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Original article

Novel Biphenyl Imidazo[2,1-*b*][1,3,4]-Thiadiazole -a versatile scaffold

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Introduction

Antimicrobial agents are the drugs, chemicals, or other substances that kill or slow the growth of microbes. The need for new antimicrobial agents is greater than ever because of the emergence of multi drug resistance in common pathogen, the rapid emergence of new infectious, and the potential for use of multidrug-resistant agents in bioweapons. Antimicrobial resistant is threatening the management of infectious such as pneumonia, tuberculosis, malaria, and AIDS. In the past, resistance could be handled by development of new drugs activity agent resistance microbes. Since the development of sulfonamides in 1930's and penicillin in the 1940's, many new classes of antibacterial compounds have been developed. Drugs active against fungi, parasites and viruses have also been introduced. Within the field of antibiotics, the emergence of resistance was soon realized to represent the concenterable the clinical problem [1].

Medicinal chemistry is concern with the invention, discovery, design, identification and preparation of biological active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and construction of structure activity relationship [2].

Anticancer drugs either kill cancer cells or modify their growth. Cancer or neoplastic disease, may be regarded as a family of related disorders. A common feature in different forms of cancer is an abnormal and uncontrolled cell division, frequently at a rate greater than that of most normal body cells. The neoplasm may be begnin or malignant. Begnin tumours do not metastasise, malignant tumours do. Metastasis is due to ability of neoplastic diseases to invade other tissues if a malignant cell floats away in the body fluids and locates in a distant place of the organism. So there occurs a secondary growth originating from the primary tumour [3].

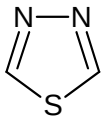
Treatment of malignant diseases with drugs is a rather recent development-started after 1940 when nitrogen mustard was used, but progress has been rapid, both in revealing pathobiology of the diseases and in discovery of new drugs. Among the heterocyclic compounds, five membered heterocyclic moieties fused with aromatic ring system with various heteroatoms like N, S, and O have possess wide spectrum of pharmacological activity. Synthesis of nitrogen containing heterocyclic compounds has been a subject of

great interest due to the wide application in agrochemical and pharmaceutical fields [4]. During recent years there has been a large investigation on different classes of imidazo thiadiazole compounds, many of which were found to possess an extensive spectrum of pharmacological activity.

The imidazo[2,1-*b*][1,3,4]-thiadiazole ring system is the core skeleton of well known immunomodulator levamisole [5]. The anti-tumor potential of the 2-amino-1, 3, 4-thiadiazole skeleton was recognized in the early 1950's and subsequently its fusion with the imidazo[2,1-*b*] ring system has resulted in compounds with potential anti-cancer, analgesic, antibacterial, antisecretary and cytotoxic activities. Thiadiazole and its derivatives are used for biological activities such as antimicrobial, antitubercular, anti-inflammatory, anticonvulsant, antihypertensive, and anticancer [6]. We reported here a review on synthesis of some novel derivatives of a relatively less studied fused system, imidazo[2,1-*b*][1,3,4]-thiadiazole for biological activity.

THIADIAZOLE

Thiadiazole is a versatile moiety that exhibits a wide variety of biological activities. It acts as "hydrogen binding domain" and "two-electron donor system" with a constrained pharmacophore.



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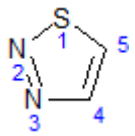
Many drugs containing thiadiazole nucleus are available in the market such as acetazolamide, methazolamide, sulfamethazole, etc. Thiadiazole can act as the bio-isosteric replacement of the thiazole moiety. So it acts like third and fourth generation cephalosporins, hence can be used in antibiotic preparations. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occur in nature in four isomeric forms *viz.* 1, 2, 3-thiadiazole; 1, 2, 5-thiadiazole; 1, 2, 4-thiadiazole and 1, 3, 4-thiadiazole.

The 1, 3, 4-thiadiazole isomer of thiadiazole series and its dihydro-derivatives provide a bulk of literature on thiadiazole. A glance at the standard reference work shows that more work has been carried out on the 1, 3, 4-thiadiazole than all other isomers. Members of this ring system have found their way into such diverse application as pharmaceuticals, oxidation inhibitors, cyanine dyes and metal complexing agents. The literature review showed that the thiadiazolenuclei have antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radioprotective, and anti-leishmanial activities [7].

Types of thiadiazole

Thiadiazole contains the five membered unsaturated ring structure composed of two nitrogen atoms and one sulfur atom. There are four isomeric types: (i) 1, 2, 3-thiadiazole (**2**); (ii) 1, 3, 4-thiadiazole (**3**); (iii) 1, 2, 4-thiadiazole **(4)** and (iv) 1, 2, 5-thiadiazole (**5**) [8].



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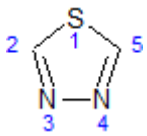

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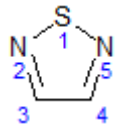

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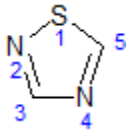

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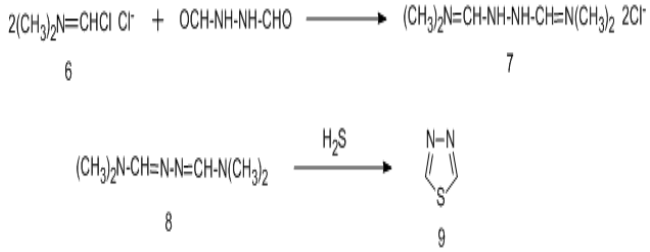
1, 3, 4-Thiadiazole

It represents an important heterocyclic system due to their pharmacological activities and are associated with diverse biocidal activities, probably by virtue of toxophoric -N=C-S- grouping [9]. The thiadiazoles have occupied an important place in drug industry. It has wide applications in many fields. The earliest uses were in the pharmaceutical area as in antibacterial with known sulphonamide drugs. These derivatives possesses wide range of therapeutic activities like antimicrobial, antifungal, diuretics, antiepileptic, anti-leshmanial, antiulcer, anti-mycobacterial, anti-inflammatory, free radical scavenging, anticonvulsant, and antileukemia agents. These compounds possess such interesting biological properties that may be conferred to them by their strong aromatic ring system. As ligands they also provide many potential binding sites for complexation and have obtained a diversified biological activity.

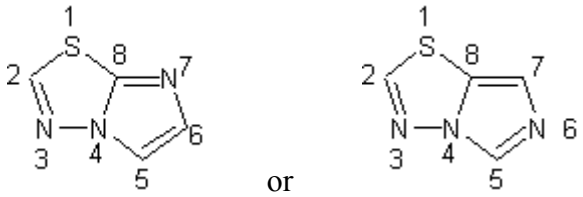
Synthesis of 1, 3, 4-Thiadiazole

It was firstly synthesized by Goerdeler, Ohm and Tegtmeyer, who used a four stage process that started from thiosemicarbazide. Jensen and Pedersen obtained the heterocycle from hydrazine and potassium dithioformate. The synthesis, by which quite large number of thiadiazole can be obtained starts from *N*, *N*-dimethylformamide azine dihydrochloride (**7**) which is formed in good yield from dimethylformamidoyl chloride (**6**) and *N*, *N*-diformylhydrazine or hydrazine dihydrochloride. Sodium ethoxide converts compound (**7**) into the free dimethylformamide azine (**8**); this reacts with H_2S at room temperature with loss of dimethylamine and formed 1, 3, 4-thiadiazole (**9**) [10].



