Tetrahedron 67 (2011) 3289–3316

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Tetrahedron report number 938

Chemistry of imidazo[2,1-*b*][1,3,4]thiadiazoles

Imtiyaz Ahmed M. Khazi [a,*], Andanappa K. Gadad [b], Ravi S. Lamani [a], Bhoomendra A. Bhongade [c]

[a] *P.G. Dept. of Studies in Chemistry, Karnatak University, Dharwad 580 003, Karnataka, India*
[b] *School of Pharmacy, Faculty of Medical Sciences, The University of the West Indies, Trinidad and Tobago*
[c] *Pharmaceutical Chemistry, RAK Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates*

ARTICLE INFO

Article history:
Received 24 February 2011
Available online 17 March 2011

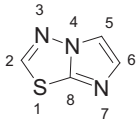
Contents

* Corresponding author. Tel.: +91 836 2215286; fax: +91 836 2771275; e-mail address: drimkorgchem@gmail.com (I.A.M. Khazi).

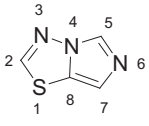
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.027

1. Introduction

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]thiadiazoles (**1**) and the imidazo [5,1-*b*][1,3,4]thiadiazoles (**2**).



1



2

The structures of imidazo[2,1-*b*][1,3,4]thiadiazoles are closely related to the biologically vibrant imidazo[1,3,4]thiazole heterocycles, in which the CH group in the thiazole ring is substituted by the isosteric nitrogen atom, but their properties often possess marked differences. The practically planar and rigid heteroaromatic imidazo[2,1-*b*][1,3,4]thiadiazole ring system may therefore have interesting physicochemical and biological properties, because of the presence of four heteroatoms and two condensed heterocycles with different π-conjugation.

Imidazo[2,1-*b*][1,3,4]thiadiazole derivatives were first discovered in the early 1950s and, since then, the research work on this heterocyclic system has led to significant developments in their chemistry and biology. Imidazo[2,1-*b*][1,3,4]thiadiazole ring systems have been extensively studied and, so far, a variety of biological activities have been reported for a large number of their derivatives, such as antitubercular, antibacterial, anticancer, anthelmintic, antifungal, anticonvulsant, anti-inflammatory, analgesic, antipyretic, local anaesthetic, cardiotonic, diuretic, leishmanicidal and herbicidal activities. In addition, they have been reported to selectively inhibit several therapeutic receptors and enzymes, extending their applications in modern drug design. During the last two decades, this area of heterocyclic chemistry has attracted growing interest from bioorganic and pharmaceutical researchers, leading to a large number of research publications and patents. Overall, much important and useful research on this bridgehead nitrogen heterocycle extending over a period of 55 years has led to some drug candidates and promising lead molecules.

There is no review available on the chemical and biological results achieved since the discovery of imidazo[2,1-*b*][1,3,4]thiadiazoles and the research papers on this type of heterocycle are rather widely scattered in the literature. Pertinent structural, synthetic and biological studies reported in the open literature as well as the biological usefulness disclosed in the patent literature have been covered in this review with the anticipation that this would act as a stimulus and guide to further developments in this field.

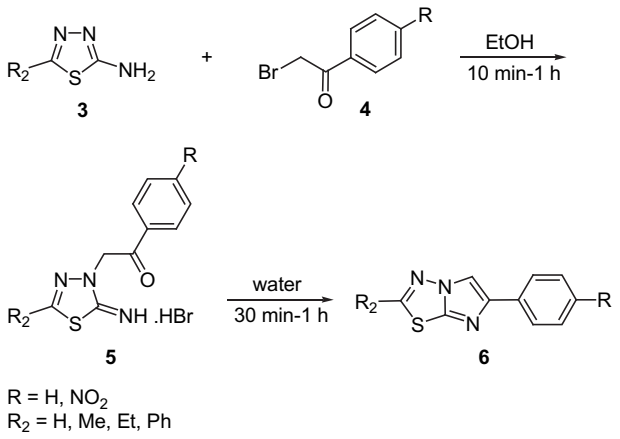
2. Synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles

For the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives the classical method involving 2-amino[1,3,4]thiadiazole derivatives with appropriate α-haloketones is widely employed. Such a synthesis is usually accomplished by using variety of reagents like chloroacetyl chloride, haloacetic acid, acetophenones, diethyl chloroacetal, dimethylformamide dimethyl amide and trichloroacetyl chloride. Besides the classical methods alternative synthetic strategies are also used to get appropriately substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles starting from 1-amino-2-(methyl)thio-4-substituted-imidazoles. A rare synthesis involving 2-amino-[1,3,4]thiadiazole with isonitrile and aldehydes has also been reported to obtain 5,6-disubstituted-imidazo[2,1-*b*][1,3,4]thiadiazoles.

2.1. Synthesis of 2- and/or 5- or 6-substituted imidazo[2,1-*b*][1,3,4]thiadiazoles

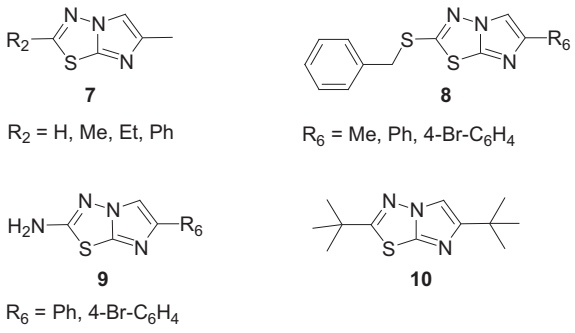
2.1.1. From 2-amino-5-(un)substituted-[1,3,4]thiadiazoles.

2.1.1.1. Reaction with α-haloketones. The first synthesis of 6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles has been reported in 1952 by Matsukawa and Ban.[1] involving the reaction of 2-amino-[1,3,4] thiadiazoles **3** (1 mol) with α-haloketones **4** (2 mol) in boiling ethanol for 30 min-1 h to yield 2-imino-3-phenacyl-5-(un)substituted-2,3-dihydro-[1,3,4]thiadiazole hydrobromide intermediates **5**, which on neutralization gave free bases. Further, intramolecular cyclization of either the hydrobromide salts **5** or the free bases in boiling water for 30 min-1 h, followed by neutralization yielded 2-(un)substituted-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **6** (Scheme 1). Similarly, the syntheses of 2-(un)substituted-6-methyl-imidazo [2,1-*b*][1,3,4]thiadiazoles **7** (R_2=H) by the condensation of 2-amino-5-(un)substituted [1,3,4]thiadiazoles **3** (R_2=H) with bromoacetone via the 2-imino-[1,3,4]thiadiazole hydrobromide intermediates **5** (R_2=H) were reported by Ban.[2]

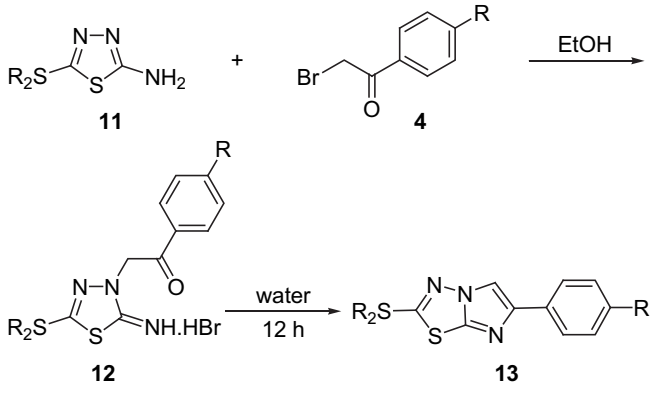


Scheme 1.

A similar methodology has been employed by other research groups for the synthesis of various 2-amino/benzylthio/*t*-butyl-6-alkyl/arylimidazo[2,1-*b*][1,3,4]thiadiazoles **7**–**10** via the intermediate hydrobromide salts **5**.[3–5]

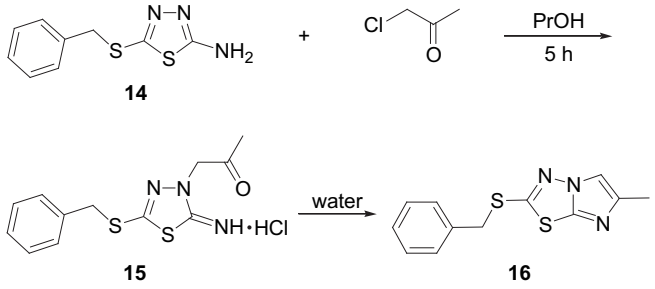


The nature of the functional groups at the 5-position of 2-amino-5-substituted [1,3,4]thiadiazoles and α-haloketones, as well as the solvents used in such reactions, influences the duration of reaction completion and yields in some cases. Eldawy et al.[6] achieved the synthesis of 2-alkylthio-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **13** in 40–88% yield by the reaction of the corresponding hydrobromides **12** in hot water for 12 h, following treatment with aqueous sodium acetate. The hydrobromides **12** were prepared by the reaction of 2-amino-5-alkylthio[1,3,4]thiadiazoles **11** with the appropriate phenacyl bromide **4** in refluxing ethanol for 1 h, followed by treatment with anhydrous ether (Scheme 2).



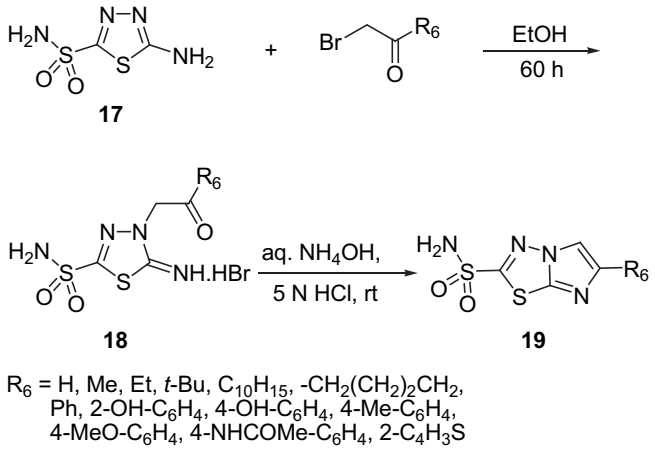
Scheme 2.

Pyl et al.[3] have also reported the reaction of 2-amino-5-benzylthio[1,3,4]thiadiazole **14** with chloroacetone in refluxing propanol for 5 h to yield the hydrochloride salt intermediate **15** after addition of diethyl ether. 2-Benzylthio-6-methylimidazo[2,1-*b*][1,3,4]thiadiazole **16** was obtained by the cyclization of the hydrochloride salt intermediate **15** in hot water, followed by neutralization with sodium hydroxide (Scheme 3).



Scheme 3.

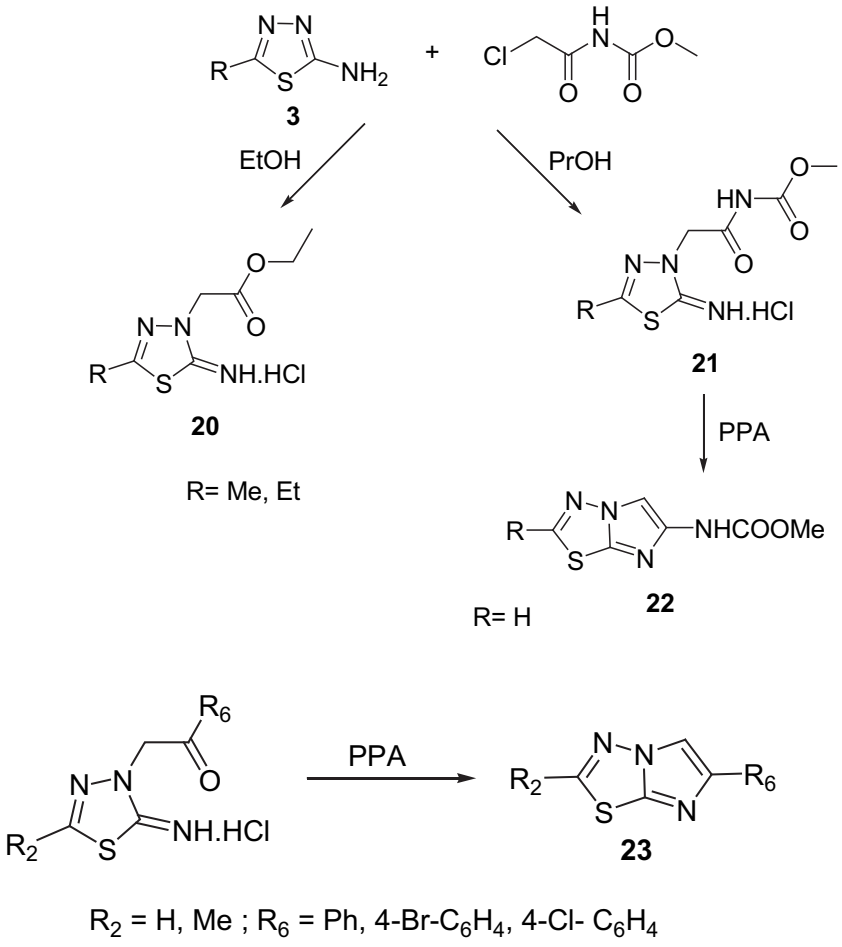
Barnish et al.[7] have reported the reaction of 2-amino-5-sulfonamido-[1,3,4]thiadiazole **17** with the appropriate α-bromoketones in refluxing ethanol for 60 h to yield the corresponding hydrobromide intermediates **18**. Ammonium hydroxide was added to an aqueous slurry of the hydrobromide salts **18** at room temperature, followed by the addition of 5 N HCl until pH 7.5, to yield the 6-alkyl/aryl-imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **19** in 14–75% yield (Scheme 4).



Scheme 4.

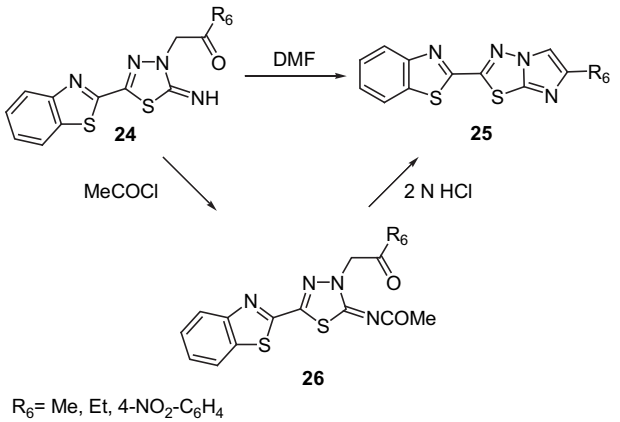
Valls et al.[8] have reported solvolysis during the condensation of 2-amino-5-methyl/ethyl-[1,3,4]thiadiazoles **3** with (2-chloroacetyl)carbamic acid methyl ester in refluxing ethanol to yield (2-imino-5-methyl/ethyl-[1,3,4]thiadiazol-3-yl)acetic acid ethyl ester hydrochloride salts **20**, while in refluxing propanol the reaction yielded [2-(2-imino-[1,3,4]thiadiazol-3-yl)-acetyl]-carbamic acid methyl ester hydrochloride salt **21**, which in polyphosphoric acid (PPA) undergoes a ring-closure reaction to yield imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl-carbamic acid methyl ester **22** (Scheme 5). Similarly, Kano[9] has reported the synthesis of 2-unsubstituted/methyl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles **23** (R_2=H, Me; R_6=Ph, 4-Br–C_6H_4, 4-Cl–C_6H_4) by treating 2-imino-3-phenacyl-5-unsubstituted/methyl-2,3-dihydro-[1,3,4]thiadiazoles with polyphosphoric acid for 2 h.

Reaction of 5-benzothiazol-2-yl-[1,3,4]thiadiazol-2-ylamine with appropriate α-bromoketones in DMF yielded 2-benzothiazol-2-yl-6-alkyl/arylimidazo[2,1-*b*][1,3,4]thiadiazoles **25** via the 5-benzothiazol-2-yl-2-imino-3-substituted-[1,3,4]thiadiazole intermediates **24**. Alternatively, the intermediates **24** were treated with acetyl chloride



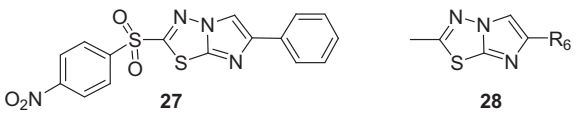
Scheme 5.

to yield the corresponding 5-acetylimino analogues **26**, which on further treatment with 2 N HCl yielded the compounds **25** (Scheme 6).[10]

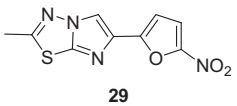


Scheme 6.

Werbel and Zamora[11] have reported the reaction of 2-amino-5-(4-nitrophenyl)sulfonyl-[1,3,4]thiadiazole with phenacyl bromide in refluxing acetone for 19 h to yield a residue, which on refluxing in ethanol for 7 h afforded 2-(4-nitrophenyl)sulfonyl-6-phenyl-imidazo[2,1-*b*][1,3,4]thiadiazole **27** in 17% yield. Andreani et al.[12] obtained 6-aryl and 6-pyridinyl derivatives of 2-methylimidazo [2,1-*b*][1,3,4]thiadiazole **28** in 60–70% and 20–30% yields, respectively, by refluxing the corresponding intermediates in 1 N HCl followed by basification with 20% NH_4OH. The intermediates were obtained by the reaction of 2-amino-5-methyl-[1,3,4]thiadiazole with α-haloketones in refluxing acetone for 1–5 h.

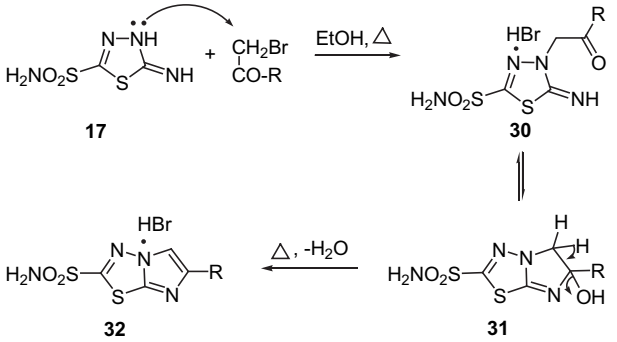


The synthesis of 2-methyl-6-[2-(5-nitrofuryl)]imidazo[2,1-*b*] [1,3,4]thiadiazole **29** in 75% yield has been reported by Saldabols et al.[13] by the reaction of equimolar quantities of 2-amino-5-methyl-[1,3,4]thiadiazole with 2-bromoacetyl-5-nitrofuran in refluxing benzene–ethanol (2:1) for 2 h to give the hydrobromide intermediate, which upon refluxing in either ethanol or propanol for 1 h gave compound **29**.



One-pot syntheses of several imidazo[2,1-*b*][1,3,4]thiadiazole derivatives have been achieved by the condensation of 2-amino-[1,3,4]thiadiazoles with α-haloketones in various solvents, while in some cases the intermediates were isolated.

Khazi et al.[14] have proposed a mechanism for the condensation between 2-amino-[1,3,4]thiadiazole-5-sulfonamide **17** and α-haloketones involving an initial electrophilic attack on the more basic *endo* nitrogen (C-3 N) of 2-amino-[1,3,4]thiadiazoles, forming the ring-chain tautomeric intermediates (**30**↔**31**) as the rate-determining step; the progress of the reaction depends on the basicity of the *endo* nitrogen and the strength of the electrophile. The second step, which is very fast, involves an intramolecular cyclization with the elimination of a water molecule to afford the hydrobromide salts of 6-substituted-imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **32** (Scheme 7).



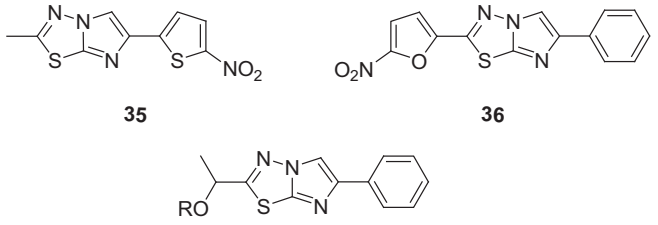
Scheme 7.

Valls[8] and Marin et al.[15] have reported the synthesis of various 2-substituted-6-carbamic acid methyl esters of imidazo[2,1-*b*][1,3,4]thiadiazoles **33** in 27–58% yield by the reaction of 2-amino-5-substituted-[1,3,4]thiadiazoles either with the appropriate methyl-*N*-chloroacetyl carbamate or with α-haloketones in DMF at 80–120 °C for 1–2 h, yielding iminium salt intermediates, which were further cyclised in PPA at 100 °C or in refluxing IPA for 1–2 h. A (6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-2-yl)carbamic acid methyl ester derivative **34** has been synthesized by the reaction of (5-amino-[1,3,4]thiadiazol-2-yl)carbamic acid methyl ester with phenacyl bromide in DMF at 85 °C for 4 h.

R = H, Me, Et, *n*- Bu, Ph, NH_2, S-*n*-Pr, S(O)Pr, $SCH_2CONHCOOMe$,

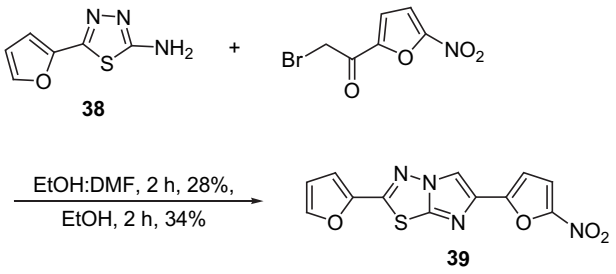
R = NHCOOMe

Arya et al.[16] have reported the reaction of 2-amino-5-methyl-[1,3,4]thiadiazole with 2-bromoacetyl-5-nitrothiophene in refluxing DMF for 30 min to yield 2-methyl-6-(5-nitro-2-thiophenyl) imidazo[2,1-*b*][1,3,4]thiadiazole **35** in 40% yield upon neutralization. Similarly, the syntheses of some 2,6-alkyl/arylimidazo[2,1-*b*][1,3,4]thiadiazole derivatives **36** and **37** were prepared in refluxing DMF for 2–5 h[11,17]



R = 4-Cl, 3-Me-C_6H_3,
4-*t*-Bu-C_6H_4, 2,4-$(Me)_2$-C_6H_3

Reaction of 2-amino-5-furyl-[1,3,4]thiadiazole **38** with 2-bromoacetyl-5-nitrofuran in refluxing ethanol/DMF for 2 h yielded 2-furyl-6-(5-nitro-2-furyl)imidazo[2,1-*b*][1,3,4]thiadiazole **39** in 28% yield, while, under similar conditions, a 34% yield was reported in refluxing ethanol by Saldabols et al.[13] (Scheme 8).



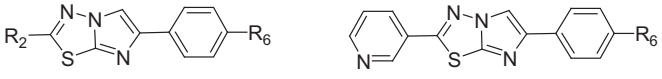
Scheme 8.

