Journal of Saudi Chemical Society (2016) **20**, S406–S410

King Saud University

**Journal of Saudi Chemical Society**

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ORIGINAL ARTICLE

# Synthesis, and antimicrobial evaluation of new pyridine imidazo [2,1b]-1,3,4-thiadiazole derivatives

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Received 30 October 2012; accepted 14 December 2012
Available online 4 January 2013

**KEYWORDS**

Synthesis;
Pyridine Imidazo-thiadiazole;
Antimicrobial activity

**Abstract** With the aim of producing new biologically active compounds, a series of New Pyridine Imidazo [2,1b]-1,3,4-thiadiazole derivatives **4(a–k)** were synthesized. All the compounds were characterized via IR, $^1$H-NMR and Mass spectral studies. The antimicrobial activity of newly synthesized compounds against various bacteria; *Bacillus pumillus, Staphylococcus aureus, Vibrio cholera, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, and* fungi; *Candida albicans* were evaluated. Among the compounds tested, **4(a)**, **4(b)**, **4(f)**, 4(h) and **4(k)** exhibited good antimicrobial activity while others responded moderately with reference to standard drugs ampicillin and amphotericin B.



## 1. Introduction

The rising prevalence of multi-drug resistant Gram positive and Gram negative bacteria continues to provide impetus for the search and discovery of novel antimicrobial agents active against these pathogens. A large number of substituted pyridines (Kallanagouda and shankar, 2011; Mohamed and Eman 2009; Massimo et al., 2000) and Imidazo [2,1-b]-1,3,4-thiadiazole have been claimed by researchers all around the world because of its versatile and eminent biological profile. Imidazo [2,1-b]-1,3,4-thiadiazole are known for cardiotonic (Andreani et al., 1996), diuretic (Andreani et al., 1987), antitubercular (Kolavi et al., 2006), anticonvulsant, analgesic (Khazi et al., 1996), and antisecretory (Andreani et al., 2000) activities. Moreover, interest of many medicinal chemist has also been focused on the antibacterial (Talath and Gadad, 2006), anticancer (Jadhav et al., 2008), antifungal (Guzeldemirci and Kucukbasmaci 2010), anti-inflammatory (Rostom et al., 2009), and herbicidal (Andreani et al., 1991) activities displayed by compounds adjoining this heterocyclic system.

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Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2012.12.007

Biheterocycles containing pyridine, thiadiazoles and chromone (Ghate et al., 2003) rings have been found to exhibit antimicrobial potential, psychotropic and anti-inflammatory activities and also heterocycles containing 1,3,4-thiadiazole are well known examples for antimicrobial biological profile (Lamani et al., 2009; Padmavathi et al., 2009; Padmavathi et al., 2008).

Over the past decade, drug resistance has become a growing problem in the treatment of infectious disease caused by bacteria, fungi and viruses. In particular, resistance of bacterial pathogens to current antibiotic has emerged as a measure health problem. It has been observed that these active pharmacophores, if linked together would generate novel molecular templates which are likely to exhibit interesting biological properties in animal models. The above cited applications prompted us to synthesize a series of new compounds which are reported in the present study.

## 2. Results and discussion

The formation of 5,5′-pyridine-2,5-diylbis-(1,3,4-thiadiazol-2-amine) (3) by the reaction of pyridine-2,5-dicarboxylic acid and thiosemicarbazide was confirmed by IR and $^1$H NMR spectral data. The spectral data of synthesized compounds were found in full agreement with the proposed structural compounds. IR spectrum showed the presence of amino band at 3427 cm$^{-1}$ ($NH_2$) and the absence of carbonyl group of carboxylic acid ~1700–1600 in compound **(3)** therefore confirming the cyclization of attached thiosemicarbazide moiety and formation of compound **(3)**. Moreover $^1$H-NMR spectrum of compound **(3)** exhibited two sharp singlets at $\delta \sim 10.11$ ppm and $\delta \sim 9.90$ ppm ($NH_2$) integrating each for 2 protons, respectively. Addition of substituted phenacyl bromide to compound 3 in the presence of ethanol under reflux condition obtained with final derivatives as **4(a–k)**. Establishment of structures of imidazo-thiadiazole derivatives **4(a–k)** was carried out by the absence of ($NH_2$) band ~3200 in IR spectrum and appearance of imidazole proton in the $^1$H NMR spectrum. The mass spectra of these compounds further confirmed the assigned structure.

