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Original article

Synthesis of some novel 3-(1-(1-substitutedpiperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)-5-substituted phenyl-1,2,4-oxadiazoles as antifungal agents

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ABSTRACT

A novel series of 3-(1-(1-substituted piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)-5-substituted phenyl-1,2,4-oxadiazoles bearing 1,2,3-triazole and piperidine ring has been synthesized in one step from amidoxime using Carbonyl diimidazole (CDI) and K_2CO_3. All the synthesized compounds (**4a**–**4r**) are novel and evaluated for their in vitro antifungal activities. SAR for the series has been developed by comparing their MIC values with miconazole and fluconazole. Some of the compounds from the series like **4j** was equipotent with miconazole against *Cryptococcus neoformans* whereas activities of compound **4m** against *Aspergillus niger* and *Aspergillus flavus* were comparable to miconazole. Also compound **4r** shows activity comparable to miconazole against *Candida albicans*, *A. niger* and *A. flavus*.

1. Introduction

1,2,3-Triazole and its derivatives are important heterocycles with different activities like potent antineoplastic [1], antimicrobial [2–4], analgesic [5], anti-inflammatory, local anesthetic [6], anticonvulsant [7], antimalarial [8] and anti HIV agents [9]. Some 1,2,3-triazole derivatives were used as DNA cleaving agents [10], potassium channel activators [11], cannabinoid CB1 receptor antagonists [12] and antitubercular agents [13].

1,2,4-Oxadiazole and its derivatives are important pharmacophore with diversified pharmacological activities like antibacterial, analgesic and anti-inflammatory [14]. Especially 3, 5 disubstituted oxadiazole have gained much attention due to its biological potential. Recently 3,5 disubstituted oxadiazole has been reported as a β amyloid-imaging probe, which plays an important role in Alzheimer's drug discovery [15]. 3,5 disubstituted oxadiazole are generally prepared from amidoximes and acid compound using base [16]. However, some of these methods suffer from one or more drawbacks like harsh reaction conditions, and low yields. Considering biological significance of 1,2,3-triazole and 1,2,4-oxadiazole and in continuation of our work on synthesis of some pharmacologically important heterocycles [17], here we wish to report synthesis and antifungal activity of novel series of 3-(1-(1-substituted piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)-5-substituted phenyl-1,2,4-oxadiazoles from amidoxime and substituted benzoic acid using CDI, K_2CO_3/DMF. From the data of activity, SAR for the series has been developed.

2. Chemistry

The starting substituted amidoxime compounds **2a**–**2r** were synthesized from the commercially available starting material *N*-Boc piperidone as described in our previous report [17d]. The amidoxime compound thus prepared on reaction with substituted benzoic acid and CDI (2 equivalents) using 2 equivalents K_2CO_3 in DMF at 110 °C gave the target compounds Scheme 1 and 2.

Optimization of the reaction was carried out considering synthesis of **4a**.

From the study it is observed that use of 2 equivalent K_2CO_3 is more advantageous giving 93% yield in 4 h. The synthetic procedure was extended for synthesis of all the compounds **4a**–**4r** using different substituted benzoic acid. Results are summarized in Table 1. The yields were obtained in the range of 89–93%. All synthesized derivatives were characterized using mass and ^{1}H NMR. ^{1}H NMR spectra were recorded on a 400 MHz Varian-Gemini spectrometer and are reported as parts per million (ppm)

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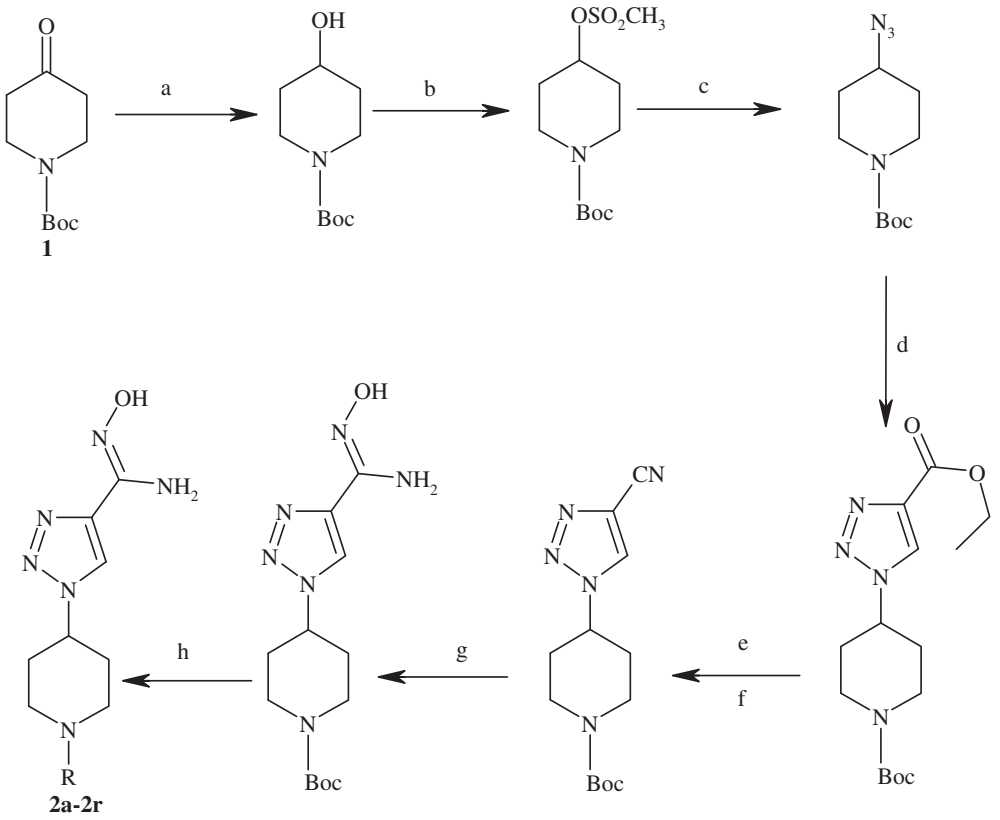


