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Research Article

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEWER BIPHENYL IMIDAZO [2,1-b] [1,3,4]THIADIAZOLE DERIVATIVES

Rakesh Yadav*[1], Amandeep Kaur[2], Divya Yadav[1], Sarvesh Kumar Paliwal[1]

1. [1]Department of Pharmacy, Banasthali University, Banasthali-304 022, Rajasthan, India.
2. [2]ASBASJSM College of Pharmacy, Bela (Ropar) 140 111, Punjab, India.

***Corresponding Author: Email**: rakesh_pu@yahoo.co.in

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ABSTRACT

In the present study, we have reported the synthesis of some novel heterocyclic derivatives comprising imidazole and 1,3,4-thiadiazole containing moiety. Imidazothiadiazoles are of interest because of their diverse biological activities and clinical applications. Reactions of biphenyl carboxylic acid with thiosemicarbazide in the presence of phosphorous oxychloride resulted in biphenyl containing 2-amino-1,3,4-thiadiazole which is then further subjected to condensation with α-bromoarylketone under reflux in dry ethanol. The structures of the newly synthesised compounds were characterized by various spectral techniques and screened for antibacterial activity against strains of *Escherichia coli, Pseudomonas aeruginosa* and *Bacillus subtilis*, and antifungal activity against *Candida albicans, Saccharomyces cerevisiae and Aspergillus niger*. The compounds exhibited moderate to good activity when compared with standards.

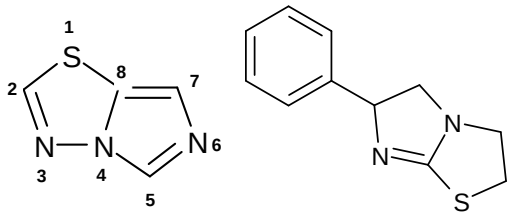
Keywords: Imidazo[2,1-*b*][1,3,4]thiadiazole; Biphenyl-4-carboxylic acid; 2-fluoro-biphenyl-4-carboxylic acid; Antimicrobial activity.

INTRODUCTION

Antimicrobial agents are the drugs, chemicals, or other substances that kill or slow the growth of microbes. The need for new antimicrobial agents is greater than ever because of the emergence of multi drug resistance in common pathogen, the rapid emergence of new infectious, and the potential for use of multidrug-resistant agents in bioweapons. Antimicrobial resistant is threatening the management of infectious such as pneumonia, tuberculosis, malaria, and AIDS. 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. 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 *pi*-conjugation.[1] The treatment of infectious diseases still remains an important and challenging problem because of a combination factors including emerging infectious diseases and increasing number of multi-drug resistant microbial pathogens with particular relevance for gram-positive bacteria.[2-7]

In spite of the large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotic resistant bacterial strains in the last decades constitutes a substantial need for the new class of antibacterial agents.[2,8] Imidazole[2,1-*b*][1,3,4]-thiadiazole derivatives have been of interest to the medicinal chemists for many years because of their anticancer[9], antitubercular[10], antibacterial[11], antifungal[12], anticonvulsant, analgesic[13] and antisecretory[14] activities. This is due to the fact that the imidazole [2,1-*b*][1,3,4]-thiadiazole (**1**) system is similar in part to levamisole (**2**), which is a well-known immune modulator.[1]



(1) **(2)**

Figure: Imidazole[2,1-*b*][1,3,4]-thiadiazole (**1**) and Levamisole (**2**)

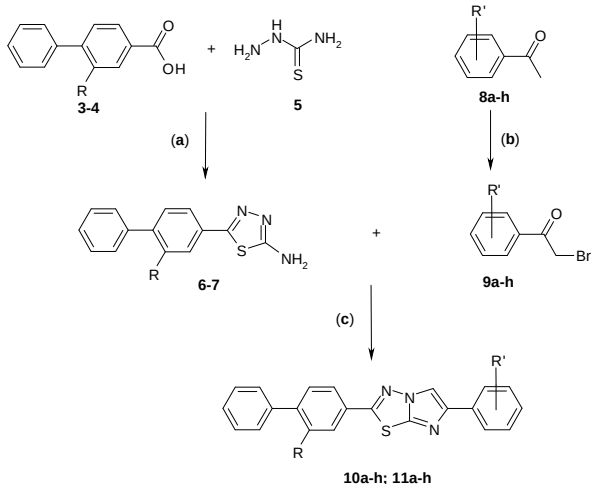
Levamisole (**2**) appears to be the most effective in patients with small tumor burdens and it acts by stimulating the responsiveness of lymphocytes to tumor antigens.[16] We reported here a study on synthesis and characterization of some novel biphenyl imidazo[2,1-*b*][1,3,4]-thiadiazole derivatives (**8a-h** and **9a-h**). These derivatives were further screened for antibacterial and antifungal activity.