The synthesized final derivatives of imidazo-thiadiazole showed potential profile against various microbes. Among the synthesized compounds **4(a)**, **4(b)**, **4(f)**, 4(h) and **4(k)** showed good antimicrobial activity against all strains. Out of these compounds, 4(a) showed maximum activity against *B. pumillus* (95.1%), *P. aeruginosa* (94.6%), *V. cholera* (91.0%), *S. aureus* (88.8%), and *P. mirabilis* (87.8%) when compared with the standard drug ampicillin. Compound **4(h)** showed maximum inhibition against *S. aureus* (92.0%) in comparison to other synthesized compounds and also showed good inhibition against *C. albicans* (84.7%). Compound **4(f)** was found to be most active against *E. coli* and *P. mirabilis* and showed (93.2% and 90.7%) inhibition respectively. Compound **4(f)** showed maximum activity against *C. albicans* (87.8%). Compounds **4(b)** and **4(k)** showed good activity against *B. pumillus* (85.2%), *P. mirabilis* (83.5%), *S. aureus* (82.7%), *C. albicans* (79.9%) and *V. cholera* (90.1%), *P. aeruginosa* (82.1%) and *B. pumillus* (81.7%), respectively. Apart from these compounds rest all showed moderate as well some showed good antimicrobial activity. Compound **4(a)** was found to be the most promising derivative of imidazo-thiadiazole as antibacterial and compound **4(f)** was the most active against fungi strain *C. albicans* with 87.8% inhibition. The results are reported as shown in Table 1.

## 3. Experimental

All chemicals and solvents were supplied by Merck, Aldrich, S.D. Fine Chemical Limited, Mumbai. All the solvents were distilled and dried before use. The reactions were monitored with the help of thin-layer chromatography using pre-coated aluminum sheets with $GF_{254}$ silica gel, 0.2 mm layer thickness (E. Merck) and solvent systems of (5:4:1); Toulene–Ethylacetate–Formic acid, (9:1); benzene-acetone. Melting points of the synthesized compounds were recorded on the Veego (VMP-MP) melting point apparatus. IR spectrum was acquired on a Shimadzu Infra Red Spectrometer, (model FTIR-8400S). $^1$H NMR (DMSO) spectra of the synthesized compounds were performed with Bruker Avance-II 400 NMR Spectrometer operating at 400 MHz in SAIF, Panjab University (Chandigarh). Chemical shifts are reported in parts per million (ppm) using tetramethylsilane as an internal standard. Mass spectra of the synthesized compounds were recorded at MAT 120 in SAIF, Panjab University.

### 3.1. Chemistry

The route of synthesis of compound **4(a–k)** is outlined in (scheme 1). 5,5′-pyridine-2,5-diylbis(1,3,4-thiadiazol-2-amine) (3) was prepared by refluxing and cyclization of Pyridine-2,5-dicarboxylic acid **(1)** treating with thiosemicarbazide **(2)** in the presence of phosphorous oxytrichloride. Using appropriate substituted phenacyl bromides under reflux condition in ethanol solvent, 2,2′-pyridine-2,5-diylbis [6-(substituted phenyl) imidazo [2,1-*b*]-1,3,4-thiadiazole] **4(a–k)** were obtained as final products. It is well established that this reaction proceeds via the intermediate iminothiadiazole, which undergoes dehydrocyclization to form the desired product (Noolvi et al., 2011). The electronic and steric factors at 5th position of 2-amino-5-substituted-1,3,4-thiadiazole are crucial in determining the course of its reaction. Thus the alkylation of this thiadiazole occurs at 3rd nitrogen with a subsequent ring closer to form the corresponding bridgehead nitrogen heterocyclic system. The yield was found to be in a range of 46%–70%. The synthesized compounds were recrystallized in appropriate solvent system and evaluated physically.