CHEMISTRY OF IMIDAZO[2,1-*b*][1,3,4]THIADIAZOLE

The fusion of a imidazole ring with a 1, 3, 4-thiadiazole nucleus give rise to a class of heterocyclic systems containing a bridgehead nitrogen atom known as imidazothiadiazoles. These may be of two types, the imidazo[2,1-*b*][1,3,4]-thiadiazole (**10**) and the imidazo[5,1-*b*][1,3,4]-thiadiazole (**11**) [11].



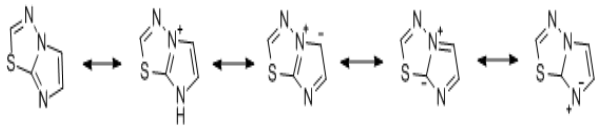
10 **11**

Both the systems contain nitrogen as a bridge head atom at 4th position. Here only imidazo[2,1-*b*][1,3,4]-thiadiazole bicyclic system is discussed. Ban and Co workers [12,13] reported the synthesis of some imidazo[2,1-*b*][1,3,4]-thiadiazole derivatives in 1952 and many have been prepared since then. But no systematic study covering all aspects of physical and chemical properties of the bicycle system was made. A brief survey of the information on the system and

chemical reactivity of this system is given on the basis of structural, chemical, ring cleavage and spectral studies.

STRUCTURAL STUDY OF IMIDAZO[2,1-*b*][1,3,4]-THIADIAZOLE

Important canonical structure of imidazo[2,1-*b*][1,3,4]-thiadiazole (**11**) is given below.



They indicate greater delocalization of π electrons in the imidazole ring, while the double bond of the thiadiazole ring is almost localized in structure as the maximum contributing group. It is pseudo-aromatic in behavior containing imidazole moiety as electron rich center. Of the three nitrogen atoms of structure (**10**) *N-7* is the most basic center. The order of basicity is *N*-7 > *N*-3 > *N*-4. Therefore, protonation occurs first at *N*-7 then at *N*-3 position. Electron charge density measurement indicated that the imidazole ring is rich in electron density having maximum at *N*-7 position and C-5 position. This accounts for the preferable electrophilic substitution reaction at C-5 position. The measurement of intermolecular bond distances and bond angles concluded that the structure (**10**) shows a small but significant deviation from the planarity, although the thiadiazole and imidazole rings are planar individually. This accounts for some overall reduction of aromaticity of (**10**). In fact this system is less stable than the corresponding electronically isosteric imidazo[2,1-*b*][1,3,4]-thiadiazole. This is further supported by measurement of magnetic susceptibility normal to the molar plan, which is the role -2.5×10^{-5} for (**10**) while it is -3.12×10^{-5} for imidazo[2,1-*b*]thiazole and -5.36×10^{-5} for imidazo[1,2-*a*]pyrimidine. These values show that the latter two systems are more aromatic than (**10**) [14].

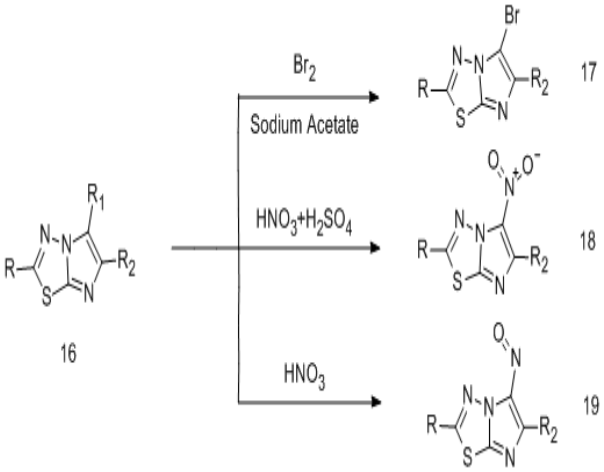
CHEMICAL REACTIVITY OF IMIDAZO[2,1-*b*][1,3,4]-THIADIAZOLE

Electophilic substitution reactions:

Kano S [15], has reported that bromination of (**12**) (R= H, R_1= Me, Ph, *p*-Cl-Ph;R_2= H takes place at 5-position of imidazo[2,1-*b*][1,3,4]-thiadiazole nucleus.

12 **13**

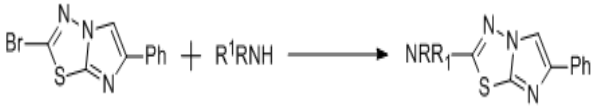
Further, **Pentiamalli L. *et al.*** [16], have also reported the following types of electrophilic substitution reactions of taking place at 5-position.



Nucleophilic displacement reactions:

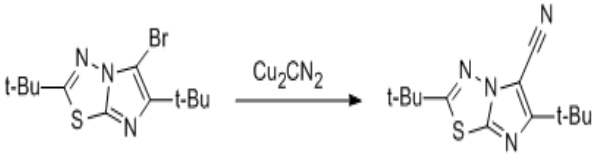
Bromine atom at position-2 (**20**) and position-5 (**22**) of imidazo[2,1-*b*][1,3,4]-thiadiazole is reported to undergo nucleophilic displacement reaction. **Ingedoh *et al.*** [17],

have prepared 2-alkylaminoimidazo[2,1-*b*][1,3,4]-thiadiazole by treating (**20**) with an appropriate alkylamine.



20 **21**

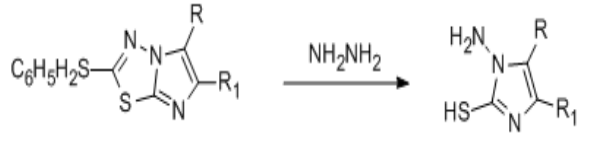
Hough [18], during the study on reactions of 5-substituted thiadiazoles he had reported that bromine of 2,6-di-*t*-butyl-5-bromo-imidazo[2,1-*b*][1,3,4]-thiadiazole could not be displaced by the reaction with ammonia or alkyl amine. He obtained 5-cyano derivative by heating the 5-bromo derivatives with cuprous cyanide in DMF.



22 **23**

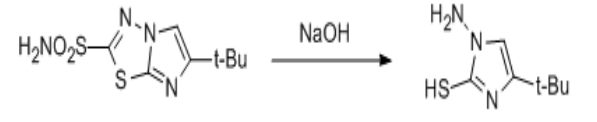
RING CLEAVAGE OF IMIDAZO[2,1-*b*][1,3,4]-THIADIAZOLES

Pyl *et al.* [19], have reported the cleavage of thiadiazole ring from imidazo[2,1-*b*][1,3,4]-thiadiazole ring of (**24**) when heated with ethenolic hydrazine hydrate.



24 **25**

Similarly, **Barnish *et al.*** [20], have reported the cleavage of thiadiazole ring by heating with 5N NaOH in the following compound (**26**).



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SPECTRAL DATA OF IMIDAZO[2,1-*b*][1,3,4]-THIADIAZOLE

Barnish and Co workers [20], have reported the X-ray crystallography and ^{13}C-NMR and mass spectral data of various imidazo[2,1-*b*][1,3,4]-thiadiazoles. Khazi *et al*., have studied mass spectral fragmentation of some 2-alkyl-6-arylimidazo[2,1-*b*][1,3,4]-thiadiazoles with the help of high resolution and metastable ion and reported McLafferty rearrangement involving transfer from alkyl chain and preferable cleavage of C-C bond between C_2 and C_3 of alkyl chain [21]. Schenetti *et al*., have reported a detailed study on the structure and protonation of the imidazo[2,1-*b*][1,3,4]-thiadiazole system by means of ^{1}H-NMR, X-ray analysis, Ring Current Model Performance and MO calculations. Some important conclusions of their study are enumerated here. The ^{1}H NMR spectra of compound (**28**) were recorded for deuteriochloroform solution and the parameters are listed in table-1.