Mazzone et al.[18] have reported the synthesis of 2-aryl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazoles **40** in refluxing ethanol/DMF (3:2) for 3 h in 75% yields by the condensation of equimolar quantities of 2-amino-5-aryl-[1,3,4]thiadiazoles with phenacyl bromide. Ethanol is the most widely used solvent for the condensation of 2-amino-[1,3,4]thiadiazoles with the appropriate α-haloketones. Abignente et al.[19] have reported the synthesis of 6-carbethoxy (methyl)-2-ethyl/methylimidazo[2,1-*b*][1,3,4]thiadiazoles **41** by reacting 2-amino-5-ethyl/methyl-[1,3,4]thiadiazoles with ethyl bromopyruvate/4-chloroacetoacetate in refluxing ethanol for 4–9 h, while the reaction of 2-amino-[1,3,4]thiadiazoles with ethyl bromopyruvate yielded the corresponding 6-carbethoxy imidazo[2,1-*b*][1,3,4]thiadiazole in refluxing ethanol for 34 h.

R = 3,4,5-$(OMe)_3$-C_6H_2,
3,4-(-O-CH_2-O-)C_6H_3,
3,5-$(OMe)_2$-C_6H_3

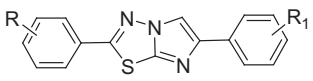
R_2 = H, Me, Et,
R_6 = COOEt, CH_2COOEt

Jag et al.[20–30] have synthesized various 2-alkyl/aryl/heteroaryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole derivatives **42**–**44** by the condensation of 2-amino-5-substituted-[1,3,4]thiadiazoles with the appropriate α-haloketones in refluxing ethanol for 4–6 h in 23–77% yield.



R_2 = *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, $C_{10}H_{15}$; R_6 = H, Cl

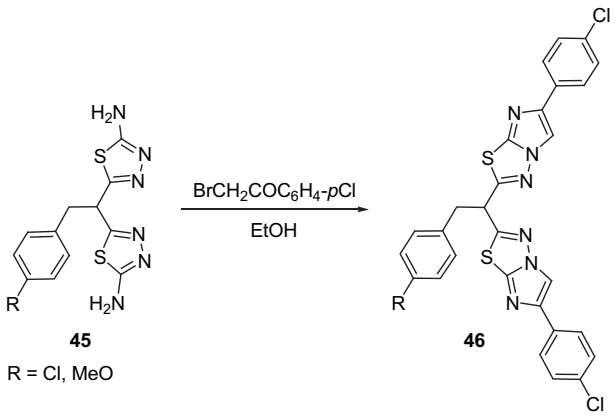
R_6 = H, Cl



R = 2-Cl, 2-Me, 2-NO_2, 2,4-Cl_2, 3-Cl, 3-Me,
3,5-$(NO_2)_2$, 4-Cl, 4-OH, 4-Me, 4-*t*-Bu,
R_1 = H, Br, Cl, NO_2, Me, Et, Ph

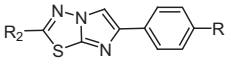
Ram et al.[31–35] synthesized various 2-substituted aryl/heteroaryl derivatives of 6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles in refluxing ethanol for 8 h. Notably, 1-bis-[6-(4-chloro-phenyl)imidazo[2,1-*b*][1,3,4]thiadiazol-2-yl]-2-(4-chloro/methoxy-phenyl)ethane **46** was

prepared by the condensation of 1-bis-[2-amino-[1,3,4]thiadiazol-5-yl]-2-(4-chloro/methoxy-phenyl)ethane **45** with 4-chlorophenacyl bromide in refluxing ethanol (Scheme 9).[31]



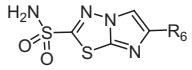
Scheme 9.

Gadad et al.[36] have reported the synthesis of various 2-alkyl (C_{6-17})-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles **47** in 64–80% yields by the reaction of 2-amino-5-alkyl-[1,3,4]thiadiazoles with α-haloketones in refluxing ethanol for 8 h, whereas, the 2-sulfonamide and 2-trifluoromethyl-6-aryl/heteroarylimidazo[2,1-*b*][1,3,4]thiadiazole derivatives **48** and **49** were synthesized in 41–61 and 31–62% yields, respectively, by the reaction of 5-sulfonamido/trifluoromethyl-2-amino-[1,3,4]thiadiazoles with α-haloketones in refluxing ethanol for 12 h followed by neutralization.[14,37,38]



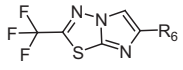
47

R_2 = Me-$(CH_2)_6$, Me-$(CH_2)_8$, Me-$(CH_2)_{10}$, Me-$(CH_2)_{12}$, Me-$(CH_2)_{14}$, Me-$(CH_2)_{16}$,Cy
R = H, Cl, Me, OMe



48

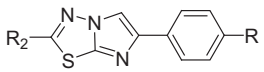
R_6 = Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 4-Ph-C_6H_4, 3,4,5-$(MeO)_3$-C_6H_2, COOEt, CH_2COOEt, 3-coumarinyl, 5-NO_2-2-thienyl, 2-furyl, 5-(4-NO_2)-2-furyl,



49

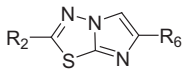
R_6 = Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-F-C_6H_4, 4-OH-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4, 3,4,5-$(MeO)_3$-C_6H_2, 3-coumarinyl, 2-furyl

Khazi et al.[39–42] have reported the syntheses of various 2-alkyl/aryl/heteroaryl-6-aryl/heteroarylimidazo[2,1-*b*][1,3,4]thiadiazoles **50** and **51** in 42–81% yield by the reaction of 2-amino-5-substituted-[1,3,4]thiadiazoles with the appropriate α-haloketones in refluxing ethanol for 6–8 h.



50

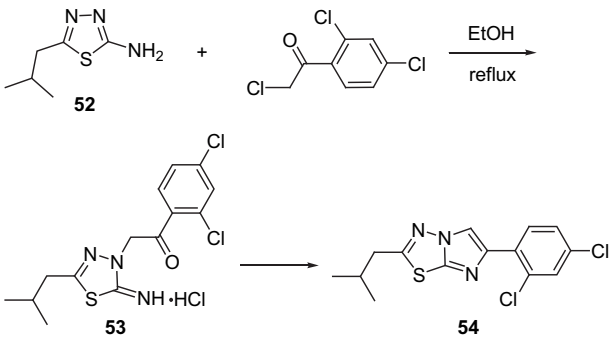
R_2 = Cy, 2-furyl, *n*-Pr, 2-thienyl
R = Br, Cl, Me, OMe



51

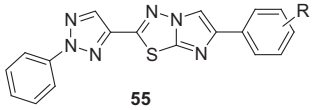
R_2 = Et, *n*-Pr, Cy, 2-furyl, 2-thienyl, Bn
R_6 = COOEt, 3-coumarinyl

Li et al.[43] have reported the reaction of 2-amino-5-*iso*-butyl-[1,3,4]thiadiazole **52** with α-chloro-2,4-dichlorophenyl-2-ethanone in refluxing ethanol for 5 h followed by neutralization to yield 2-*iso*-butyl-6-(2,4-dichlorophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole **54**. From their X-ray crystallographic studies, they have demonstrated that the endocyclic nitrogen atom of the 2-amino-[1,3,4]thiadiazole **52** displaced the chlorine atom to give the intermediate **53** (Scheme 10).



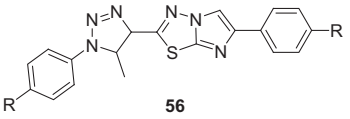
Scheme 10.

Cui et al.[44] have reported the synthesis of 2-(2-phenyl-1,2,3-triazol-4-yl)-6-arylimidazo-[2,1-*b*]-[1,3,4]thiadiazoles **55** by the reaction of 2-amino-5-(2-phenyl-1,2,3-triazol-4-yl)-[1,3,4]-thiadiazoles with α-bromoacetophenones in refluxing ethanol. The synthesis of 2-substituted triazole, oxazole and benzofuran derivatives of 6-heteroarylimidazo[2,1-*b*][1,3,4]thiadiazoles **56**–**58** by the reaction of the appropriate 2-amino-5-substituted-[1,3,4]thiadiazoles with α-bromoketones in refluxing ethanol was reported by Zhang,[45] Liu[46] and Jadhav et al.,[47] respectively.



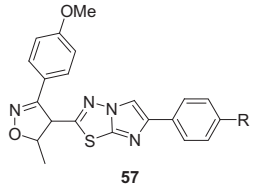
55

R = H, Me



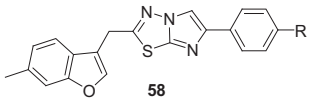
56

R = H, Me



57

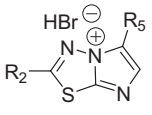
R = H, Br, Cl, OMe, Me



58

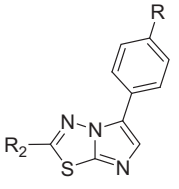
R = Br, Cl, NO_2

Joshi et al.[48] have assigned the structures as 2-alkyl-5-arylimidazo[2,1-*b*][1,3,4]thiadiazole hydrobromides **59** for the compounds obtained by the reaction of equimolar quantities of 2-amino-5-alkyl-[1,3,4]thiadiazoles with α-haloketones in refluxing ethanol (95%) for 8 h, whereas Dehuri and Nayak[49] have assigned the structures as 2,5-diaryl-[1,3,4]thiadiazolo[3,2-*b*]imidazoles **60** for the compounds obtained by the reaction of 2-amino-[1,3,4]thiadiazoles with α-haloketones in refluxing ethanol for 6 h followed by neutralization with ammonia.



59

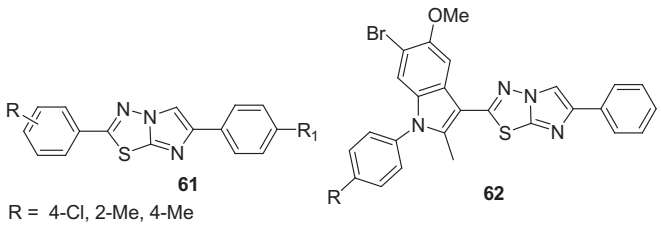
R_2 = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *n*-C_5H_{11}
R_5 = 3-Cl-4-F-C_6H_3, 4-F-2-Me-C_6H_3, 4-F-3-Me-C_6H_3, 4-F-$C_{10}H_6$



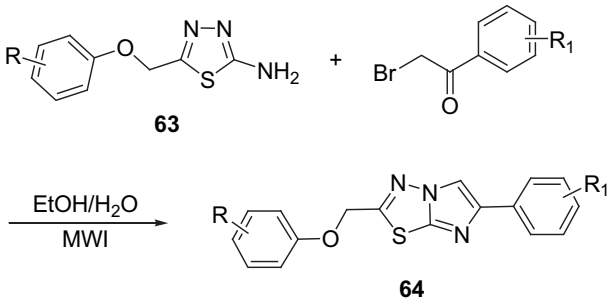
60

R = H, Cl
R_2 = H, Ph, 4-Me-C_6H_4

Some 2,6-diarylimidazo[2,1-*b*][1,3,4]thiadiazoles **61** and **62** were synthesized by condensation of the appropriate 2-amino-5-aryl[1,3,4]thiadiazoles[50,51] with α-haloketones in refluxing methanol for 4–6 h.

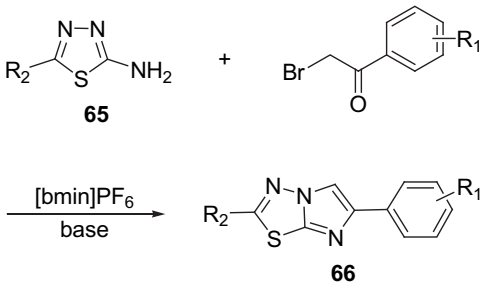


Wang et al.[52,53] have reported the synthesis of various 2-aryloxymethyl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles **64** in 70–83% yield by the condensation of 2-amino-5-aryloxymethyl-[1,3,4]thiadiazoles **63** with α-haloketones in ethanolic and aqueous media, using a microwave irradiation (MWI) method, in 7–16 min (Scheme 11).



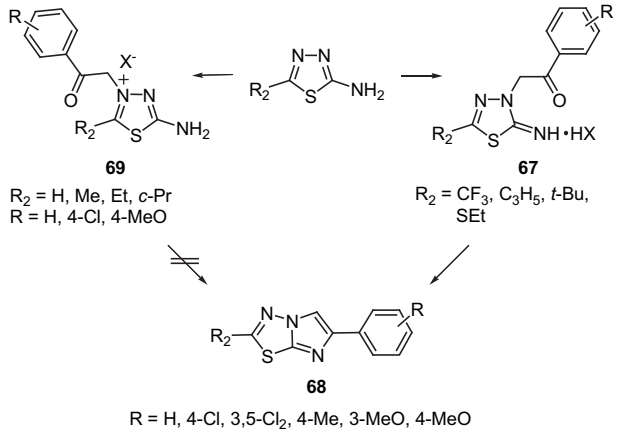
Scheme 11.

Kidwai et al.[54] have reported the reaction of 2-amino-5-(un)substituted-[1,3,4]thiadiazoles **65** with α-haloketones in a 1-butyl-3-methylimidazolium hexaflurophosphate ([bmin]PF_6) ionic liquid in the presence of a water-soluble base at 60 °C for 45–80 min to give the imidazo[2,1-*b*]-[1,3,4]thiadiazole derivatives **66** with improved yields (77–82%), compared to those obtained by the conventional method in refluxing ethanol for 3–5 h (60–65%) (Scheme 12).



Scheme 12.

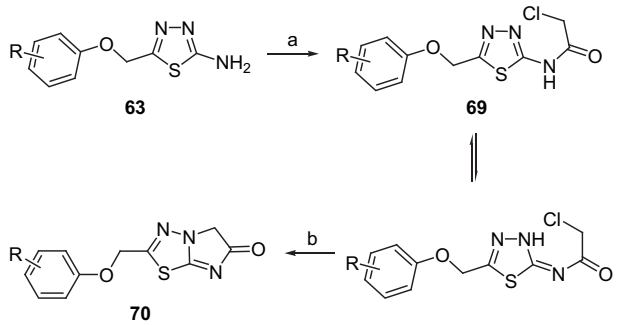
DeStevens et al.[55] studied the steric and electronic effects controlling the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazoles. The condensation of α-haloketones with 2-amino-[1,3,4]thiadiazoles is normally considered to involve alkylation of a ring nitrogen at the 3-position, forming an intermediate **67**, which readily cyclises to the condensed heterocycle **68**. DeStevens, however, isolated the halide salt **69** formed by alkylation of the more nucleophilic ring nitrogen at the 4-position, demonstrating that the nature of electronic and steric factors at the 5-position of 2-amino-5-substituted-[1,3,4]thiadiazoles determines the course of the reaction with α-haloketones. Electronegative groups at C-5 by virtue of their inductive effects impart less nucleophilic character to the nitrogen at the 4-position, while bulky groups by virtue of the influence of steric factors prevent the α-haloketones from attacking the more nucleophilic N-4 and, as a consequence, allow the reaction to occur at N-3, followed by ring closure to the desired fused imidazo[2,1-*b*][1,3,4]thiadiazoles **68** (Scheme 13).



Scheme 13.

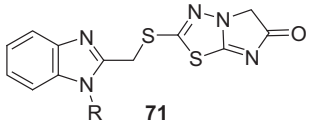
Several other 2,6-substitutedimidazo[2,1-*b*][1,3,4]thiadiazole derivatives have been reported by condensation of 2-amino-5-substituted-[1,3,4]thiadiazoles with the appropriate α-haloketones.[56–68]

2.1.1.2. Reaction with chloroacetyl chloride. Chaturvedi et al.[69] have reported the synthesis of 2-aryloxymethyl-[1,3,4]thiadiazo[5,1-*b*] imidazol-6-one derivatives **70**. Reacting 2-amino-5-aryloxy methyl-[1,3,4]thiadiazoles **63** with chloroacetyl chloride in ice-cold acetone and then allowing the reaction mixture to stand at room temperature for 2 h results in the formation of 2-chloroacetamido-5-aryloxymethyl-[1,3,4]thiadiazole intermediates **69**, and these were further cyclized in dry pyridine on standing overnight at room temperature to give the compounds **70** (Scheme 14).



Scheme 14.

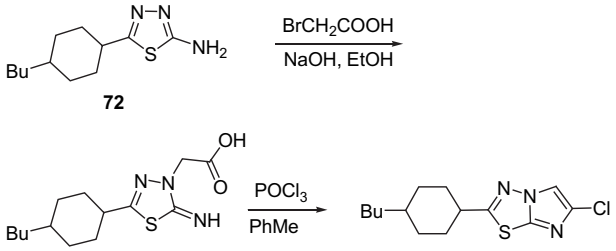
Employing a similar methodology, Ashour et al.[70] have reported the synthesis of 2-(1-benzyl/ethyl-1*H*-benzimidazol-2-ylmethylsulfanyl) imidazo[2,1-*b*][1,3,4]thiadiazol-6-ones **71**.



71

R = Et, Bn

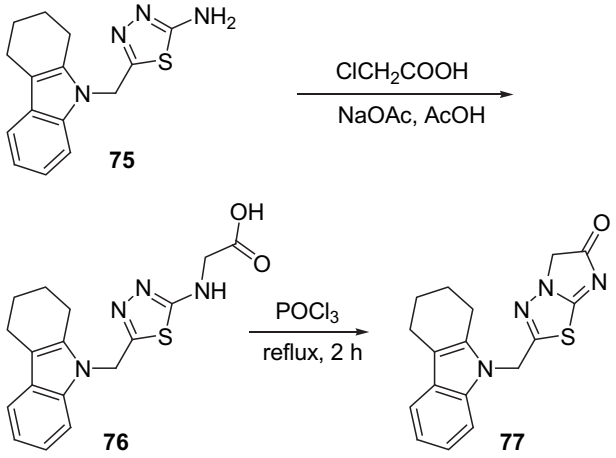
2.1.1.3. Reaction with haloacetic acid. Ivashchenko et al.[71] have reported the synthesis of 2-(4-butylcyclohexyl)-6-bromoimidazo[2,1-*b*][1,3,4]thiadiazole **74** by the reaction of 2-amino-5-(4-butylcyclohexyl)-[1,3,4]thiadiazole **72** with bromoacetic acid in ethanolic NaOH followed by cyclization of the [5-(4-butylcyclohexyl)-2-imino-[1,3,4]thiadiazol-3-yl]acetic acid intermediate **73** in $POCl_3$ (Scheme 15).



72 73 74

Scheme 15.

Shafi and Radhakrishan[72] have reported the reaction of 2-amino-5-[1,2,3,4-tetrahydrocarbazol-9-yl-methyl]-[1,3,4]thiadiazole **75** (0.01 mol) and chloroacetic acid (0.02 mol) in the presence of sodium acetate in refluxing glacial acetic acid to give 5-[1,2,3,4-tetrahydrocarbazol-9-yl-methyl]-[1,3,4]thiadiazole-2-aminoacetic acid **76**, which on refluxing with phosphoryl chloride for 2 h, yielded 5-[1,2,3,4-tetrahydrocarbazol-9-yl-methyl]-imidazo[2,1-*b*][1,3,4]thiadiazol-5-one **77** (Scheme 16).



75 76 77

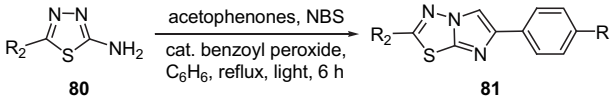
Scheme 16.

Andotra et al.[73], however, have assigned the structures as 2-(2,4-dialkoxy-5-alkylphenyl)-imidazo[2,1-*b*][1,3,4]thiadiazol-5-ones **78** for the compounds obtained by the reaction of 2-amino-5-(2,4-dialkoxy-5-alkylphenyl)-[1,3,4]thiadiazoles with chloroacetic acid along with sodium acetate in refluxing methanol for 8–10 h. Similarly, Jag and Anupama[26] have reported the synthesis of 2-[4-*tert*-butyl-phenyl]imidazo[2,1-*b*][1,3,4]thiadiazol-5-one **79** by the reaction of 2-amino-5-[4-*tert*-butyl-phenyl]-[1,3,4]thiadiazole and chloroacetic acid along with sodium acetate in refluxing EtOH for 10 h.

78 79

R = 2,4-$(MeO)_2$-5-Et, 2,4-$(EtO)_2$-5-Et, 2,4-$(MeO)_2$-5-Pr, 2,4-$(EtO)_2$-5-Pr, 2,4-$(MeO)_2$-5-Bu, 2,4-$(EtO)_2$-5-Bu, 2-MeO-4-EtO-5-Et

2.1.1.4. Reaction with acetophenones. Jag et al. synthesized various 2,6-substituted-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **81** by the reaction of equimolar quantities of 2-amino-5-substituted-[1,3,4]thiadiazoles **80**, acetophenones and *N*-bromosuccinimide (NBS) in the presence of catalytic benzoyl peroxide and light in refluxing benzene for 6 h, followed by neutralization (Scheme 17).[21,23,25–29]

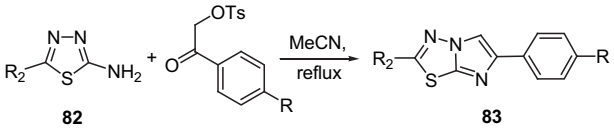


80 81

R = H, Br, Cl, NO_2, Ph, Me, Et;
R_2 = 2,4-Cl_2-C_6H_3,2-Me-C_6H_4, 3-Cl-C_6H_4, 3-Me-C_6H_4, 4-Cl-C_6H_4, $C_{10}H_{15}$, 4-*t*-Bu-C_6H_4, 3,5-$(NO_2)_2$-C_6H_3

Scheme 17.

Jag et al.[22,24,50] have also reported the synthesis of 2,6-substituted-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **83** by the reaction of acetophenones and [hydroxy(tosyloxy)iodo]benzene (HTIB) in refluxing acetonitrile for 45 min, followed by the addition of 2-amino-6-substituted-[1,3,4]thiadiazoles **82**, and then refluxing the reaction mixture for 4 h (Scheme 18).

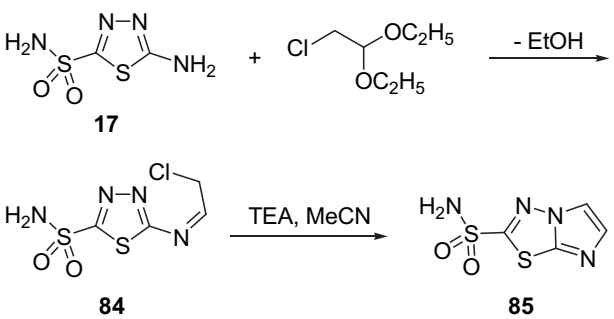


82 83

R = H, Br, Cl, Ph;
R_2 = $Me(CH_2)_{n\ (n\ =\ 4\text{-}6)}$, 2-Cl-$C_6H_4$, 2-Me-$C_6H_4$,2-$NO_2$-$C_6H_4$, 3-Me-$C_6H_4$, 4-Cl-$C_6H_4$;

Scheme 18.

