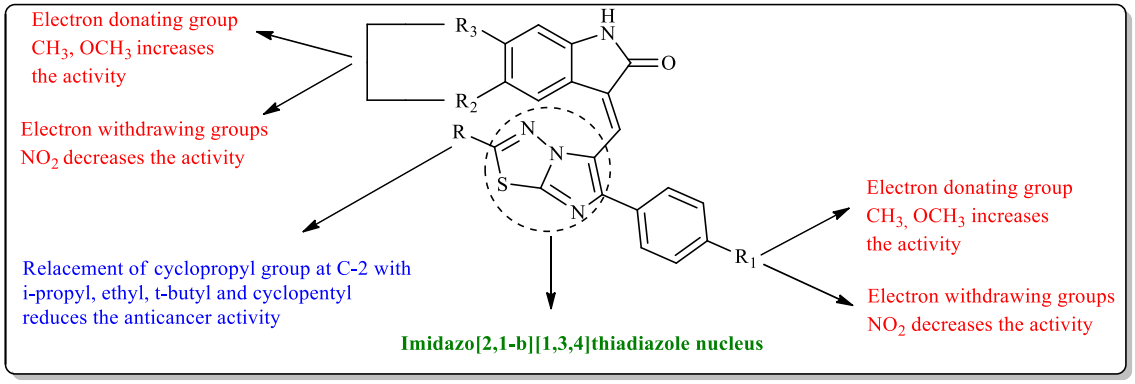

Figure 8: SAR of imidazo[2,1-b][1,3,4]thiadiazole derivatives as anticancer agent

Anti-microbial activity (Antibacterial and antifungal activity):

Fang *et al*., 2021 reported the synthesis of three series of imidazole-fused imidazo[2,1-b][1,3,4]thiadiazole ,and their antibacterial and antifungal activity are evaluated. All the target compounds showed sturdy antifungal activity and high property for the check lant candida over gram-positive and gram-negative microorganisms. Compound 34 showed the highest activity against C. *albicians* (MIC_{50}= 0.16 µg/mL), thirteen and three times that of the positive control compound gatifloxacin and fluconazole, respectively. This compound was safe as the positive control compounds in haemolysis test[29].

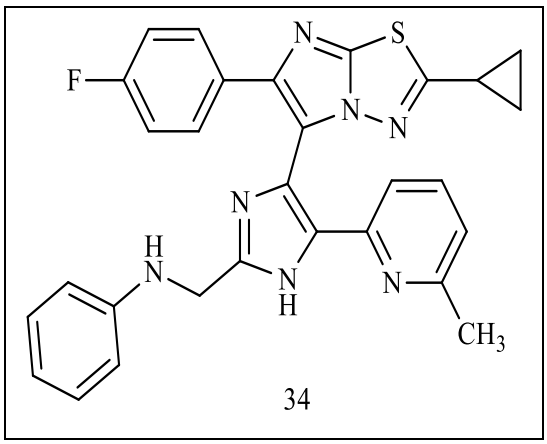

Figure 9: Structure formulae of imidazole-fused imidazo[2,1-b][1,3,4]thiadiazole derivatives

Mustafa Er. *et al*., 2019 reported Substituted Benzothiazole and Imidazo[2,1-b][1,3,4]thiadiazole derivatives for antibacterial activities. At various concentrations, the compounds were most effective against Escherichia coli (MIC_{50}=625-10,000 µg/mL). The compounds were also effective against Yersinia enterocolitica (MIC= 1250-20,000 µg/mL) and Salmonella typhimurium (MIC_{50}= 5000 µg/mL). Except for 35t (MIC_{50}=10,000 µg/mL), none of the other compounds were effective against Klebsiella pneumoniae[30].