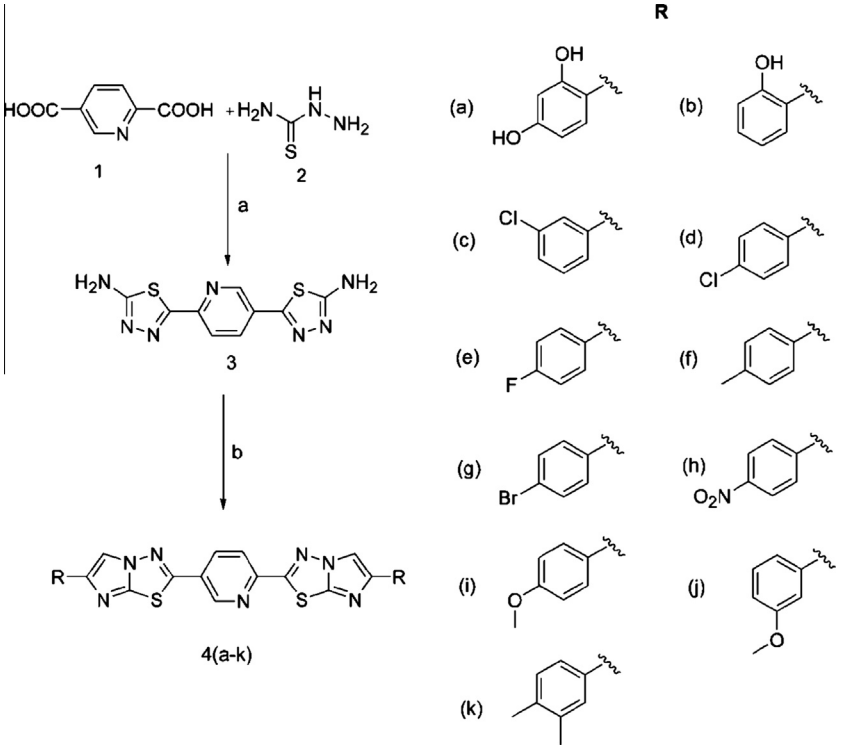
### 3.2. Pharmacology: Antimicrobial activity

The synthesized compounds 4(a–k) were screened for their antimicrobial activity using cup-plate agar diffusion method. Both bacterial culture of *B. pumillus, S. aureus, V. cholera, E. coli, P. mirabilis,* and *P. aeruginosa,* in nutrient agar medium and fungal culture of *C. albicans* in sabouraund's dextrose agar medium were utilized for the study (Holla et al., 2002). Compounds **4(a–k)** tested for antibacterial activity utilizing culture of *B. pumillus, S. aureus, V. cholera, E. coli, P. mirabilis,* and *P. aeruginosa* were compared with positive control, the standard drug Ampicillin (50 μg/mL) and for antifungal activity utilizing culture of *C. albicans* against the standard drug amphotericin B (50 μg/mL) moreover with negative control, the DMSO poured disk. DMSO was used

**Table 1** Antimicrobial Activity data for synthesized compounds 4(a-k).

| Compounds | % Inhibition | | | | | | |
|---|---|---|---|---|---|---|---|
| | *B. pumillus* | *S. aureus* | *V. cholera* | *E. coli* | *P. mirabilis* | *P. aeruginosa* | *C. albicans* |
| 4(a) | 95.1 | 88.8 | 91.0 | 73.5 | 87.8 | 94.6 | 79.2 |
| 4(b) | 85.2 | 82.7 | 75.1 | 79.4 | 83.5 | 66.5 | 79.9 |
| 4(c) | – | – | 43.5 | 71.2 | – | 32.8 | 66.1 |
| 4(d) | 48.6 | – | 59.7 | 37.2 | 63.2 | 70.5 | 58.9 |
| 4(e) | 23.7 | – | 61.5 | 72.6 | 80.3 | – | – |
| 4(f) | 92.0 | 89.9 | 81.6 | 93.5 | 90.7 | 72.0 | 87.8 |
| 4(g) | 72.1 | 75.3 | 48.9 | 50.8 | 67.6 | 56.5 | 49.3 |
| 4(h) | 89.9 | 92.0 | 88.3 | 90.1 | 79.2 | 86.4 | 84.7 |
| 4(i) | – | 72.2 | 63.0 | – | 57.5 | 73.2 | 65.2 |
| 4(j) | 75.0 | 53.1 | – | 51.1 | 72.3 | 53.1 | 49.7 |
| 4(k) | 81.7 | 79.8 | 90.1 | 72.5 | 77.6 | 82.1 | 70.1 |
| Standard | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

(–) No zone of inhibition
Standard: Ampicillin for bacteria and Amphotericin B for fungi