2.1.1.5. Reaction with diethyl chloroacetal. Scozzafava and Supuran[74] have reported the synthesis of imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide **85** in 69% yield by the reaction of 2-amino-[1,3,4]thiadiazole-5-sulfonamide **17**, triethylamine (TEA) and diethyl chloroacetal in acetonitrile at room temperature for 5 h, and then refluxing for 24 h, followed by neutralization. The reaction was hypothesized to proceed via a Schiff base **84**, which undergoes intramolecular cyclization in the presence of TEA (Scheme 19). Barnish



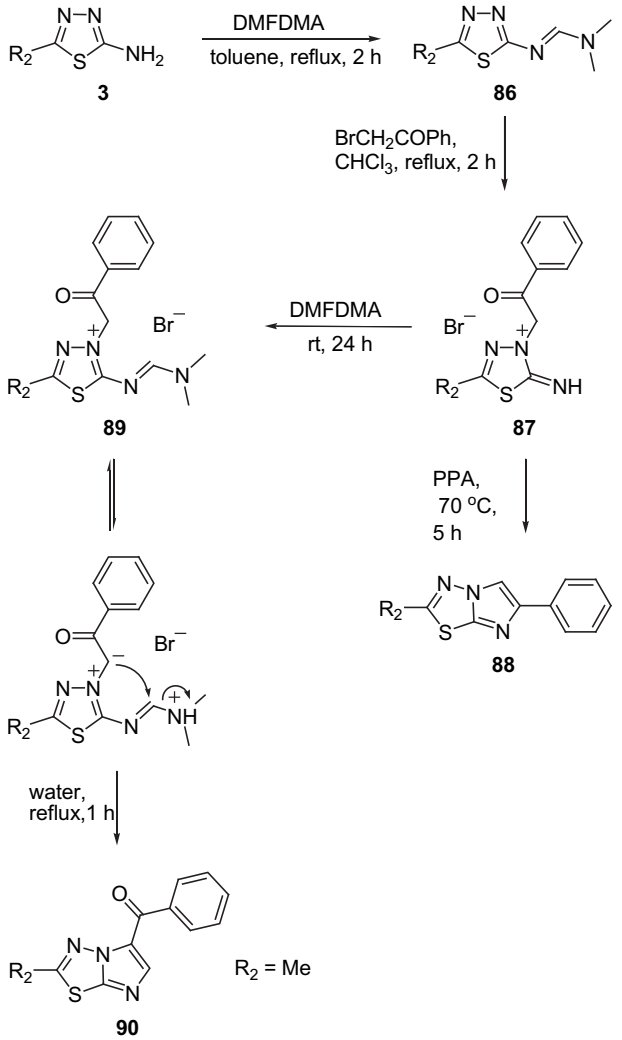
17 84 85

Scheme 19.

et al.[7] have reported the synthesis of the hydrobromide salt of compound **85** in 26% yield by a similar reaction, but without using TEA.

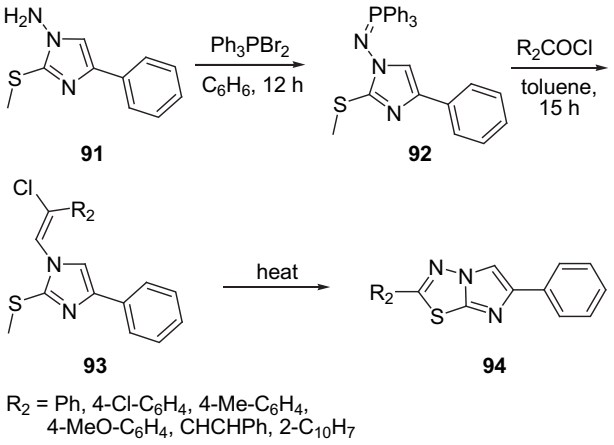
2.1.1.6. Reaction with N,N-dimethylformamide dimethyl acetal. Fajgelj et al.[75] have reported the syntheses of 2-methyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole **88** and 5-benzoyl-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole **90**, starting from 2-amino-5-methyl-[1,3,4]thiadiazole and dimethylformamide dimethyl acetal (DMFDMA) (Scheme 20). The reaction of 2-amino-5-methyl-[1,3,4] thiadiazole **3** (R_2=Me) with DMFDMA in refluxing toluene for 2 h yielded 2-(*N*,*N*-dimethylaminomethyleneamino)-5-methyl-[1,3,4] thiadiazole **86**, which on quaternization with phenacyl bromide in refluxing ethanol for 2 h, gave 2-imino-5-methyl-3-phenacyl-[1,3,4]thiadiazolium bromide **87**. Further, compound **87** in PPA at 70 °C for 5 h yielded the cyclised product **88**.

When compound **87** was stirred with DMFDMA for 24 h at room temperature, however, 2-(*N*,*N*-dimethylaminomethyleneamino)-5-methyl-3-phenacyl-[1,3,4]thiadiazolium bromide **89** was formed and, on heating under reflux in aqueous solution, this compound underwent cyclodehydration by intramolecular nucleophilic attack of the anion of the quaternary group on the carbon atom of the amidine group, followed by elimination of dimethylamine or protonated diamine, to give compound **90** (Scheme 20).



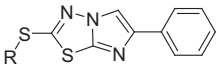
Scheme 20.

2.1.2. From 1-amino-2-substituted-4-phenylimidazole. Molina et al.[76] have described a method of annelation of the [1,3,4]thiadiazole ring on a pre-existing imidazole ring based on an initial aza-Wittig reaction. The reaction of 1-amino-2-methylthio-4-phenylimidazole **91** with triphenylphosphine dibromide in dry benzene under reflux for 12 h gave 2-methylthio-4-phenyl-1-triphenylphosphoranylidenamino-1*H*-imidazole **92** in 95% yield. The aza-Wittig reaction between iminophosphorane **92** and aroyl chlorides in dry toluene at refluxing temperature for 15 h yielded aryl-*N*-[2-methylthio-4-phenylimidazol-1-yl]imidoyl chloride intermediates **93**, which underwent cyclization with elimination of methyl chloride on heating at temperatures just above their melting points (180–210 °C) under reduced pressure to give the corresponding 2-aryl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazoles **94** in 55–77% yield. Alternatively, compounds **94** were also obtained by the reaction of iminophosphorane **92** with aroyl chlorides in dry toluene at refluxing temperature for 60 h (Scheme 21).



Scheme 21.

Shukurov et al.[77] have reported the synthesis of 2-(alkyl/aryl/arylalkylthio)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazoles **95** by the condensation of 1-amino-2-mercapto-4-phenylimidazole with the appropriate thiocyanates in polyphosphoric acid.



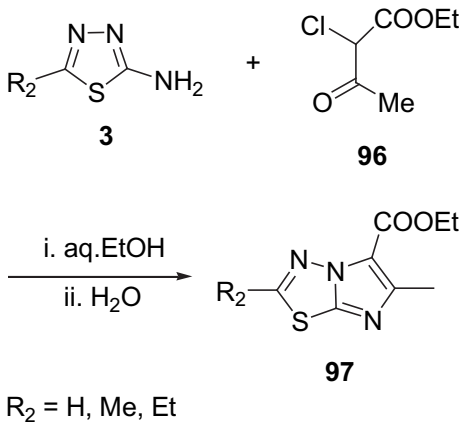
95

R = Me, Ph, Bn

2.2. Synthesis of 5,6- or 2,5,6-substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles

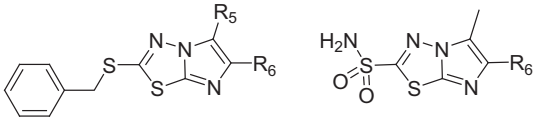
2.2.1. From 2-amino-5-(un)substituted-[1,3,4]thiadiazoles. 2.2.1.1. Reaction with substituted haloketones. Ban et al.[2] have reported the first synthesis of 5-carbethoxyethyl-6-methyl-2-(un)substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles **97** by the reaction of 2-amino-5-(un)substituted-[1,3,4] thiadiazoles **3** with 2-chloroacetoacetate ethyl ester **96** in hot aqueous alcohol for 2–5 h and the residues thus obtained were further heated in water for 30 min to yield the compounds **97** (Scheme 22).

Pyl et al.[3] have synthesized some 2-benzylthio-5,6-substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles **98** by the reaction of 2-amino-5-benzylthio-[1,3,4]thiadiazoles with 2-bromo-1-phenyl/(4-bromophenyl)propan-1-ones in boiling propanol for 1 h, followed by heating in hot water for several hours, or with 2-chloro-1,2-diphenylethanone in boiling propanol for 35 h and with 2-chloro-3-oxobutyric acid ethyl ester in ethanol for 40 h. Barnish et al.[7] have reported the synthesis of 6-alkyl/aryl-5-methylimidazo[2,1-*b*][1,3,4] thiadiazole-2-sulfonamides **99** in 17–37% yield by the reaction of 2-



Scheme 22.

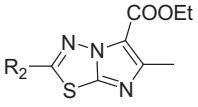
amino-5-sulfonamido-[1,3,4]thiadiazole with substituted bromoketones in refluxing ethanol for 60 h to yield the hydrobromide salt intermediates, which were further treated at room temperature with ammonium hydroxide solution followed by 5 N HCl until pH 7.5.



R_5 = Me, Ph, COOEt
R_6 = Me, Ph, 4-Br-C_6H_4

R_6 = Me, Et, Ph

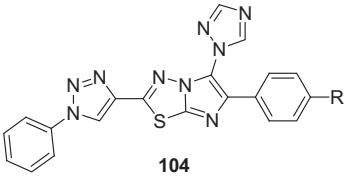
Abignente et al.[19] have reported the synthesis of 5-carbethoxyethyl-2-unsubstituted/methyl-6-methylimidazo[2,1-*b*][1,3,4]thiadiazoles **100** by the reaction of 2-amino-5-unsubstituted/methyl-[1,3,4]thiadiazoles with 2-chloroacetoacetate in refluxing ethanol for 10–34 h.

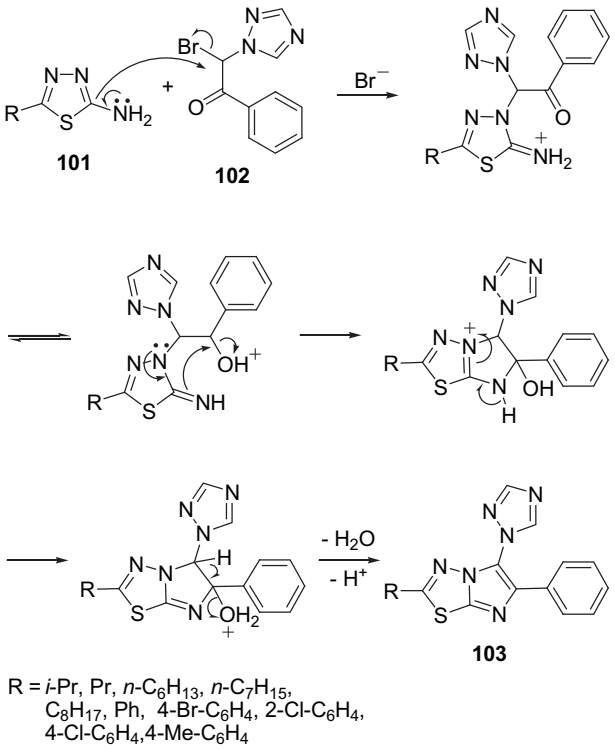


R_2 = H, Me

Zhang et al.[78] have reported the synthesis of 2-alkyl/aryl-6-phenyl-5-[1,2,4]triazol-1-yl-imidazo[2,1-*b*][1,3,4]thiadiazoles **103** by the reaction of 2-amino-5-alkyl/aryl-[1,3,4]thiadiazoles **101** with 2-bromo-1-phenyl-2-[1,2,4]triazol-1-yl-ethanone **102** via various unisolated intermediates (Scheme 23).

Cui et al.[44] have reported the synthesis of 2-(2-phenyl-1,2,3-triazol-4-yl)-5-(1*H*-1,2,4-triazol-1-yl)-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles **104** by the reaction of 2-amino-5-(2-phenyl-1,2,3-triazol-4-yl)-[1,3,4]thiadiazoles with ω-bromo-ω-(1*H*-1,2,4-triazol-1-yl)acetophenones in refluxing ethanol.

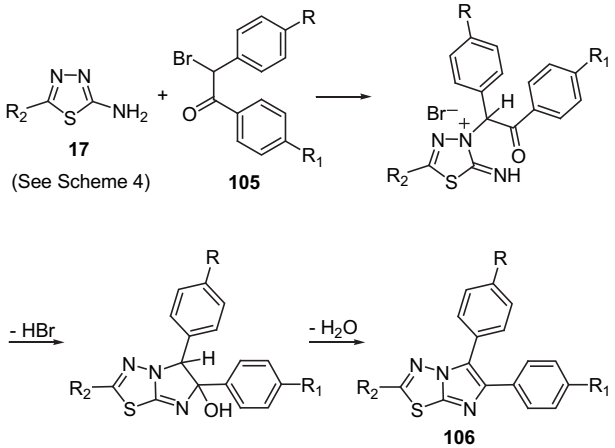




R = *i*-Pr, Pr, *n*-C_6H_{13}, *n*-C_7H_{15}, C_8H_{17}, Ph, 4-Br-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4,4-Me-C_6H_4

Scheme 23.

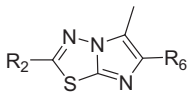
Gadad et al.[79] have reported the synthesis of 2-sulfonamido/trifluoromethyl-5,6-diaryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **106** in 40–72% yield by the reaction of 2-amino-5-sulfonamido/trifluoromethyl-[1,3,4]thiadiazoles **17** with the appropriate α-bromo-1,2-(4-(un)-substituted)diaryl-1-ethanones **105** in refluxing ethanol for 4–6 h, followed by the addition of phosphorus pentoxide and further refluxing for 4–6 h to obtain hydrobromide salts, which on neutralization with sodium carbonate yielded free bases (Scheme 24).



R = H, OMe
R_1 = H, F, Me, OMe, SMe, SO_2Me
R_2 = CF_3, SO_2NH_2

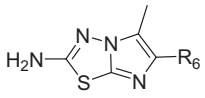
Scheme 24.

Pentimalli,[58] Paul[80] and Kukaniev et al.[68] have reported some 2,5,6-substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles **107**, **108** and **109**, respectively, by the reaction of 2-amino-5-substituted-[1,3,4]thiadiazoles with the appropriate α-bromo-1,2-substituted-1-ethanones.



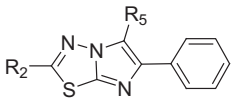
107

R_2 = H, Me
R_6 = Me, Ph, etc



108

R_6 = Me, Et, Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4,

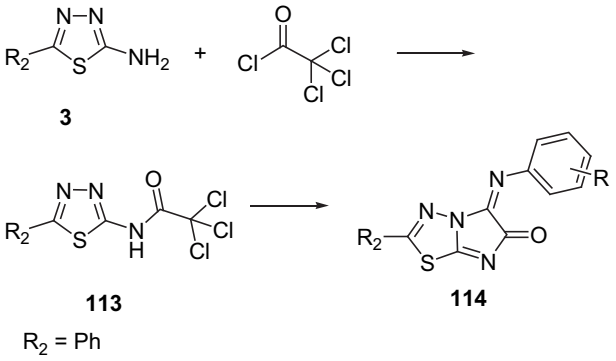


109

R_2 = Br, morpholino
R_5 = Br, morpholinomethyl

2.2.1.2. Combinatorial synthesis. Bienayme and Bouzid[81] have reported the combinatorial synthesis of a 5,6-disubstituted-imidazo[2,1-*b*][1,3,4]thiadiazole **110** by the reaction of 2-amino-[1,3,4]thiadiazole **3** (R_2=H) with *tert*-butyl isonitrile and benzaldehyde in the presence of a catalytic amount of $HClO_4$ by a three-component reaction in a non-nucleophilic solvent (trifluoroethanol). A plausible mechanism was proposed to involve a nonconcerted [4+1] cycloaddition between the protonated Schiff base **111** (which is both electrophilic and nucleophilic) and the isonitrile which behaves like a vinylidene carbenoid **112**, and a subsequent prototropic shift to give the final aromatic fused heterocycle (Scheme 25).

with primary arylamines via the ring closure of an isolable 2,2,2-trichloro-*N*-(5-phenyl-[1,3,4]thiadiazol-2-yl)-acetamide intermediate **113** (Scheme 26).



3

113

R_2 = Ph

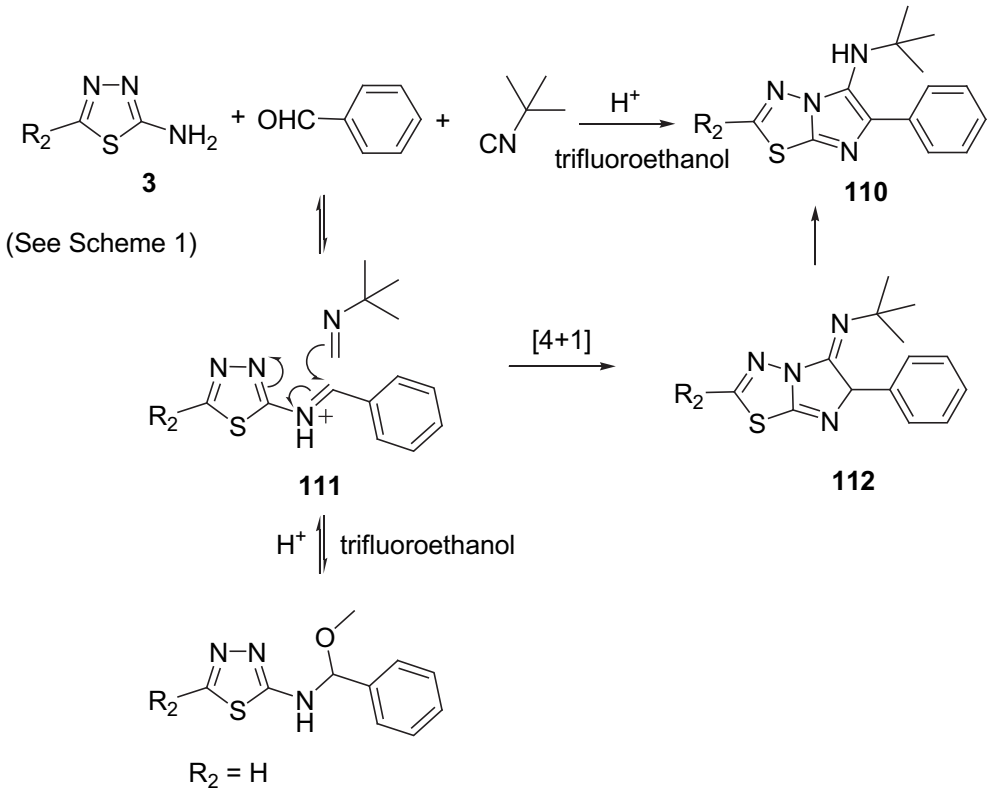
114

Scheme 26.

3. Structure and physicochemical properties

3.1. X-ray structural studies

The structural features of many imidazo[2,1-*b*][1,3,4]thiadiazoles have been determined by X-ray diffraction techniques. Schenetti et al.[83] have performed an X-ray analysis of 5,6-dimethyl-imidazo[2,1-*b*][1,3,4]thiadiazole **115** and its hydrobromide salt and suggested that the protonation of the free base occurred at N-7. In



3

(See Scheme 1)

trifluoroethanol

110

111

[4+1]

112

H^+ trifluoroethanol

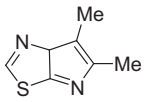
R_2 = H

Scheme 25.

2.2.1.3. Reaction with trichloroacetyl chloride. Yadav and Vaish[82] have reported the synthesis of 2-phenyl-5-aryliminoimidazo[2,1-*b*][1,3,4] thiadiazol-6-ones **114** by the reaction of 2-amino-5-phenyl-[1,3,4]thiadiazole **3** (R_2=Ph) with trichloroacetyl chloride and then

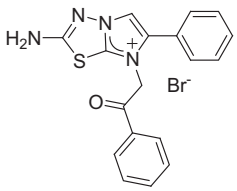
both the free base and the hydrobromide salt, the S–C distances from the imidazole ring [(S-1)–C(8) 1.720 (3) and 1.711 (4) Å] were significantly shorter than those involving C(2) [S(1)–C(2) 1.740 (4) and 1.737 (5) Å], suggesting π-delocalization was more favoured

through C(2). Both molecules exhibited a significant deviation from planarity, whereas the individual rings were planar. The packing of the free base showed all the contacts were consistent with the van der Waals radii, while in the protonated compound the water was involved in contacts with N(7).



115

Andreani et al.[84] have studied the X-ray crystal structure of 2-amino-7-(2-oxo-2-phenylethyl)-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazolium bromide **116**. The asymmetric unit was formed by two independent molecules and stabilized by intermolecular hydrogen bond and stacking interactions. The N–N bond distance was equal to 1.396 (9) and 1.379 (8) Å in the two molecules of the asymmetric unit. The planar imidazothiadiazole ring and its appended phenyl group formed dihedral angles of 39.1 and 43.2°, respectively. The phenyl bond to the CH_2CO-group was close to being orthogonal to the imidazothiadiazole ring with the dihedral angle equal to 75.26 and 71.40° in the two molecules of the asymmetric unit.



116

Li et al.[43] have determined the crystal structure of 2-isobutyl-6-(2,4-dichlorophenyl)-imidazo[2,1-*b*][1,3,4]thiadiazole **54** by single-crystal X-ray diffraction and this showed almost coplanar imidazothiadiazole ring atoms and a dihedral angle of 16.8(0.2)° between the phenyl group and the heterocycle.

Anilkumar et al.[85] have reported the X-ray crystal structure of 6-(4-chloro-phenyl)imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide **48** (R_6=4-Cl–C_6H_4) with essential planarity (Fig. 1). The crystal structure exhibited an intermolecular C12–H12···N1 hydrogen bonding between an imidazole ring nitrogen and a phenyl proton, whilst an intermolecular N–H···O hydrogen bonding between oxo and amino groups of the sulfonamides stabilized the crystal structure (Fig. 2). The torsion angle of 5.2(1)° suggested the coplanarity of the phenyl ring with the imidazole ring.

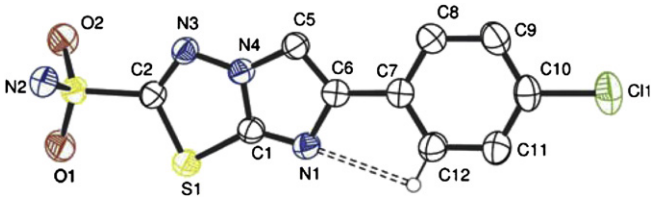


Fig. 1. View of compound **48** (R_6=4-Cl–C_6H_4), with displacement ellipsoids drawn at 50% probability level; broken line indicates intramolecular hydrogen bond.

A non-coplanar imidazothiadiazole ring system and a 6-methoxyphenyl ring with an angle of 31.60(7)° between their mean planes was reported by Begum et al.[86] in the X-ray crystal structure of 2-ethyl-6-(4-methoxyphenyl)imidazo[2,1-*b*][1,3,4] thiadiazole-5-carbaldehyde **117**. In the crystal structure,

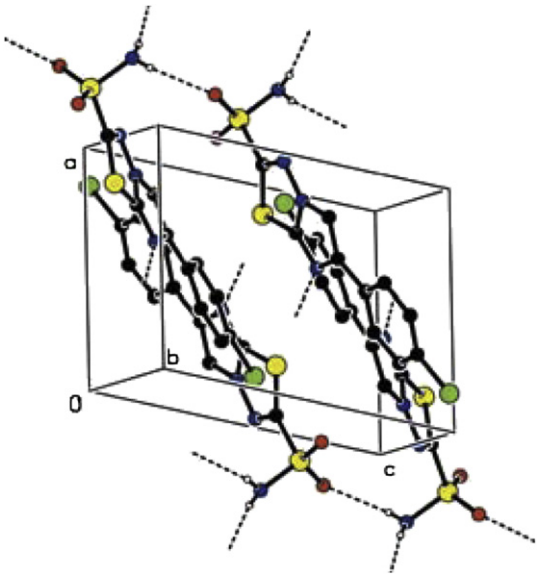
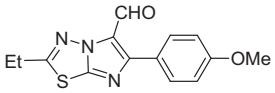
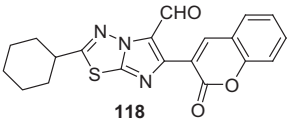


Fig. 2. Packing diagram for compound **48** (R_6=4-Cl–C_6H_4), with N–H···O hydrogen bonds shown as dashed lines.

intermolecular C–H···O hydrogen bonding linked the molecules into dimmers, while π–π staking interactions reinforced the crystal cohesion.



