



BIOLOGICAL ACTIVITIES OF IMIDAZO[2,1-b][1,3,4]THIADIAZOLE DERIVATIVES: A REVIEW

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Abstract-1,3,4-Thiadiazole skeleton forms an integral part of various medicinal agents and depicts a vast array of biological activities such as antimicrobial, anti-inflammatory, analgesic, antileishmanial, antitumor, anti-tuberculosis, antileptic, antiviral and other activities. 1,3,4-Thiadiazole moiety has many desirable features which makes them pharmaceutically suitable as it can act as “hydrogen binding domain” and “two electron donor system”. On the other hand imidazole nucleus is one of the most important and well-known five-membered heterocycle, which is abundant in natural products and responsible for biological activities displayed by vast majority of compounds containing this nucleus. In the recent years, a lot of reports have indicated that the fused imidazo[2,1-b][1,3,4]thiadiazoles emerged out as a new class of compounds possessing wide and interesting biological properties. In the present study we have reviewed the different biological activities of imidazo[2,1-b][1,3,4]thiadiazoles and thus highlighting the importance of this scaffold in medicinal chemistry.

Keywords: biological activities, 1,3,4-thiadiazole, imidazole, imidazo[2,1-b][1,3,4]thiadiazole.

Introduction

During the past few decades, small ring heterocycles containing two or more hetero atoms such as thiazole, oxazole, pyrazole, triazole have received tremendous amount of attention and have been considered as a reliable source for discovering novel biologically active molecules. Thiadiazole is a five-membered ring system containing two nitrogen atoms and one sulphur atom with conjugated p and π electrons. 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 (Fig 1). Thiadiazoles can act as bioisosteres of oxadiazole, oxazole and benzene, and substitution of these heterocycles with a thiadiazole moiety can lead to analogues with improved biological activities because sulfur atom can improve the lipo solubility of a molecule.¹

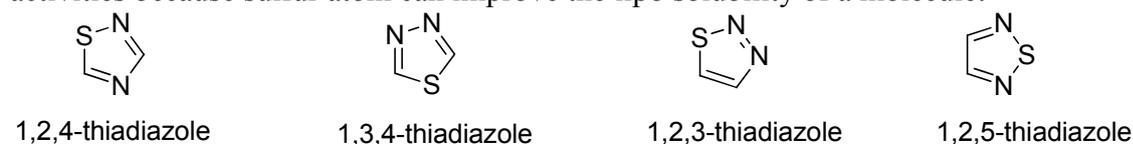


Fig1.

Among all the derivatives of thiadiazole, 1,3,4-thiadiazole scaffold has gained much importance in pharmaceutical chemistry owing to its wide and interesting biological properties such as anticonvulsant,^{ii,iii} antihypertensive,^{iv,v} local anesthetic,^{vi} anticancer,^{vii,viii} antimicrobial,^{ix,x} anti-HIV,^{xi} anti-inflammatory,^{xii,xiii} hypoglycemic activities.^{xiv} A number of 1,3,4-thiadiazole based drugs are currently available in the market for example acetazolamide (1) is a carbonic anhydrase inhibitor and used for the treatment of glaucoma, epileptic seizure, periodic paralysis and dural ectasia. Methazolamide (2) also act as carbonic anhydrase inhibitor^{xv} and used in the treatment of glaucoma. It lowers the high pressure inside the eye and helps to prevent blindness, vision loss and nerve damage. 1,3,4-thiadiazole can act as bioisostere of thiazole ring therefore it is used in the preparation of third and fourth generation of cephalosporins, e.g. cefazolin sodium (CFZL; 3) and cefazedone (CFZD, 4). ARRY-520 (5) also known as filanesib, is a kinesin spindle protein inhibitor and is currently under clinical trials for the treatment of cancer.^{xvi} Megazol (6) is widely used for the treatment of African trypanosomes also known as sleeping sickness.^{xvii} Tebuthiuron (7) is a non-selective broad spectrum herbicide. It is used to control weeds, woody and herbaceous plants (Fig. 2).

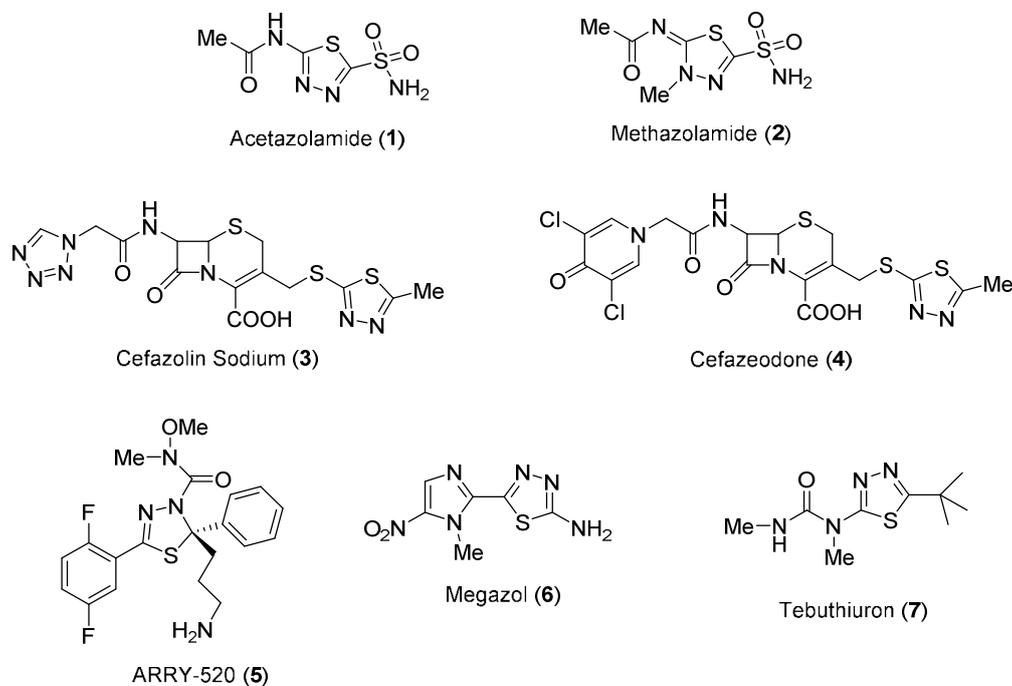
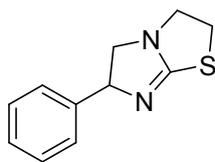
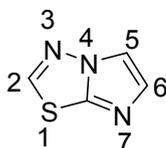


Fig 2

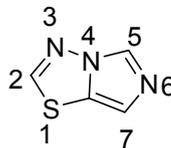
After the discovery of broad spectrum anthelmintic tetramisole (8), a great deal of interest was also pursued in replacing thiazole ring in tetramisole with bioisosteric thiadiazole motif which resulted in the formation of imidazo[2,1-*b*][1,3,4]thiadiazoles.^{xviii} Two types of bicycle imidazo[2,1-*b*][1,3,4]thiadiazole ring systems are possible 9 and 10. Both the system contains nitrogen as a bridgehead atom at 4th position.