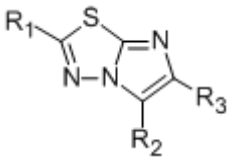

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Table 1

Chemical shifts and J values of Compound (28)

COMPOUND-28	SOLVENT	δ-2	δ-5	δ-6	$J_{5,6}$	$J_{2,6}$
R_1=R_2=R_3=H	$CDCl_3$	8.56	7.82	7.38	1.42	0.97
R_1=R_2=H; R_3=Me	$CDCl_3$	8.47	7.54	2.36	0.92	-
R_1=H; R_2=R_3=Me	$CDCl_3$	8.44	2.43	2.31	0.67	-
R_1=R_3=Me; R_2=H	$CDCl_3$	2.66	7.41	2.33	0.93	-

NOTE: *H-2/H-5 of parent 1, 3, 4-thiadiazole appears at 9.32 ppm; H-4 and H-5 of N-methyl imidazole appeared at 7.00 and 6.90 ppm, respectively [10].*

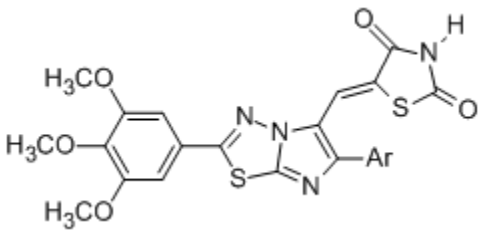
The chemical shifts of the hydrogen atoms bonded to the ring show that in the fused system H-2 falls at higher field and H-5 and H-6 at lower field with respect to the parent thiadiazole and imidazole or *N*-methylimidazole heterocycles. The difference in the chemical shift relative to the free base suggests that the effect of protonation is higher on H-2, followed by H-5 and H-6. This behavior was not conclusive for determining the site of protonation [22].

BIOLOGICAL ACTIVITIES OF IMIDAZO[2,1-*b*][1,3,4]-THIADIAZOLE

Imidazo thiadiazole are known to exhibits a variety of biological activities such as antimicrobial, antitubercular, antibacterial, anti-cancer and anti-inflammatory.

Antimicrobial Activity

Alagawadi K. R. *et al*., synthesized a series of new 2,4-thiazolidinones derivatives. The compounds were tested for their *in vitro* antimicrobial activity against the Gram-positive *Staphylococcus aureus*, *Enterococcus faecalis*, Gram-negative *Escherichia coli*, *Pseudomonas aeruginosa bacteria* and *Candida albicans*, *Aspergillus flavus*, *Aspergillus niger*. The presence of 6-*p*-chlorophenyl and 6-*p*-bromophenyl derivatives showed increased activity [23].



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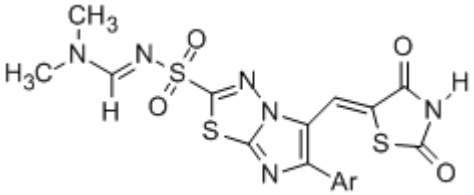

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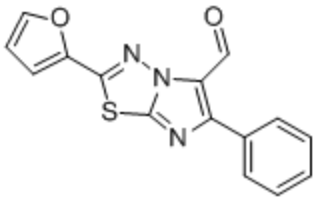
Antitubercular Activity

Kolavi G. *et al.*, synthesis aseries of 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]thiadiazoles and screened for antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$ using the BACTEC 460 radiometric system. Among the tested compound (**31**) and (**32**) had shown the highest (100%) inhibitory activity [6].



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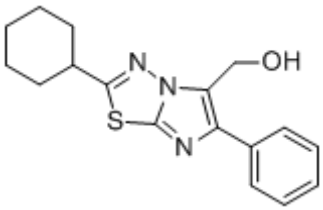

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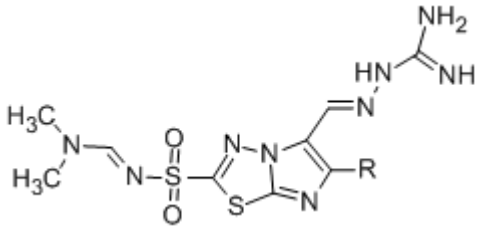
Antibacterial Activity

Gadad A. K. *et al.* [24], synthesized series of 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide derivatives. Compounds (**33**) and (**34**) showed a high degree of antibacterial activity against both *Escherichia coli* and *Staphylococcus aureus* comparable to that of sulfamethoxazole and Norfloxacin.



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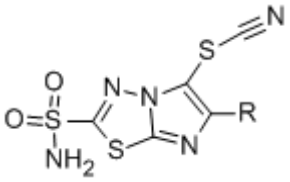

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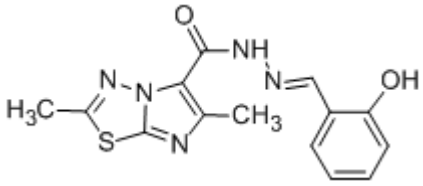
However, they were found to show moderate activity against *Salmonella typhi, Pseudomonas aeruginosa* and *Pneumococci*.

Anticancer Activity

Terzioglu N. *et al.* [5], synthesized some novel 2, 6-dimethyl-*N*'-substituted phenylmethylene-imidazo[2,1-*b*][1,3,4]-thiadiazole-5-carbohydrazides. Compounds (**35**) and (**36**) which passed the criteria for activity in this assay (20-29% growth percentages) were scheduled automatically for evaluation against the full panel of 60 human tumor cell lines at a minimum of five concentrations at 10-fold dilutions.



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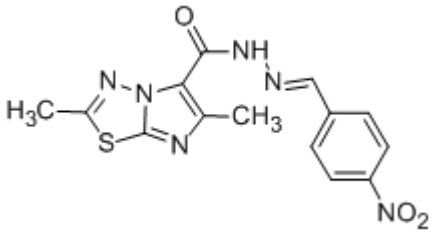

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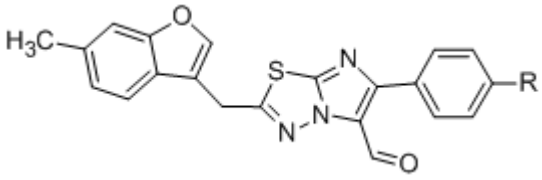
Anti-Inflammatory Activity

Jadhav V. B. *et al.* [25], synthesized a series of 6-substituted and 5,6-disubstituted 2-(6-methyl-benzofuran-3-ylmethyl)-imidazo[2,1-*b*][1,3,4]-thiadiazoles. The new compounds have been tested for their *in vivo* analgesic, anti-inflammatory activities. Some of the compound showed good anti-inflammatory activity.