117



118

In the single-crystal X-ray crystal structure of 2-cyclohexyl-6-(2-oxo-2*H*-chromen-3-yl)imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde **118**, the imidazothiadiazole and coumarin ring systems have reported to be planar and inclined at an angle of 31.60(7)° towards each other, whilst the crystal structure was stabilized by intermolecular C–H···O interactions (Figs. 3 and 4).[87]

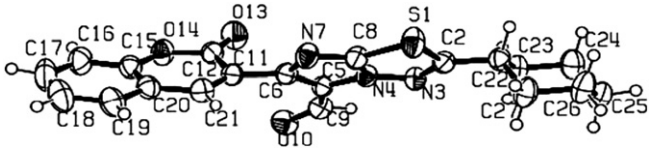


Fig. 3. Molecular structure and atom-labelling scheme for compound **118**.

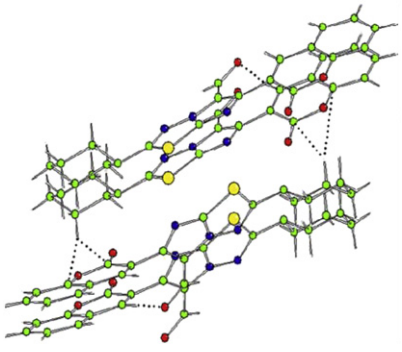
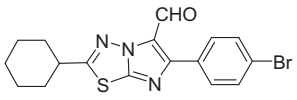


Fig. 4. View of (i) C–H···O interaction (ii) intermolecular short contacts between cyclohexyl proton and coumarin ring of compound **118**.

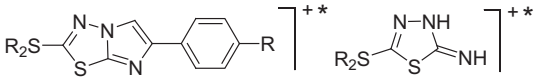
The single X-ray crystal structure of 6-(4-bromo-phenyl)-2-cyclohexylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde **119** has also been reported.[88]



119

3.2. Mass spectral fragmentation

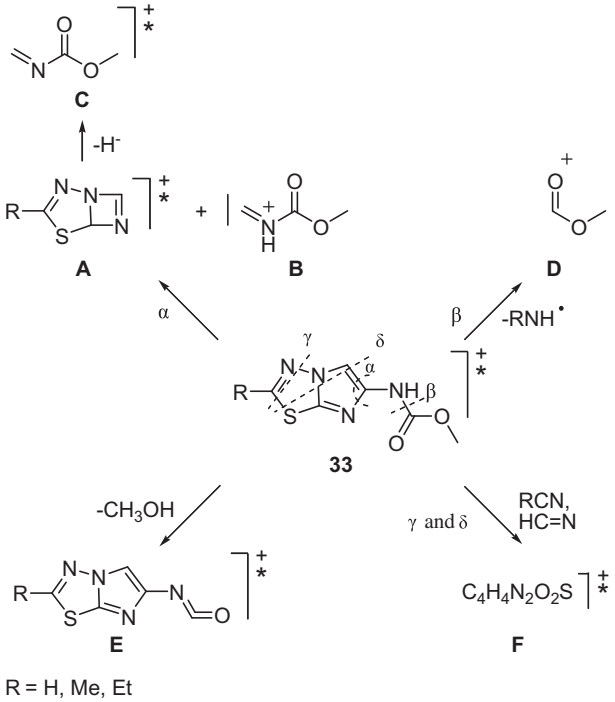
The mass spectral fragmentation of 2-methylthio-6-phenyl-imidazo[2,1-*b*][1,3,4]thiadiazole **13** (R_2=Me; R=H) has been studied by electron impact and chemical ionization techniques in methane by Eldawy et al.[6] The molecular ion peak **13** in the electron impact mass spectrum is observed at 247 in addition to peaks at 248 and 249 corresponding to (m+1) and (m+2) peaks, respectively. The peaks at 232, 200, 175 and 105 may be produced by fragmentation of the molecular ion, while the base peak at 147 may be formed by double protonation of fragment **120** having an *m*/*e* value of 145. The chemical ionization mass spectrum in methane showed base peak at 248. This is attributed to the quasimolar ion (*m*+1) in addition to the molecular ion peak at 247 and *m*+29 peak (for methane) at 276.



13 m/e 247 **120** m/e 147

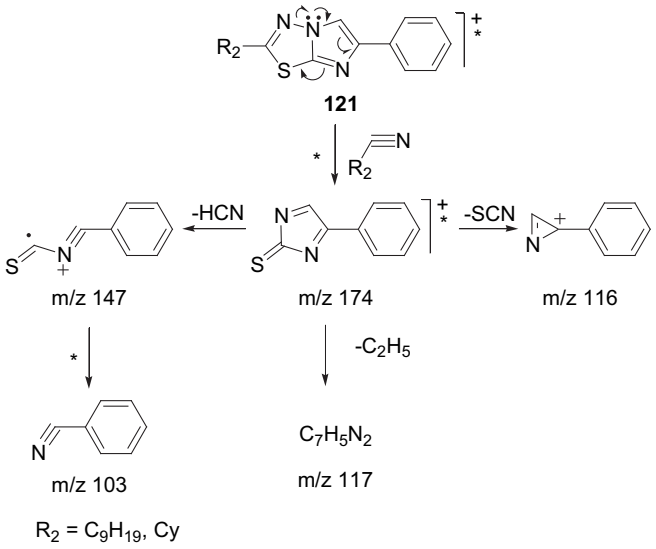
R = Me; R_4 = H

Valls et al.[8] have studied the mass spectral fragmentation for (2-(un)substituted-imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-carbamic acid methyl ester derivatives **33**, which showed molecular ion peaks with remarkable intensity. The fragmentation pattern of these compounds is shown in Scheme 27. Peaks **A** and **C** have been attributed to cleavage of the imidazole ring (marked α). The base peak fragment **C** appeared to be more stable than the ion **B**, which would be produced by loss of hydride. The peak **D** arises from β rupture, while peak **E** arises from the molecular ion by the loss of methanol. The common peak **F** arose from γ and δ cleavage by the elimination of neutral molecules: HCN; HCN and acetonitrile; HCN and propionitrile.



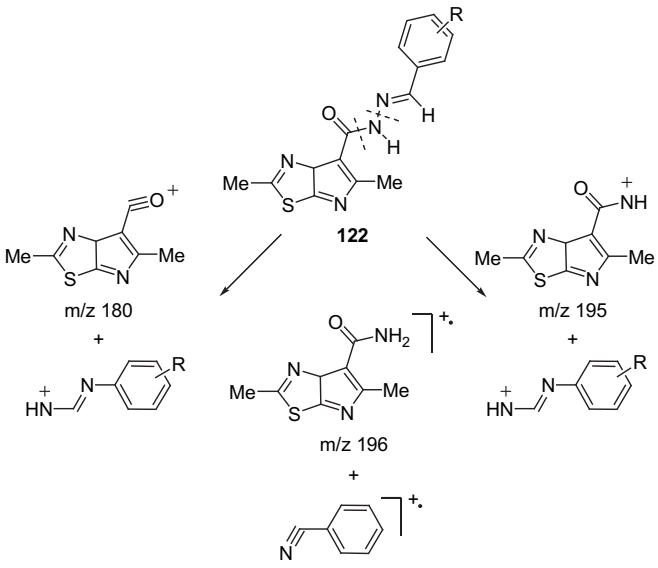
Scheme 27.

The high-resolution and metastable ion mass spectral fragmentation of 2-alkyl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles **121** was reported by Khazi et al.[89], demonstrating the loss of alkyl radicals of formula C_nH_{2n+1} from the molecular ion and the McLafferty rearrangement involving dominant ring cleavage which may be due to the localization of positive charge in the heterocyclic ring (Scheme 28).



Scheme 28.

The major fragmentation pathway involving cleavage of the N–N bond and migration of a C–H proton to the nitrogen atom in the electron impact mass spectra of 2,6-dimethyl-5-substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles **122** was proposed by Terzioglu and Gursoy[90] (Scheme 29).

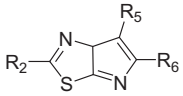


Scheme 29.

3.3. Nuclear magnetic resonance (NMR) spectra

Although a considerable amount of NMR data for imidazo[2,1-*b*][1,3,4]thiadiazoles are available in the literature, little work has been done in a systematic way to correlate substituent effects with NMR spectra. The presence of a characteristic singlet for the C-5 proton in the ^{1}H NMR spectra of 2-alkoxythio-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles at around δ 7.88–7.75 ppm was assigned for the first time by Eldawy et al.[6]

Schenetti et al.[83] have studied the ^{1}H NMR spectra of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **115** and **123**–**125** in $CDCl_3$ and trifluoroacetic acid (TFA) in order to determine the basicity of the ring nitrogen atoms. In the ^{1}H NMR ($CDCl_3$) spectra, C_2–H resonated at higher field, while C_5–H and C_6–H resonated at lower fields with respect to the parent thiadiazole and imidazole or *N*-methyl-imidazole heterocycles. Comparison of the ^{1}H NMR (TFA) spectra of the protonated forms with those of the free bases suggested the highest effect of protonation was on C_2–H followed by C_5–H and C_6–H. NMR studies using a lanthanide shift reagent, Eu(fod)$_3$, indicated N(7) as the most basic atom, which was also supported by X-ray analysis.



115: R_2 = H, R_5 = R_6 = Me
123: R_2 = R_5 = R_6= H
124: R_2 = R_5 = H, R_6 = Me
125: R_2 = Me, R_5 = H, R_6 = Me

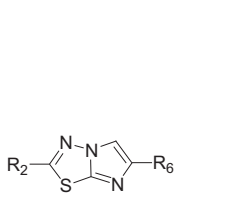
Valls et al.[8] have reported that the ring carbon atoms in the ^{13}C NMR spectra (DMSO-d_6) of imidazo[2,1-*b*][1,3,4]thiadiazole-2-carbamic acid methyl ester **33** (R=H) resonated at δ 140.1, 100.8, 142.6 and 148.4 ppm, respectively, corresponding to C_2, C_5, C_6 and C_8. A solvent effect of TFA was observed in the ^{13}C NMR spectra of 2-methyl/ethylimidazo[2,1-*b*][1,3,4]thiadiazole-2-carbamic acid methyl esters. The C_2, C_5, C_6 and C_8 carbons resonated at δ 136.5, 104.9, 142.8–141.7 and 174.0–168.3 ppm, respectively.

3.4. UV spectra

Barnish et al.[7] have reported a UV spectral band in methanol at 262 nm for 6-*tert*-butyl-imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide **19** (R_6=*t*-Bu). Gadad et al. have reported UV spectral data for a series of imidazo[2,1-*b*][1,3,4]thiadiazoles.[36–38] 2-Alkyl-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **47** exhibited UV spectral bands at 255 nm (log ϵ, 3.70) and at 277 nm (log ϵ, 3.45).[36] The UV spectra of 5-guanylhydrazone-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-2-[*N*-(dimethylaminomethino)]sulfonamides in ethanol exhibited three bands in the regions of 288–349, 248–292 and 225–226 nm.[37] 6-Arylimidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **48** showed three UV bands in the regions of 314–326, 254–270 and 232–234 nm in ethanol, while the 2-trifluoromethyl derivatives **49** exhibited bands in the regions of 304–340, 250–288 and 228–240 nm.[38]

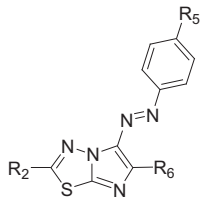
3.5. Liquid crystals

Ivashchenko[71,91] and Torgova et al.[92–94] have reported the synthesis of various liquid-crystalline imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **126** containing alkyl, *trans*-alkylcyclohexyl and aryl substituents in the 2 and 6 positions by the reaction of 2-amino-5-substituted-[1,3,4]thiadiazoles with the appropriate α-bromoketones. These mesogens possess a wide mesophase range and high thermal stability. The mesophase type was reported to depend on the nature of the substituents, in particular the cyclohexane ring, and also their position in the thiadiazole or imidazole part of the molecule. A nematic phase was produced by attaching a cyclohexyl group to the imidazole ring.[92] Various 5-arylazo-2,6-diarylimidazo[2,1-*b*][1,3,4]thiadiazoles **127** were reported[91] as dichronic T-dyes useful for liquid crystal display applications.



126

R_2 = Et, *n*-C_5H_{11}, *n*-C_9H_{19}, 4-Bu-C_6H_{10}, 4-Bu-C_6H_4;
R_6 =4-Br-C_6H_4, 4-CN-C_6H_4, 4-Bu-C_6H_4,4-Bu-C_6H_{10}, 4-(4-Bu-C_6H_{10})-C_6H_4, 4-(4-n-C_5H_{11}-C_6H_{10})-C_6H_4,



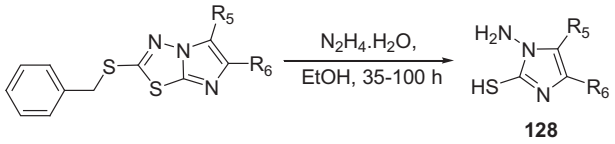
127

R_2 = *n*-C_5H_{11}, 4-Bu-C_6H_{10}, 4-C_7H_{15}-C_6H_4;
R_5 =Br, CN, Me, Et, C_5H_{11};
R_6 =4-Br-C_6H_4, 4-CN-C_6H_4, 4-(4-Pr-C_6H_{10})-C_6H_4, 4-(4-n-C_5H_{11}-C_6H_{10})-C_6H_4,

4. Reactivity

4.1. Ring cleavage

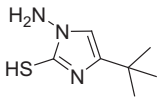
During the reaction of 2-benzylthio-5-and/or 6-(un) substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles **16** and **98** with hydrazine hydrate in hot ethanol for 35–100 h, the thiadiazole ring cleavage resulting in the corresponding 1-amino-2-mercaptoimidazole derivatives **128** has been reported by Pyl et al.[3] (Reaction 1).



128

8: R_5 = H; R_6 = Me, Ph, 4-Br-C_6H_4
98: R_5 = Me, Ph, COOEt;
R_6 = Me, Ph, 4-Br-C_6H_4

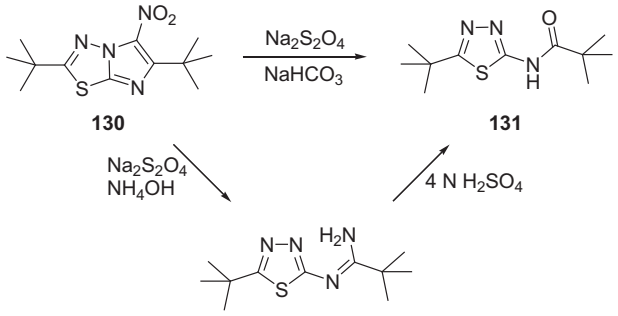
Reaction 1.



129

Similarly, Sitte et al.[4] have reported ring cleavage during the reaction of 2-amino-6-alkyl/aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **9** with boiling hydrazine hydrate. Barnish et al.[7] have reported the formation of 1-amino-2-mercapto-4-*tert*-butylimidazole **129** in 91% yield by the thiadiazole ring cleavage of 6-*tert*-butylimidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide **19** (R_6=*t*-Bu) in 5 N NaOH at 95 °C for 6 h after neutralization with 5 N HCl.

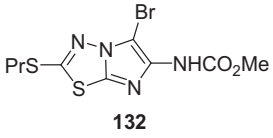
Hough[5] has reported the formation of *N*-(5-*tert*-butyl-1,3,4-thiadiazol-2-yl)pivalamide **131** in 42% yield by cleavage of the imidazole ring during the reaction of 2,6-di-*tert*-butyl-5-nitroimidazo[2,1-*b*][1,3,4]thiadiazole **130** and sodium bicarbonate in aqueous EtOH at 50 °C with sodium dithionite, followed by reflux for 1 h. A similar reaction in the presence of concentrated ammonium hydroxide instead of sodium bicarbonate gave *N*-(5-*tert*-butyl-1,3,4-thiadiazol-2-yl)pivalamine in 61% yield, which on reflux in 4 N H_2SO_4 for a few minutes gave compound **131** (Reaction 2).



Reaction 2.

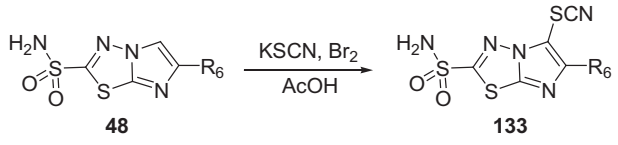
4.2. Electrophilic substitution reactions

Electrophilic substitution reactions of imidazo[2,1-*b*][1,3,4]thiadiazoles with bromine have been widely reported in the literature. The reaction of various imidazo[2,1-*b*][1,3,4]thiadiazoles with bromine in the presence of catalytic anhydrous sodium acetate in boiling AcOH yielded the corresponding the 5-bromo derivatives of imidazo[2,1-*b*][1,3,4]thiadiazoles.[5,14,15,20,21,23,25,26,28,30,36,38,58,66,71] Marin et al.[15] have reported the synthesis of (5-bromo-2-propylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-carbamic acid methyl ester **132** by the reaction of (2-propylsulfanylimidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)carbamic acid methyl ester HBr salt with m-chloroperbenzoic acid in DCM at −5 °C for 15 min, and then at room temperature for 2.5 h, followed by the addition of a saturated solution of Na_2CO_3.



132

Gadad et al.[37] have reported the reaction of 6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **48** and KSCN with bromine in AcOH at 0–5 °C, and then at 15–18 °C for 30 min and at room temperature for 30 min to give 5-thiocyanato-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **133** in 60–75% yield (Reaction 3).

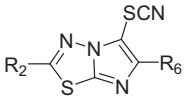


48 **133**

R_6 = Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-NO_2-C_6H_4

Reaction 3.

Similarly, Kano[9] has also reported the thiocyanation of some 2-(un)substituted-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles by the bromine method to yield the corresponding 5-thiocyanato derivatives **134**.



134

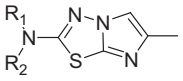
R_2 = H, Me
R_6 = Me, Ph, 4-Br-C_6H_4,4-Cl-C_6H_4

4.3. Nucleophilic displacement reactions

Displacement of a bromo substituent at the 2- and 5-position in imidazo[2,1-*b*][1,3,4]thiadiazoles by various nucleophiles has been achieved under appropriate reaction conditions.

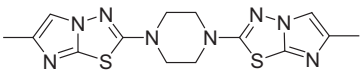
Shukurov et al.[77] have reported the reaction of 2-bromo-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole with benzenethiol to yield 2-phenylsulfanyl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole **95** (R=Ph).

Khodzhibaev and Kukaniev[95] have reported the reaction of 2-bromo-6-methylimidazo[2,1-*b*][1,3,4]thiadiazole with various secondary alkyl amines to give the corresponding 2-alkylamino derivatives **135**, whereas the reaction with piperazine HCl yielded 1,4-bis-(6-methylimidazo [2,1-*b*][1,3,4]thiadiazol-2-yl)piperazine **136**.



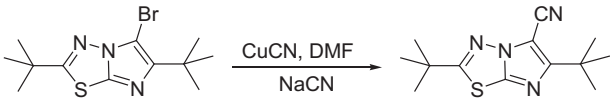
135

R_1 = H, R_2 = Me, Et, EtOH, CH_2COOH;
R_1 = R_2 = Me, Et;
R_1R_2 = -$(CH_2)_2$-, -$(CH_2)_4$-NH-



136

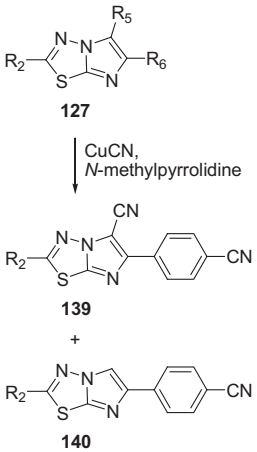
Hough[5] has reported the reaction of 5-bromo-2,6-di-*tert*-butylimidazo[2,1-*b*][1,3,4]thiadiazole **137** with CuCN in DMF at 160 °C, followed by treatment with aqueous NaCN to yield the corresponding 5-carbonitrile derivative **138** (Reaction 4).



137 **138**

Reaction 4.

Ivashchenko et al.[71] have reported the reaction of 5-bromo-6-(4-bromo-phenyl)-2-(4-butylcyclohexyl)imidazo[2,1-*b*][1,3,4]thiadiazole **127** (R_2=4-Bu–C_6H_{10}; R_5=Br; R_6=4-Br–C_6H_{10}) with CuCN in *N*-methylpyrrolidine to give the corresponding dinitrile derivative **139** and 5-unsubstituted derivative **140** (Reaction 5).



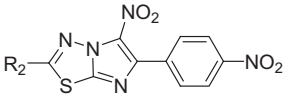
R_2 = 4-Bu-C_6H_{10}, ; R_5 = Br; R_6 = 4-Br-C_6H_4

Reaction 5.

4.4. Nitration

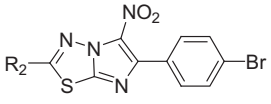
Pentimalli et al.[58] have reported the nitration of 6-phenyl-2-(un) substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles to yield the corresponding 2-(un)substituted-5-nitro-6-(4-nitro-phenyl)imidazo[2,1-*b*][1,3,4]thiadiazoles **141**, while Andotra et al.[66] have reported the nitration of 6-(4-bromophenyl)-2-substituted-imidazo[2,1-*b*][1,3,4] thiadiazoles to give 2-substituted-5-nitro-6-(4-bromophenyl)-imidazo[2,1-*b*][1,3,4]thiadiazoles **142**.

Similarly, Hough[5] has reported the synthesis of 2,6-di-*tert*-butyl-5-nitroimidazo[2,1-*b*][1,3,4]thiadiazole **143** in 86% yield by the reaction of 2,6-di-*tert*-butylimidazo[2,1-*b*][1,3,4]thiadiazole with HNO_3/H_2SO_4 for 15 min.