Tetramisole (8)

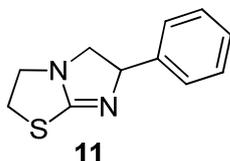


imidazo[2,1-*b*][1,3,4]thiadiazole (9)

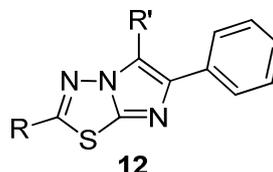


imidazo[5,1-*b*][1,3,4]thiadiazole (10)

There are several reports in literature which demonstrated that the fusion of 1,3,4-thiadiazole with imidazo[2,1-*b*] ring system resulted in the compounds having a broad spectrum of biological activities. 2-Amino-1,3,4-thiadiazole skeleton had a wide variety of literary importance owing to its antitumor potential and subsequently it is found that its fusion with the imidazo[2,1-*b*] ring system has resulted in compounds with potential anti-cancer, analgesic, antibacterial, antisecretory and cytotoxic activities. For example Levamisole (11) which contains imidazo[2,1-*b*][1,3]thiazole as a basic nucleus, acts as an anthelmintic agent, and also found to be an immuno-stimulant in 1972 by Rebnoux. It appears to be the most effective in patients with small tumor burdens and it generally act by stimulating the responsiveness of lymphocytes to the tumor antigen.^{xix} In addition, the imidazo[2,1-*b*]thiazole derivatives (12) of Levamisole have also been reported as potential antitumor agents.^{xx}



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A lot of reports cited in literature have revealed that fused imidazo[2,1-*b*][1,3,4]thiadiazole derivatives possess wide and interesting biological activities and their coupling with other heterocyclic rings furnishes novel and complex organic molecules possessing different biological properties. In the present review we discussed the different biological activities possessed by imidazo[2,1-*b*][1,3,4]-thiadiazole derivatives till now.

Biological Activity

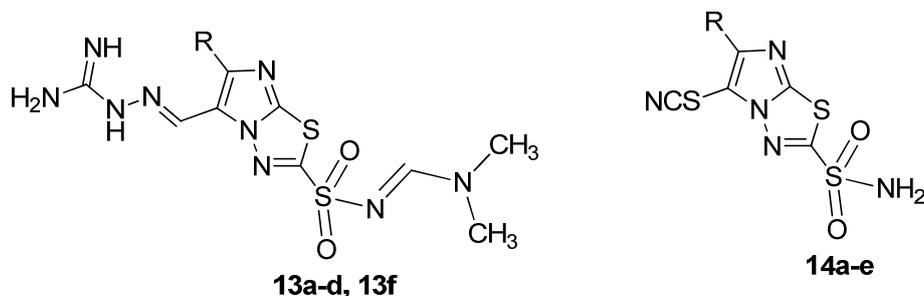
A large number of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives have been synthesized and reported to possess a vast array of biological activities such as antibacterial, antifungal, antitubercular, anticancer and antisecretory. Apart from this, some of the compounds incorporating this nucleus have also shown significant anti-inflammatory, cardiotoxic, diuretic and herbicidal activities.

- Antibacterial and antifungal activity
- Anticancer Activity
- Antitubercular Activity
- Anti-inflammatory Activity
- Analgesic Activity

- Anticonvulsant activity
- Antihyperlipidemic
- Other biological activities

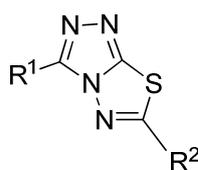
Antibacterial and antifungal activity

A series of 5-guanylhyazone/thiocyanato-6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide derivatives was reported^{xxi} and the newly synthesized compounds were tested for their antibacterial studies using Cup plate method. Tests were carried out against one Gram-positive bacterium (*Staphylococcus aureus*) and four Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* and *Pneumococci*). Bioassay activity results showed that most of the synthesized compounds exhibited significant activity against all the bacterial stains. Interestingly, amongst all, compounds **13b**, **13c**, **14b**, **14c** and **14e** showed comparable activity to the reference drug Sulfamethoxazole and Norfloxacin against bacterial strains *Escherichia coli* and *Staphylococcus aureus* at all concentrations. Compounds **14b**, **14c** and **14e** were found to possess superior activity against *S. aureus* even at 50 µg concentration.



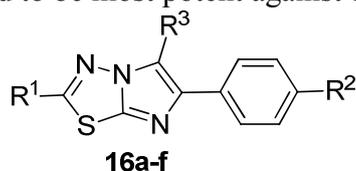
- a:** R= C₆H₅; **b:** R= 4-Cl-C₆H₄
c: R= 4-Br-C₆H₄; **d:** R= 4-CH₃-C₆H₄
e: R= 4-NO₂-C₆H₄; **f:** R= 3-coumarinyl

A new series of 4,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives were synthesized^{xxii} and all the newly synthesized compounds were evaluated for their *in vitro* antibacterial studies against Gram-positive bacteria (*Bacillus subtilis*) and four Gram-negative bacteria (*Escherichia coli* and *Pseudomonas fluorescens*, *Xanthomonas campestris pvs* and *Xanthomonas oryzae*) and antifungal activity against four fungal strains (*Aspergillus niger*, *Aspergillus flavus*, *Fusarium oxysporum* and *Trichoderma sp*) by disc diffusion method. Streptomycin and Tetracycline used as reference drugs against bacteria and Nystatin was used as reference drug against fungi. Compounds **15a**, **15b** and **15c** bearing electron donating groups ethyl, phenyl and *p*-tolyl respectively at 3rd position showed excellent activity against all the tested bacterial and fungal strains while *p*-chlorophenyl substituted **15d** was found to be inactive. Compounds **15e-g** having electron donating alkyl groups at both 3rd and 6th position showed significant activity against all the screened strains.

**15a-g**

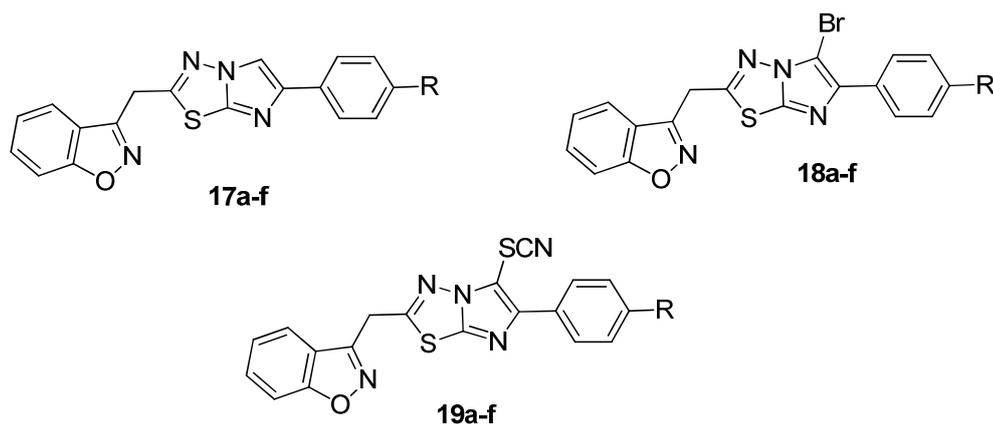
- a:** R¹ = C₂H₅, R² = 2-Cl-C₆H₅ **e:** R¹ = C₂H₅, R² = CH(C₃H₇)₂
b: R¹ = C₆H₅, R² = 2-Cl-C₆H₅ **f:** R¹ = C₆H₅, R² = CH(C₃H₇)₂
c: R¹ = 4-CH₃-C₆H₅, R² = 2-Cl-C₆H₅ **g:** R¹ = 4-CH₃-C₆H₅, R² = CH(C₃H₇)₂
d: R¹ = 4-Cl-C₆H₅, R² = 2-Cl-C₆H₅