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Compound	R	Comp	R	Comp	R
35a	-H	35h	-3,4-Cl	35o	$-OCH_3$
35b	-F	35i	-Ph	35p	$-NO_2$
35c	-Cl	35j		35q	-CN
35d	-Br	35k	-H	35r	-3,4-Cl
35e	$-OCH_3$	35l	-F	35s	-Ph
35f	$-NO_2$	35m	-Cl	35t	
35g	-CN	35n	-Br		

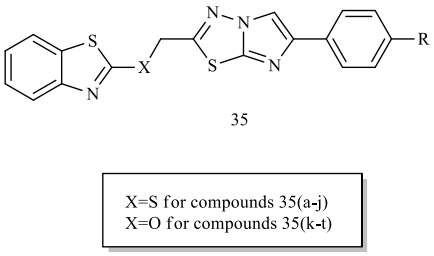

Figure 10: Structure formulae of Benzothiazole and Imidazo[2,1-b][1,3,4]thiadiazole derivatives

Er. M. *et al.*, 2017 reported antifungal activity of compounds containing the nucleus imidazo[2,1-b][1,3,4]thiadiazole derivatives against plant pathogens. The majority of the synthesized compounds were discovered to have antifungal activity. Compound 36 was discovered to have the most potent antifungal activity. The highest antifungal activity was related to compounds 36e, 36f, 36g, 36h, and 36m for Alternaria solani; compounds 36c, 36g, 36h, 36j, 36p, and 36q for Fusarium *oxysporum* f. *sp.*[31].

Compound	R
36a, 36j	-H
36b, 36k	-Br
36c, 36l	-Cl
36d, 36m	-F
36e, 36n	-OCH3
36f, 36o	-NO2
36g, 36p	-CN
36h, 36q	-Ph
36i, 36r	

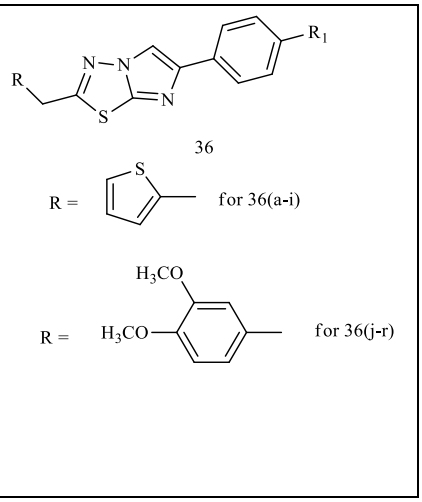

Figure 11: Structure formulae of Imidazo[2,1-b][1,3,4]thiadiazole derivatives

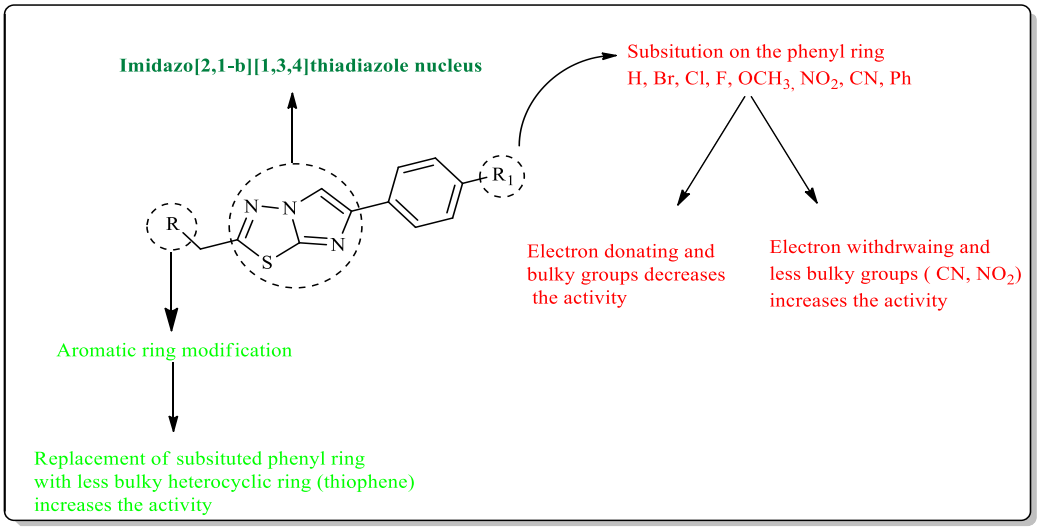

Figure 12: SAR of imidazo[2,1-b][1,3,4]thiadiazole derivatives as antimicrobial agent