**Scheme 1** Synthesis of compounds 4(a-k); (a) Phosphorous oxytrichloride, $H_2O$, reflux (b) Substituted phenacylbromide, ethanol, reflux.

as a solvent for all the compounds, and as a control. The poured sterilized agar medium was allowed to solidify in petri-dishes. All the synthesized compounds (50 μg/mL) were placed in sequence in the cavities with the help of micropipette and allowed to diffuse for 1 h. For the antibacterial and antifungal activities, all the plates were incubated at 37 °C for 24 h and 28 °C for 48 h, respectively. The zone of inhibition was observed around the cup after respective incubation and following which the zone of inhibition was measured, and % inhibition was calculated to compare the potency of test with that of standard.

### *3.3. Spectral characterization*

#### *3.3.1. Synthesis of 5,5′-pyridine-2,5-diylbis(1,3,4-thiadiazol-2-amine) (3)*

Pyridine-2,5-dicarboxylic acid **(1) (0.1 M)** was refluxed with thiosemicarbazide **(2) (0.2 M)** and phosphorous oxytrichloride (5 mL) for 2 h. After 2 h the mixture was cooled and diluted with water (10 mL) and again refluxed for additional 4 h. Then the mixture was filtered and filtrate was neutralized with potassium hydroxide solution. The precipitate was filtered off and recrystallized from ethanol.

Yellow solid; yield 58%; mp: 316–318 °C; IR (KBr, $cm^{-1}$): 3427, 2924, 1414, 1349, 710; $^1$HNMR ($DMSOd_6$) δ ppm: 8.02 (s, 1H of pyridine), 8.50 (s, 1H of pyridine), 8.85 (s, 1H of pyridine), 9.90 (s, 2H, $NH_2$), 10.11 (s, 2H, $NH_2$); MS (*m/z%*): 277.32 [$M^+$].

*3.3.2. General procedure for synthesis of 2,2′-pyridine-2,5-diylbis[6-(substituted phenyl) imidazo [2,1-b]-1, 3, 4-thiadiazole]* ***4(a–k)***

A mixture of 5,5′-pyridine-2,5-diylbis (1,3,4-thiadiazol-2-amine) **(3)** (0.01 mol) and substituted bromoacetyl compound **(a–k)** (0.02 mol) was refluxed in dry ethanol for 18 h. The excess of solvent was distilled off and separated solid hydrobromide was collected by filtration, suspended in water and neutralized by aqueous sodium carbonate solution to get free base. It was filtered, washed with water, dried and recrystallized from ethanol.

*3.3.2.1. 2,2′-pyridine-2,5-diylbis[6-(2, 4-dihydroxyphenyl) imidazo [2,1-b]-1, 3, 4-thiadiazole]* ***4(a)***. Yellowish solid; yield 60%; mp: 320–322 °C; IR (KBr, $cm^{-1}$): 3501, 3422, 2873, 1650, 1238, 730; $^1$HNMR ($DMSOd_6$) δ ppm: 10.52 (s, 2H, OH), 10.10 (s, 2H, OH), 7.10–8.78 (m, 9H, Ar-H), 6.81 (s, 2H, Ar-H); MS (*m/z%*) $C_{25}H_{15}N_7O_4S_2$: 542.57 [M + 1]$^+$.

*3.3.2.2. 2,2′-pyridine-2,5-diylbis[6-(2-hydroxyphenyl) imidazo [2,1-b]-1, 3, 4-thiadiazole]* ***4(b)***. Yellow solid crystal; yield 54%; mp: 282–284 °C; IR (KBr, $cm^{-1}$): 3420, 2888, 1664, 1267, 711; $^1$HNMR ($DMSOd_6$) δ ppm: 10.61 (s, 1H, OH), 10.04 (s, 1H, OH), 7.13–8.92 (m, 13H, Ar-H); MS (*m/z%*) $C_{25}H_{15}N_7O_2S_2$: 509.57 [$M^+$]

*3.3.2.3. 2,2′-pyridine-2,5-diylbis[6-(3-chlorophenyl)imidazo [2,1-b]-1,3,4-thiadiazole]* ***4(c)***. Brown solid; yield 62%; mp: 324–326 °C; IR (KBr, $cm^{-1}$): 2925, 1643, 1402, 715, 691; $^1$HNMR ($DMSOd_6$) δ ppm: 8.93 (s, 2H, pyridine), 8.80 (s, 1H, pyridine), 8.69–7.31 (m, 10H, Ar-H); MS (*m/z%*) $C_{25}H_{13}Cl_2N_7S_2$: 546.48 [$M^+$].

