European Journal of Medicinal Chemistry 71 (2014) 316–323

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and biological evaluation of novel substituted 1,3,4-thiadiazole and 2,6-di aryl substituted imidazo [2,1-*b*] [1,3,4] thiadiazole derivatives

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ARTICLE INFO

Article history:
Received 5 May 2013
Received in revised form
20 October 2013
Accepted 22 October 2013
Available online 30 October 2013

Keywords:
1,3,4-Thiadiazole
2,6-Diaryl imidazo [2,1-*b*] [1,3,4] thiadiazole
Antibacterial
Antifungal activity

ABSTRACT

A new series of *N*-[5-(4-(alkyl/aryl)-3-nitro-phenyl)-[1,3,4-thiadiazol-2-yl]-2,2-dimethyl-propionamide **4** (**a**–**l**) and 6-(4-Methoxy-phenyl)-2-(4-alkyl/aryl)-3-nitro-phenyl)-Imidazo [2,1-*b*] [1,3,4] thiadiazole **6** (**a**–**l**) were synthesized starting from 5-(4-Fluoro-3-nitro-phenyl)-[1,3,4] thiadiazole-2-ylamine. The synthesized compounds were characterized by IR, NMR, mass spectral and elemental analysis. All the compounds were tested for antibacterial and antifungal activities. The antimicrobial activities of the compounds were assessed by well plate method (zone of inhibition). Compounds **4a**, **4c** and **6e**, **6g** displayed appreciable activity at the concentration 0.5–1.0 mg/mL.

1. Introduction

In last few decades, there is tremendous growth in the development of antimicrobial drugs. However development of the resistance against these antimicrobials is also at an alarming stage. During recent years, there have been intense investigation on thiadiazole and 2,6-imidazo [2,1-*b*] [1,3,4] thiadiazole compounds, many of which are known to possess interesting biological properties such antimicrobial [1] anti-inflammatory [2,3], anticonvulsant [4], antituberculosis [5,6], antifungal [7,8], antiviral [9], antibacterial [10–12], antitumour [13], anticancer [14,15] activities.

The various biological activities of imidazo [2,1-*b*] [1,3,4] thiadiazole and their derivatives have been known from early 1950s and since then, the research work on this heterocyclic system has led to significant developments in their chemistry and biology [16].

The literature review revealed that substituted 2-amino-5-aryl-1,3,4-thiadiazole analogues (Fig. 1) especially its phenyl substituent, exhibit significant *in-vitro* antiproliferative activity [17]. Moreover Levamisole appears to be the most effective in patient's drugs against small tumour burdens as it acts by stimulating the responsiveness of lymphocytes toward tumour antigens [18]. The 2,6-Aryl imidazo [2,1-*b*] thiazole derivatives of Levamisole and another 2,6-Aryl imidazo [1,2-*b*] [1,3,4] thiadiazole analogue has been reported as potential antitumour agents [19].

The continuous and widespread use of antimicrobial agents has resulted in the development of resistance to these drugs by pathogenic microorganisms, hence there is urgent need for newer class of drugs [20]. Thus, intense efforts in antimicrobial drug discovery are still needed to develop more promising and effective antifungal agents for use in the field of clinical research [21].

Prompted by the scope for the newer class of antimicrobial drugs and in continuation of our research on biologically active heterocycles [22,23], we hereby report the synthesis of some new 1,3,4-thiadiazole and 2,6-di aryl substituted imidazo [2,1-*b*] [1,3,4] thiadiazole derivatives. Moreover, nitrogen-containing heterocycles are also of broad pharmaceutical interest and significance,

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http://dx.doi.org/10.1016/j.ejmech.2013.10.056

which justifies our continuing efforts in designing new heterocyclic molecules of biological importance [24].

2. Results and discussion

2.1. Chemistry

The title compounds were prepared according to the synthetic strategy described in Scheme 1. The key scaffold in the present study is 5-(4-Fluoro-3-nitro-phenyl)-[1,3,4] thiadiazole-2-ylamine **2** and was synthesized from 4-Fluoro-3-nitrobenzoic acid by treating with phosphorous oxychloride and thiosemicarbazide using the reported procedure [25,26]. The compound was then converted into **3** by protecting $-NH_2$ group by pivaloyl chloride followed by treating different aliphatic/aromatic amines under microwave conditions to afford different substituted 1,3,4-Thiadiazole derivatives **4** (**a**–**l**).

Similarly the compound was also converted in to **5** by cyclization reaction with 4-methoxy phenacyl bromide according to the reported literature [27] and followed by Micro wave reaction using different amines to afford different substituted 2,6-Aryl imidazo [2,1-*b*] [1,3,4] thiadiazol **6** (**a**–**l**) derivatives (Scheme 1).