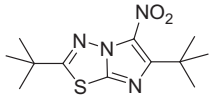
141

R_2 = H, Me



142

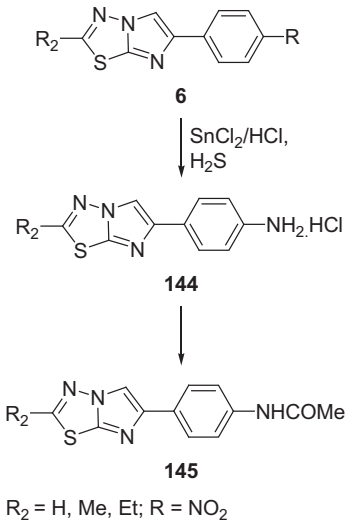
R_2 = 3-Et-4,6-$(MeO)_2$-C_6H_2, 3-Et-6-EtO-4-MeO-C_6H_2, 3-Pr-4-EtO-6-MeO-C_6H_2, 3-Pr-4,6-$(EtO)_2$-C_6H_2, 3,4-(-O-CH_2-O-)-6-NO_2-C_6H_2



143

4.5. Reduction

Matsukawa et al.[96] have reported the reaction of 2-(un)substituted/alkyl-6-(4-nitrophenyl)-imidazo[2,1-*b*][1,3,4]thiadiazoles **6** in hot aqueous $SnCl_2$/HCl for 20 min, followed by saturation of the reaction mixture with H_2S in hot water, to give the 2-(un)substituted/alkyl-6-(4-aminophenyl)-imidazo[2,1-*b*][1,3,4]thiadiazole HCl salts **144**, which on neutralization yielded 2-(un)substituted/alkyl-6-(4-acetylaminophenyl) imidazo[2,1-*b*][1,3,4]thiadiazoles **145** (Reaction 6).



6

$SnCl_2$/HCl, H_2S

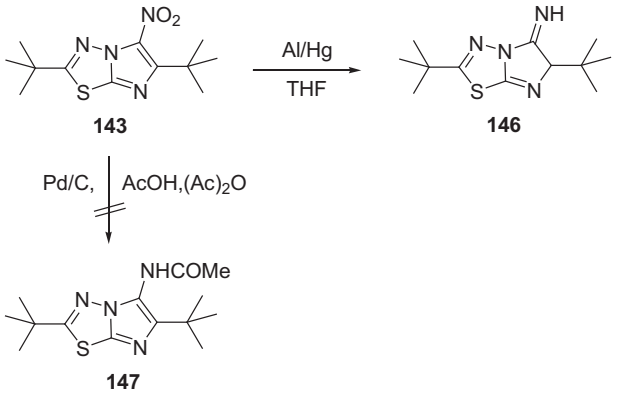
144

145

R_2 = H, Me, Et; R = NO_2

Reaction 6.

Hough[5] has reported the reduction of 2,6-di-*tert*-butyl-5-nitro-imidazo[2,1-*b*][1,3,4]thiadiazole **143** with aluminium amalgam in THF for 5 h to give 2,6-di-*tert*-butyl-5-imino-5,6-dihydro-imidazo [2,1-*b*][1,3,4]thiadiazole **146** in 36% yield. The reaction of compound **143** in acetic acid/acetic anhydride with palladium/charcoal, however, did not give the expected amine **147** (Reaction 7).

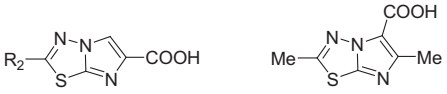


143 **146** **147**

Reaction 7.

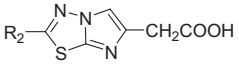
4.6. Hydrolysis

Abignente et al.[19] reported the hydrolysis of 2-alkylimidazo[2,1-*b*][1,3,4]thiadiazole-6-carboxylic acid ethyl esters **41** and 2,6-dimethylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carboxylic acid ethyl ester **100** in refluxing NaOH (1 M) or ethanolic NaOH for 1–3 h, followed by treatment with dilute HCl to give the corresponding acids **148** and **149**, respectively. 2-Unsubstituted-carboxylic acid ethyl ester derivatives of compounds **41** and **100** were, however, resistant to acid hydrolysis while, in alkaline solutions, they underwent decomposition. Hydrolysis of 2-substituted-imidazo[2,1-*b*][1,3,4]thiadiazole-5-acetic acid ethyl esters to the corresponding 5-acetic acid **150** was achieved by their reaction either with 1 M NaOH in aqueous EtOH at room temperature for 1 h, followed by acidification with dilute HCl, or by refluxing in dilute HCl for 2 h, and then treatment with 10% NaOH.



148 **149**

R_2 = Me, Et



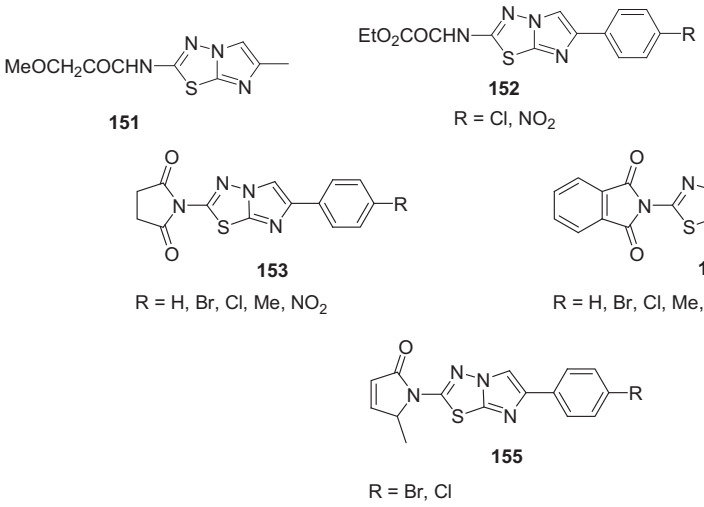
150

R_2 = H, Me, Et

4.7. Reactions of 2-amino group

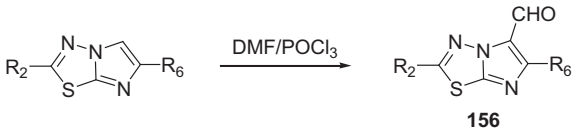
Paul and Sitte[97] have studied the behaviour of 2-amino-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole **9** (R_6=Ph) towards NaOH and EtONa. Treatment of ethanolic compound **9** with NaOH and EtONa in absolute ethanol yielded the colourless, granular, strongly hygroscopic di-sodium salt of compound **9**, which was reported to exist as the resonance-stabilized thiadiazole ring-opened form.

Paul and Sitte[60] have further reported the reaction of 2-amino-6-methyl-imidazo[2,1-*b*][1,3,4]thiadiazole with 3-oxo-butyric acid *tert*-butyl ester in acetone to give *N*-(6-methyl-imidazo[2,1-*b*][1,3,4] thiadiazol-2-yl)-3-oxo-butyramide **151**. Similarly, Paul and Wessel[98] have reported the reaction of 2-amino-6-arylimidazo[2,1-*b*][1,3,4] thiadiazoles with ethyl oxalate in PPA to yield 2-(ethoxycarbonyl-formylamino)-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles **152**, while the reactions with ethyl succinate, ethyl phthalate and ethyl levulinate in PPA yielded the corresponding 2-cyclic-amino derivatives **153**–**155**, respectively.



4.8. Vilsmeier–Haack reactions

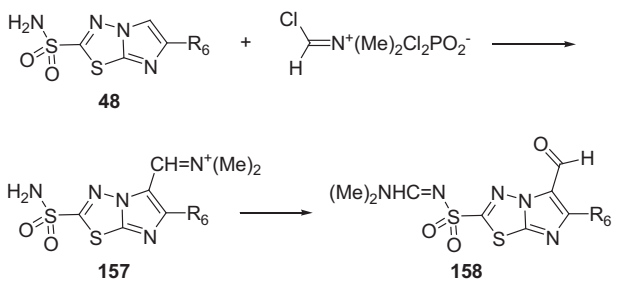
Vilsmeier–Haack reactions of various imidazo[2,1-*b*][1,3,4]thiadiazoles have been reported with DMF/$POCl_3$, which involve attack of the electrophilic chloroimmonium ion at C-5 of the imidazo[2,1-*b*][1,3,4]thiadiazoles to give the corresponding 5-carbaldehyde derivatives **156** (Reaction 8).[39,40,42,99]



R_2 = Me, Et, Pr, Cy, Ph, 4-Br-C_6H_4, Bn, 2-furyl, 2-thieny
R_6 = Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4
3-coumarinyl

Reaction 8.

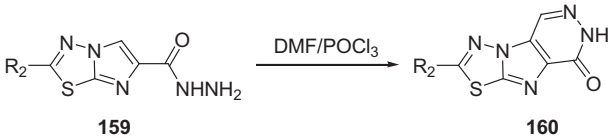
Gadad et al.[100] have reported the Vilsmeier–Haack reaction of 6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **48** with DMF/$POCl_3$ to give 6-aryl-5-carbaldehyde-imidazo[2,1-*b*][1,3,4]thiadiazole-2-*N*-(dimethylaminomethino)sulfonamides **158** in 40–82% yields, probably via the unisolated 2-chloroimine/amine intermediates **157** (Reaction 9).



R_6 = Ph, 4-Br-C_6H_4,
4-Cl-C_6H_4, 4-NO_2-C_6H_4, 4-Ph-C_6H_4,
3-coumarinyl,
5-(4-NO_2-C_6H_4)-2-furyl,

Reaction 9.

Kolavi et al.[41] have reported the synthesis of 2-alkyl/aryl-[1,3,4]thiadiazolo[2′,3′:2,3]imidazo[4,5-d]pyridazin-8(7*H*)-ones **160** in 39–58% yields by the Vilsmeier–Haack reaction of 2-alkyl/aryl-imidazo[2,1-*b*][1,3,4]thiadiazole-6-carboxylic acid hydrazides **159** with DMF/$POCl_3$ at 0 °C for 30 min, and then for 2 h at room temperature and 60 °C, respectively, followed by stirring the reaction mixture at 90 °C for 2 h in sodium carbonate solution (Reaction 10).

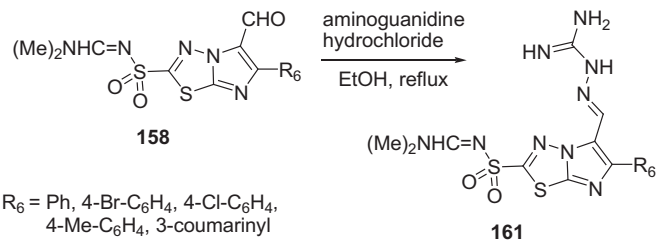


R_2 = Et, *n*-Pr, Cy, Bn, 2-furyl, 2-thienyl

Reaction 10.

4.9. Reactions of 5-carbaldehydes

Gadad et al.[37] have reported the reaction of 6-aryl-5-carbaldehyde-imidazo[2,1-*b*][1,3,4]thiadiazole-2-*N*-(dimethylaminomethino)sulfonamides **158** with aminoguanidine hydrochloride in refluxing EtOH for 30 min to give the corresponding 5-guanylhydrazone-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-2-*N*-(dimethylaminomethino)sulfonamides **161** in 65–70% yields (Reaction 11).

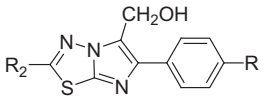


R_6 = Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4,
4-Me-C_6H_4, 3-coumarinyl

Reaction 11.

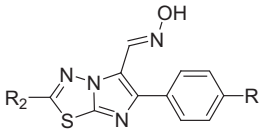
Kolavi et al.[39] have reported the reactions of 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes **156** with sodium borohydride and hydroxylamine hydrochloride. Reduction of compounds **156** with sodium borohydride in methanol at room temperature for 5 h yielded various (2-alkyl/aryl-6-arylimidazo

[2,1-*b*][1,3,4]thiadiazol-5-yl)methanol derivatives **162** in 63–85% yields. Compounds **156** with hydroxylamine hydrochloride in refluxing pyridine for 6 h, however, gave 2-alkyl/aryl-6-arylimidazo [2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde oximes **163** in 76–83% yields. Further, Hegde et al.[42] have reported the reaction of compounds **156** with 2-aminothiophenol in DMSO to give 2-(2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)-1,3-benzothiazoles **164** in 71–82% yields.



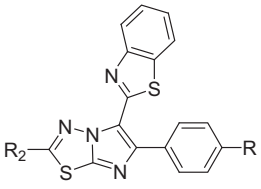
162

R = H, Br
R_2 = Cy, 2-furyl, 2-thienyl



163

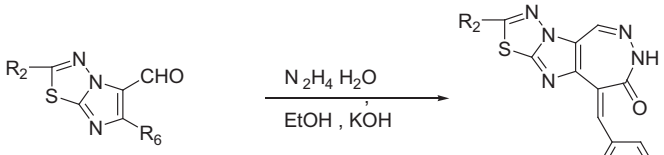
R = H, Br
R_2 = Cy, 2-furyl, 2-thienyl



164

R = Cl, Me, OMe
R_2 = Pr, Cy, 2-thienyl

Kolavi et al.[40] have also reported the reaction of **156** with hydrazine hydrate in refluxing ethanolic KOH for 6 h to give 2-alkyl/aryl-9-(2-hydroxybenzylidene)-7,9-dihydro-8*H*-[1,3,4]thiadiazolo [2′,3′:2,3]imidazo[4,5-d][1,2]diazepin-8-ones **165** in 24–36% yields by ring opening and cyclization via an intramolecular amidation (Reaction 12).



156

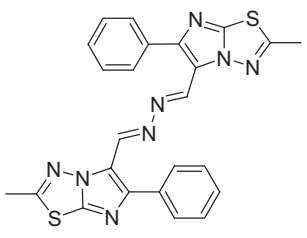
R_2 = Et, n-Pr, Cy, Bn, 2-furyl, 2-thienyl

R_6 =

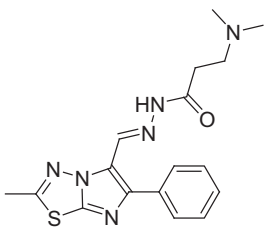
165

Reaction 12.

Andreani et al.[99] have reported 2-methyl-6-phenylimidazo[2,1-*b*] [1,3,4]thiadiazol-5-yl-methylene hydrazine derivatives **166** and **167**.



166

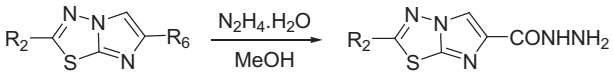


167

4.10. Reactions with hydrazine hydrate

Imidazo[2,1-*b*][1,3,4]thiadiazoles have been reported to undergo ring cleavage[3,4] or hydrazinolysis[41,90] depending on the nature of the substitutions at either C-5 or C-6 positions. Terzioglu and Gursoy[90] have reported the reaction of 2-unsubstituted/alkyl-6-methylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carboxylic acid ethyl esters **100** with hydrazine hydrate (80%) in EtOH at room temperature, and then at 80 °C (R_2=H, 5 min.; R_2=Me, Et, 2 h) to give 2-unsubstituted/alkyl-6-methylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carboxylic acid hydrazides (R_2=H, Me, Et).

Kolavi et al.[41] have reported the reaction of 2-alkyl/aryl-imidazo [2,1-*b*][1,3,4]thiadiazole-6-carboxylic acid ethyl esters **51** with hydrazine hydrate in refluxing MeOH for 6 h to yield the corresponding 6-carboxylic acid hydrazides **168** in 77–90% yields (Reaction 13).



51 **168**

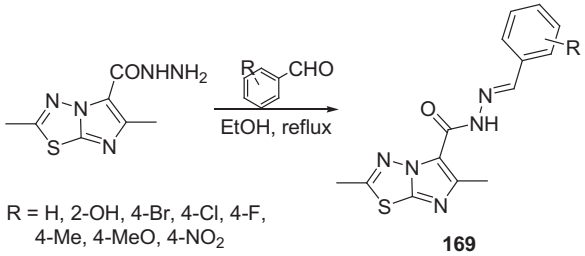
R_2 = Et, Pr, Cy, Bn, 2-furyl, 2-thienyl

R_6 = COOEt

Reaction 13.

4.11. Reactions of 5-carbohydrazides

Terzioglu and Gursoy[90] have reported the synthesis of 2,6-dimethyl-*N*′-substituted-phenylmethylidene-imidazo[2,1-*b*][1,3,4] thiadiazole-5-carbohydrazides **169** in 40–87% yields by the reaction of 2,6-dimethylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbohydrazides with the appropriate aldehydes in refluxing ethanol for 5 h (Reaction 14).



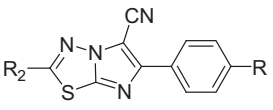
R = H, 2-OH, 4-Br, 4-Cl, 4-F, 4-Me, 4-MeO, 4-NO_2

169

Reaction 14.

4.12. Reactions of 5-carbaldehyde oximes

Kolavi et al.[39] have reported the dehydration reaction of 2-alkyl/aryl-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde oximes **163** in refluxing thionyl chloride for 5 min, followed by neutralization with sodium carbonate, to yield 2-alkyl/aryl-6-arylimidazo[2,1-*b*] [1,3,4]thiadiazole-5-carbonitriles **170** in 68–90% yields.

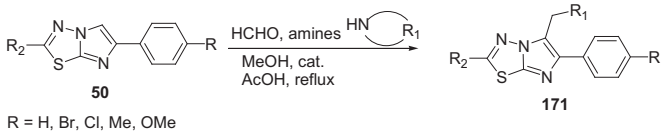


170

R = H, Br
R_2 = Cy, 2-furyl, 2-thienyl

4.13. Mannich and Schiff bases

Kolavi, Hegde et al.[39,42] have reported the Mannich reaction of 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles **50** with cyclic amines and formaldehyde in the presence of AcOH in refluxing methanol for 8 h to give 2-alkyl/aryl-5-(substituted aminomethyl)-6-arylimidazo[2,1-*b*][1,3,4]thiadiazoles **171** (Reaction 15).

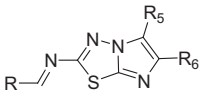


50 **171**

R = H, Br, Cl, Me, OMe
R_2 = Cy, 2-furyl, Pr, 2-thienyl
R_1 = 4-morpholinyl, 1-piperidinyl, 1-pyrrolidinyl

Reaction 15.

Paul et al.[80] have reported the reaction of 2-amino-5-unsubstituted/methyl-6-alkyl/aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles with various aldehydes to yield the corresponding Schiff bases **172**.

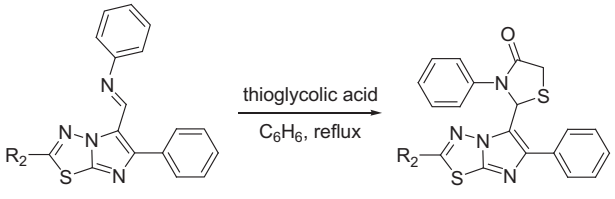


172

R = Ph, 4-$(Me)_2$N-C_6H_4, 4-NO_2-C_6H_4
R_5 = H, Me
R_6 = Me, Et, Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4

4.14. Reactions of Schiff bases

Kolavi et al.[39] have reported the reaction of (2-alkyl/aryl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-ylmethylene)phenylamine Schiff bases with thioglycolic acid in refluxing benzene for 5 h to yield 2-(2-alkyl/aryl-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)-3-phenyl-1,3-thiazolidin-4-ones **173** in 64–66% yields (Reaction 16). Although the structures of the Schiff bases were not characterized by the authors, they were isolated from the reaction of 2-alkyl/aryl-6-phenyl-imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes **156** with aniline in refluxing EtOH in the presence of catalytic acetic acid and used for the reaction with thioglycolic acid.



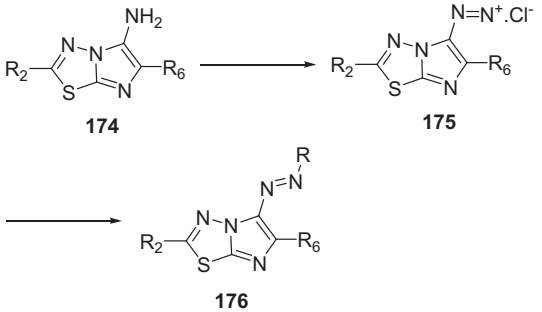
173

R_2 = Cy, 2-furyl, 2-thienyl

Reaction 16.

4.15. Diazotization

Ivashchenko et al.[91] have reported the synthesis of some 5-arylazo-2,6-bis-(4-hexyl-phenyl)-imidazo[2,1-*b*][1,3,4]thiadiazole liquid crystals **176** from the corresponding amino derivatives **174** via the formation of the diazonium salts **175** (Reaction 17).



174 **175** **176**

R = 2-OH-$C_{10}H_6$, 2-OH-5-Pr-C_6H_3, 2-OH-5-(4-C_8H_{17}-C_6H_4)-C_6H_3
R_2 = R_6 = 4-C_6H_{13}-C_6H_4

Reaction 17.

4.16. Metal complexes

Scozzafava et al.[74] have reported various coordination complexes of imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides with Zn(II), Cd(II), Hg(II), Co(II), Ni(II), Cu(II), V(IV), Fe(III) and Ag(I) metals, which were prepared by heating the sodium salts of imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides with the aqueous metal salts in methanol.

5. Biological activities

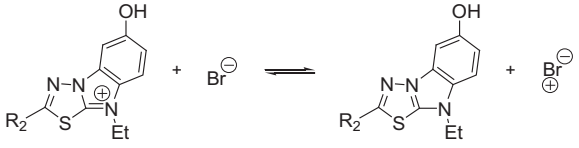
The imidazo[2,1-*b*][1,3,4]thiadiazole nucleus is reported to be associated with a wide range of biological activities, viz., antibacterial and antifungal,[56,57,62,66,67,69,70,82] antitubercular,[16,39,42] anthelmintic,[15,105–107] anticonvulsant,[7,14] anti-inflammatory and analgesic,[14,19,62,79] calcium channel blocking,[101] cardiotonic,[12] carbonic anhydrase inhibitory[7,102] diuretic,[99] leishmanicidal,[32] anticancer[90,100,103,104] and a variety of other activities.[66,108–110]

6. Ring-fused imidazo[2,1-*b*][1,3,4]thiadiazoles

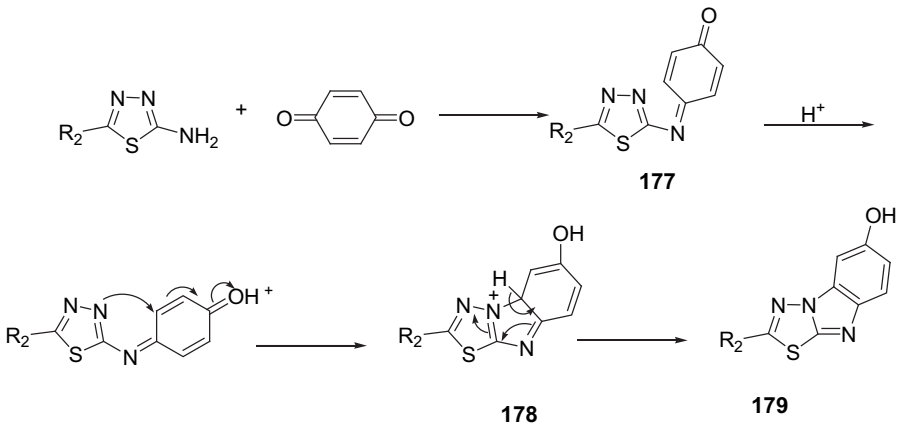
6.1. [1,3,4]Thiadiazolo[2,3-*b*]benzimidazoles

Soni and Saxena[111] and Sahu et al.[112] have reported the acid-catalyzed cyclodehydration of 2-amino-5-(un)substituted-[1,3,4]thiadiazoles with *p*-benzoquinone in AcOH either at room temperature for 2 days, followed by treatment with 50% HCl, or at 80 °C for 8 h and then keeping the reaction mixture overnight at room temperature, to give the corresponding 2-(un) substituted-6-hydroxy-[1,3,4]thiadiazolo[2,3-*b*]benzimidazoles **179**. The reaction involves an initial nucleophilic attack of the amino group at the carbonyl carbon to give the unstable intermediate **177**, which undergoes cyclodehydration through the imino nitrogen **178** (Scheme 30).