*3.3.2.4. 2,2′-pyridine-2,5-diylbis[6-(4-chlorophenyl) imidazo [2,1-b]-1,3,4-thiadiazole]* ***4(d)***. Light brown solid; yield 69%; mp: 336–338 °C; IR (KBr, $cm^{-1}$): 2899, 1662, 1440, 727, 700; $^1$HNMR ($DMSOd_6$) δ ppm: 9.12 (s, 2H of pyridine), 8.89 (s, 1H of pyridine), 8.79–7.21 (m, 10H, Ar-H); MS (*m/z%*) $C_{25}H_{13}Cl_2N_7S_2$: 546.48 [$M^+$].

*3.3.2.5. 2,2′-pyridine-2,5-diylbis[6-(4-florophenyl) imidazo [2,1-b]-1,3,4-thiadiazole]* ***4(e)***. White solid; yield 52%; mp: 312–314 °C; IR (KBr, $cm^{-1}$): 2936, 1657, 1451, 681, 1017; $^1$HNMR ($DMSOd_6$) δ ppm: 9.31 (s, 1H of pyridine), 8.97 (s, 2H of pyridine), 8.81–7.42 (m, 10H, Ar-H); MS (*m/z%*) $C_{25}H_{13}F_2N_7S_2$: 514.55 [M + 1]$^+$.

*3.3.2.6. 2,2′-pyridine-2,5-diylbis[6-(4-methylphenyl) imidazo[2,1-b]-1,3,4-thiadiazole]* ***4(f)***. Brown solid; yield 57%; mp: 306–308 °C; IR (KBr, $cm^{-1}$): 2997, 1671, 1460, 714; $^1$HNMR ($DMSOd_6$) δ ppm: 9.25 (s, 1H of pyridine), 9.11 (s, 1H of pyridine), 8.94 (s, 1H of pyridine), 8.83–8.21 (m, 5H, Ar-H), 8.01–7.54 (m, 5H, Ar-H), 2.60 (s, 6H, $CH_3$); MS (*m/z%*) $C_{27}H_{19}N_7S_2$: 505.70 [$M^+$].

*3.3.2.7. 2,2′-pyridine-2,5-diylbis[6-(4-bromophenyl) imidazo [2,1-b]-1,3,4-thiadiazole]* ***4(g)***. Dark brown solid; yield 61%; mp: 316–318 °C; IR (KBr, $cm^{-1}$): 2960, 1658, 1449, 723, 675; $^1$HNMR ($DMSOd_6$) δ ppm: 9.16 (bs, 3H of pyridine), 8.76–8.28 (m, 7H, Ar-H), 8.11 (s, 2H, Ar-H), 7.60 (s, 1H, Ar-H); MS (*m/z%*) $C_{25}H_{13}Br_2N_7S_2$: 635.46 [$M^+$].

*3.3.2.8. 2,2′-pyridine-2,5-diylbis[6-(4-nitrophenyl) imidazo [2,1-b]-1,3,4-thiadiazole]* ***4(h)***. Orange solid crystals; yield 70%; mp: 324–326 °C; IR (KBr, $cm^{-1}$): 2924, 2216, 1625, 1510, 1047, 784; $^1$HNMR ($DMSOd_6$) δ ppm: 9.17 (bs, 3H of pyridine), 9.03–8.36 (m, 8H, Ar-H), 7.04 (s, 2H, Ar-H); MS (*m/z%*) $C_{25}H_{13}N_9O_4S_2$: 567.66 [$M^+$].

*3.3.2.9. 2,2′-pyridine-2,5-diylbis[6-(4-methoxyphenyl) imidazo[2,1-b]-1,3,4-thiadiazole]* ***4(i)***. White solid crystals; yield 66%; mp: 320–322 °C; IR (KBr, $cm^{-1}$): 2987, 1668, 1466, 683; $^1$HNMR ($DMSOd_6$) δ ppm: 9.13 (s, 2H of pyridine), 9.02 (s, 1H of pyridine), 8.96–7.99 (m, 7H, Ar-H), 7.21 (s, 3H, Ar-H), 3.80 (s, 6H, $CH_3O$); MS (*m/z%*) $C_{27}H_{19}N_7O_2S_2$: 538.69 [M + 1]$^+$.