MATERIALS AND METHODS

Chemistry

Melting points were determined on an electrothermal capillary melting point apparatus and are uncorrected. The infrared (IR) spectra were recorded on Perkin Elmer IR spectrophotometer (ν_{max} in cm^{-1}) using potassium bromide pellets. Proton (^1H) nuclear magnetic resonance spectroscopy was performed using a Bruker AC-400F, 400 MHz spectrometer for solutions in deuteriochloroform ($CDCl_3$) and deuterated dimethylsulfoxide (DMSO-d_6) and are reported in parts per million (ppm) downfield from tetramethylsilane (Me_4Si) as internal standard. Mass spectra were recorded on MAT 120. Chemical and solvents used were of LR grade and obtained from Merck, Sigma Aldrich, Loba chem., SD fine chemicals ltd., CDH etc. Precoated plates with silica gel G (E. Merck 60 F_{254}, 0.25 mm) were used for thin layer chromatography (TLC). Chromatographic spots were visualized by ultra-violet light in the UV cabinet (Perfit, India) and iodine chambers. Anhydrous sodium sulfate was utilized as drying agent. All solvents were freshly distilled and dried prior to use according to standard procedures.

Various imidazo[2,1-*b*][1,3,4]-thiadiazole derivatives of 2-fluorobiphenyl-4-carboxylic acid and biphenyl-4-carboxylic acid derivatives were synthesized using reaction *scheme 1*.



R = H (3, 6, 10a-h) or F (4, 7, 11a-h)
R' = **a**: H; **b**: 4'Cl; **c**: 4'F; **d**: 2',4'diCl; **e**: 4'NH_2; **f**: 2',4'diOH; **g**: 4'Br; **h**: 2'OH

***General procedure for the synthesis of 5-(3-fluorobiphenyl-4-yl)-1,3,4-thiadiazol-2-amine (6 and 7)*:**

Biphenyl-4-carboxylic acid (**3**) / 2-Fluorobiphenyl-4-carboxylic acid (**4**) (0.05 mol) was refluxed with thiosemicarbazide (0.05 mol) (**5**) in the presence of phosphorus oxychloride (15 ml) for 1 h. The reaction mixture was cooled and diluted with water and again refluxd for 4 h.[17] The reaction was monitored by thin layer chromatography and filtered after completion. The filtrate was basified with potassium hydroxide and the precipitate

so obtained was filtered off and crystallized from ethanol to gave the desired compound **6** and **7**.

*5-(Biphenyl-4-yl)-1,3,4-thiadiazol-2-amine (**6**)*: Yield 80%; m.p. 289-295 °C; IR (KBr) cm^{-1}: 3150 (CH), 1600 (C=C), 3283 (N-H); ^1H NMR (DMSO-d_6): δ 7.27-8.07 (m, 9H, Ar-H) and 3.37 ppm (s, 2H, NH_2).

*5-(3-Fluorobiphenyl-4-yl)-1,3,4-thiadiazol-2-amine (**7**)*:Yield 85%; m.p. 278-280 °C; IR (KBr) cm^{-1}: 3278 (N-H), 2964 (CH), 1579 (C=C), 1072 (C-F); ^1H NMR (DMSO-d_6): δ 7.36-7.82 (m, 8H, Ar-H) and 3.50 ppm (br s, 2H, NH_2).