A series of 2,6-disubstituted and 2,5,6-trisubstituted imidazo[2,1-b][1,3,4]thiadiazoles was synthesized^{xxiii} and the compounds (**16a-f**) were tested for their preliminary *in vitro* antibacterial activity against *Escherichia coli* and *Bacillus cirrhosis* and antifungal activity against *Aspergillus niger* and *Penicillium wortmanni* using cup plate method at a concentration of 25–100 µg/mL in presence of DMF as solvent. Aldehydes **16a** and **16b** showed promising antibacterial activity against the tested bacterial strains. Against the fungal strains compounds **16c** and **16d** showed better antifungal activity, however pyrrolidine containing **16e** was found to be most potent against both the tested fungal strains.

**16a-f**

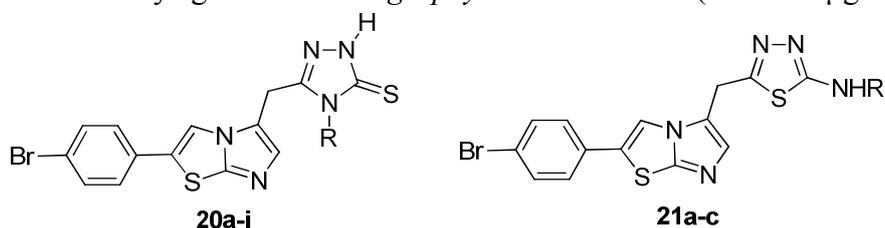
- 16a;** R¹ = cyclohexyl ; R² = Br; R³ = CHO
16b; R¹ = 2-furyl ; R² = H; R³ = CHO
16c; R¹ = 2-furyl ; R² = H; R³ = CH₂OH
16d; R¹ = 2-thienyl ; R² = H; R³ = CH₂OH
16e; R¹ = cyclohexyl ; R² = H; R³ = —H₂C—N

The synthesis, evaluation and SAR studies of a novel series^{xiv} of methylene bridged benzisoxazolyl imidazo[2,1-b][1,3,4]thiadiazoles was carried out. Compounds **17b**, **17d**, **18b**, **18e** and **19b** showed very promising activity against *Bacillus subtilis* and *Escherichia coli*. Compound **19b** was found to be active against all the bacterial strains, however compounds **17b** and **17d** containing electron withdrawing chloro and bromo functional groups respectively showed significant activity against *Escherichia coli* as compared to Ampicilin (reference drug). Bioassay results of antifungal activities indicated that compounds **17d**, **17f** and **19e** possess good activity against *Candida albicans*. Against *Aspergillus fumigatus*, compound **17d** displayed excellent activity comparable to standard drug Clotrimazole, while compounds **17a**, **17e** and **19f** also showed promising activity against this strain.



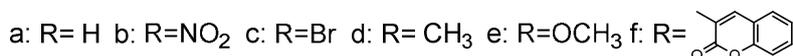
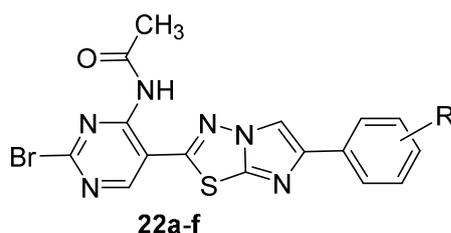
a: R= H; b: R=Cl; c: R=NO₂:
d: R= Br; e: R= OCH₃; f: R=3-coumarinyl

Two groups of structure hybrids comprising basically the triazole moiety attached to polysubstituted thiazole or 2,5-disubstituted-1,3,4-thiadiazole counterparts through various linkages.^{xv} Twelve compounds were evaluated for their *in vitro* antimicrobial activity assessed by the microbroth dilution technique. Preliminary results revealed that some of the compounds exhibited promising antimicrobial activities. Compound **20d** containing *N*-butyl substituent found to be most active against two bacterial strains *S. aureus* and *E. coli*. Compound **21b** was also found to possess prominent activity against *E. coli* while compounds **20b**, **20c**, **21a** and **21b** were most effective against *T. tonsurans*. Compound **20a** showed excellent activity against *T. mentagrophytes var. erinacei* (MIC = 8 µgcm⁻³).

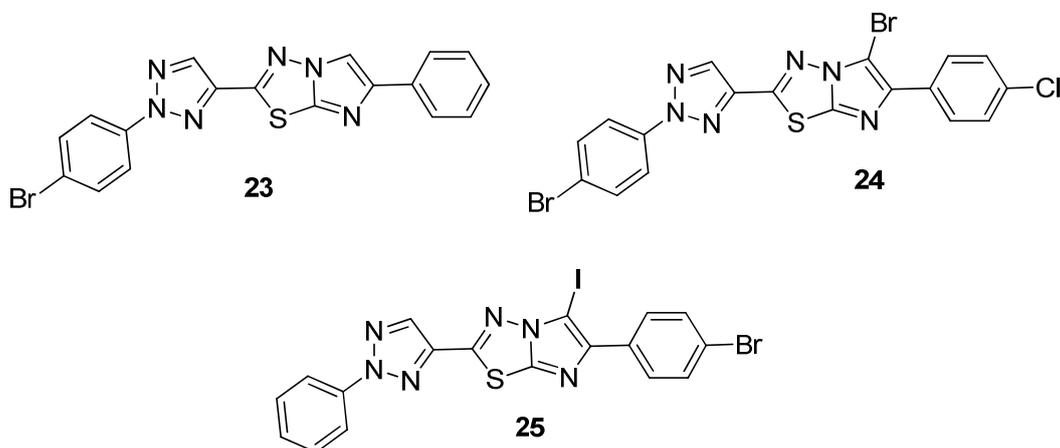


a: R= CH₃ b: R= C₂H₅ c: R= C₃H₇ d: R= C₄H₉ e: R= CH₂CH=CH₂
f: R= C₆H₅ g: R= 4-Br-C₆H₄ h: 4-Cl-C₆H₄ i: 4-CH₃-C₆H₄

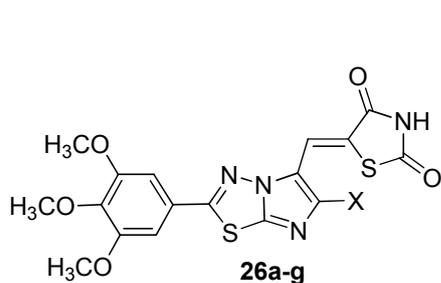
A novel series of *N,N'*-(5-(6-(4-substitutedphenyl)imidazo[2,1-b][1,3,4]-thiadiazol-2-yl)pyrimidine-2,4-diyl)diacetamide was synthesized and screened for antibacterial activities using cup-plate-agar-diffusion method. Results of antibacterial assay showed that the compounds **22b**, **22e** and **22f** possess very good activity against both gram positive (*E. coli* and *Staphylococcus aureus*) and gram-negative (*Bacillus subtilis* and *Pseudomonas aeruginosa*) bacterial pathogens as compared to the standard drug Methotrexate. The structure activity relationship (SAR) studies revealed that the presence of methoxy and halo group in para position at aromatic ring (R = OCH₃, Br) of the nucleus has significant effect on the antibacterial activity.^{xvi}