*3.3.2.10. 2,2′-pyridine-2,5-diylbis[6-(3-methoxyphenyl) imidazo [2,1-b]-1,3,4-thiadiazole]* ***4(j)***. Yellow solid crystals; yield 57%; mp: 314–316 °C; IR (KBr, $cm^{-1}$): 3005, 1656, 1447, 671; $^1$HNMR ($DMSOd_6$) δ ppm: 9.02 (bs, 3H of pyridine), 8.83–7.14 (m, 8H, Ar-H), 6.71 (s, 2H, Ar-H), 3.62 (s, 6H, $CH_3O$); MS (*m/z%*) $C_{27}H_{19}N_7O_2S_2$: 537.80 [$M^+$].

*3.3.2.11. 2,2′-pyridine-2,5-diylbis[6-(3,4-dimethylphenyl) imidazo [2,1-b]-1,3,4-thiadiazole]* ***4(k)***. White solid; yield 46%; mp: 330–332 °C; IR (KBr, $cm^{-1}$): 3015, 1665, 1469; $^1$HNMR ($DMSOd_6$) δ ppm: 9.13 (s, 2H of pyridine), 8.94 (s, 1H of pyridine), 8.63 (s, 3H, Ar-H), 7.81–7.15 (m, 5H, Ar-H), 2.72 (s, 3H, $CH_3$); MS (*m/z%*) $C_{29}H_{23}N_7S_2$: 533.81 [$M^+$].

## 4. Conclusion

Irrefutably, we hereby report eleven synthesized derivatives containing imidazo-thiadiazole moiety **4(a–k)** which were prosecuted for antibacterial activity against the standard drug ampicillin and antifungal activity against amphotericin B as the standard drug. Among the synthesized compounds, **4(a)**, **4(b)**, **4(f)**, 4(h) and **4(k)** were found to be the most promising candidates against *B. pumillus*, *S. aureus*, *V. cholera*, *E. coli*, *P. mirabilis*, *P. aeruginosa* and *C. albicans*. Different substitutions and structural diversity of the reported compounds were found to play an eminent role in their biological profiling. The % inhibition of all the compounds was determined by observing the zone of inhibition formed around the cup after 24 h of incubation for antibacterial and 48 h for antifungal activities. Keeping in mind of their biological diversity further developments on this area of subject are still under progress.

**Acknowledgment**

The authors are thankful to the Head, Sophisticated Analytical Instrument Facility, Panjab University, Chandigarh, for providing IR, $^1$H-NMR, and Mass spectral data and microbiological section of department of Biotechnology, Bioinformatics and Pharmacy for availing the facilities for screening of compounds.

## References


Andreani, A., Leoni, A., Locatelli, A., Morigi, R., Rambaldi, M., Simon, W.A., Senn-Bilfinger, J., 2000. Synthesis and antisecretory activity of 6-substituted 5-cyanomethylimidazo[2,1-b] thiazoles and 2,6-dimethyl-5-hydroxymethylimidazo[2,1-b][1,3,4]thiadiazole. Arzneim-Forsch. Drug. Res. 50, 550–553.

Andreani, A., Rambaldi, M., Leoni, A., Locatelli, A., Bossa, R., Chiericozzi, M., Galatulas, I., Salvatore, G., 1996. Synthesis and cardiotonic activity of imidazo[2, l-b]thiazoles bearing a lactam ring. Eur. J. Med. Chem. 31, 383–387.

Andreani, A., Rambaldi, M., Locatelli, A., 1991. Herbicidal activity of 5-haloimidazo[2,1-*b*]thiazoles. Collect. Czech. Chem. Commun. 56, 2436–2447.

Andreani, A., Rambaldi, M., Mascellani, G., Rugarli, P., 1987. Synthesis and diuretic activity of imidazo[2,1-b]thiazole acetohydrazones. Eur. J. Med. Chem. 22, 19–22.

Ghate, M., Manohar, D., Kulkarni, V., Shobha, R., Kattimani, S.Y., 2003. Synthesis of vanillin ethers from 4-(bromomethyl) coumarins as anti-inflammatory agents. Eur. J. Med. Chem. 38, 297–302.