General procedure for the *synthesis of substituted phenacyl bromides (9a-h)*: Various acetophenone derivatives **8a-h** (0.25 mol) were dissolved in 30 ml of chloroform and added bromine (0.25 mol) very slowly from dropping funnel with continuous stirring. During the addition the temperature was maintained below 20 °C and then cooled the mixture to afford **9a-h**.[18]

General procedure for the synthesis of 2-(biphenyl-4-yl)-6-substituted[2,1-b][1,3,4]thiadiazole derivatives (10a-h and 11a-h):

A mixture of equimolar quantities **6** and **7** (0.01 mol) and bromoacetyl compound (**9a-h**) (0.01 mol) was refluxed in dry ethanol for 12 h.[17] The excess of solvent was removed under reduced pressure and the precipitate so obtained was collected by filtration, suspended in water and neutralized by aqueous sodium carbonate solution to gave the desired compounds **10a-h** and **11a-h**.

***2-(Biphenyl-4-yl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazole (10a)*:** Yield 85%; m.p. 263-260 °C; IR (KBr) cm^{-1}: 3029 (CH), 1596 (C=C); ^1H NMR (DMSO-d_6): δ 8.54 (s, 1H, C_5-H) and 7.39-8.16 ppm (m, 14H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 145.33, 13133.69, 133.57, 129.92, 128.60, 128.53, 127.92, 127.75, 127.37, 126.74 and 126.61ppm; MS *m/z*: 254.1 (M^+), 255.1 (M+1), 256.1 (M+2).

***2-(Biphenyl-4-yl)-6-(4-chlorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (10b)*:** Yield 76%; m.p. 271-274 °C; IR (KBr) cm^{-1}: 3055 (CH), 1595 (C=C), 725 (C-Cl); ^1H NMR (DMSO-d_6): δ 8.50 (s, 1H, C_5-H) and 7.28-7.58 ppm (m, 13H, Ar-H).

***2-(Biphenyl-4-yl)-6-(4-fluorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (10c)*:** Yield 79%; m.p. 261-264 °C; FTIR (KBr) cm^{-1}: 3089 (CH), 1587 (C=C), 1150 (C-F); ^1H NMR (DMSO-d_6): δ 8.45 (s, 1H, C_5-H) and 7.25-7.68 ppm (m, 13H, Ar-H).

***2-(Biphenyl-4-yl)-6-(2,4-dichlorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (10d)*:** Yield 80%; m.p. 255-259 °C; FTIR (KBr) cm^{-1}: 3080 (CH), 1580 (C=C), 736 (C-Cl); ^1H NMR (DMSO-d_6): δ 8.54 (s, 1H, C_5-H) and 7.38-8.07 ppm (m, 12H, Ar-H).

***4-(2-(Biphenyl-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)aniline (10e)*:** Yield 73%; m.p. 263-267 °C; FTIR (KBr) cm^{-1}: 3055 (CH), 1595 (C=C), 3255 (N-H); ^1H NMR (DMSO-d_6): δ 8.51 (s, 1H, C_5-H), 7.36-8.01 (m, 13H, Ar-H) and 3.35 ppm (br s, 2H, NH_2).

***4-(2-(Biphenyl-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl) benzene-1,3-diol (10f)*:** Yield 75%; m.p. 266-269 °C; FTIR (KBr) cm^{-1}: 3057 (CH), 1589 (C=C), 3367 (O-H); ^1H NMR (DMSO-d_6): δ 8.25 (s, 1H, C_5-H), 7.35-8.07 (m, 12H, Ar-H) and 5.34 ppm (s, 2H, OH).

***2-(Biphenyl-4-yl)-6-(4-bromophenyl)imidazo[2,1-b][1,3,4]thiadiazole (10g)*:** Yield 81%; m.p. 254-259 °C; FTIR (KBr) cm^{-1}: 3056 (CH), 1585 (C=C), 876 (C-Br); ^1H NMR (DMSO-d_6): δ 8.28 (s, 1H, C_5-H) and 7.28-7.99 ppm (m, 13H, Ar-H).

***2-(2-(Biphenyl-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)phenol (10h)*:** Yield 79%;

m.p. 253-257 °C; FTIR (KBr) cm^{-1}: 3089 (CH), 1580 (C=C), 3348 (O-H); ^1H NMR (DMSO-d_6): δ 8.45 (s, 1H, C_5-H), 7.36-8.01 (m, 13H, Ar-H) and 5.30 ppm (s, 1H, OH).