Further, Soni and Saxena[111] have reported the quaternization of compounds **179** with ethyl bromide in refluxing ethanol/acetone (1:1) for 3 h to yield the corresponding 9-ethyl derivatives **180**. Compounds **180** in their absorption spectra in EtOH at different pH values exhibited a bathochromic shift of the absorption band to longer wavelengths, which was more pronounced in a basic medium. The quaternized derivatives exhibited a further red shift in the absorption band in the visible region confirming their dipolar nature.



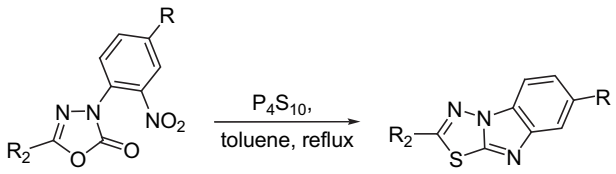
180



R_2 = H, Me, Et, Pr, *i*-Pr, $(CH_2)_4CH$, Ph

Scheme 30.

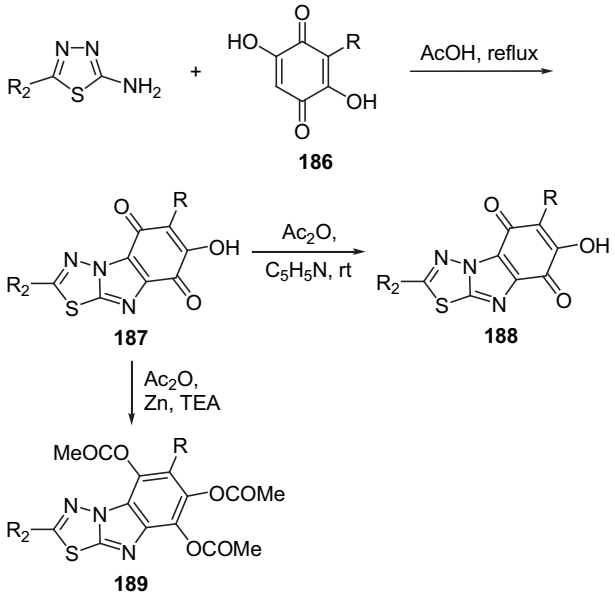
Pilgram[113] has reported the reaction of 5-substituted-3-(2-nitro-4-(un)substituted phenyl)-3*H*-[1,3,4]oxadiazol-2-ones **181** with P_4S_{10} in refluxing xylene to give 2,7-(un)substituted-[1,3,4]thiadiazolo[2,3-*b*]benzimidazoles **182** (Scheme 31). A similar reaction with 5-(1-cyclopropylethyl)-3-(2-nitro-4-trifluoromethylphenyl)-3*H*-[1,3,4] oxadiazol-2-one **183**, however, gave 5-(1-cyclopropylethyl)-3-(2-nitro-4-trifluoromethylphenyl)-3*H*-[1,3,4] oxadiazol-2-thione **184** and 2-(1-cyclopropylethyl)-7-trifluoromethyl-[1,3,4]thiadiazolo[2,3-*b*]benzimidazole **185** in 19 and 29% yield, respectively (Scheme 32).



R_2 = *t*-Bu, $CH_2C(Me)_3$; R = H, CF_3

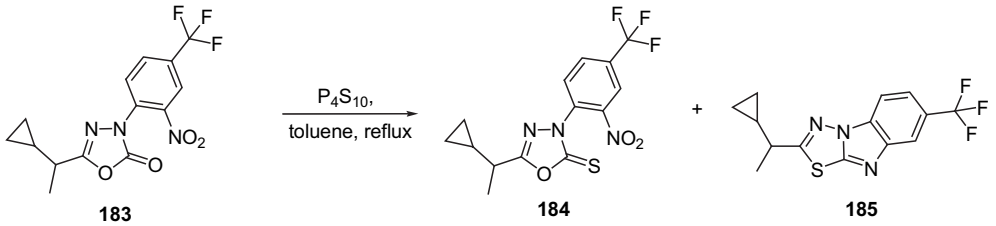
Scheme 31.

Rao and Rao[114] have reported the synthesis of 2-alkyl-7-hydroxy-6-undecyl-[1,3,4]thiadiazolo [3,2-*a*]benzimidazol-5,8-diones **187** by the condensation of 2-amino-5-alkyl-[1,3,4]thiadiazoles with 2,5-dihydroxy-3-undecyl-1,4-benzoquinone (embelin) **186** in refluxing glacial AcOH for 3 h. Further, the reaction of compounds **187** with acetic anhydride in the presence of a catalytic amount of pyridine at room temperature for 24 h gave 7-acetoxy-2-alkyl-6-undecyl-[1,3,4] thiadiazolo[3,2-*a*]benzimidazol-5,8-diones **188**, while the reductive acetylation of compounds **187** with catalytic zinc and TEA in refluxing acetic anhydride for 2 h yielded 5,7,8-triacetoxy-2-alkyl-6-undecyl-[1,3,4]thiadiazolo[3,2-*a*]benzimidazoles **189** (Scheme 33).



R_2 = H, Me, Et, *n*-Pr, Bu, C_5H_{11}; R = undecyl

Scheme 33.

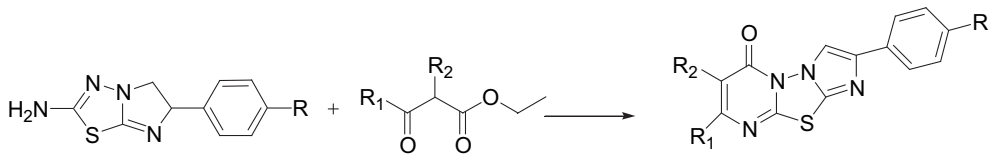


Scheme 32.

6.2. Imidazo[2,1-*b*][1,3,4]thiadiazolo[3,2-*a*]pyrimidinones

Paul et al.[115] have reported the reaction of 2-amino-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **190** with R_1COCHR_2COOEt to yield 7,8-disubstituted-2-aryl-imidazo[1′,2′:4,5][1,3,4] thiadiazolo[3,2-*a*] pyrimidin-6-ones **191** (Scheme 34).

Paul et al.[98] have further reported the reaction of 2-acetoacetylamino-6-alkyl/aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles **192** in hot

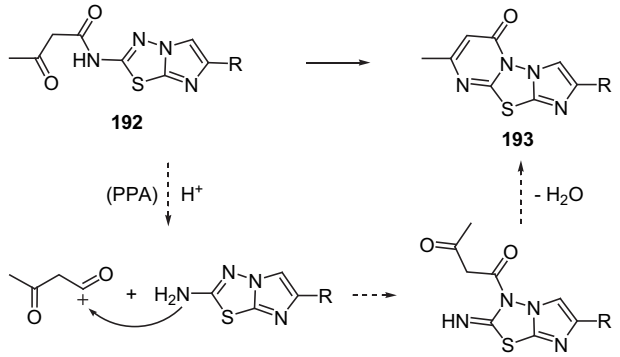


190 **191**

R = H, Br, Cl, Me, MeO; R_1 = Pr, Ph, 4-NO_2-C_6H_4; R_2 = H; R_1, R_2 = $(CH_2)_3$, $(CH_2)_4$.

Scheme 34.

polyphosphoric acid to yield 2,8-substituted-imidazo[1′,2′:4,5][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-6-ones **193** via the proposed mechanism depicted in Scheme 35. These compounds were found to be devoid of antiviral activity against *Vaccinia* viruses, except the 2-(4-methoxy-phenyl) derivative, which was reported to inhibit the growth of *Vaccinia* viruses.

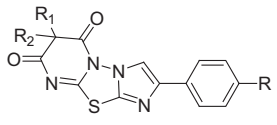


192 **193**

R = Me, Ph, 4-Br-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4

Scheme 35.

Further, Paul and Wessel[98] have reported the synthesis of 2-aryl-6,8-dioxo-dihydro-6*H*-imidazo[2,1-*b*][1,3,4]thiadiazolo[3,2-*a*]pyrimidinones and their 7,7-diethyl derivatives **194** by the reaction of 2-amino-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles in polyphosphoric acid with ethyl malonate and ethyl diethylmalonate, respectively.

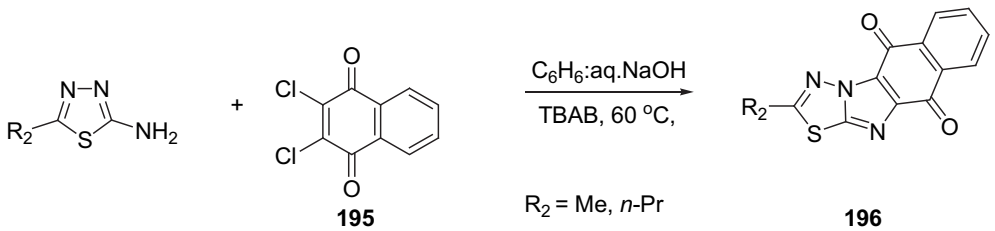


194

R = Br, Cl; R_1 = R_2 = H, Et

6.3. Naphth[2,3-*d*]imidazo[2,3-*b*]thiadiazolo-5,10-diones

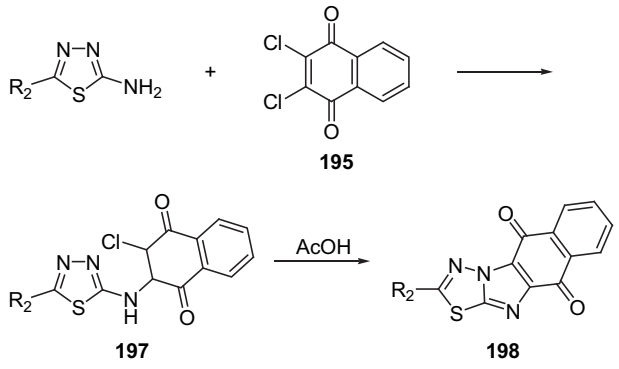
El-Shafei et al.[116] have reported the synthesis of 2-alkyl/aryl-naphth[2,3-d]imidazo[2,3-*b*]thiadiazolo-5,10-diones **196** by the reaction of 2-amino-5-alkyl-[1,3,4]thiadiazoles with 2,3-dichloronaphthoquinone **195** in benzene:50% aqueous NaOH (1:3) in the presence of tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst at 60 °C for 4–6 h (Scheme 36).



195 **196**

Scheme 36.

Soni[117] has reported the reaction of 2-amino-5-(un)substituted-[1,3,4]thiadiazoles with 2,3-dichloronaphthoquinone **195** to give 2-chloro-3-(5-(un)substituted-[1,3,4]thiadiazol-2-ylamino)-2,3-dihydro-[1,4]naphthoquinone intermediates **197** in 33–46% yields, which were further cyclized in acetic acid to give 2-alkyl-naphth[2,3-*d*]imidazo[2,3-*b*]thiadiazolo-5,10-diones **198** in 24–37% yields (Scheme 37).

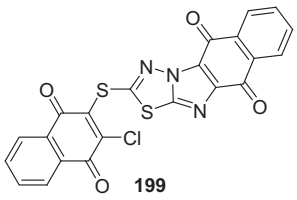


195 **197** **198**

R = H, Me, Et, *n*-Pr, *i*-Pr

Scheme 37.

Similarly, Zoorob et al.[118] have reported the synthesis and antibacterial and antifungal activities of 2-(3-chloro-1,4-dioxo-1,4-dihydro-naphthalen-2-ylsulfanyl)naphth[2,3-*d*]imidazo[2,3-*b*] thiadiazolo-5,10-dione **199**.

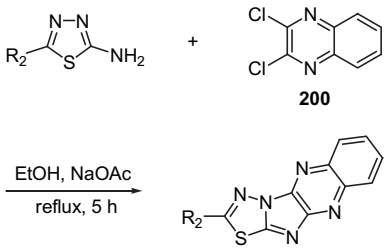


199

6.4. Thiadiazolo[2″,3″:2,1]imidazo[4,5-*b*]quinoxalines

Jag et al.[20,25,30] have reported the synthesis of some 2-alkyl/arylthiadiazolo[2″,3″:2,1]imidazo- [4,5-*b*]quinoxalines **201** by the reaction of 2-amino-5-alkyl/arylimidazo[2,1-*b*][1,3,4]thiadiazoles with 2,3-dichloroquinoxaline **200** in the presence of anhydrous sodium acetate in refluxing ethanol for 5 h (Scheme 38). These compounds were reported to exhibit poor or no antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans*.

El-Shafei et al.[119] and Langer et al.[120] have also reported the synthesis of some 2-alkyl/aryl-thiadiazolo[2″,3″:2,1]imidazo[4,5-*b*] quinoxaline derivatives.



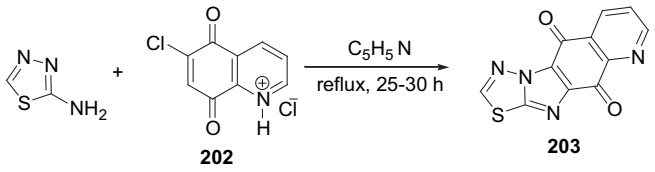
200 201

R_2 = $Me(CH_2)_5$, 4-OH-C_6H_4, 2,4-Cl_2-C_6H_3

Scheme 38.

6.5. Thiadiazolo [3′,2′:2,1]imidazolo[5,4-*g*]quinolinediones

Yanni[121,122] has reported the synthesis of thiadiazolo[3′,2′:2,1] imidazolo[5,4-*g*]quinoline-5,10-dione **203** by the reaction of 2-amino-[1,3,4]thiadiazole with 6-chloroquinoline-5,8-dione hydrochloride **202** in refluxing pyridine for 25–30 h (Scheme 39). This compound was inactive against *C. albicans* fungus and *Bacillus cereus*, *Micrococcus roses*, *Micrococcus luteus*, *E. coli* and *S. aureus* microbes.



202 203

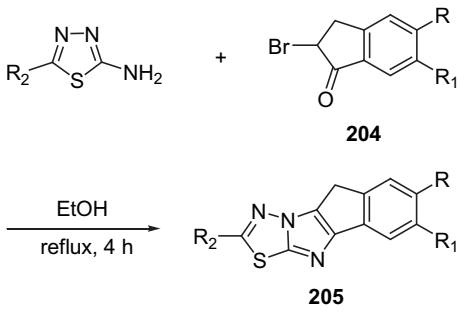
Scheme 39.

6.6. Indeno[1′,2′:4,5]imidazo[2,1-*b*][1,3,4]thiadiazoles

Gupta et al.[123] have reported the synthesis of various 7,8-dialkyloxy-2-aryl-indeno[1′,2′:4,5]- imidazo[2,1-*b*][1,3,4]thiadiazoles **205** by the reaction of 2-amino-5-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles with 2-bromo-5,6-dialkoxyindan-1-one **204** in refluxing ethanol for 4 h, followed by neutralization with potassium carbonate (Scheme 40). No significant antifungal activity against *Aspergillus niger*, *C. albicans* and *Aspergillus flavus* and antibacterial activity against *E. coli* and *S. aureus* was reported at 5 mg/ml concentration.

6.7. [1,3,4]Thiadiazolo[2′,3′:2,3]imidazo[4,5-*d*]diazepin-8-ones

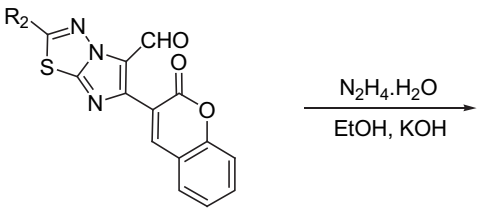
Kolavi et al.[40] have reported the synthesis of 2-alkyl/aryl-9-(2-hydroxybenzylideno)-7,9-dihydro-8*H*-[1,3,4]thiadiazolo[2′,3′:2,3] imidazo[4,5-*d*]diazepin-8-ones **165** by the intramolecular amida tion of 2-alkyl/aryl-6-(2-oxo-2*H*-chromen-3-yl)-imidazo[2,1-*b*] [1,3,4]thiadiazole-5-carbaldehydes **156** with hydrazine hydrate in refluxing ethanolic KOH for 6 h (Scheme 41). The proposed reaction



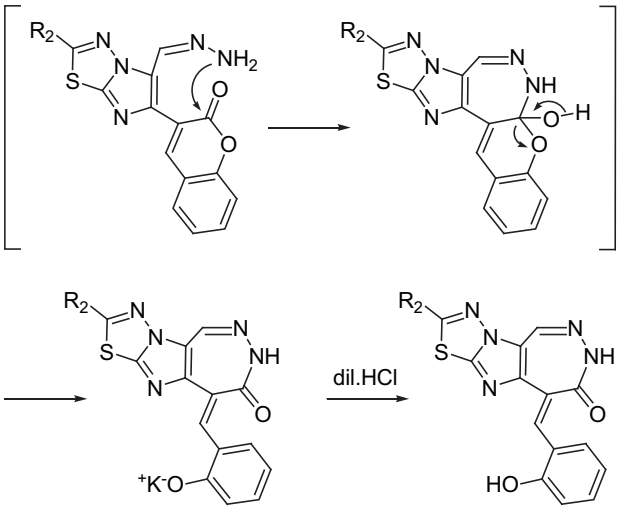
204 205

R = MeO; R_1 = EtO
R_2 = Ph, 2-Cl-C_6H_4, 4-MeO-C_6H_4, Bn

Scheme 40.



156 (See Reaction 8)



165

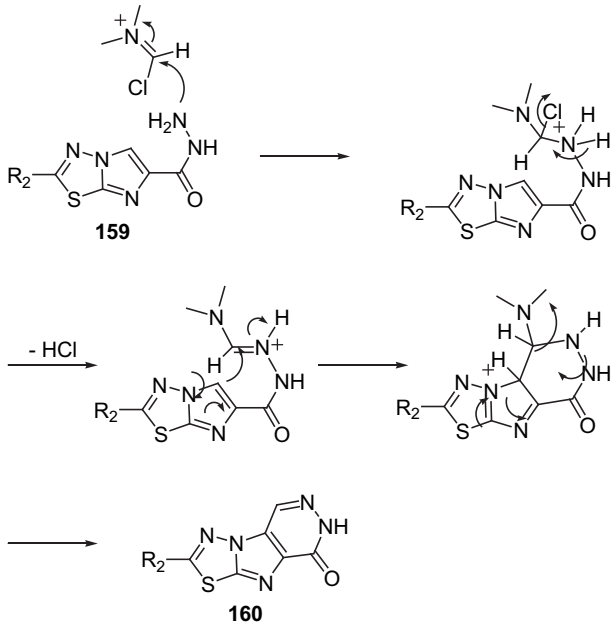
R_2 = Et, *n*-Pr, Cy, Bn, 2-furyl, 2-thienyl

Scheme 41.

mechanism involved an initial intramolecular nucleophilic attack at the lactone carbonyl of coumarin by the primary amino group, leading to the formation of a lactam/diazepinone.

6.8. [1,3,4]Thiadiazolo[2′,3′:2,3]imidazo[4,5-*d*]pyridazin-8 (7*H*)ones

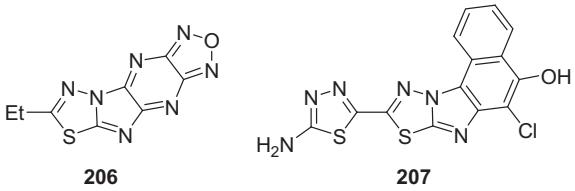
Kolavi et al.[41] have reported the synthesis of 2-alkyl/aryl-[1,3,4] thiadiazolo[2′,3′:2,3] imidazo[4,5-*d*]pyridazin-8(7*H*)-ones **160** by the reaction of 2-alkyl/aryl-imidazo[2,1-*b*][1,3,4]thiadiazole-6-carboxylic acid hydrazides **159** with DMF/$POCl_3$ at 0 °C for 30 min, and then for 2 h at room temperature and 60 °C, respectively, followed by stirring the reaction mixture at 90 °C in sodium carbonate solution for 2 h (Scheme 42).



Scheme 42.

6.9. Other fused imidazo[2,1-*b*][1,3,4]thiadiazoles

Starchenkov et al.[124] have reported 2-ethyl-6-oxa-1-thia-3,3a,4,5,7,8,9-heptaazocyclopenta(a)-*s*-indaenes **206** by the reaction of 5,6-dichlorofurazano[3,4-*b*]pyrazine with 5-ethyl-2-amino-[1,3,4] thiadiazole in cold acetonitrile in the presence of triethylamine. Aly et al.[125] have reported 9-(5-amino[1,3,4]thiadiazol-2-yl)-6-chloro-8-thia-7,10,10a-triaza-pentaleno[1,2-*a*]naphthalen-5-ol **207**.

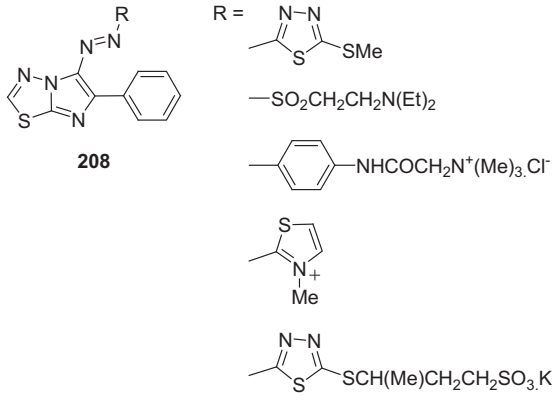


206 **207**

7. Patents

The purpose of this subsection is to further outline the applications of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives disclosed in the patent literature.

Various 5-arylazo-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazoles **208** have been disclosed as dyes for hydrophobic fibres, acid-modified polyesters, acrylic fibres and polyacrylonitrile yarn.[126–130]



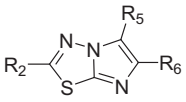
208

Carpenter et al.[131–133] have disclosed 1,3-diethyl-2-{2-[6-(4-nitro-phenyl)imidazo[2,1-*b*][1,3,4]-thiadiazol-5-yl]vinyl}-2,3-dihydro-1*H*-imidazo[4,5-*b*]quinoxaline tosylate as a sensitizing dye for organic photoconductor layers and silver halide emulsions.

Glenn et al.[134] have disclosed keratin dyeing derivatives of imidazo[2,1-*b*][1,3,4]thiadiazole. Several cyclic hexa peptides and polycyclic peptides containing imidazo[2,1-*b*][1,3,4]thiadiazoles or their salts as antimicrobial and antifulngal agents and their stabilized pharmaceutical compositions in lyophilized form have been disclosed.[135–142]

Berger et al.[143] have disclosed the synthesis and antimicrobial activity of 6-*N*′-[*N*,*N*-(dimethyl)-formamidin]-2-(5-nitro-furan-2-yl)imidazo[2,1-*b*][1,3,4]thiadiazole. Various cephem[144–146] and carbapenem[147] derivatives of imidazo[2,1-*b*][1,3,4]thiadiazole have been disclosed as antibacterial agents.