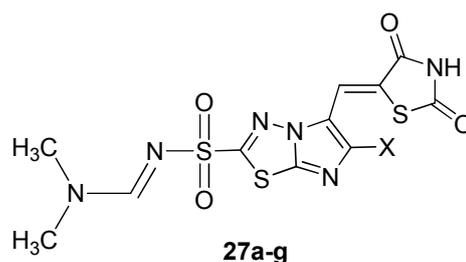
A new series of thiadiazole derivatives containing 1,2,3-triazoles was presented.^{xvii} All the newly synthesized compounds were evaluated for their *in vitro* antifungal and antibacterial activities by following agar diffusion method. The results showed that some of the compounds possess strong antifungal activities. Derivatives **23** and **24** were found to be moderately active against *Escherichia coli*, while **25** was also found moderately potent against *Pseudomonas aeruginosa*.



The synthesis of 5-imidazo[2,1-b][1,3,4]thiadiazol-substituted thiazolidine-2,4-diones **26a-g** and **27a-g** were prepared.^{xxviii} The compounds were screened for their *in vitro* antimicrobial activity and showed variable inhibitory effects against the tested bacterial and fungal strains. Compounds **26e**, **26f**, **27e** and **27f** having 4-bromophenyl and 4-chlorophenyl groups at 6th position showed significant activity against *S. aureus* and *E. faecalis* and moderate activity against *E. coli* and *P.aeruginosa*, while 4-methylphenyl, 4-methoxyphenyl and 4-nitrophenyl substituted compounds **26a**, **26b**, **26c**, **26d**, **26g**, **27a**, **27b**, **27c**, **27d** and **27g** showed only weak to moderate activity. The compounds **26e**, **26f**, **27e** and **27f** also exhibited remarkable activity against all the tested fungal strains.

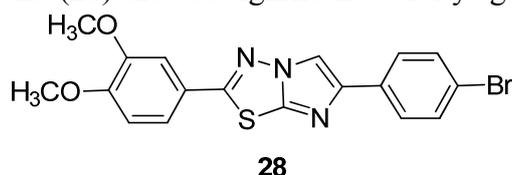


X= a: C₆H₅, b: 4-CH₃-C₆H₄, c: 4-OCH₃-C₆H₄,
d: 4-NO₂-C₆H₄, e: 4-Br-C₆H₄, f: 4-Cl-C₆H₄,
g: 2,5-(OCH₃)₂C₆H₃

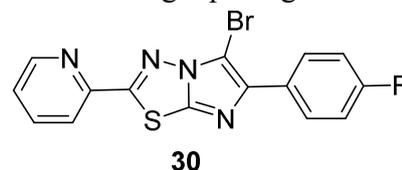
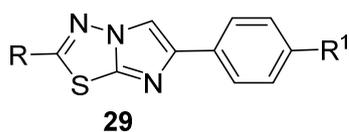


X= a: C₆H₅, b: 4-CH₃-C₆H₄, c: 4-OCH₃-C₆H₄,
d: 4-NO₂-C₆H₄, e: 4-Br-C₆H₄, f: 4-Cl-C₆H₄,
g: 2,5-(OCH₃)₂C₆H₃

Imidazo[2,1-*b*][1,3,4]thiadiazole derivatives were synthesized from cyclocondensation reaction of 5-phenyl-1,3,4-thiadiazol-2-amine with bromoester.^{xxix} Investigation of synthesized compounds for antimicrobial activity was carried out by agar dilution method against two bacterial strains: *Staphylococcus aureus*, *Escherichia coli* and three fungal strains: *Candida albicans*, *Candida tropicalis* and *Tryptococcus neoformans*. The synthesized compounds were found to be less effective against bacterial strains as compared to the fungal strains. Particularly compound (**28**) showed significant activity against all the fungal strains.



The synthesis of 2-alkyl/(hetero)aryl-6-aryl imidazo[2,1-*b*][1,3,4]thiadiazoles **29** and their 5-bromo derivatives **30** were also evaluated for antibacterial and antifungal properties. Some of these compounds were found to be active against tested bacterial and fungal pathogens.^{xxx-xxxv}



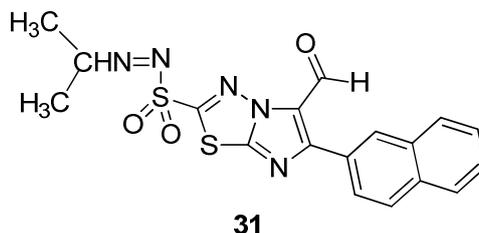
R = 4-Cl-C₆H₄, R¹ = C₆H₅, 4-Cl-C₆H₄, 4-Ph-C₆H₄
R = 2-CH₃-C₆H₄, R¹ = C₆H₅, 4-Br-C₆H₄, 4-Cl-C₆H₄, 4-Ph-C₆H₄
R = 2,4-Cl₂-C₆H₃, R¹ = C₆H₅
R = 4-^tBu-C₆H₄, R¹ = 4-Cl-C₆H₄
R = 2-OH-C₆H₄, R¹ = C₆H₅, 4-Br-C₆H₄, 4-Cl-C₆H₄

R = H, Cl, Br

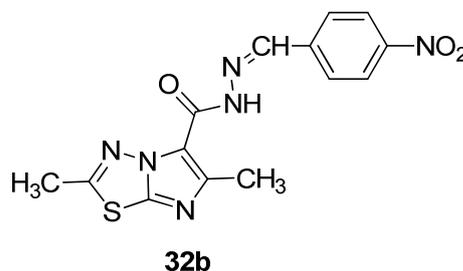
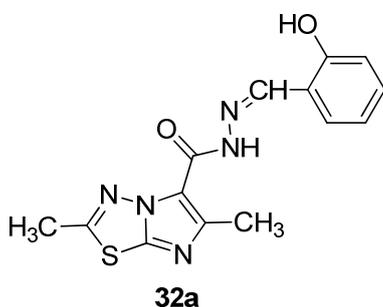
Anticancer Activity

Another series of novel 5-formyl-6-arylimidazo(2,1-*b*)-1,3,4-thiadiazole-2-*N*-(dimethylaminomethyl)sulfonamides was synthesized and compounds were evaluated for their *in vitro* cytotoxic effects against a panel of 60 human tumor cell lines. All the screened compounds showed significant *in vitro* cytotoxic effects against a variety of human tumor cell lines including cells derived from solid tumors such as colon, non-small cell lung, central nervous system, ovarian, melanoma, prostate and breast cancer, and also few cell lines of renal cancer and leukemia. Substitution of a formyl group at the 5- and substituted aromatic group at 6-position generated compounds **31** with potent antitumor activity whereas