The formation of substituted 1,3,4-thiadiazole and 2,6-Aryl imidazo [2,1-*b*] [1,3,4]-thiadiazole derivatives were confirmed by recording their IR, ^{1}H NMR, ^{13}C NMR, elemental analysis and mass spectral data. IR spectrum of **4a** shows absorption at 3516 cm^{-1} which is due to amide –NH stretch. An absorption band at 2933, 2836 cm^{-1} which is due to aromatic stretching, band at 1587 cm^{-1} is due to C=N group, band at 1461 cm^{-1} is stretching of phenyl rings. The ^{1}H NMR of compound **4a** showed broad singlet in the region of δ 12.18 cm^{-1}, which is due to amide –NH proton, the singlet at δ 8.33–8.32 cm^{-1}, multiplet in the region of δ 8.08–8.06 cm^{-1} and doublet in the region of δ 7.42–7.39 cm^{-1} with *J* value 8.76 Hz for the aromatic phenyl ring protons. In the aliphatic region, the multiplet observed in the region of δ 3.71–3.69 cm^{-1} and δ 3.10–3.08 cm^{-1} is due to the morpholine ring protons. Similarly singlet at δ 1.26 cm^{-1} for *tert*-butyl (9) protons. The mass spectrum of **4a** showed a molecular ion peak at $m/z = 392$ (M^+), which is in agreement with the molecular formula $C_{17}H_{21}N_5O_4S$. Similarly the spectral values for all the compounds and C, H, N analyses are given in the experimental part.

Similarly IR spectrum of compound **6a** showed absorption at 2965, 2856 cm^{-1} which is due to aromatic stretching, band at 1614 cm^{-1} is due to C=N group, peak observed at 1486, 1465 cm^{-1} is stretching of phenyl rings. The ^{1}H NMR spectrum of compound **6a** showed singlet in the region of δ 8.60 due to the imidazole ring proton, the singlet at δ 8.31 multiplet in the region of δ 8.06–8.04 and doublet in the region of δ 7.44–7.42 with *J* value 8.72 Hz for aromatic nitro phenyl ring protons. The doublet appeared in the region of δ 7.81–7.79 and δ 6.99–6.96 due to methoxy phenyl protons. The multiplet observed in the region of δ 3.71–3.70 and δ 3.14–3.10 is due to morpholine ring protons. Similarly singlet at δ 3.77 is because of methoxy protons. The mass spectrum of compound **6a** showed a molecular ion peak at $m/z = 438$ (M^+), which is in agreement with the molecular formula $C_{21}H_{19}N_5O_4S$. Similarly the spectral values for all the compounds and C, H, N analyses are given in the experimental part and the characterization is provided in Table 1 and Table 2.

2.2. Pharmacology

2.2.1. Antibacterial studies

The *in-vitro* antibacterial activity of newly synthesized compounds **4** (**a**–**l**) and **6** (**a**–**l**) was determined by well plate method [28,29]. The following Gram positive and negative bacteria were used as test organism: *Escherichia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa* to investigate the activity. The test compounds were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 and 0.5 mg/mL.

The antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains. The result indicated that among the synthesized compounds, **4a** and **6e** showed good activity against *E. coli* at concentrations of 1 and 0.5 mg/mL compared to standard drug Streptomycin. The remaining compounds showed moderated activity against all the three tested bacterial strains.

The details of antibacterial results are furnished in Table 3 and Table 4.

2.2.2. Antifungal activity

The fungal strains used in this study were *Candida albicans*, *Aspergillus flavus* and *Chrysosporium keratinophilum* because of their infectious nature. The study was determined by well plate method [30] at concentrations of 1, 0.5 mg/mL using DMSO solvent. Among the tested compounds, the compound **4c** and **6e** were emerged as active against *A. flavus* compared with standard drug Fluconazole. Whereas other compounds showed less activity against all the tested microorganisms compared to standard.

The result of antifungal studies have been furnished in Table 5 and Table 6

3. Conclusion

All the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, mass spectrometry and IR studies. Compounds were screened for their *in-vitro* antibacterial and antifungal studies. Antibacterial activity for the derivatives **4** (**a**–**l**) and **6** (**a**–**l**) was evaluated by well plate method. The preliminary in-vitro antimicrobial screening of new 1,3,4-thiadiazole and imidazo [2,1-*b*] [1,3,4-thiadiazole derivatives, reported in the article, evidenced that many of the compounds from the both series have emerged as potent antibacterial and antifungal agents endowed with moderate to good activity. The possible improvements in the activity can be further achieved by slight modification of thiadiazole to imidazo [2,1-*b*][1,3,4-thiadiazole. Hence, it can be concluded that, new class of compounds certainly holds a greater pledge in discovering a potent antimicrobial agent.

More potent compounds among the synthesized series have been presented in Fig. 2.

4. Experimental

4.1. Chemistry

All the Chemicals were procured from Aldrich Co. Reactions were monitored and purity of the products was checked by TLC which was performed on MERCK 60F-254 silica gel plates. Melting

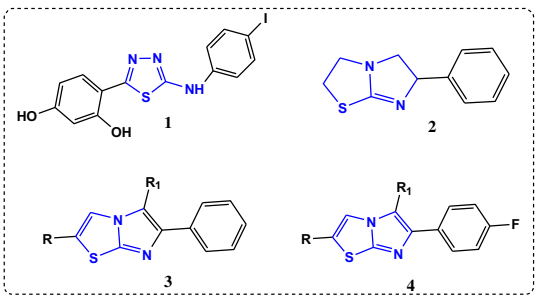

Fig. 1. Structures of some literature reviewed active molecules.