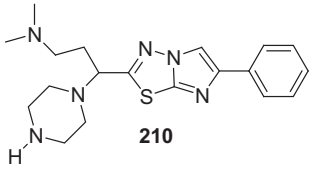
Camaggi et al.[148] have disclosed the synthesis of some 2,5,6-substituted-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **209** having preventive fungicidal activities exceeding 90% compared to control at a concentration of 500 ppm against cucumber oidium (*Sphaerotheca fuliginea*), barley helminthosporiosis (*Helminthosporium teres*) and vine peronospora (*Plasmopara viticola*).



209

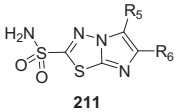
R_2 = *t*-Bu, CF_3, 4-MeO-C_6H_4
R_5 = COCOOMe, C(=OMe)COOMe, C(=CHOMe)COOMe, C(=CHOMe)OOMe, C(=NOMe)COOMe, CH_2O-4-Cl-C_6H_4
R_6 = Me, C(=CHOMe)COOMe

Tomcufcik et al.[149,150] have obtained patents on the synthesis and anthelmintic activity of 2-[4-[3-(dimethylamino)propyl]-1-piperazinyl]-6-phenylimidazo[2,1-*b*][1,3,4]thiadiazole **210** against trypanosomes.



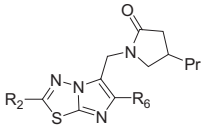
210

Barnish et al.[151] have disclosed various 5,6-(un)substituted-imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **211** as anticonvulsant agents. Kenda et al.[152–153] have disclosed the preparation of some 5-(4-propylpyrrolidin-2-one)methyl-2,6-(un)substituted-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **212** as anticonvulsant agents.



211

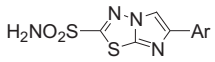
R_5 = H, Me, Et, COOEt, Ph, alkyl, aryl, 1-admantyl, thienyl,
R_6 = 3-pyridinyl, heteroarylmethyl



212

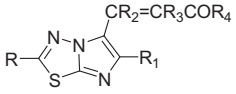
R_2 = H, Pr
R_6 = Me, Ph, 4-MeO-C_6H_4

Schwartz et al.[154] have patented 6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamides **213** and their use in the treatment and/or prophylaxis of neuropathic pain.



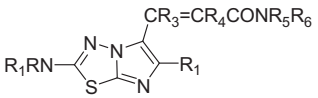
213

Meyer et al.[155,156] have disclosed the synthesis of several imidazo[2,1-*b*][1,3,4]thiadiazole derivatives **214** and their use as diuretics, antihypertensives and uricosurics.

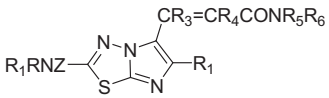


214

Ingendoh et al. have patented several imidazo[2,1-*b*][1,3,4]thiadiazole alkenecarboxamidine derivatives **215** as antihypertensives and diuretics[157] and (aminoalkyl)imidazo[2,1-*b*][1,3,4]-thiadiazole alkenecarboxylic acid amide derivatives **216** as diuretic and uricosuric agents.[158]



215

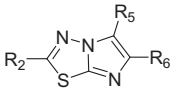


216

Press and Urbanski[159] have obtained a patent on the synthesis of 6-(4-dibutylaminopropoxy phenyl)-2-methyl-imidazo[2,1-*b*][1,3,4] thiadiazole as a calcium channel blocker useful in the treatment of cardiovascular conditions such as hypertension or angina. This compound exhibited 80, 50 and 27% inhibition of calcium-dependent smooth muscle contraction at 10, 1, 0.5 μM concentrations, respectively, and exhibited an IC_{50} value of 1.1 μM in a nitrendipine binding assay.

Shiokawa et al.[160] have disclosed the synthesis and adenosine antagonist activity of 3-(2-methyl-imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-2-phenyl-pyrazolo[1,5-*a*]pyridine.

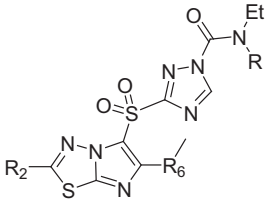
Horstmann et al.[161] have disclosed various imidazo[2,1-*b*][1,3,4] thiadiazole derivatives **217** (R_2=(substituted)naphthyl, furyl, thienyl, phenyl or phenylalkyl; R_5=H, alkyl, (substituted) phenyl; R_6=(substituted) phenyl) as antithrombic agents.



217

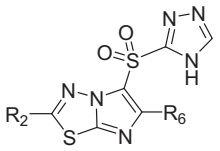
Yasuo et al.[162] have disclosed the synthesis and herbicidal activity of (6-methyl-imidazo[2,1-*b*][1,3,4]thiadiazol-5-sulfonyl)-(4,6-dimethoxy-pyrimidin-2-yl)-urea.

Fusaka et al.[163] have disclosed the preparation and herbicidal activity against *Echinochloa oryzicola* and *Cyperus difformis* of some 3-(2,6-substituted-imidazo[2,1-*b*][1,3,4]thiadiazol-5-sulfonyl)-[1,2,4] triazole derivatives **218**–**220**.



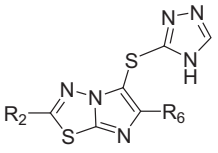
218

R_2 = H, Me, Et
R_6 = Cl, Me, Et
R = Et, Cy



219

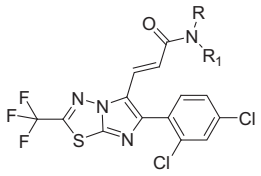
R_2 = Me, Et
R_6 = Cl, Me, Et



220

R_2 = H, Me, Et
R_6 = Cl, Me, Et

Schwarz[164] and Hewitt et al.[165] have disclosed the synthesis and insecticidal activity of 3-[6-(2,4-dichloro-phenyl)-2-trifluoromethyl-imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]-*N*-substituted-acrylamides **221**. Some of these compounds exhibited 83–100% protection after 7 days in a *Phaedon cochleariae* protection assay at 500 ga.i./ha (sic).



221

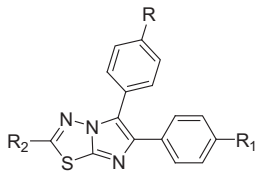
R, R_1 = alkyl, aryl

Jaquith et al.[166–168] have disclosed several 6-substituted-arylimidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide/sulfoxide/sulfone derivatives useful in the treatment of neuronal disorders of the central and peripheral nervous system and in the treatment of proliferative diseases. These compounds were reported to protect superior cervical ganglion (SCG) neurons from several neurotoxic insults, including nerve growth factor (NGF) withdrawal and treatment with chemotherapeutics such as Taxol, cisplatin and vincristine. These compounds were also reported to protect cortical motor neurons from malonate-induced death and to aid in the regeneration of neuronal damage.

Barker et al.[169] have further disclosed an HSP90-probe complex-based assay method for identifying inhibitors that modulate neuronal apoptotic pathways.

In recent years, several patent applications have disclosed the preparation and selective enzyme and receptor inhibitory activity of various imidazo[2,1-*b*][1,3,4]thiadiazole derivatives.

Bernauer et al.[170] have disclosed 5-imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl-3-nitro-pyrocatechol derivatives as catechol-*O*-methyltransferase inhibitors. Winn et al.[171] have disclosed 6-amino/butylaminoimidazo[2,1-*b*][1,3,4]thiadiazole-5-carboxylic acid butyl esters as angiotensin II receptor antagonists. Gauthier et al.[172] have disclosed some 5,6-aryl-2-(un)substituted-imidazo[2,1-*b*][1,3,4] thiadiazoles **222** as selective cyclooxygenase-2 inhibitors.



222

R = H, SO_2Me; R_1 = H, F, SO_2Me; R_2= H, Me

Zhu et al.[173] have disclosed 3-(2-amino-2-phenyl-ethyl)-1-(2, 6-difluoro-benzyl)-6-methyl-5-(2-methyl-imidazo[2,1-*b*][1,3,4]thiadiazol-6-yl)-1*H*-pyrimidin-2,4-dione as a gonadotropin-releasing hormone receptor antagonist. Wang et al.[174] have disclosed 2-(4-methoxy/nitro-phenyl)-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazole derivatives as tyrosine phosphatase inhibitors. Campbell et al.[175] have disclosed 6-[3-methoxy-4-(pyridin-2-yl)phenyl]imidazo[2,1-*b*][1,3,4] thiadiazole as a metabotropic glutamate-5 modulator. Blumberg et al.[176] have disclosed 5-aryl-6-(6-methyl-pyridin-2-yl)imidazo[2,1-*b*][1,3,4]thiadiazole derivatives as transforming growth factor (TGF) inhibitors. Claffey et al.[177] have disclosed the synthesis of aryl-substituted-imidazo[2,1-*b*][1,3,4]thiadiazoles as antagonists of the mammalian C3a receptor and their use for the treatment of chronic inflammatory diseases. Several imidazo[2,1-*b*][1,3,4]thiadiazole derivatives have been disclosed as leukotriene biosynthesis inhibitors useful for the treatment of atherosclerotic diseases,[178] tyrosine kinase modulators,[179] mineraralocorticoid receptor antagonists,[180] IKK enzyme inhibitors useful for the treatment of inflammatory diseases and cancer,[181] and Btk kinase inhibitors.[182]

Goldman[183] has disclosed the synthesis of 2,5,7-trimethyl-5*H*-[1,3,4]thiazolo[2,3-*f*]purine-6,8-dione as a 3′,5′-nucleotidephosphodiesterase inhibitor. This compound was also tested for bronchodilating, diuretic and anti-inflammatory activity.

Methods for the preparation of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives have also been disclosed.[184–187]

8. Conclusions

The imidazo[2,1-*b*][1,3,4]thiadiazoles constitute a rather small, yet growing and increasingly important class of heterocyclic ring system. The early developments of imidazo[2,1-*b*][1,3,4]thiadiazoles were highlighted by the synthesis of various derivatives and their biological evaluation. This has resulted in the discovery of some biologically potent molecules, most notably, 3-(2-diethylaminomethyl-6-phenyl-imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)-1-piperidin-1-yl-propenone, a uricosuric drug candidate, and 6-*tert*-butyl-imidazo[2,1-*b*][1,3,4] thiadiazole-2-sulfonamide, a potent diuretic as well as anticonvulsant agent.

The last decade has witnessed substantial developments in the chemistry and biology of imidazo[2,1-*b*][1,3,4]thiadiazoles, resulting in a variety of new and interesting reactions, evaluation as enzyme inhibitors and the synthesis of potential molecules reaching clinical developments. 6-Aryl-imidazo[2,1-*b*][1,3,4]thiadiazole-2-sulfonamide/sulfoxide/sulfone derivatives are among the most promising clinical candidates in this class of compounds for the treatment of neuronal disorders and proliferative diseases.

It is of interest to note that 2-(2-furyl)-6-phenyl-5-carbaldehyde-imidazo[2,1-*b*][1,3,4]-thiadiazole and (2-cyclohexyl-6-phenyl-imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl)methanol as antitubercular agents and 5-(4-methoxy)phenyl-6-(4-sulfonylmethyl)phenyl-imidazo [2,1-*b*]-[1,3,4]thiadiazole-2-sulfonamide as a selective cyclo-oxygenase-2 inhibitor are among the most potent molecules yet reported in this class of heterocycles.

A diverse range of biological activities are exhibited by this heterocyclic class of compounds, yet the cellular biology and the interactions of these molecules with receptors have not been extensively studied. Finally, knowledge concerning the molecular interactions with enzyme receptors, pharmacokinetics and metabolic studies of this class of heterocyclic compounds is not well advanced and these represent yet other fascinating areas for future investigation, which may provide some interesting mechanistic playing fields for the future design and synthesis of selective therapeutic agents. The inhibitory potential of various enzymes and receptors manifested by the imidazo[2,1-*b*][1,3,4] thiadiazole derivatives has provided bioorganic medicinal chemists with new challenging goals and there is every anticipation that molecular modelling, drug design and synthetic developments in this area will continue to provide new useful molecules to penetrate the multiple modes of action that these molecules display.

Acknowledgements

IMK acknowledges financial support from UGC New Delhi and B.A.B. thanks The University of West Indies, St. Augustine and Government of Trinidad and Tobago for financial support.

References and notes

1. Matsukawa, T.; Ban, S. *Yakugaku Zasshi* **1952**, *72*, 610; *Chem. Abstr.* **1952**, *47*, 6409g.
2. Ban, S. *Yakugaku Zasshi* **1954**, *74*, 658; *Chem. Abstr.* **1954**, *49*, 11630c.
3. Pyl, T.; Wasehk, F.; Beyer, H. *Justus Liebigs Ann. Chem.* **1963**, *663*, 113; *Chem. Abstr.* **1963**, *59*, 5160d.
4. Sitte, A.; Paul, H.; Hilgetag, G. *Z. Chem.* **1967**, *7*, 341; *Chem. Abstr.* **1967**, *67*, 108608b.
5. Hough, T. L. *J. Heterocycl. Chem.* **1983**, *20*, 1003.
6. Eldawy, M. A.; Shams El-Dine, S. A.; El-Brembaly, K. M. *Pharmazie* **1979**, *34*, 144.
7. Barnish, I. T.; Cross, P. E.; Dickinson, R. P.; Gadsby, B.; Parry, M. J.; Randall, M. J.; Sinclair, I. W. *J. Med. Chem.* **1980**, *23*, 117.
8. Valls, N.; Marin, A.; Alcalde, E.; Elguero, J. *Farmaco, Ed. Sci.* **1985**, *40*, 34.
9. Kano, S. *Yakugaku Zasshi* **1972**, *92*, 935; *Chem. Abstr.* **1972**, *76*, 85728K.
10. Russo, F.; Santagati, M. *Farmaco, Ed. Sci.* **1976**, *31*, 41; *Chem. Abstr.* **1976**, *84*, 90090r.
11. Werbel, L. M.; Zamora, M. L. *J. Heterocycl. Chem.* **1965**, *2*, 287.
12. Andreani, A.; Rambaldi, M.; Locatelli, A.; Bossa, R.; Salvatore, G.; Galatulas, I. *Eur. J. Med. Chem.* **1994**, *29*, 339.
13. Saldabols, N.; Hillers, S.; Alekseeva, L. N.; Brizga, B. *Khim. -Farm. Zh.* **1967**, *1*, 27; *Chem. Abstr.* **1967**, *68*, 2856m.
14. Khazi, I. M.; Mahajanshetti, C. S.; Gadad, A. K.; Tarnalli, A. D.; Sultanpur, C. M. *Arzneim. Forsch.* **1996**, *46*, 949.
15. Marin, A.; Valls, N.; Javier, B. F.; Alonson, M. T.; Ramon, M. A.; Mercedes, M. M.; Elguero, J. *Farmaco* **1992**, *47*, 63.
16. Arya, V. P.; Fernandes, F.; Sudarsanam, V. *Indian J. Chem.* **1972**, *10*, 598.
17. Srivastava, S. K.; Pathak, R. B.; Bahel, S. C. *Indian J. Chem* **1991**, *30*, 620.
18. Mazzone, G.; Bonina, F.; Puglisi, G.; Reina, R.; Arrigo.; Cosentino, C.; Blandino, G. *Farmaco, Edizione Scientifica* **1982**, *37*, 685.
19. Abignente, E.; Arena, F.; Luraschi, E.; Saturnino, C.; Marmo, E.; Cazzola, M.; Rossi, F.; Lampa, E. *Farmaco, Edizione Scientifica* **1985**, *40*, 190.
20. Jag, M.; Anjaneyulu, G. S. R.; Kiran. *J. Indian Chem. Soc.* **1989**, *66*, 118.
21. Jag, M.; Anjaneyulu, G. S. R.; Kiran. *Indian J. Chem.* **1989**, *28*, 500.
22. Jag, M.; Singh, V.; Kumar, V.; Kataria, S. *J. Chem. Res., Synop.* **1994**, *1*, 38.
23. Jag, M.; Singh, V.; Kataria, S. *Indian J. Heterocycl. Chem.* **1993**, *3B*, 43.
24. Jag, M.; Singh, V.; Kumar, V.; Kataria, S. *Indian J. Chem.* **1994**, *33B*, 692.
25. Jag, M. *Indian J. Heterocycl. Chem.* **1999**, *9*, 143.
26. Jag, M.; Anupama. *Indian J. Heterocycl. Chem.* **2000**, *9*, 255.
27. Jag, M. *Indian J. Heterocycl. Chem.* **2000**, *10*, 65.
28. Jag, M.; Kumar, A. *Indian J. Heterocycl. Chem.* **2002**, *12*, 41.
29. Jag, M.; Kumar, A. *Indian J. Heterocycl. Chem.* **2003**, *13*, 101.
30. Jag, M.; Shikha. *Indian J. Heterocycl. Chem.* **2005**, *14*, 365.
31. Ram, V. J.; Nath, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *105*, 11.
32. Ram, V. J.; Haque, N. *Indian J. Chem.* **1996**, *35B*, 238.
33. Ram, V. J.; Nath, M.; Singh, S. K. *Indian J. Chem.* **1996**, *35B*, 273.
34. Ram, V. J.; Goel, A.; Kandpal, M.; Mittal, N.; Goyal, N.; Tekwani, B. L.; Guru, P. Y.; Rastogi, A. K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 651.
35. Ram, V. J.; Nath, M. *Indian J. Chem.* **1997**, *36B*, 394.
36. Gadad, A. K.; Khazi, I. M.; Mahajanshetti, C. S. *Indian J. Heterocycl. Chem.* **1992**, *2*, 125.
37. Gadad, A. K.; Mahajanshetti, C. S.; Nimbalkar, S.; Raichurkar, A. *Eur. J. Med. Chem.* **2000**, *35*, 853.