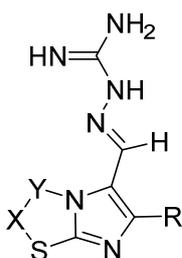
introduction of bromo functionality at 5- and ester group at 6-position leads to compounds with lower activity.^{xxxvi}



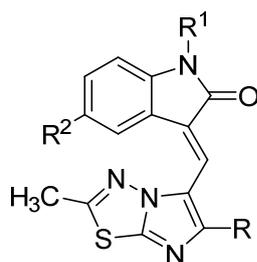
A new series of compounds 2,6-dimethyl-*N*-substituted phenylmethylene-imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbohydrazides was reported.^{xxxvii} The newly synthesized compounds were screened for their *in vitro* cytotoxic activity against lung, breast and CNS cell lines. The hydroxyl derivative **32a** and nitro derivative **32b** showed prominent cytotoxic activity and reduced the growth of cell lines upto 32% and these compounds were further evaluated against the full panel of 60 human tumor cell lines. The biological activity data revealed that compound **32a** was highly active against ovarian cancer cell line (OVCAR-3, $\log_{10}GI_{50}$ value -5.51) and breast cancer cell line (MCIC $\log_{10}GI_{50}$ value = -4.51). The nitro derivative **32b** demonstrated an excellent activity against two CNSC cell lines (SF-539, $\log_{10}GI_{50}$ value = -4.50 and U251, $\log_{10}GI_{50}$ value = -4.63), an OC cell line (SK-OV-3, $\log_{10}GI_{50}$ value = -4.55) and a BC cell line (MDA-MD-231/ATCC, $\log_{10}GI_{50}$ value -4.62). Compounds **32a** and **32b** showed superior activity than standard drugs chlorambucil, 5-fluorouracil and melfalan against an OC cell line, OVCAR-3 and SKOV-3, respectively.



A series of guanyl hydrazones **33** was reported from imidazo-[2,1-*b*]-thiazoles ($x = CH$) and thiazolines ($x = CH_2$) bearing substituents at position 6. The synthesized compounds were evaluated in mice bearing Ehrlich ascites tumor cells.^{xxxviii-xxxix} The results displayed that the presence of 4-chlorophenyl group at position 6 showed better antitumor activity as compared to compounds just bearing chlorine group at the same position. There is not much effect of the double bond at position 2, 3. However compounds **33a** and **33d** were found to be slightly more active than corresponding 2,3-dihydro analogs **33f** and **33i**. Further, the introduction of more than one chlorine atom on the phenyl ring in compounds **33k-n**, did not lead to any enhancement in the antitumor activity shown by monochlorophenyl derivatives.

**33****33a** X-Y = CH=CH, R = Cl**33b** X-Y = CH=CH, R = CH₃**33c** X-Y = CH=CH, R = C₆H₅**33d** X-Y = CH=CH, R = 4-ClC₆H₄**33e** X-Y = CH=CH, R = 4-CH₃C₆H₄**33f** X-Y = CH₂-CH₂, R = Cl**33g** X-Y = CH₂-CH₂, R = CH₃**33h** X-Y = CH₂-CH₂, R = C₆H₅**33i** X-Y = CH₂-CH₂, R = 4-ClC₆H₄**33j** X-Y = CH₂-CH₂, R = 4-CH₃C₆H₄**33k** X-Y = CH=CH, R = 2,4-Cl₂C₆H₃**33l** X-Y = CH=CH, R = 2,3,4-Cl₃C₆H₂**33m** X-Y = CH₂-CH₂, R = 2,4-Cl₂-C₆H₃**33n** X-Y = CH₂-CH₂, R = 2,3,4-Cl₃C₆H₂

Further in continuation, same group^{x1} reported some new analogues containing indole and imidazothiazole ring. On the basis of preliminary *in vitro* anticancer activity fifteen compounds were selected and tested further for full five dose assay. The results were expressed as the negative log of the molar concentration at three assay end points: the 50% growth inhibitory power (pGI50), the cytostatic effect (pTGI) total growth inhibition), and the cytotoxic effect (pLC50). Vincristine sulfate is used as the reference drug. Interestingly, it was noted that introduction of carboxyl group at position 5 (compound **34a**) in the indolinone system led to a decrease in activity while the presence of fluorine at the same position in **34b**, was found to enhance the activity and showed a mean growth inhibition of 5.22 and it was found to be particularly effective against colon tumors (pGI = 5.62). Imidazothiadiazole derivative **34c** having N-methyl group was found to be most active against prostate cancer (pGI = 6.00) and leukemia (pGI = 5.84) while N-methylindole derivative **34d** containing 2,5-dimethoxyphenyl group at position 6 was found to be mainly active against leukemias (pGI₅₀ = 5.13) with relatively low cytotoxicity (pLC₅₀ = 4.01). 2-Methylimidazothiazole derivatives **34e-g** and **34h-k** bearing 4-methylphenyl or a 4-chlorophenyl group at position 6 gave better results. Particularly compound **34h** was found to be highly active against kidney tumors (pGI50 = 5.11), **34e** showed marked antitumor activity against prostate cancers and leukemias, and compound **34f** was most active toward CNS tumors.



34a-k

34a: R= CH₃, R¹= H, R²= COOH

34b: R= CH₃, R¹= H, R²= F

34c: R= CH₃, R¹= CH₃, R²= Cl

34d: R= 2,5-(OCH₃)₂-C₆H₃, R¹= CH₃, R²= Cl

34e: R = 4-CH₃-C₆H₄, R¹= H, R²= OCH₃

34f: R = 4-CH₃-C₆H₄, R¹= H, R²= Cl

34g: R = 4-CH₃-C₆H₄, R¹= H, R²= OH

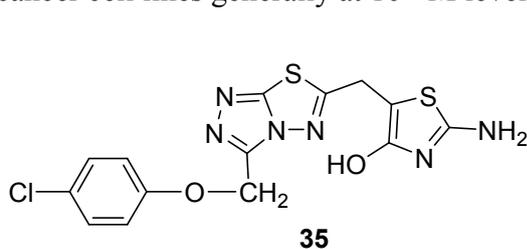
34h: R = 4-Cl-C₆H₄, R¹= H, R²= H

34i: R = 4-Cl-C₆H₄, R¹= H, R²= OCH₃

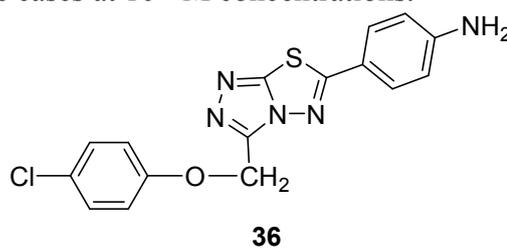
34j: R = 4-Cl-C₆H₄, R¹= H, R²= Cl

34k: R = 4-Cl-C₆H₄, R¹= H, R²= OH

A new set of 3,6-disubstituted[1,2,4]triazolo[3,4-b][1,3,4]-thiadiazoles was produced and screened for their anticancer activity against a panel of 60 human cancer cell lines.^{xlii} Compounds **35** and **36** were found to have inhibitory effects on the growth of a wide range of cancer cell lines generally at 10⁻⁵ M level and in some cases at 10⁻⁷ M concentrations.