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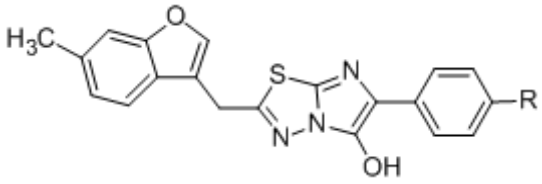

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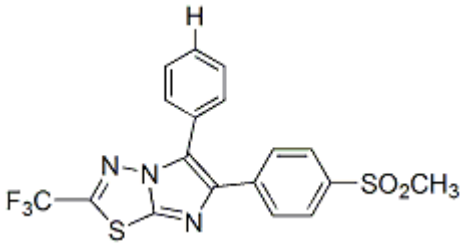
Gadad A. K. *et al.* [26], synthesized a series of 2-trifluoromethyl/sulfonamide-5,6-diarylsubstituted imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives. The compounds showed



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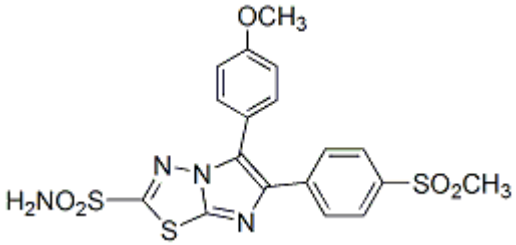

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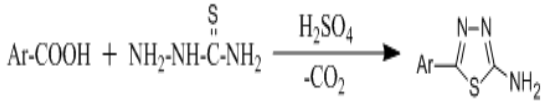
selective inhibitory activity toward COX-2 over COX-1, amongst them compounds (**39**) and (**40**) showed appreciable COX-2 selective inhibitory activity. These compounds also exhibited anti-inflammatory activity.

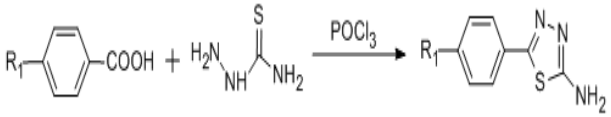
LITERATURE REVIEW

Pattan S. R. et al., reported synthesis and biological evaluation of some 1, 3, 4-thiadiazole derivatives [27]. A mixture of thiosemicarbazide (**42**), aryl carboxylic acid (**41**), in the presence of sulphuric acid was refluxed for 1 hr and poured onto crushed ice. The solid separated out was filtered, washed with water & recrystallized from ethanol.



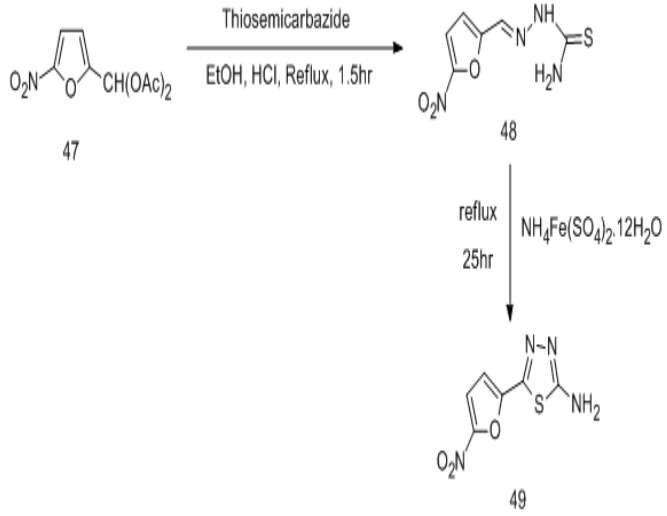
41 **42** **43**

Xu W. F. *et al.*, reported novel aminopeptidase N inhibitors derived from 1,3,4-thiadiazole scaffold [28]. A stirring mixture of benzoic acid (**44**), N-aminothiourea (**45**) and $POCl_3$ was heated at 75 ˚C for 0.5 hr. After cooling, the mixture was basified to pH 8 by the dropwise addition of 50% NaOH solution under stirring. The precipitate was filtered and recystallized from ethanol.

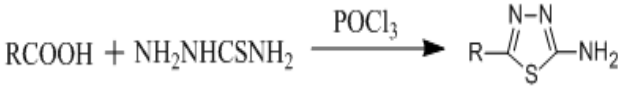


44 45 46

Foroumadi A. *et al.*, reported synthesis and in vitro anti-*Helicobacter pylori* activity of 2-(substituted benzylthio)-5-(5-nitro-2- furyl)-1,3,4-thiadiazole derivatives [29]. Reaction of 5-nitrofuran-2-carboxaldehyde diacetate (**47**) with thiosemicarbazide in refluxing ethanol yielded thiosemicarbazone. In the next step, oxidative cyclization of (**48**) in the presence of ammonium ferric sulfate afforded amino-1, 3, 4-thiadiazole.



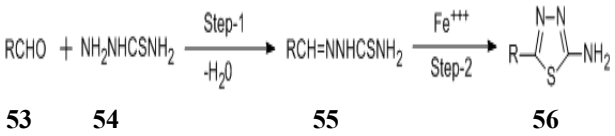
Zheng K. B. *et al.*, reported synthesis and antitumor activity of N^1-acetylamino-(5-alkyl/aryl-1,3,4-thiadiazole-2-yl)-5-fluorouracil derivatives [30]. The synthesis of 2-amino-alkyl/aryl-1,3,4-thiadiazoles (**52**) was achieved conveniently by treating carboxylic acid (**50**) directly with thiosemicarbazide (**51**) in the presence of phosphorus oxychloride.



50 51 52

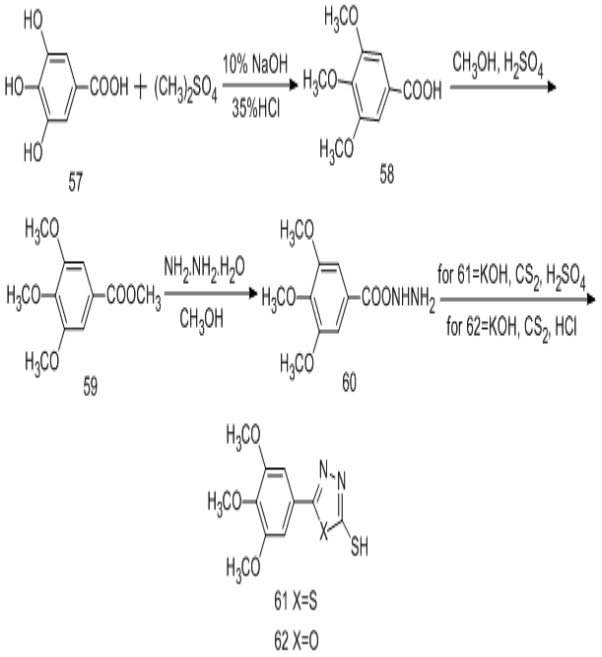
Jatav V. *et al.*, reported synthesis and CNS depressant activity of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3*H*)-ones [31]. The synthesis of 2-amino-5alkyl/aryl-1,3,4-thiadiazoles (**56**) was done by slowly heating an aromatic aldehyde (**53**) and thiosemicarbazide (**54**) with constant stirring. The formed thiosemicabazone (**55**) was suspended in distilled water and ferric chloride was added to it and heated at 80-90 ˚C. After cooling, the

whole solution was neutralized with the help of 10% aqueous ammonia solution. The crude precipitate that got separated was filtered and washed several times with distilled water and dried. Final products were recrystalized from hot water or ethanol.