Scheme 1. Synthesis of amidoxime compounds (**2a**–**2r**) from *N*-Boc piperidone. (a) $NaBH_4$, ethanol, rt, 2 h; (b) Methanesulfonyl chloride, triethylamine, dichloromethane; (c) NaN_3, DMF, 80 °C, 8 h; (d) Ethyl Propiolate, CuI, acetonitrile, rt, 12 h; (e) ammonia, ethanol, rt, 12 h; (f) TFAA, dichloromethane, rt, 2 h; (g) Hydroxylamine hydrochloride, sodium bicarbonate, methanol, reflux, 14 h (h) TFA, dichloromethane, rt, 14 h; triethylamine, R-X or RCOX, tetrahydrofuran, 0–5 °C to rt, 2 h.

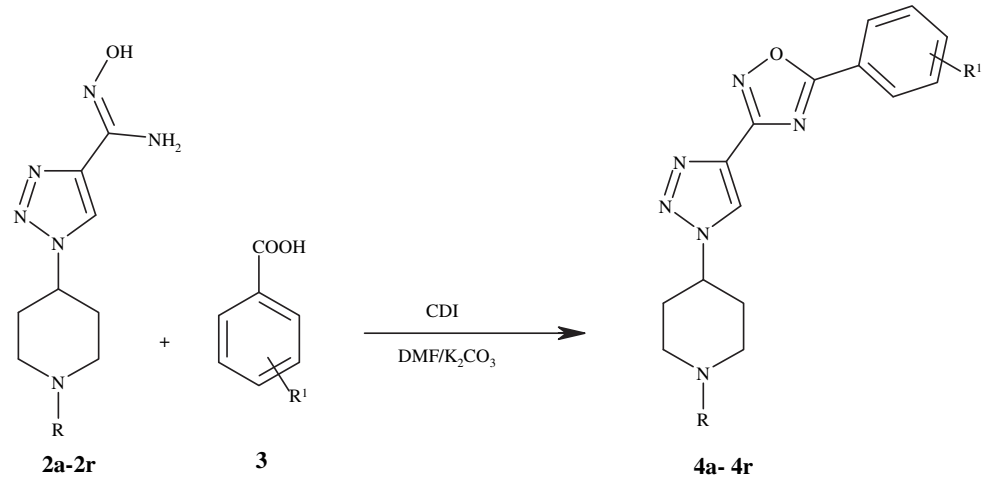
downfield from a tetramethylsilane internal standard. Mass spectra were taken with Micromass - QUATTRO-II of WATER mass spectrometer.

3. Antifungal activity

All the synthesized novel compounds were screened for in vitro antifungal activity. The antifungal activity was evaluated against different fungal strains such as *Candida albicans*, *Fusarium oxysporum*, *Aspergillus flavus*, *Aspergillus niger*, *Cryptococcus neoformans*. Minimum inhibitory concentration (MIC) values were determined using standard agar method [18]. Miconazole and fluconazole were used as a standard for the comparison of antifungal activity. MIC values of the tested compounds are presented in Table 2.

4. Results and discussion

Many of the newly synthesized compounds were found to show good antifungal activity. From the antifungal activity data (Table 2), it was observed that compound **4j**, **4m** and **4r** are the most active compounds. *N*-protected compound **4a** shows very less antifungal activity comparable to miconazole and fluconazole. Deprotected



Scheme 2. Synthesis of 3-(1-(1-substituted piperidin-4-yl)-1*H*-1,2,3-triazol-4-yl)-5-substituted phenyl-1,2,4-oxadiazoles (**4a-4r**) from amidoximes (**2a**–**2r**).