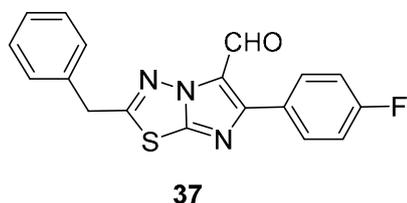


35

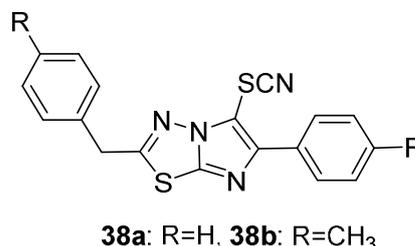


36

Fourteen novel derivatives of imidazo[2,1-b][1,3,4]thiadiazoles were synthesized by reacting 2-amino-5-aryl-1,3,4-thiadiazoles with 4-fluoro-phenacylbromide. The synthesized compounds were evaluated against the human T-cell leukemia cells for the study of preliminary anti-cancer activity. Amongst all, compounds **37**, **38a** and **38b** exhibited strong cytotoxic activity.^{xliii}

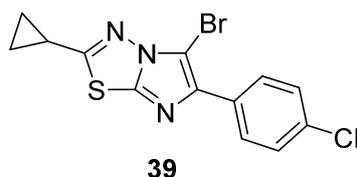


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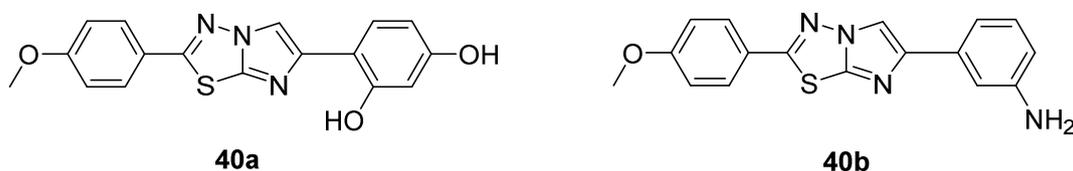


38a: R=H, 38b: R=CH₃

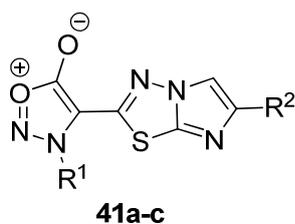
A series of 2-cyclopropylimidazo[2,1-b][1,3,4]thiadiazoles was prepared and compounds were tested for their anti-tumor activity.^{xliiii} 5-Bromo-6-(4-chlorophenyl)-2-cyclopropylimidazo[2,1-b][1,3,4]thiadiazole (**39**) exhibited significant anticancer activity against most of the tested cell lines representing nine different subpanels with GI₅₀ values between 1.79-43.4 μM.



The same group reported some novel 2,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazoles synthesized from 5-substituted-1,3,4-thiadiazol-2-amine. The newly synthesized compounds were evaluated in the National Cancer Institute for single dose *in vitro* primary cytotoxicity assay.^{xliv} After preliminary examination, compound **40a** and **40b** were selected and evaluated against the full panel of 60 human tumor cell lines at a minimum of five concentrations at 10-fold dilutions. 3-(2-(4-Methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)aniline (**40b**) exhibited significant *in vitro* anticancer activity against Non Small Cell Lung Cancer HOP-92 cell line ($GI_{50} = 0.114$ mM) and Renal Cancer CAKI-1 cell line ($GI_{50} = 0.743$ mM). Compounds **40a** and **40b** were also found to be more selective towards breast cancer cell lines as compared to other cell lines.

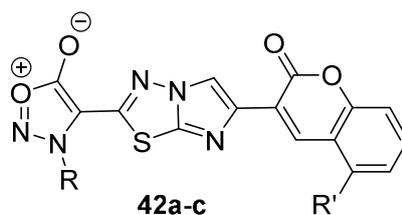


In 2011, a new series of 3-aryl-4-(6'-aryl-imidazo[2,1-b][1,3,4]thiadiazol-2'-yl)-sydnones was prepared. All the newly synthesized compounds were evaluated for their anticancer activity against cervical cancer cell lines (Hela) by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay. It was established that among the studied compounds, thiadiazoles **41a**, **41b** and **41c** found to have the maximum inhibition against cancerous cells.^{xlv}



- 41a:** R= *p*-tolyl, R'= *p*-nitrophenyl
41b: R= *p*-chlorophenyl, R'= *p*-nitrophenyl
41c: R= *p*-anisyl, R'= *p*-chlorophenyl

In continuation, same group reported a new set of 3-aryl-4-[6'-(6"-substituted-coumarin-3"-yl)imidazo[2,1-b][1,3,4]thiadiazol-2'-yl]-sydnones. The coumarin substituted imidazo[2,1-b][1,3,4]thiadiazoles were screened for their anticancer activity against cell line HT-29-human colorectal adenocarcinoma using cisplatin drug as standard and DNA cleavage analyses. The compounds **42a**, **42b** and **42c** exhibited very good anticancer activity, and the compound **42c** was shown to cleave the DNA completely.^{xlvi}

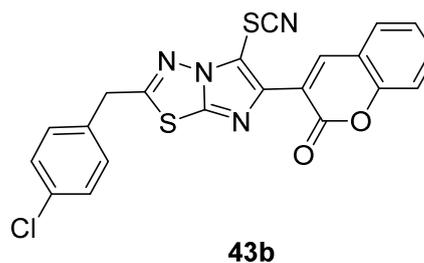
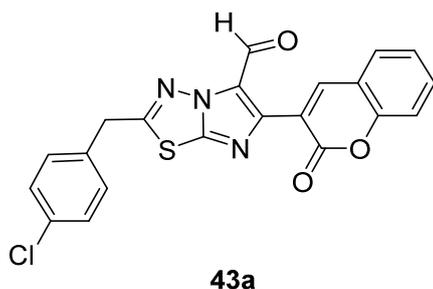


42a: R= phenyl, R'= H

42b: R= *p*-tolylphenyl, R'= chloro

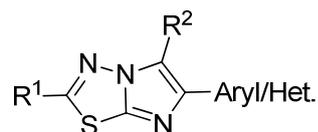
42c: R= *p*-chlorophenyl, R'= chloro

A new series of 2-(4'-chlorobenzyl)-5,6-disubstituted imidazo[2,1-b][1,3,4]thiadiazoles^{xlvii} was synthesized and compounds were evaluated towards human cervix carcinoma HeLa and T-lymphocyte CEM cells and also towards murine leukemia L1210 cells to investigate if the compounds were cytotoxic to human transformed cells. Among the tested compounds, two derivatives namely 2-(4-chlorobenzyl)-6-(2-oxo-2H-chromen-3-yl)imidazo[2,1-b][1,3,4]thiadiazole-5-carbaldehyde **43a** and 2-(4-chlorobenzyl)-6-(2-oxo-2H-chromen-3-yl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl thiocyanate **43b** was found to be most potent against all the cell lines.