38. Gadad, A. K.; Noolvi, M. N.; Karpoormath, R. V. *Bioorg. Med. Chem.* **2004**, *12*, 5651.
39. Kolavi, G. D.; Hegde, V. S.; Khazi, I. M.; Gadad, P. *Bioorg. Med. Chem.* **2006**, *14*, 3069.
40. Kolavi, G. D.; Hegde, V. S.; Khazi, I. M. *Tetrahedron Lett.* **2006**, *47*, 2811.
41. Kolavi, G. D.; Hegde, V. S.; Khazi, I. M. *Synth. Commun.* **2006**, *36*, 1837.
42. Kolavi, G. D.; Hegde, V. S.; Lamani, R. S.; Khazi, I. M. *J. Sulf. Chem.* **2006**, *27*, 553.
43. Li, M.; Wen, L.-R.; Fu, W.-J.; Yang, H.-Z. *Jiegou Huaxue* **2004**, *23*, 11.
44. Cui, L.; Chen, J.-S.; Liu, F.-M.; Xie, Z.-F.; Sun, Y.-D.; Wang, H.-Y. *Youji Huaxue* **2006**, *26*, 963.
45. Zhang, Y.; Sun, X.-W.; Hui, X.-P.; Zhang, Z.-Y.; Wang, Q.; Zhang, Q. *Chin. J. Chem.* **2002**, *20*, 168.
46. Liu, F.-M.; Ablajan, K.; Wang, H.-Y.; Shao, L. *Gaodeng Xuexiao Huaxue Xuebao* **2004**, *25*, 1673.
47. Jadhav, V. B.; Kulkarni, M. V.; Rasal, V. P.; Biradar, S. S.; Vinay, M. D. *Eur. J. Med. Chem.* **2008**, *43*, 1721.
48. Joshi, K. C.; Pathak, V. N.; Panwar, M. P. *J. Indian Chem. Soc.* **1979**, *56*, 716.
49. Dehuri, S. N.; Nayak, A. *J. Indian Chem. Soc.* **1982**, *59*, 1170.
50. Mohan, J.; Singh, V.; Kataria, S. *J. Chin. Chem. Soc.* **1994**, *41*, 617.
51. Gadaginamath, G. S.; Kavali, R. R.; Shyadligeri, A. S.; Doddamani, H. P. *Indian J. Heterocycl. Chem.* **1999**, *9*, 33.
52. Wang, X.-C.; Wang, M.-G.; Yang, Z.; Quan, Z.-J.; Wang, F.; Li, Z. *J. Chem. Res.* **2005**, 744.
53. Wang, X.; Wang, M.; Quan, Z.; Li, Z. *Synth. Commun.* **2005**, *35*, 2881.
54. (a) Kidwai, M.; Rastogi, S. *Lett. Org. Chem.* **2006**, *3*, 149; (b) Kidwai, M.; Rastogi, S. *Indian J. Chem.* **2006**, *45B*, 2321.
55. DeStevens, G.; Eager, M.; Tarby, C. *Heterocycles* **1993**, *35*, 763.
56. Weuffen, W.; Pyl, T.; Gruebner, W.; Juelich, W. D. *Pharmazie* **1965**, *20*, 629; *Chem. Abstr.* **1965**, *64*, 5488e.
57. Tattler, G.; Weuffen, W. *Pharmazie* **1966**, *21*, 425; *Chem. Abstr.* **1966**, *64*, 20546g.
58. Pentimalli, L.; Milani, G.; Biavati, F. *Gazz. Chim. Ital.* **1975**, *105*, 777.
59. Baboulene, M.; Sturtz, G. *Sci. Chim.* **1977**, *284*, 799.
60. Paul, H.; Sitte, A. *Z. Chem.* **1977**, *17*, 176; *Chem. Abstr.* **1977**, *87*, 167947x.
61. Paul, H.; Sitte, A.; Wessel, R. *Arch. Pharmacol.* **1981**, *314*, 359; *Chem. Abstr.* **1981**, *95*, 80873m.
62. Mazzone, G.; Bonina, F.; Panico, A. M.; Puglisi, G.; Marchetta, G.; Amico Roxas, M.; Caruso, A.; Blandino, G. *Farmaco, Edizione Scientifica* **1984**, *39*, 585.
63. Rajeswar, R. V.; Rao, M. S.; Padmanabha, R. T. V. *Collect. Czech. Chem. Commun.* **1986**, *51*, 2214.
64. Ashour, F. A. *Alexandria J. Pharm. Sci.* **1991**, *5*, 16.
65. Papadaki-Valiraki, A.; Siatra-Papastaikoudi, T.; Tsitsa, P.; Delitheos, A. *Chim. Chron.* **1990**, *19*, 225.
66. Andotra, C. S.; Langer, T. C.; Dham, S.; Kour, P. *Proc. Indian Natl. Sci. Acad.* **1993**, *63*, 589.
67. Kumar, P.; Mohan, J.; Makrandi, J. K. *Indian J. Heterocycl. Chem.* **2006**, *16*, 139.
68. Kukaniev, M. A.; Rakhmonov, R.; Safarov, V.; Khodzhibaev, Y.; Osimov, D. M. *Chem. Heterocycl. Compd.* **2007**, *43*, 499.
69. Chaturvedi, B.; Tiwari, N.; Nizamuddin, A. *Indian J. Chem.* **1989**, *28B*, 358.
70. Ashour, F. A.; Habib, N. S.; El Taibbi, M.; El Dine, S.; El Dine, A. S. *Farmaco* **1990**, *45*, 1341.
71. Ivashchenko, A. V.; Torgova, S. I.; Karamysheva, L. A.; Abolin, A. G. *Liq. Cryst.* **1990**, *7*, 475.
72. Shafi, S. S.; Radhakrishnan, T. R. *Indian J. Heterocycl. Chem.* **1998**, *7*, 231.
73. Andotra, C. S.; Langer, T. C.; Kotha, A. *J. Indian Chem. Soc.* **1997**, *74*, 125.
74. Scozzafava, A.; Supuran, C. T. *Met. -Based Drugs* **1997**, *4*, 19.
75. Fajgelj, S.; Stanovnik, B.; Tisler, M. *Heterocycles* **1986**, *24*, 379.
76. Molina, P.; Lorenzo, A.; Vilaplana, M. J.; Aller, E.; Planes, J. *Heterocycles* **1988**, *27*, 1935.
77. Shukurov, S. S.; Kukaniev, M. A.; Osimov, D. M.; Artykova, D. A. *Khim. Geterotsikl. Soedin.* **1994**, *3*, 421.
78. Zhang, Y.; Liu, D.; Dai, C.-F.; Zhang, Z.-Y.; Xu, P.-F.; Hui, X.-P.; Wang, Q. *Gaodeng Xuexiao Huaxue Xuebao* **2002**, *23*, 1882.
79. Gadad, A. K.; Palkar, M. B.; Anand, K.; Noolvi, M. N.; Boreddy, T. S.; Wagwade, J. *Bioorg. Med. Chem.* **2008**, *16*, 276.
80. Paul, H.; Sitte, A.; Wessel, R. *Monatsh. Chem.* **1977**, *108*, 665; *Chem. Abstr.* **1977**, *87*, 201420g.
81. Bienayme, H.; Bouzid, K. *Angew. Chem.* **1998**, *37*, 2234.
82. Yadav, L. D. S.; Vaish, A. *Bull. Pol. Acad. Sci., Chem.* **1994**, *41*, 89.
83. Schenetti, M. L.; Taddei, F.; Greci, L.; Marchetti, L.; Milani, G.; Andreetti, G. D.; Bocelli, G.; Sgarabotto, P. *J. Chem. Soc., Perkin Trans. 2* **1980**, *2*, 421.
84. Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Giorgi, G.; Salvini, L. *ARKIVOC* **2002**, *11*, 32.
85. Anilkumar, G. N.; Kokila, M. K.; Puttaraja, K. S. S.; Kulkarni, M. V. *Acta Crystallogr.* **2006**, *E62*, 2014.
86. Begum, N. S.; Vasundhara, D. E.; Kolavi, G. D.; Khazi, I. M. *Acta Crystallogr.* **2007**, *E63*, 1955.
87. Begum, N. S.; Vasundhara, D. E.; Girija, C. R.; Kolavi, G. D.; Hegde, V. S.; Khazi, I. M. *J. Chem. Crystallogr.* **2007**, *37*, 193.
88. Arjuna Gouda, K. V.; Kolavi, G. D.; Khazi, I. M. *Acta Crystallogr.* **2005**, *61*, 293.
89. Khazi, I. M.; Gadad, A. K.; Mahajanshetti, C. S.; Vairamani, M. *Indian J. Chem.* **1994**, *33B*, 585.
90. Terzioglu, N.; Gursoy, A. *Eur. J. Med. Chem.* **2003**, *38*, 781.
91. Ivashchenko, A. V.; Petrova, O. S.; Titov, V. V. *Mol. Cryst. Liq. Cryst.* **1987**, *145*, 25.
92. Torgova, S. I.; Abolin, A. G.; Karamysheva, L. A.; Ivashchenko, A. V. *Zh. Org. Khim.* **1988**, *24*, 192.
93. Torgova, S. I.; Abolin, A. G.; Roitman, K. V.; Karamysheva, L. A.; Ivashchenko, A. V. *Zh. Org. Khim.* **1988**, *24*, 199.
94. Torgova, S. I.; Shtykov, N. M.; Abolin, A. G.; Karamysheva, L. A.; Ivashchenko, A. V.; Barnik, M. I. *Zh. Org. Khim.* **1988**, *24*, 1306.
95. Khodzhibaev, Yu.; Kukaniev, N. A. *Bashk. Khim. Zh.* **1998**, *5*, 23.
96. Matsukawa, T.; Ban, S.; Shirakawa, K.; Yoneda, M. *Yakugaku Zasshi* **1953**, *73*, 159.
97. Sitte, A.; Paul, H. *Z. Chem.* **1973**, *13*, 373.
98. Paul, H.; Wessel, R. *Arch. Pharmacol.* **1982**, *315*, 12.
99. Andreani, A.; Rambaldi, M.; Locatelli, A.; Malandrino, S.; Pifferi, G. *Arzneim. Forsch.* **1994**, *44*, 618.
100. Gadad, A. K.; Karki, S. S.; Rajurkar, V. G.; Bhongade, B. A. *Arzneim. Forsch.* **1999**, *49*, 858.
101. Sanfilippo, P. J.; Urbanski, M.; Press, J. B.; Dubinsky, B.; Moore, J. B. *J. Med. Chem.* **1988**, *31*, 2221.
102. Sigrist, G.; Greven, J.; Fuchs, B. *Dev. Nephrol.* **1987**, *18*, 547.
103. Kamiya, S.; Tanno, M.; Miyahara, M. *Eisei Shikensho Hokoku* **1983**, *101*, 71.
104. Miyahara, M.; Kamiya, S.; Nakadate, M.; Sueyoshi, S.; Tanno, M.; Miyahara, M. *Eisei Shikensho Hokoku* **1982**, *100*, 163.
105. Alonso, M. T.; Berenguer, F. J.; Pujol, M. T.; Gallego, J. *Rev. Iber. Parasitol.* **1986**, *46*, 195.
106. Pumarola, D.; Alonso, M. T.; Berenguer, F. J.; Gallego, J. *Rev. Iber. Parasitol.* **1987**, *47*, 403.
107. Cativiela, C.; Garcia, J. I.; Marin, A.; Valls, N.; Elguero, J. *Farmaco* **1989**, *44*, 671.
108. Ohta, K.; Itoh, S.; Kandou, Y.; Yoshikawa, H.; Ishida, Y. *Nippon Noyaku Gakkaishi* **1994**, *19*, 137.
109. Salehi, A. H.; Morris, S. J.; Ho, W.-C.; Dickson, K. M.; Doucet, G.; Milutinovic, S.; Durkin, J.; Gillard, J. W.; Barker, P. A. *Chem. Biol.* **2006**, *13*, 213.
110. Conroy, C. W.; Schwam, H.; Maren, T. H. *Drug Metab. Dispos.* **1984**, *12*, 614.
111. Soni, R. P.; Saxena, J. P. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2033.
112. Sahu, M.; Sahu, J. K.; Nayak, A. *Indian J. Chem.* **1986**, *25B*, 1266.
113. Pilgram, K. H. *Phosphorus, Sulfur Silicon Relat. Elem.* **1988**, *36*, 139.
114. Rao, V. R.; Rao, T. V. P. *Indian J. Chem.* **1994**, *33B*, 1189.
115. Paul, H.; Wessel, R.; Huschert, G. *Monatsh. Chem.* **1981**, *112*, 209.
116. El-Shafei, A. K.; Sultan, A.; Vernin, G. *Heterocycles* **1982**, *19*, 333.
117. Soni, R. P. *Proc. Indian Natl. Sci. Acad.* **1982**, *48*, 1081.
118. Zoorob, H. H.; Berghot, M. A.; Abou-Elzahab, M. M.; Amer, F. A. *Mansoura Sci. Bull., A: Chem.* **2002**, *29*, 129.
119. El-Shafei, A. K.; El-Kashef, H. S.; Ahmed, A. B.; Ghattas, G. *Gazz. Chim. Ital.* **1981**, *111*, 409.
120. Langer, T. C.; Dham, Sumita; Andotra, C. S. *J. Nepal Chem. Soc.* **1992**, *11*, 15.
121. Yanni, A. S. *J. Indian Chem. Soc.* **1991**, *68*, 529.
122. Yanni, A. S. *Rev. Roum. Chim.* **1994**, *39*, 967.
123. Gupta, R.; Sharma, M.; Paul, S.; Sudan, S.; Kachroo, P. L. *J. Indian Chem. Soc.* **1993**, *70*, 649.
124. Starchenkov, I. B.; Andrianov, V. G. *Chem. Heterocycl. Compd.* **1997**, *33*, 1352.
125. Aly, A. A.; Hassan, A. A.; Mohamed, N. K.; Mourad, A. F. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *116*, 261.

Patents

126. Fisher, J. G.; Straley, J. M. GB 1159691, 1969; *Chem. Abstr.* **1970**, *72*, 56682c.
127. Fisher, J. G.; Clark, G. T. U.S. Patent 3,804,823, 1974; *Chem. Abstr.* **1974**, *81*, 51119a.
128. Dawson, J. F.; Teale, E. GB 1401968, 1975; *Chem. Abstr.* **1976**, *84*, 19161.
129. Fisher, J. G.; Straley, J. M. U.S. Patent 3,928,311, 1975; *Chem. Abstr.* **1976**, *84*, 91634.
130. Weaver, M. A.; Coates, C. A. U.S. Patent 4,396,547, 1983; *Chem. Abstr.* **1983**, *99*, 141532f.
131. Carpenter, J. W.; Mee, J. D.; Heseltine, D. W. FR 2006142, 1969; *Chem. Abstr.* **1971**, *74*, 8370u.
132. Carpenter, J. W.; Mee, J. D.; Heseltine, D. W. U.S. Patent 3,615,639, 1971; *Chem. Abstr.* **1972**, *77*, 103346.
133. Carpenter, J. W.; Mee, J. D.; Heseltine, D. W. U.S. Patent 3,615,639, 1974; *Chem. Abstr.* **1974**, *81*, 51156k.
134. Glenn, R. W.; Lim, M.; Rees, C. W.; Rakitin, O. A.; Laidig, W. D.; Shaffer, J. S.; Gardlik, J. M.; Murphy, B. P. WO 20050901, 2005; *Chem. Abstr.* **2005**, *143*, 253456.
135. Ohki, H.; Tomishima, M.; Yamada, A.; Takasugi, H. WO 9823637, 1998; *Chem. Abstr.* **1998**, *129*, 54604.
136. Tojo, T.; Ohki, H.; Shiraishi, N.; Matsuya, T.; Matsuda, H.; Murano, K.; Barrett, D.; Ogino, T.; Matsuda, K.; Ichihara, M.; Hashimoto, N.; Kanda, A.; Ohigashi, A. WO 2000064927, 2000; *Chem. Abstr.* **2000**, *133*, 335462z.
137. Sawai, S.; Kasai, A.; Otomo, K. WO 20010111, 2001; *Chem. Abstr.* **2001**, *134*, 105851s.
138. Toda, A.; Matsuya, T.; Mizuno, H.; Matsuda, H.; Murano, K.; Barrett, D.; Ogino, T.; Matsuda, K. WO 20010823, 2001; *Chem. Abstr.* **2001**, *135*, 180954b.
139. Miyake, K.; Ohtomo, K.; Kasai, A. PCT Int. Appl. WO 2002053584, 2002; *Chem. Abstr.* **2002**, *137*, 98997a.
140. Toda, A.; Mizuno, H.; Matsuya, T.; Matsuda, H.; Murano, K.; Barrett, D.; Ogino, T.; Matsuda, K. WO 20020919, 2002; *Chem. Abstr.* **2002**, *137*, 247927g.
141. Mizuno, H.; Matsuda, H.; Toda, A.; Matsuya, T.; Barrett, D.; Matsuda, K. WO 20030821, 2003; *Chem. Abstr.* **2003**, *139*, 197770.
142. Ohnaka, C.; Nakai, M. U.S. Patent 20,031,127, 2003;
143. Berger, H.; Gall, R.; Merdes, H.; Stach, K.; Sauer, W.; Voemel, W. Ger. Offen. 2109577, 1972; *Chem. Abstr.* **1972**, *77*, 164657.
144. Miyake, A.; Kondo, M.; Fujino, M. PCT Int. Appl. WO 8505620, 1985; *Chem. Abstr.* **1986**, *105*, 60475.
145. Yoshida, C.; Tanaka, K.; Santo, T.; Komatsu, M.; Kishimoto, S.; Watanabe, Y.; Tai, M.; Saikawa, JP 62181284, 1987.
146. Tawada, H.; Nakao, M. JP 07061987, 1995; *Chem. Abstr.* **1995**, *122*, 286514.

147. Ishibashi, Y.; Imamura, S.; Miwa, T. WO 9725325, 1997; *Chem. Abstr.* **1997**, *127*, 161635.
148. Camaggi, G.; Filippini, L.; Gusmeroli, M.; Mormile, S.; Venturini, I.; Garavaglia, C.; Signorini, E. EP 662477, 1995.
149. Tomcufcik, A. S.; Fabio, P. F.; Hoffman, A. M. U.S. Patent 19,640,311, 1964; *Chem. Abstr.* **1965**, *62*, 66595.
150. Tomcufcik, A. S.; Fabio, P. F.; Hoffman, A. M. U.S. Patent 3,331,843, 1967; *Chem. Abstr.* **1967**, *67*, 90839.
151. Barnish, I. T.; Cross, P. E.; Dickinson, R. P.; Gadsby, B. GB 1464259, 1977; *Chem. Abstr.* **1977**, *87*, 102336.
152. Kenda, B.; Quesnel, Y.; Ates, A.; Michel, P.; Turet, L.; Mercier, J. WO 20061207, 2006; *Chem. Abstr.* **2006**, *146*, 27722.
153. See Ref. 152; *Chem. Abstr.* **2006**, *146*, 45393.
154. Schwarz, H. G.; Scherkenbeck, J.; Holmwood, G.; Wieschemeyer, J.; Loesel, P.; Malsam, O.; Drewes, M. W.; Kuck, K. H.; Wachendorff, N. U.; Arnold, C.; Salgado, V. L. Ger. 20,060,907, 2006; *Chem. Abstr.* **2006**, *145*, 314992.
155. Meyer, H.; Horstmann, H.; Moeller, E.; Garthoff, B. Ger. 3,020,421, 1981 *Chem. Abstr.* **1982**, *96*, 85561.
156. Meyer, H.; Horstmann, H.; Moller, E.; Garthoff, B. EP 19811209, 1981; *Chem. Abstr.* **1982**, *96*, 122803.
157. Ingendoh, A.; Meyer, H.; Garthoff, B. Ger. 19830915, 1983; *Chem. Abstr.* **1984**, *100*, 156587.
158. Ingendoh, A.; Meyer, H.; Garthoff, B. Ger. 19850228, 1985; *Chem. Abstr.* **1985**, *103*, 22596w.
159. Press, J. B.; Urbanski, M. U.S. Patent 4880824, 1989; *Chem. Abstr.* **1999**, *112*, 235304.
160. Shiokawa, Y.; Akahane, A.; Katayama, H.; Mitsunaga, T. EP 19900801, 1990; *Chem. Abstr.* **1991**, *114*, 62080.
161. Horstmann, H.; Meng, K.; Seuter, F.; Moeller, E. Ger. 2823686, 1979; *Chem. Abstr.* **1980**, *92*, 215440.
162. Yasuo, I.; Kazunari, O.; Tatsuo, N.; Harutoshi, Y. EP 19870923, 1987; *Chem. Abstr.* **1988**, *108*, 204632.
163. Fusaka, T.; Ujikawa, O.; Kajiwara, T.; Tanaka, Y. WO 9711075, 1997; *Chem. Abstr.* **1997**, *126*, 293354p.
164. Schwarz, H. G.; Scherkenbeck, J.; Holmwood, G.; Wieschemeyer, J.; Loesel, P.; Malsam, O.; Drewes, M.W.; Kuck, K.H.; Ulrike, W. N.; Arnold, C.; Salgado, V. L. Ger. 20,060,907, 2006; *Chem. Abstr.* **2006**, *145*, 314992.
165. Hewitt, K.; Durkin, J.; Winocour, P. CA 2584745, 2007; *Chem. Abstr.* **2007**, *147*, 462300.
166. Jaquith, J. B.; Villeneuve, G.; Boudreault, A.; Morris, S.; Durkin, J.; Gillard, J. W.; Hewitt, K.; Marsh, N. H. WO 20030626, 2003; *Chem. Abstr.* **2003**, *139*, 69270.
167. Jaquith, J. B.; Gillard, J. W. WO 20041223, 2004; *Chem. Abstr.* **2004**, *142*, 74577.
168. Jaquith, J. B.; Bureau, J.; Scott, G; John, W. WO 20041223, 2004; *Chem. Abstr.* **2004**, *142*, 1127389.
169. Barker, P. A.; Jaquith, J. B.; Morris, S. J.; Salehi, A. WO 20070809, 2007; *Chem. Abstr.* **2007**, *147*, 250626.
170. Bernauer, K.; Borgulya, J.; Bruderer, H.; Da Prada, M.; Zurcher, G. AU 19901129, 1990; *Chem. Abstr.* **1990**, *112*, 118359h.
171. Winn, M.; De, B.; Zydowsky, T. M.; Kerkman, D. J.; Debernardis, J. F.; Rosenberg, S.H.; Shiosaki, K.; Basha, F. Z.; Spina, K. P. WO 9317681, 1993; *Chem. Abstr.* **1994**, *120*, 134512.
172. Gauthier, J. Y.; Lau, C. K.; Leblanc, Y.; Li, C. S.; Roy, P.; Therien, M.; Wang, Z. WO 9621667, 1996; *Chem. Abstr.* **1996**, *125*, 195659b.
173. Zhu, Y. F.; Chen, C.; Tucci, F. C.; Guo, Z.; Gross, T. D.; Rowbottom, M.; Struthers, R. Scott. WO 20010802, 2001; *Chem. Abstr.* **2001**, *135*, 152816q.
174. Wang, J.; Rideout, D.; Ramnarayan, K.; Tsai, C.Y.; Yalamoori, V. V.; Wu, F.; Loweth, C.; Elabdellaoui, H.; Fung, L.; Brady, T. P. WO 20030424, 2003; *Chem. Abstr.* **2003**, *138*, 338152.
175. Campbell, B. T.; Munoz, B.; Stearns, B. A.; Vernier, J. M. A.; Wang, B.; Gunzner, J. L. WO 20040325, 2004; *Chem. Abstr.* **2004**, *140*, 287390.
176. Blumberg, L. C.; Munchhof, M. J.; Shavnya, A. U.S. Patent 20,040,909, 2004.
177. Claffey, M. M.; Goldstein, S. W.; Jung, S.; Nagel, A.; Shulze, V. WO 20070329, 2007; *Chem. Abstr.* **2007**, *146*, 358852.
178. Armstrong, H. M.; Chang, L. L.; Chu, L.; Sisco, R.; Ok, H. O.; Xu, J.; Ujjainwalla, F. WO 20070518, 2007; *Chem. Abstr.* **2007**, *146*, 521694.
179. Anikin, A. V.; Gantla, V. R.; Gregor, V. E.; Jiang, L.; Liu, Y.; Mcgee, D. P. C.; Mikel, C. C.; Pickens, J. C.; Webb, T. R.; Zheng, Y.; Zhu, T.; Kadushkin, A.; Zozulya, S.; Chucholowski, A.; Mcgrath, D. E.; Sviridov, S. WO 20070518, 2007; *Chem. Abstr.* **2007**, *146*, 521800.
180. Fukumoto, S.; Matsunaga, N.; Ohra, T.; Ohyabu, N.; Hasui, T.; Motoyaji, T.; Siedem, C. S.; Tang, T. P.; Demeese, L. A.; Gauthier, C. WO 20070712, 2007; *Chem. Abstr.* **2007**, *147*, 166327.
181. Pitts, W. J.; Kempson, J.; Guo, J.; Das, J.; Langevine, C. M.; Spergel, S. H.; Watterson, S. H. WO 2006122137, 2006; *Chem. Abstr.* **2006**, *145*, 505488.
182. Currie, K. S.; Kropf, J. E.; Darrow, J. W.; Desimone, R. W. U.S. Patent 2,006,178,367, 2006.
183. Goldman, I. M. Ger. 1,809,013, 1969; *Chem. Abstr.* **1970**, *72*, 12771b.
184. Matsukawa, T; Ban, S. JP 28005879, 1953; *Chem. Abstr.* **1953**, *49*, 4724i.
185. Kano, S.; Noguchi, T. JP 19710731, 1971; *Chem. Abstr.* **1971**, *75*, 140865j.
186. Stubbe, M.; Samaan, S. Ger. 3,502,264, 1986; *Chem. Abstr.* **1986**, *105*, 191089e.
187. Wang, X.; Zhu, J.; Yang, Z.; Song, A.; Quan, Z. CN 101037445, 2007; *Chem. Abstr.* **2007**, *147*, 427352.

Biographical sketch

Dr. Imtiyaz Ahmed M. Khazi was born in Rattihalli, Haveri, India. He received his M.Sc. Degree in 1990. He did his Ph.D. under the supervision of Prof. C. S. Mahajanshetty at Karnatak University, Dharwad, India. He was the recipient of an international fellowship as visiting scientist at Korea Research Institute of Chemical Technology, South Korea (2006–2007). Dr. Khazi was the recipient of a prestigious commonwealth fellowship tenable at University of Reading (UK) for the year 2009–2010. He has over 13 years of teaching and research experience. Presently, he is an Associate Professor in Organic Chemistry at Karnatak University, Dharwad. His research interests include synthesis and pharmacological evaluation of a number of fused tricyclic/tetracyclic and polycyclic heterocyclic systems, syntheses and evaluation of thia/oxazolidine diones as possible antidiabetic agents, organic light-emitting materials, organic semiconductors and solid lipid nanoparticle studies.

Dr. Ravi S. Lamani was born in Santholli, Sirsi, India. He obtained his B.Sc. (2002) and M.Sc. (2004) degrees from Karnatak University, Dharwad, India. He did his Ph.D. on heterocyclic compounds of biological interest under the supervision of Dr. Imtiyaz Ahmed M. Khazi at Karnatak University, Dharwad, India. Presently he is working as a Dr. D. S. Kothari Postdoctoral fellow at Bangalore University, Bangalore. His research interests are synthesis and pharmacological evaluation of sulfur and nitrogen heterocycles, thiazolidine-2,4-dione derivatives, peptides and peptidomimetics.

Professor Andanappa K. Gadad was born in Gajendrgad, Dharwad, India. He received his M. Pharm. Degree in 1984 from Gujarat University and did his Ph.D. under the supervision of Prof. C. S. Mahajanshetty at Karnatak University, Dharwad, India. He worked as a research fellow at the Indian Institute of Science, Bangalore, India and at the University of Sunderland, UK. He has over 24 years of teaching and research experience in India and abroad. He has worked as a Professor and Chairperson of pharmaceutical chemistry at RAK Medical and Health Sciences University, Ras Al Khaimah, UAE. Presently, he is a professor of pharmaceutical chemistry at the University of the West Indies, Trinidad and Tobago. His research interests include computer-aided drug design, carbo/hetero cyclic drug synthesis and prodrug development.

Dr. Bhoomendra A. Bhongade was born in Umarzari, Bhandara, India. He received his B. Pharm. Degree in 1995 from Nagpur University, India and M. Pharm. Degree in 1997 from Karnatak University, Dharwad, India. He earned his Ph.D. in 2006 from RGUHS Karnataka, Bangalore, India under the supervision of Prof. A. K. Gadad. He was the recipient of a senior research fellowship from the CSIR, New Delhi, India. He worked as a postdoctoral researcher with Prof. Gurdial Singh at the University of the West Indies, Trinidad and Tobago. Then he moved to the International Medical University, Kuala Lumpur, Malaysia to work as lecturer in pharmaceutical chemistry. Presently he is working as a Lecturer in Pharmaceutical Chemistry Department at RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, Ras Al Khaimah. His research areas are molecular modelling, drug design and synthesis of small-molecule inhibitors of therapeutic interest.