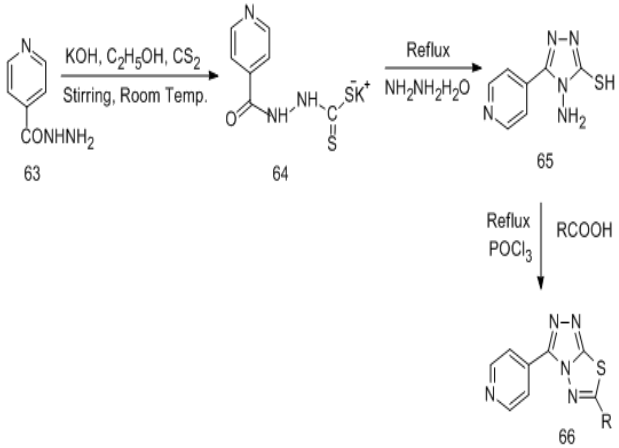
53 **54** **55** **56**

Liu F. *et al.*, reported synthesis and antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-thiadiazole and 1,3,4-oxadiazole moiety [32]. 5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazole-2-thiol (**61**) was synthesized from gallic acid in five steps including etherification, esterification, hydrazidation, salt formation, and cyclization.

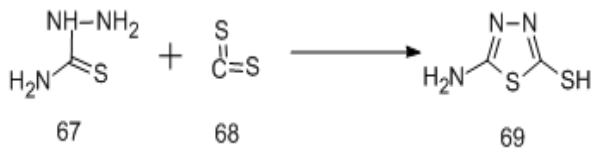


Gilani S. J. *et al.*, reported synthesis and pharmacological evaluation of condensed heterocyclic 6-substituted 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole and 1,3,4-oxadiazole derivatives of isoniazid [33]. 6-Substituted-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole (**66**) was prepared according to the procedure outlined.

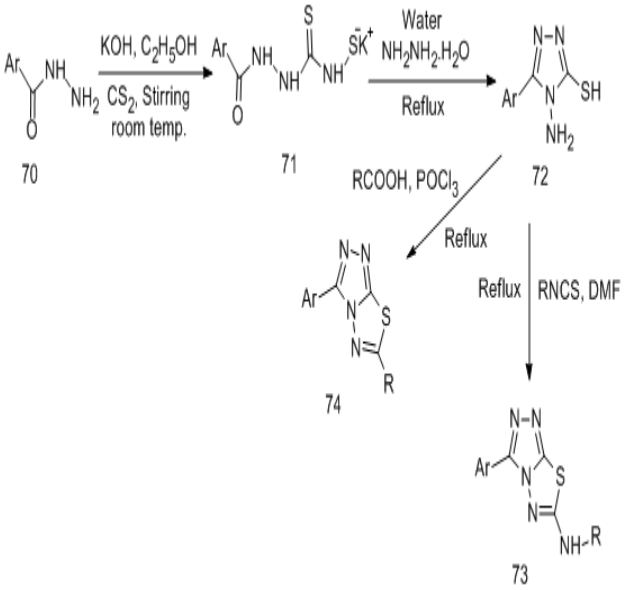
The required dithiocarbazinate was synthesized by reacting acid hydrazide with carbon disulfide and potassium hydroxide in ethanol. After that resultant triazole (**65**) was then converted to (**66**), by condensation with aromatic acids in the presence of $POCl_3$.



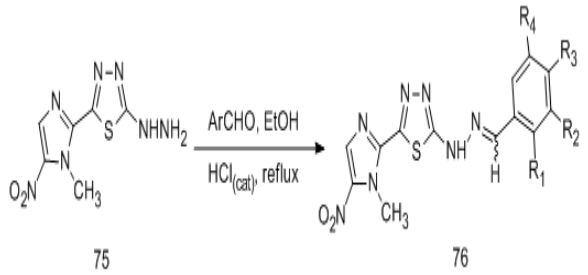
Yusuf M. *et al.*, reported synthesis and anti-depressant activity of 5-amino-1,3,4-thiadiazole-2-thiol imines and thiobenzyl derivatives [34]. Thiosemicarbazide (**67**) was suspended in absolute ethanol and anhydrous sodium carbonate and carbon disulphide (**68**) were added slowly. The mixture was stirred under reflux for 1 hr and later heated at 75–80 ˚C for 4 hr. The residue was dissolved in water, acidified with conc. HCl to give the product.



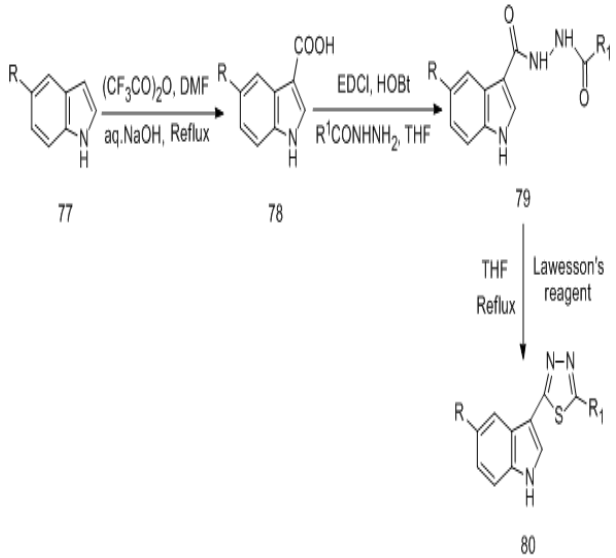
Amir M. *et al*., reported condensed bridgehead nitrogen heterocyclic system of 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole derivatives of ibuprofen and biphenyl-4-yloxyacetic acid [35]. These were prepared by condensation with aromatic acids in the presence of phosphorus oxychloride and with aryl/alkyl isothiocyanates in the presence of DMF.



Carvalho S. A. *et al*., reported studies toward the structural optimization of new brazilizonerelated trypanocidal 1,3,4-thiadiazole-2-arylhydrazone derivatives [36]. 1,3,4-thiadiazolylhydrazine (**75**) in absolute ethanol containing a catalytic amount of hydrochloric acid was added of corresponding aromatic aldehyde derivative. The mixture was stirred at room temperature for 30 min, when extensive precipitation was observed. The mixture was then poured into cold water, neutralized with 10% aqueous sodium bicarbonate solution.

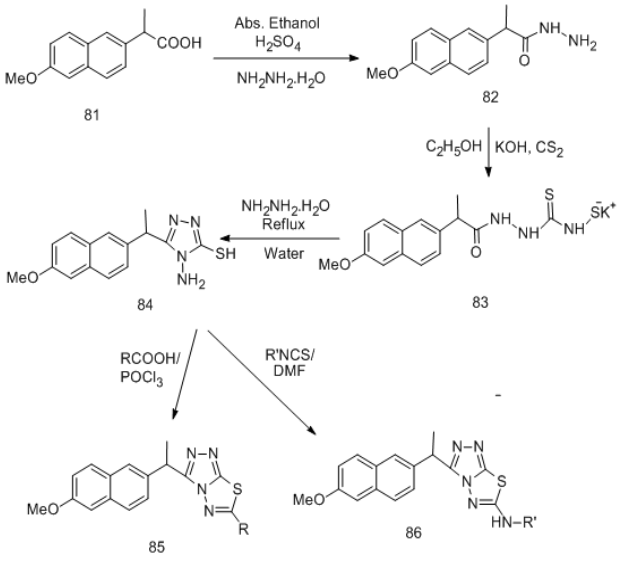


Kumar D. *et al*., reported synthesis and anticancer activity of 5-(3-indolyl)-1,3,4-thiadiazoles [37]. A mixture of indole-3-carboxylic acid (**78**), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and 1-hydroxy-benzotriazole in dry tetrahydrofuran was stirred at room temperature for 15 min. To this reaction mixture, appropriate arylhydrazide was added and continued stirring at room temperature for 6 hrs. Then the solid 1,2-diacylhydrazine (**79**) was filtered off. A mixture of 1,2-diacylhydrazines (**79**) and Lawesson's reagent in tetrahydrofuran was refluxed at 80 ˚C for 5 hrs.