Antitubercular Activity

Literature revealed that a series of 2-sulfonamido/trifluoromethyl-6-(4'-substituted aryl/heteroaryl)imidazo[2,1-b]-1,3,4-thiadiazole (**44a-e**) was prepared by reaction of 2-amino-5-sulfonamido/trifluoromethyl-1,3,4-thiadiazoles with an appropriate α -haloaryl/heteroaryl ketones.^{xlviii} The newly synthesized compounds were screened for their preliminary *in vitro* anti-tuberculosis activity against Mycobacterium tuberculosis H37Rv strain following radiometric BACTEC and broth dilution assay procedures. Compounds substituted with phenyl group at 6th position and ganunylhydrazone at 5th position, showed moderate to significant anti-tuberculosis activity at a MIC >6.25 μ g/mL. The replacement of sulfonamido by trifluoromethyl group at 2nd position showed no greater change in the anti-tuberculosis activity.

**44a-e**

44a: R¹ = SO₂NH₂ ; R² = SCN; Aryl = 4'-CH₃-C₆H₄

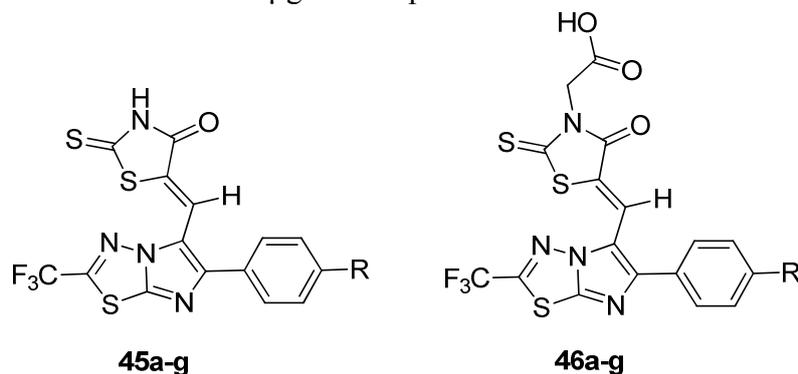
44b: R¹ = SO₂N=CH-N(CH₃)₂ ; R² = CH=N-NH-C=NH(NH₂); Aryl = 4'-CH₃-C₆H₄

44c: R¹ = SO₂N=CH-N(CH₃)₂ ; R² = CH=N-NH-C=NH(NH₂); Aryl = 4'-Cl-C₆H₄

44d: R¹ = CF₃ ; R² = H; Aryl = 4'-OCH₃-C₆H₄

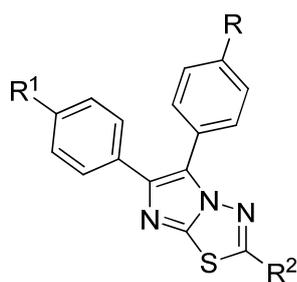
44e: R¹ = CF₃ ; R² = H; Aryl = 4'-NO₂-C₆H₄

In 2012, a new class of novel 2-(trifluoromethyl)-6-arylimidazo[2,1-b][1,3,4]thiadiazole derivatives was prepared by both conventional as well as microwave assisted method. The compounds were evaluated for their *in vitro* anti-tubercular activity against *M. tuberculosis* H₃₇Rv (ATCC 27294) using the Micro plate Alamar Blue assay (MABA) method. From SAR studies, it was revealed that introduction of rhodanine and rhodanine-3-acetic acid moiety instead of thiazolidinedione in compounds **45a-e** and **46a-e** respectively, results in an increase in antimycobacterial activity and are considered as promising lead scaffolds for further generation of new potent antitubercular agents. Compounds **45a**, **45b**, **45c**, **45d** and **45e** showed promising antitubercular activity at MIC value 6.25 µg/ml. Compound **45c** was found to be most active at 3.12 µg/ml. Compounds **46b**, **46c**, **46d**, **46e** and **46f** were found to be active with MIC of 1.56–3.12 µg/ml. Compound **46f** was found to exhibit excellent activity against MTB at a MIC 1.56 µg/ml comparable to that of Isoniazid.^{xlix}

**45a-g****46a-g**

Anti-inflammatory Activity

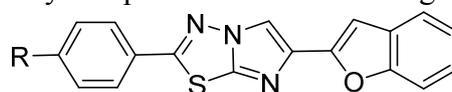
In 2008, a series of 2-trifluoromethyl/sulfonamido-5,6-diarylsubstituted imidazo[2,1-b]-1,3,4-thiadiazole derivatives **47a-f** were synthesized and the selected compounds were screened for their preliminary *in vitro* cyclooxygenase inhibitory activity against COX-2 and COX-1 enzymes using colorimetric method. The screened compounds showed selective inhibitory activity towards COX-2 over COX-1. Structure Activity Relationship showed that compounds **47d** and **47f** containing 4''-SO₂CH₃ group are more active as compared to compounds **47a** and **47b** having 4''-SCH₃. Compounds **47a-f** were also screened for their *in vivo* anti-inflammatory activity using carrageenan-induced rat paw edema method and most of the compounds showed significant anti-inflammatory activity comparable to standard Celecoxib.¹

**47a-f**

- 47a:** R=H, R¹=SCH₃, R²=CF₃
47b: R=OCH₃, R¹=SCH₃, R²=CF₃
47c: R=OCH₃, R¹=OCH₃, R²=CF₃
47d: R=H, R¹=SO₂CH₃, R²=CF₃
47e: R=OCH₃, R¹=F, R²=SONH₂
47f: R=OCH₃, R¹=SO₂CH₃, R²=SO₂NH₂

Analgesic Activity

A series of imidazo[2,1-*b*]-1,3,4-thiadiazoles was reported^{li} and compounds were screened for their analgesic activity. Compounds **48a** and **48b** proved to be potent analgesic agents, as they exhibited significant activity comparable to standard drug.

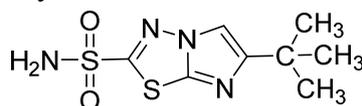


48a: R= CH₃

48b: R= Cl

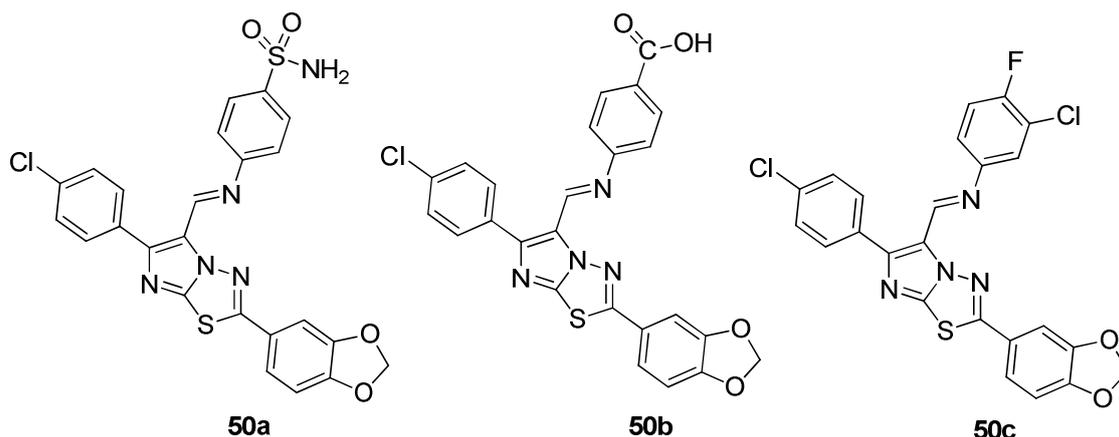
Anticonvulsant Activity

2-Sulfamoyl-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives were synthesized and evaluated for anticonvulsant activity using Acetazolamide and Methazolamide as standard drugs. Compounds were examined in the maximal electroshock (MES) test method at a dose of 2.5, 6.25 and 16 mg/kg in male mice. The most active compound 6-*tert*-butylimidazo[2,1-*b*][1,3,4] thiadiazole-2-sulfonamide (**49**) exhibited an oral ED₅₀ value of 2.6 mg/kg and showed good anticonvulsant activity in the test models.^{lii}