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Anti-Tubercular activity:

Syed M.A *et al*., 2018 describe the synthesis of imidazo[2,1-b][1,3,4]thiadiazoles derivatives and evaluated for the antifungal and antitubercular activity. Compound 37a, 37b, 37c, 37d, 37e ,and 37f had the highest activity against the Mycobacterium tuberculosis H37Rv strain of Mycobacterium tuberculosis. Compounds were also evaluated for antifungal activity and Compounds 37a, 37b, 37g, and 37h demonstrated antifungal activity with MIC values of 5µg/mL[32].

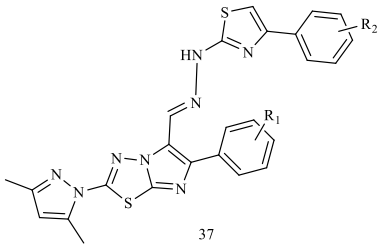
Compound	R_1	R_2	
37a	p-NO_2	p-OCH_3	
37b	p-NO_2	p-NO_2	
37c	p-NO_2	p-CH_3	
37d	p-OCH_3	p-NO_2	
37e	p-OCH_3	m-NO_2	
37f	p-Cl	p-OCH_3	
37g	p-NO_2	p-Cl	
37h	p-NO_2	p-Br	

Figure 13: Structure formulae of Imidazo[2,1-b][1,3,4]thiadiazole derivatives

Rajiv Dua. *et al.,* 2018 reported the evaluation of antitubercular activity of New Imidazo[2,1-b][1,3,4] thiadiazole-Phenothiazine derivatives. All the final synthesized compounds were screened for their antitubercular activity screened against M. tuberculosis H37Rv using Lowenstein-Jensen (L.J.) Agar method at 50 and 100 µg/mL concentrations. The standard antitubercular drugs isoniazid showed 100% activity at both the above concentrations. The MIC value of synthesized compound 38a-38c ranges from 4-12gµ/mL[33].

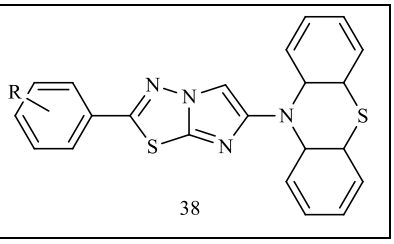
Compound	R	
38a	3-$NO_2C_6H_4$	
38b	4-$NO_2C_6H_4$	
38c	2-$NO_2C_6H_4$	

Figure 14: Structure formulae of Imidazo [2,1-b][1,3,4] Thiadiazole-Phenothiazine derivatives

Patel H.M *et al*., 2017 synthesized a series of imidazo[2,1-b][1,3,4]thiadiazoles derivatives and tested them for the antitubercular activity against the Mycobacterium tuberculosis H37Rv strain. Compound, 39f was found to be the most potent of all the compounds tested with a MIC value of 3.14µg/ml[34].

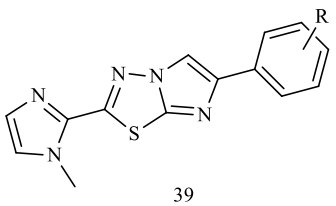
Compound	R	
39a	3-NO_2	
39b	4-Br	
39c	4-Cl	
39d	4-F	
39e	H	
39f	4-NO_2	

Figure 15: Structure formulae of Imidazo [2,1-b][1,3,4]thiadiazole derivatives

e-ISSN: 2582-5208
International Research Journal of Modernization in Engineering Technology and Science
(Peer-Reviewed, Open Access, Fully Refereed International Journal)
Volume:03/Issue:09/September-2021 Impact Factor- 6.752 www.irjmets.com