***2-(3-Fluorobiphenyl-4-yl)-6-phenylimidazo[2,1b][1,3,4]thiadiazole (11a)*:** Yield 85%; m.p. 242-245 °C; FTIR (KBr) cm^{-1}: 3057 (CH), 1580 (C=C), 1118 (C-F); ^1H NMR (DMSO-d_6): δ 8.67 (s, 1H, C_5-H) and 7.29-8.21 ppm (m, 13H, Ar-H); ^{13}C NMR (DMSO-d_6): δ 164.75, 145.98, 142.24, 141.71, 138.97, 133.91, 132.65, 132.14, 129.97, 128.68, 127.17, 126.94, 126.90, 122.43, 120.28, 119.00 and 114.49 ppm; MS *m/z*: 272.1 (M^+), 273.1 (M+1), 274.1 (M+2).

***6-(4-Chlorophenyl)-2-(3-fluorobiphenyl-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (11b)*:** Yield 75%; m.p. 248-250 °C; FTIR (KBr) cm^{-1}: 3128 (CH), 1580 (C=C), 1092 (C-F), 734 (C-Cl); ^1H NMR (DMSO-d_6): δ 8.50 (s, 1H, C_5-H) and 7.39-7.89 ppm (m, 12H, Ar-H).

***2-(3-Fluorobiphenyl-4-yl)-6-(4-fluorophenyl)imidazo[2,1-b][1,3,4]thiadiazole (11c)*:** Yield 78%; m.p. 253-258 °C; IR

(KBr) cm^{-1}: 3138 (CH), 1570 (C=C), 1108 (C-F); ^1H NMR (DMSO-d_6): δ 8.45 (s, 1H, C_5-H) and 7.36-7.88 ppm (m, 12H, Ar-H).

***6-(2,4-Dichlorophenyl)-2-(3-fluorobiphenyl-4-yl)imidazo[2,1-b][1,3,4]thiadiazole (11d)*:** Yield 71%; m.p. 261-264 °C; FTIR (KBr) cm^{-1}: 3094 (CH), 1583 (C=C), 725 (C-Cl); ^1H NMR (DMSO-d_6): δ 8.20 (s, 1H, C_5-H) and 7.37-7.79 ppm (m, 11H, Ar-H).

***4-(2-(3-Fluorobiphenyl-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)aniline (11e)*:** Yield 80%; m.p. 243-246 °C; FTIR (KBr) cm^{-1}: 3120 (CH), 1580 (C=C), 3246 (N-H); ^1H NMR (DMSO-d_6): δ 8.45 (s, 1H, C_5-H), 7.39-8.01 (m, 12H, Ar-H) and 3.50 ppm (br s, 2H, NH_2).

***4-(2-(3-Fluorobiphenyl-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)benzene-1,3-diol (11f)*:** Yield 73%; m.p. 252-256 °C; FTIR (KBr) cm^{-1}: 3125 (CH), 1575 (C=C), 3357 (O-H); ^1H NMR (DMSO-d_6): δ 8.39 (s, 1H, C_5-H), 7.35-7.86 (m, 11H, Ar-H) and 5.30 ppm (s, 2H, OH).

***2-(2-(3-Fluorobiphenyl-4-yl)imidazo[2,1-b][1,3,4]thiadiazol-6-yl)phenol (11h)*:** Yield 77%; m.p. 267-270 °C; FTIR (KBr) cm^{-1}: 3089 (CH), 1575 (C=C), 3367 (O-H); ^1H NMR (DMSO-d_6): δ 8.40 (s, 1H, C_5-H), 7.37-7.68 (m, 12H, Ar-H) and 5.31 ppm (s, 1H, OH).

ANTIMICROBIAL SUSCEPTIBILITY TEST

The newly synthesized compounds were screened for their antibacterial and antifungal screening using agar diffusion method. The antibacterial activity of test compounds were evaluated against gram-positive bacteria, *Bacillus subtilis* and gram-negative bacteria, *Escherichia coli*; *Pseudomonas aeruginosa*. Antifungal activity was also screened against three fungal strain, *Candida albicans*; *Saccharomyces cerevisiae* and *Aspergillus niger*.