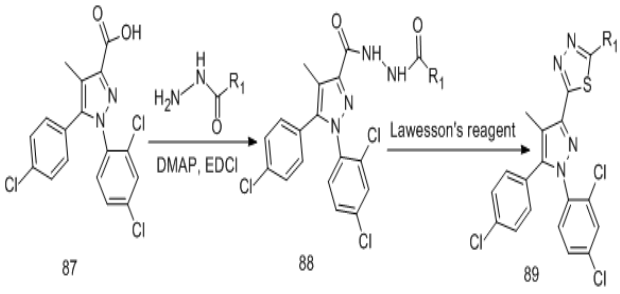


Amir M. *et al*., reported synthesis and pharmacological evaluation of condensed heterocyclic 6-substituted-1,2,4-triazolo[3,4-

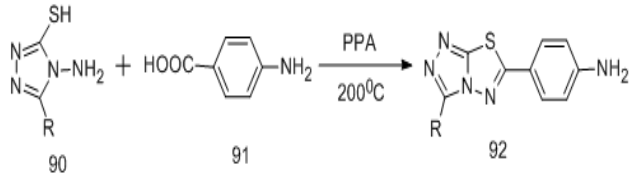
b]-1,3,4-thiadiazole derivatives of naproxen [38]. Synthesis of compounds (**85**) was prepared by condensation with aromatic acids in the presence of $POCl_3$ and compounds (**86**) were accomplished by reacting the triazole (**84**) with aryl/alkyl isothiocyanates in the presence of DMF.



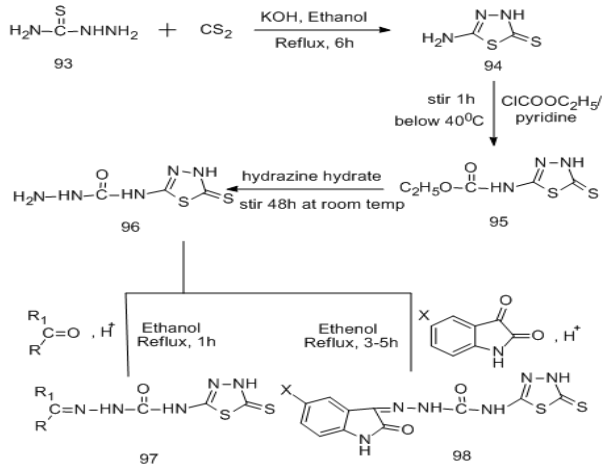
Lee J. *et al*., reported discovery of 2-(4-((1*H*-1,2,4-triazol-1-yl)methyl)-5-(4-bromophenyl)-1-(2-chlorophenyl)-1*H*-pyrazol-3-yl)-5-*tert*-butyl-1,3,4-thiadiazole (GCC -2680) as a potent, selective and orally efficacious cannabinoid-1 receptor antagonist [39]. Compounds (**89**) were prepared by (i) reaction of carboxylic acid (**87**) with a hydrazide compound in the presence of coupling reagents (EDCI, DMAP) and (ii) thionation–cyclization of the resulting product (**88**) using Lawesson's reagent to obtain a 1,3,4-thiadiazole (**89**).



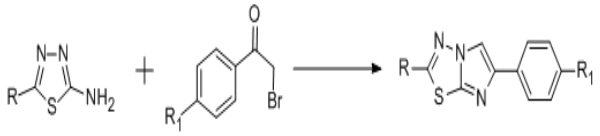
Ibrahim D. A., reported synthesis and biological evaluation of 3,6-disubstituted [1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazole derivatives as a novel class of potential anti-tumor agents [40]. Synthesis of 4-(3-substituted-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazol-6-yl) aniline derivatives (**92**) was achieved when 4-amino-5-substituted [1,2,4]-triazole-3-thiol (**90**) and 4-amino benzoic acid (**91**) were heated at 180–200 ˚C in PPA.



Abdel-Hamid M. K. *et al*., reported design, synthesis, and docking studies of new 1,3,4-thiadiazole-2-thione derivatives with carbonic anhydrase inhibitory activity [41]. 4-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)-1-(α-substituted/α,α-disubstitutedmethylene) semicarbazides (**97**), were obtained by condensing the semicarbazide (**96**) with different aldehydes and ketones. Similarly, the derivatives 4-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)-1-(2-oxoindolin-3-ylidene)semicarbazides (**98**) were prepared by refluxing the semicarbazide (**96**) with the appropriate isatin derivative.

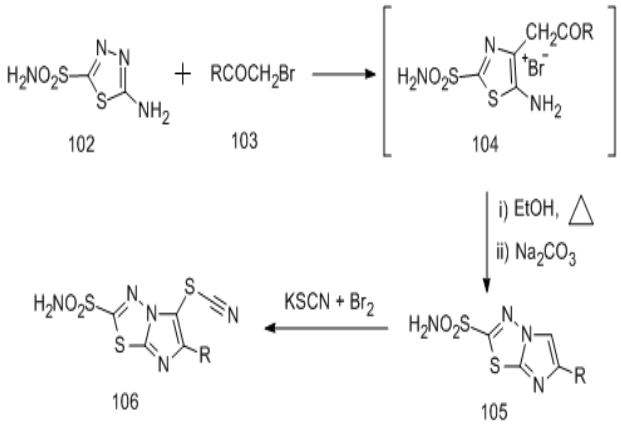


Kolavi G. *et al*., reported synthesis and evaluation of antitubercular activity of imidazo[2,1-*b*][1,3,4]-thiadiazole derivatives [6]. Synthesis of the basic nucleus imidazo[2,1-*b*][1,3,4]-thiadiazole is brought about by the condensation of 2-amino-1,3,4-thiadiazole with α-bromoarylketone under reflux in dry ethanol.



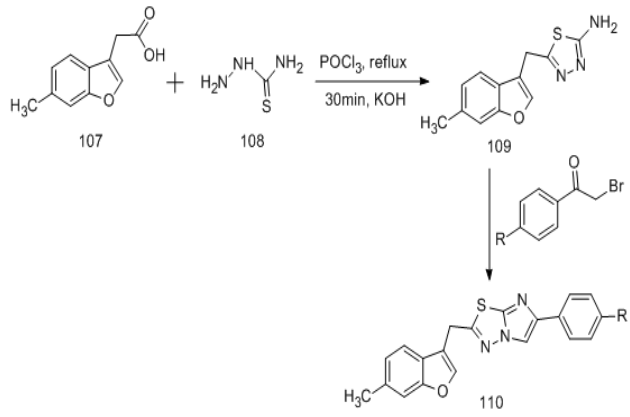
99 100 101

Gadad A. K. *et al*., reported synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanato-6-arylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide derivatives [27]. The condensation of (**102**) and (**103**) involved attack of an electrophile α-bromoketone on the more basic *endo* nitrogen (3-N) of 2-amino-1,3,4-thiadiazole–5-sulfonamide (**102**) followed by dehydrocyclisation of the intermediate in boiling anhydrous ethanol to yield 6-arylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamides which upon reaction with KSCN in the presence of bromine produced 5-thiocyanato derivative (**106**).