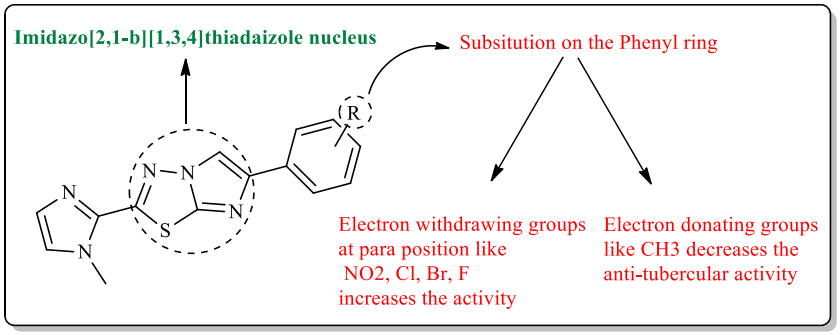
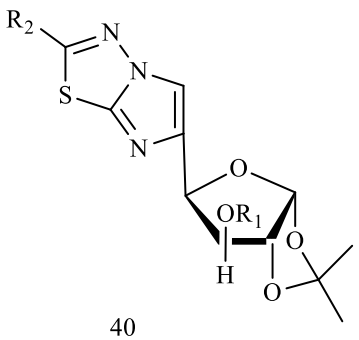


Figure 16: SAR of imidazo[2,1-b][1,3,4]thiadiazole derivatives as anti-tubercular agent

Anti-viral activity

Fascio M.L., *et al.*, 2019 describe the synthesis of imidazo[2,1-b][1,3,4]thiadiazoles from carbohydrates with D-ribo and D-Xylo configuration evaluated for the antiviral activity. A virus yield inhibition assay was used to assess antiviral activity. The effective concentration of 50% (EC_{50}) was determined as the concentration required to reduce virus yield by 50% in compound-treated cultures versus untreated control cultures. In a simultaneous antiviral assay, Ribavirin (RIB) (Sigma-Aldrich, USA) was used as a positive anti-arenavirus control35.

Compound	R1	R2
40a	CH_3	CH_2CH_3
40b	CH_3	
40c	CH_3	3,4,5-OCH3Ph
40d	CH_3	
40e		
40f		3,4,5-OCH3Ph
40g		



40

Figure 17: Structure formulae of imidazo[2,1-b][1,3,4]thiadiazoles derivatives from carbohydrates

SAR of imidazo[2,1-b][1,3,4]thiadiazole derivatives as anti-viral agent

Compounds with electron-withdrawing groups outperformed derivatives with electron donor substituents in antiviral activity. The antiviral activity of the *p*-Chloro derivatives (40b and 40e) against JUNV infection of Vero cells was moderate and selective. The presence of a carbonyl group between the heterocyclic ring and the carbohydrate moiety may account for their increased efficacy and SI against JUNV infection.

IV. CONCLUSION

The Synthetic and biological studies on imidazo[2,1-b][1,3,4]thiadiazole heterocycles have yielded some potentially therapeutic analogs. The imidazo[2,1-b][1,3,4]thiadiazole derivatives demonstrated exciting biological activities and emerged as potential leads for further development as drug candidates. During the last decade, research efforts have primarily focused on the synthesis and evaluation of imidazo[2,1-b][1,3,4]thiadiazole derivatives as antibacterial, anti-TB, and anticancer agents, anti-viral agents. The nature and type of substituents at positions 2- and 6- of the imidazo[2,1-b][1,3,4]thiadiazole nucleus had a significant

impact on the spectrum and potency of biological activities. As a result, additional systematic structure-activity studies could provide insights into the development of more potent derivatives as drug candidates. To summarise, traditional synthetic efforts yielded some potential lead molecules; however, rational drug design techniques may speed up drug discovery in the chemical class of imidazo[2,1-b][1,3,4]thiadiazoles in the future.

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