The bacterial cultures were inoculated and the nutrient agar media was made as per the reported procedure and sterilized by autoclaving at 121 °C for 15 min at 15-*psi* pressure. Afterwards the mixture was cooled to 45 °C and then inoculums were added to the above cooled media, mixed properly and poured into the sterile petridishes for solidifying. Bores were made on the medium using sterile borer and 0.1 ml of test solution and standard solution of 50 µg/ml concentration were taken. The standard antibiotics (Ampicillin) for bacteria and (Amphotericin B) for fungi were maintained with same concentration in each plate alongwith a control. The petridishes were incubated at 37 °C for 24 h and zones of inhibition were observed, measured and results are tabulated in the table 1.

Table 1: Antibacterial and antifungal activities of compounds (10a-h and 11a-h)

Compound No.	Zone of Inhibition (mm)					
	P. aeruginosa (ATCC-**17933**)	*B. subtilis* (ATCC-**77374**)	*E. coli* (ATCC-**87064**)	*C. albicans* (ATCC-**10231**)	S. cerevisiae (ATCC-**9763**)	*A. niger* (ATCC-**16404**)
10a	9.1	7.2	10.5	4.4	-	3.2
10b	8.5	8.5	9.4	5.8	-	4.5
10c	8.9	9.3	6.7	-	-	-
10d	7.9	9.8	8.8	-	-	-
10e	9.9	6.5	8.2	3.7	-	-
10f	9.5	7.8	7.8	-	-	2.7
10g	10.2	6.9	7.3	4.3	-	-
10h	9.6	9.4	9.7	-	-	-
11a	7.5	9.1	8.9	3.4	-	4.4
11b	8.5	8.5	9.4	4.8	-	-
11c	9.0	9.3	6.7	-	-	-
11d	7.9	7.4	9.4	-	-	-
11e	6.5	6.5	8.2	4.4	-	3.8
11f	9.5	7.8	8.7	-	-	-
11g	8.8	8.4	7.3	4.3	-	-
11h	9.6	6.9	9.7	-	-	-
STD	14.5	13.0	15.5	14.0	13.0	15.0

Control: DMSO; **(-):** No zone of inhibition (mm)

RESULTS AND DISCUSSION

The synthetic route of the newly synthesized compounds **10a-h** and **11a-h** is outlined in *Scheme 1*. 2-Amino-5-alkyl/aryl-1,3,4-thiadiazole **1** was obtained by direct cyclisation of a alkyl/aryl moiety and thiosemicarbazide in the presence of phosphorus oxychloride, the latter refluxed with substituted α-haloaryl ketones in dry ethanol yielded the imidazothiadiazoles in good yield. 2-Amino-5-alkyl/aryl-1,3,4-thiadiazole **2** was obtained by direct cyclisation of a alkyl/aryl moiety and thiosemicarbazide in the presence of phosphorus oxychloride, the latter refluxed with substituted α-haloaryl ketones in dry ethanol yielded the imidazothiadiazoles in good yield.

All the compounds were confirmed spectral techniques viz, IR, NMR. The absorption at 3128-3029 cm^{-1} are characteristic of (C-H) and (C=C) respectively. The appearance of imidazole proton (C_5-H) around δ 8.0 and the aromatic proton signals showed 7.1-8.2 ppm in the ^1H NMR spectra. The ^{13}C-NMR and mass spectral data on synthesized compounds are also in accordance with the proposed structures. The imidazo[2,1-*b*][1,3,4]thiadiazole derivatives were assayed *in vitro* for their antimicrobial activity against a panel of selected gram-positive, gram-negative bacteria and fungi in table 1, in comparison with those of the standard drugs ampicillin and amphotericin B. The antibacterial activity data reveals that the compounds **10a-h** and **11a-h** exhibited good antibacterial activity against various strains of bacteria as compared to standard drug ampicillin.

The antifungal screening results showed moderate activity against *Candida albicans* and *Aspergillus niger* strains as compared to standard Amphotericin B and no activity against *Saccharomyces cerevisiae*.

CONCLUSION

All the newly synthesized biphenyl imidazo[2,1-*b*][1,3,4]thiadiazole derivatives were characterized with different spectral techniques and screened *in vitro* for their antibacterial activity against both *Gram-positive* and *Gram-negative* strains of bacteria and also subjected for the antifungal activity. The results of antibacterial screening reveals all compounds exhibited good activity against all strains and moderate activity against *Candida albicans* and *Aspergillus niger* strains and no activity against *Saccharomyces cerevisiae* strains. Further studies of these compounds are in progress

Conflicts of interest

There is no conflict of interest.

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