Guzeldemirci, N.U., Kucukbasmaci, O., 2010. Synthesis and antimicrobial activity evaluation of new 1,2,4-triazoles and 1,3,4-thiadiazoles bearing imidazo[2,1-*b*]thiazole moiety. Eur. J. Med. Chem. 45, 63–68.

Holla, S., Poojary, N.K., Rao, B.S., Shivananda, M.K., 2002. New bis aminomercaptotriazoles and bis-triazolothiadiazoles as possible anticancer agents. Eur. J. Med. Chem. 37, 511–517.

Jadhav, V.B., Kulkarni, M.V., Rasal, V.P., Biradar, S.S., Vinay, M.D., 2008. Synthesis and anti-inflammatory evaluation of methylene bridged benzofuranyl imidazo[2,1-*b*][1,3,4]thiadiazoles. Eur. J. Med. Chem. 43, 1721–1729.

Kallanagouda, R.A., Shankar, G.A., 2011. Synthesis, characterization and antimicrobial activity evaluation of new 2,4-Thiazolidinediones bearing imidazo[2,1-*b*][1,3,4]thiadiazole moiety. Arabian J. Chem. 4, 465–472.

Khazi, I.A.M., Mahajanshetti, C.S., Gadad, A.K., Tarnalli, A.D., Sultanpur, C.M., 1996. Synthesis, anticonvulsant and analgesic activities of some 6-substituted imidazo(2,1-b)-1,3,4-thiadiazole-2-sulfonamides and their 5-bromo derivatives. Arzneim-Forsch. Drug. Res. 46, 949–952.

Kolavi, G., Hegde, V., Khazi, I.A., Gadad, P., 2006. Synthesis and evaluation of antitubercular activity of imidazo[2,1-*b*][1,3,4]thiadiazole derivatives. Bioorg. Med. Chem. 14, 3069–3080.

Lamani, R.S., Shetty, N.S., Kamble, R.R., Khazi, I.A.M., 2009. Synthesis and antimicrobial studies of novel methylene bridged benzisoxazolyl imidazo[2,1-*b*][1,3,4]thiadiazole derivatives. Eur. J. Med. Chem. 44, 2828–2833.

Massimo, P., Marco, T., Daniela, U., Giuseppe, P., Pietro, B., Fiorenzo, P., Fabrizio, Z., 2000. 3*H*-[1,2] dithiolo [3,4-*b*] pyridine-3-thione and its derivatives synthesis and antimicrobial activity. II. Farmaco 55, 669–679.

Mohamed, A.A.R., Eman, M.H.A., 2009. Synthesis of some pyridine, thiopyrimidine, and isoxazoline derivatives based on the pyrrole moiety. Monatsh Chem. 140, 229–233.

Noolvi, M.N., Patel, H.M., Singh, N., Gagad, A.K., Cameotra, S.S., Badiger, A., 2011. Synthesis and anticancer evaluation of novel 2-cyclopropylimidazo[2,1-*b*][1,3,4]-thiadiazole derivatives. Eur. J. Med. Chem. 46, 4411–4418.

Padmavathi, V., Reddy, G.S., Padmaja, A., Kondaiah, P., Ali-Shazia, 2009. Synthesis, antimicrobial and cytotoxic activities of 1,3,4-oxadiazoles, 1,3,4-thiadiazoles and 1,2,4-triazoles. Eur. J. Med. Chem. 44, 2106–2112.

Padmavathi, V., Thriveni, P., Reddy, G.S., Deepti, D., 2008. Synthesis and antimicrobial activity of novel sulfone-linked bis heterocycles. Eur. J. Med. Chem. 43, 917–924.

Rostom, S.A.F., El-Ashmawy, I.M., Razik, H.A.A.E., Badr, M.H., Ashour, H.M.A., 2009. Design and synthesis of some thiazolyl and thiadiazolyl derivatives of antipyrine as potential non-acidic anti-inflammatory, analgesic and antimicrobial agents. Bioorg. Med. Chem. 17, 282–295.

Talath, S., Gadad, A.K., 2006. Synthesis, antibacterial and antitubercular activities of some 7-[4-(5-amino-[1,3,4]thiadiazole-2-sulfonyl)-piperazin-1-yl] fluoroquinolonic derivatives. Eur. J. Med. Chem. 41, 918–924.