**49**

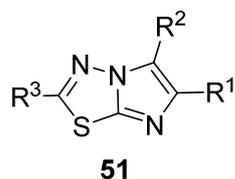
Antihyperlipidemic Activity

The synthesis of a novel series of 2,5,6-trisubstituted-imidazo[2,1-*b*][1,3,4]thiadiazoles was reported^{liii} All the compounds were screened for their *in vitro* antihyperlipidemic activity using standard drug Fenofibrate by following triton induced hyperlipidemic model. Biological activity data showed that in comparison to standard drug Fenofibrate, compounds **50a**, **50b** and **50c** demonstrated a significant decrease in the serum, TCH (Total Cholesterol), LDL (low-density lipoprotein), VLDL (very low density lipoprotein) and TG (Triglycerides) values along with an increase in serum HDL (high density lipoprotein) levels as compared to standard drug. The treated groups also showed significant decrease in the atherogenic index, LDL:HDL risk ratios which are a reliable risk assessment factor of coronary heart disease. Compounds were also evaluated for Hepatotoxicity by measuring alanine transferase, aspartate transferase and alkaline phosphatase levels in serum and none of the compound was found to be hepatotoxic.



Other Biological Activities

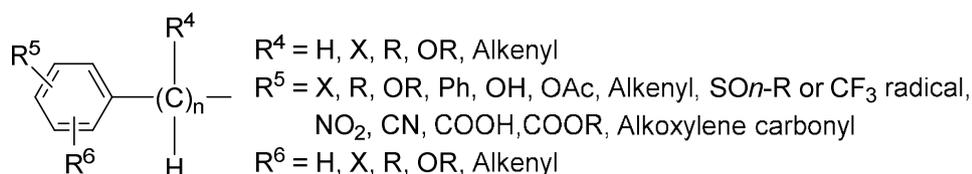
An invention related to the synthesis of a new series of imidazo[2,1-b][1,3,4]thiadiazoles of the general formula (51) and their use as thrombolytic agents was described. Many compounds were found to show effective thrombolytic activity.^{liv}



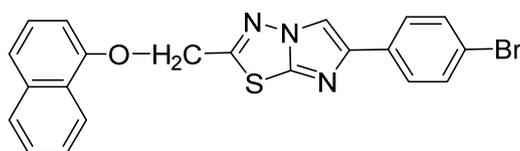
R¹ = Aryl radical which contains substituents such as X(F, Cl, Br, I), CF₃, R (Alkyl), alkenyl, Ph, OR, NO₂, CN, sulphonamido and SO_n-R

R² = H, R, Alkenyl or Aryl radical which contains substituents X, R, OR, alkenyl

R³ = Naphthyl, Furyl, Thienyl, Pyridyl, which is optionally substituted by one or two alkyl radical or a radical of the general formula



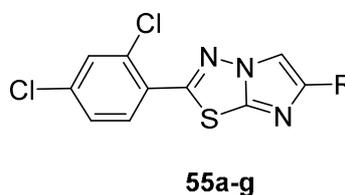
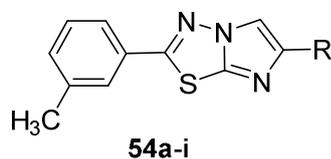
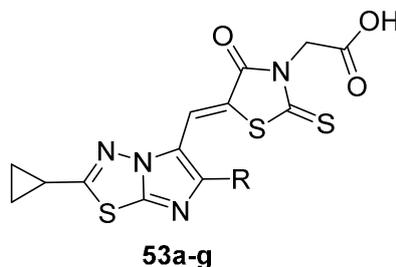
A new series of imidazo[2,1-b][1,3,4]thiadiazole containing 2-naphthyl ethers were synthesized and evaluated for protective activity against DNA damage induced by bleomycin-iron complex method. Compound 52 showed moderate to low activity against DNA damage.^{lv}



52

A new series of imidazo[2,1-b][1,3,4]thiadiazoles 53a-g, 54a-i and 55a-h were synthesized and compounds were evaluated for ALK5 inhibitory activity in an enzyme assay and their TGF- β -induced Smad 2/3 phosphorylation inhibitory activity in a cell-based assay. Amongst all, 2-(5-((2-cyclopropyl-6-(4-fluorophenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-

4-oxo-2- thioxothiazolidin-3-yl) acetic acid (**53d**), showed prominent ALK5 inhibition ($IC_{50} = 0.0012 \mu\text{M}$) with significant percentage of inhibition (91%) at $10 \mu\text{M}$. The binding mode of compound **53d** by XP docking studies showed that it fits well into the active site cavity of ALK5 by forming broad and tight interactions. Lipinski's rule and in silico ADME pharmacokinetic parameters are within the acceptable range defined for human use thereby indicating their potential as a drug-like molecules.^{lvi}



53a, 54a, 55a R = C₆H₅
53b, 54b, 55b R = 2,4-Cl₂-C₆H₃
53c, 54c, 55c R = 4-Br-C₆H₄
53d R = 4-F-C₆H₄
53e R = 4-Cl-C₆H₄

53f, 55d R = 3-NH₂-C₆H₄
53g, 55e R = 2,4-(OH)₂-C₆H₃
54g, 55f R = 4-OCH₃-C₆H₄
54h, 55g R = 2-OH-C₆H₄
54i, 55h R = 4-NH₂-C₆H₄

Conclusion

The present review summarizes ongoing efforts in investigating imidazo[2,1-b][1,3,4]thiadiazoles as lead molecules. The broad biological activities of imidazo[2,1-b][1,3,4]thiadiazoles has indicated that in the last decade an enormous amount of research efforts has been focused on the synthesis and evaluation of imidazo[2,1-b][1,3,4]thiadiazole derivatives especially as antibacterial, antituberculosis, anti-inflammatory, anticonvulsant, analgesic, antihyperlipidemic and anticancer agents. They are also reported to show protective activity against DNA damage, thrombolytic activity and ALK5 inhibitory activity. Therefore there is an opportunity for researchers to look forward for exploring imidazo[2,1-b][1,3,4]thiadiazoles as therapeutically potential analogs for newer biological activities by rational drug design techniques which may accelerate the process of drug discovery in future.

Acknowledgments

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