102 103 104 105 106

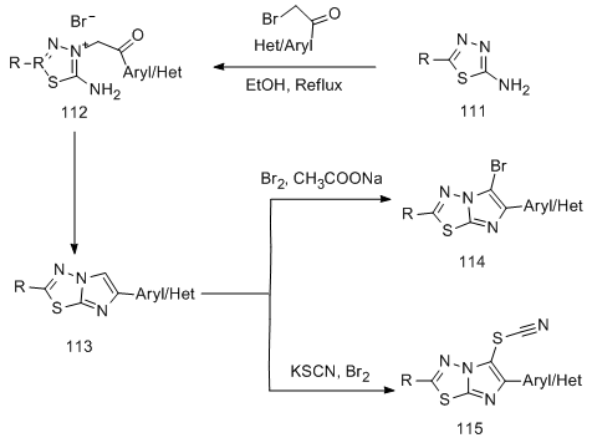
Jadhav V. B. *et al*., reported synthesis and anti-inflammatory evaluation of methylene bridged benzofuranyl imidazo[2,1-*b*][1,3,4]thiadiazoles [29]. Benzofuran-3-acetic acid upon reaction with thiosemicarbazide in presence of $POCl_3$ yielded (**109**). The imidazo[2,1-*b*][1,3,4]-thiadiazole was obtained by the condensation of (**109**) with α-bromoarylketones under reflux in dry ethanol.



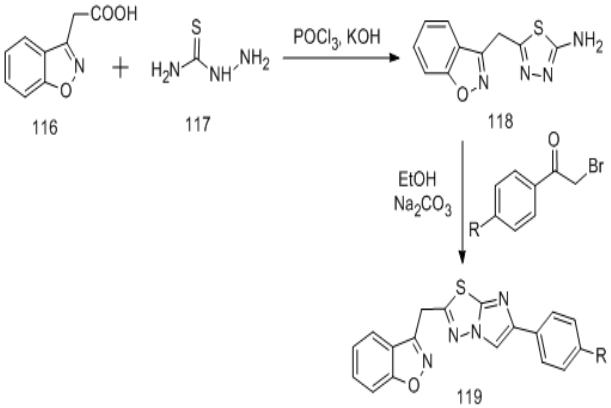
107 108 109 110

Gadad A. K. *et al*., reported synthesis and anti-tubercular activity of a series of 2-sulfonamido/trifluoromethyl-6-substituted imidazo-[2,1-*b*]-1,3,4-thiadiazole derivatives [42]. The synthesis of the imidazo[2,1-*b*]-1,3,4-thiadiazoles was carried out by the condensation of (**111**) with a α-haloaryl/heteroaryl ketone under reflux in ethanol.

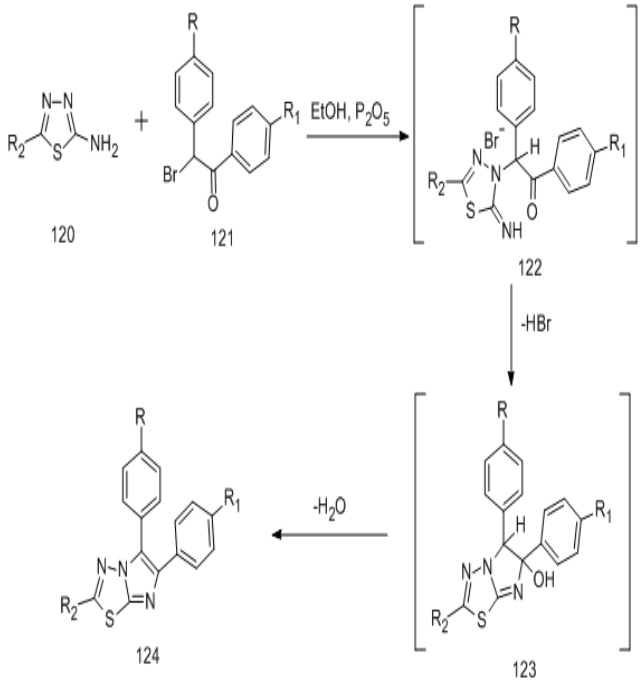
Thus obtained 2-sulfonamido/ trifluoromethyl-6-aryl/ heteroaryl-imidazo [2,1-*b*]-1,3,4-thiadiazole derivatives were subjected to electrophilic substitution reaction at the fifth position with bromine in the presence of sodium acetate in acetic acid to obtain 5-bromo derivative (**114**) and 5-thiocyanato derivatives (**115**).



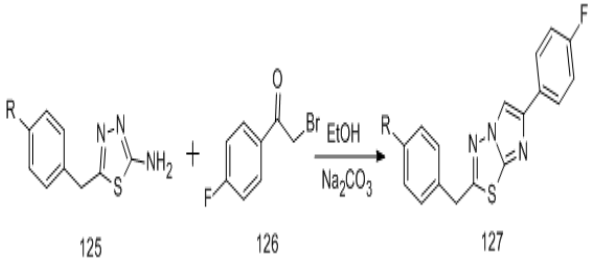
Lamani R. S. *et al*., reported synthesis and antimicrobial studies of novel methylene bridged benzisoxazolyl imidazo[2,1-*b*][1,3,4]thiadiazole derivatives [43]. Reaction of 1,2-benzisoxazole-3-acetic acid (**116**) with thiosemicarbazide in refluxing phosphorous oxychloride afforded the desired 2-amino-5-benzoisoxazol-3-ylmethyl-[1,3,4]-thiadiazole (**118**), which upon condensation with α-haloaryl ketones under reflux in dry ethanol yielded the imidazothiadiazoles (**119**) in good yield.



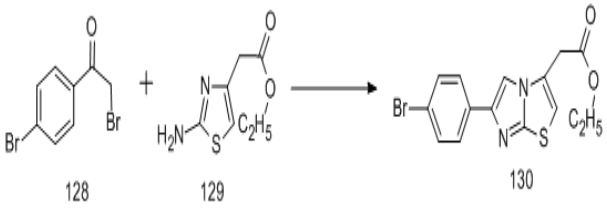
Gadad A. K. *et al*., reported synthesis and biological evaluation of 2-trifluoromethyl/sulfonamido-5,6-diaryl substituted imidazo[2,1-*b*]-1,3,4-thiadiazoles: A novel class of cyclooxygenase-2 inhibitors [30]. The synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazole derivatives (**124**) was carried out by the condensation of (**121**) with 2-amino-5-substituted-1,3,4-thiadiazole under reflux in dry ethanol. This reaction proceeds via intermediate iminothiadiazole (**122**), which spontaneously undergoes ring closer to (**123**) under reflux temperature to afford the desired fused heterocycles in good yields.



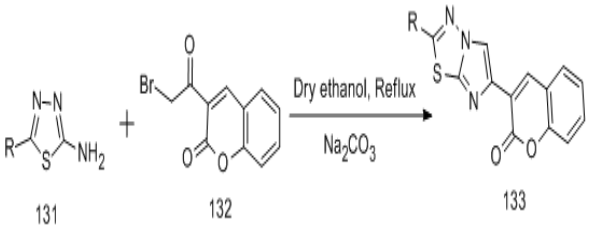
Karki S. S. *et al*., reported synthesis and biological evaluation of novel 2-aralkyl-5-substituted-6-(4'-fluorophenyl)-imidazo[2,1-*b*][1,3,4]-thiadiazole derivatives as potent anticancer agents [44]. The derivatives of imidazo[2,1-*b*][1,3,4]-thiadiazoles (**127**) containing aralkyl group at 2nd position by reacting 2-amino-5-aralkyl-1,3,4-thiadiazoles (**125**) with 4-fluoro phenacyl bromide (**126**).



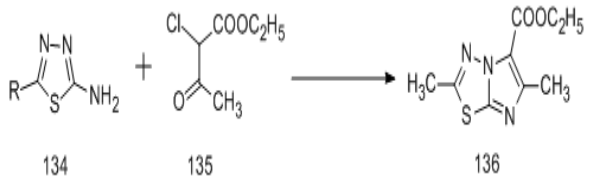
Guzeldemirci N. U. *et al*., reported synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-*b*]thiazole moiety [45]. 2-Amino-1,3-thiazole (**129**), upon reaction with α-bromoarylketone (**128**) under reflux in dry ethanol produced the basic nucleus imidazo[2,1-*b*]-thiazole moiety.



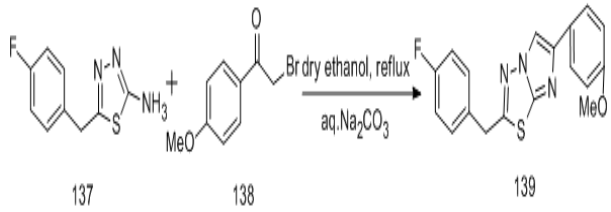
Kolavi G. *et al*., reported synthesis of novel imidazo[2,1-*b*][1,3,4]-thiadiazole and imidazo[2,1-*b*][1,3]-thiazole fused diazepinones [46]. The synthesis of basic nucleus imidazo[2,1-*b*]-1,3,4-thiadiazole is brought about by the condensation of 2-amino-1,3,4-thiadiazole with 3-(bromoacetyl)coumarin under reflux in dry ethanol.



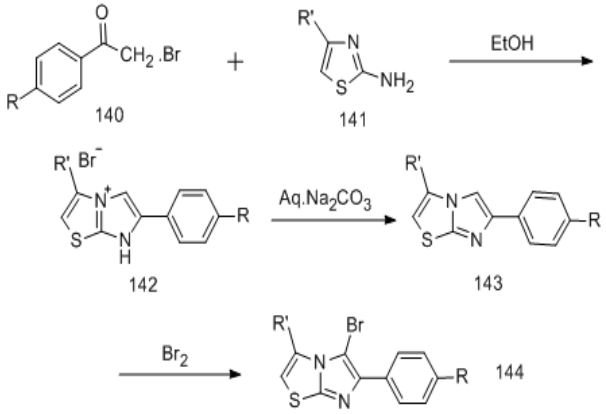
Terzioglu N. *et al*., reported synthesis and anticancer evaluation of some new hydrazone derivatives of 2,6-dimethylimidazo[2,1-*b*]-[1,3,4]-thiadiazole-5-carbohydrazide [5]. The reaction of 2-amino-5-methyl-1,3,4-thiadiazole and ethyl 2-chloroacetoacetate under reflux afforded the basic nucleus imidazo[2,1-*b*][1,3,4]-thiadiazole.



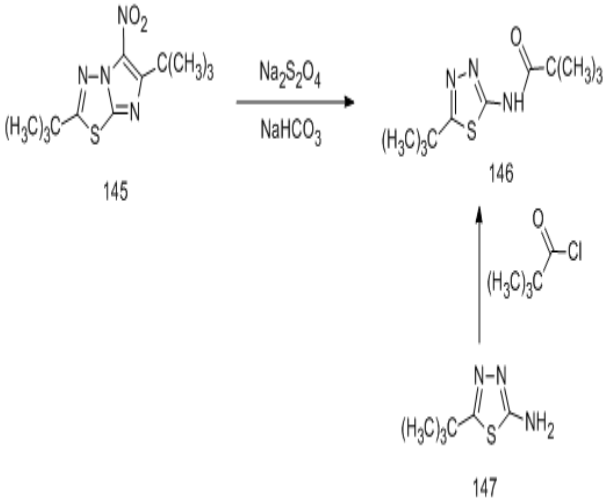
Banu A. *et al*., reported synthesis, spectroscopic and crystal structure analysis of 2-(4-fluorobenzyl)-6-(4-methoxyphenyl)imidazo[2,1-*b*][1,3,4]-thiadiazole and its morpholin- nomethyl derivative [47]. A mixture of 5-(4-fluorobenzyl)-1,3,4-thiadiazol-2-amine (**137**) and *p*-methoxy phenacyl bromide (**138**) was refluxed in dry ethanol for 12 hrs. The excess of solvent was distilled off and the solid hydrobromide salt that separated was collected by filtration, suspended in water and neutralized by aqueous sodium carbonate solution to get free base (**139**).



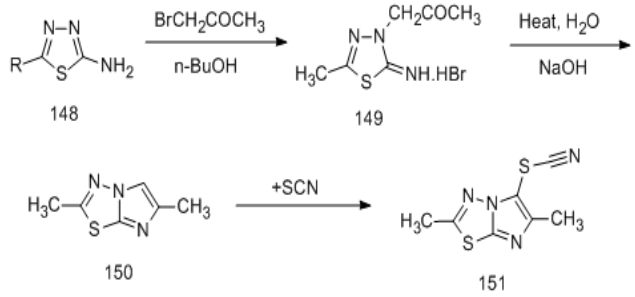
Khazi M. I. *et al*., studied synthesis and biological activity of some 3-methyl/ethoxycarbonyl-6-arylimidazo[2,1-*b*]-thiazoles and their 5-bromo/5-formyl derivatives [48]. A mixture of phenacyl bromide and 2-aminothiadiazole in anhydrous ethanol was heated on steam bath for 6 hrs and the solvent removed under the reduced pressure. The product that separated on addition of crushed ice was filtered and washed with ethanol. Compound was sparingly soluble in water, hence purified by recrystallisation from ethanol.



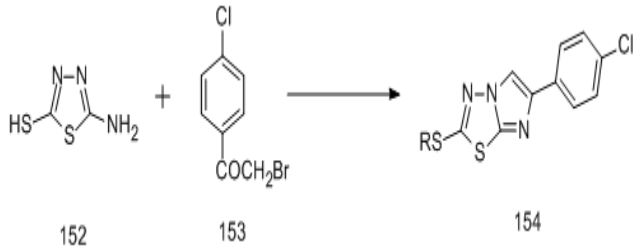
Hough T. L., reported the reaction of some 5-substituted imidazo[2,1-*b*]-1,3,4-thiadiazoles [18]. Reduction of (**145**) with sodium dithionite resulted in the unexpected cleavage of the imidazole ring. In the aqueous ethanolic bicarbonate solution, the thiadizolyl amide (**146**) was obtained.



Kano S., reported synthesis of imidazo[2,1-*b*]-1,3,4-thiadiazole and thiazolo[3,2-*b*]-triazole derivatives and thiocyanation and bromination of their compounds [15]. 6-methylimidazo[2,1-*b*][1,3,4]thiadiazole (**150**) was prepared in good yield by treatment of 2-amino-1,3,4-thiadiazole (**148**) with bromoacetone in H_2O for 1 hr. Thiocyanation of (**150**) was carried out by the bromine method and the urea method, and corresponding 5-thiocyanato derivatives were obtained.



Ram V. J. *et al*., reported synthesis of 1,3,4-thiadiazole[3,2-*a*]-pyrimidines and imidazo[2,1-*b*]-1,3,4-thiadiazole as leishmanicides [49]. The interaction of 5-alkylthio-2- amino-1,3,4-



thiadiazole (**152**) with ω-bromo-4-chloro-acetophenone in ethanol at reflux temperature produces 2-alkylthio-6-(4-chlorophenyl)-imidazo[2,1-*b*][1,3,4]thiadiazole.

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