European Journal of Medicinal Chemistry 95 (2015) 96–103

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

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

Original article

# Synthesis, biological evaluation and molecular docking of some substituted pyrazolines and isoxazolines as potential antimicrobial agents

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ARTICLE INFO

*Article history:*
Received 9 September 2014
Received in revised form
2 March 2015
Accepted 15 March 2015
Available online 16 March 2015

*Keywords:*
2-pyrazolines
Isoxazolines antimicrobial
Molecular docking
14α-sterol demethylases

ABSTRACT

A series of substituted pyrazolines (**2a**–**e**, **3a**–**h** and **6a**–**c**) and isoxazolines (**4a**–**e**) were synthesized and their structures were established on the basis of IR, $^{1}$H NMR, $^{13}$C NMR and mass spectra. All the synthesized compounds were tested against two bacterial and four fungal strains and found to exhibit moderate to potent antifungal activity. Compounds **2b**, **4c**, **4d** and **6a**–**c** exhibited significant activity against all tested fungal strains. MIC values of all the active compounds were comparable with standard drug fluconazole. The results of the *in silico* molecular docking study supported the antifungal activity of the synthesized compounds.



## 1. Introduction

Despite significant progress made in the treatment of infectious diseases, caused by bacteria and fungi, it remains a major worldwide health problem due to rapid development of resistance against the existing antimicrobial drugs. Developing novel antimicrobial agents with different mode of action than that of existing drugs is one of the main challenges to overcome the antimicrobial resistance. In view of these facts, it is important to develop more effective antimicrobial agents. Thus, the synthesis and discovery of more efficient antimicrobial agents has been intensively considered during the last decade. Different heterocyclic compounds containing nitrogen, sulphur and oxygen as hetero atoms have been explored for the development of new antimicrobial agents [1–7]. Compounds containing five membered heterocyclic ring systems like pyrazolines and isoxazolines continue to attract considerable interest due to the wide range of biological activities they posses. Pyrazolines have been reported to exhibit a variety of biological activities including anti-tumour [8,9], anti-inflammatory [4,10–15], antiparasitary [16], anticonvulsant [17], antimicrobial [18–22], antinociceptive [23], antimalarial [24], nitric oxide synthase inhibitory, inflammatory arthritis [25], antidepressant [26,27], anticancer [28–30], antibacterial [18], analgesic [31], antioxidant [32], antiamoebic, cytotoxic [33–35], antifungal [36,37], antimycobacterial [38], antihepatotoxic [39] and pesticidal properties [40]. Isoxazoline derivatives have been reported to possess antimicrobial [20,21,41,42], anticonvulsant [43], anti-inflammatory [44], anti-viral [45], analgesic [46] and antitumour activity [47,48]. Penicillin derivatives containing isoxazole ring have been found to possess antibacterial activity [49]. Isoxazoline derivatives also show a good potency in animal models of thrombosis [50]. In addition, isoxazoline derivatives have played a vital role in the theoretical development of heterocyclic chemistry and are also extensively used in organic synthesis [51,52].

Computational biology and bioinformatics play a major role in designing the drug molecules and have the potential of speeding up the drug discovery process. Molecular docking of the drug molecule with the receptor (target) gives important information about drug receptor interactions and is commonly used to find out the binding orientation of drug candidates to their protein targets in order to predict the affinity and activity. Cytochrome $P_{450}$ 14α-sterol

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http://dx.doi.org/10.1016/j.ejmech.2015.03.031
0223-5234/

demethylases (CYP51) are essential enzymes in sterol biosynthesis in eukaryotes. Being a key enzyme of sterol biosynthesis, CYP51 has been found to be a target for antifungal [53] and cholesterol-lowering [54] drug design.

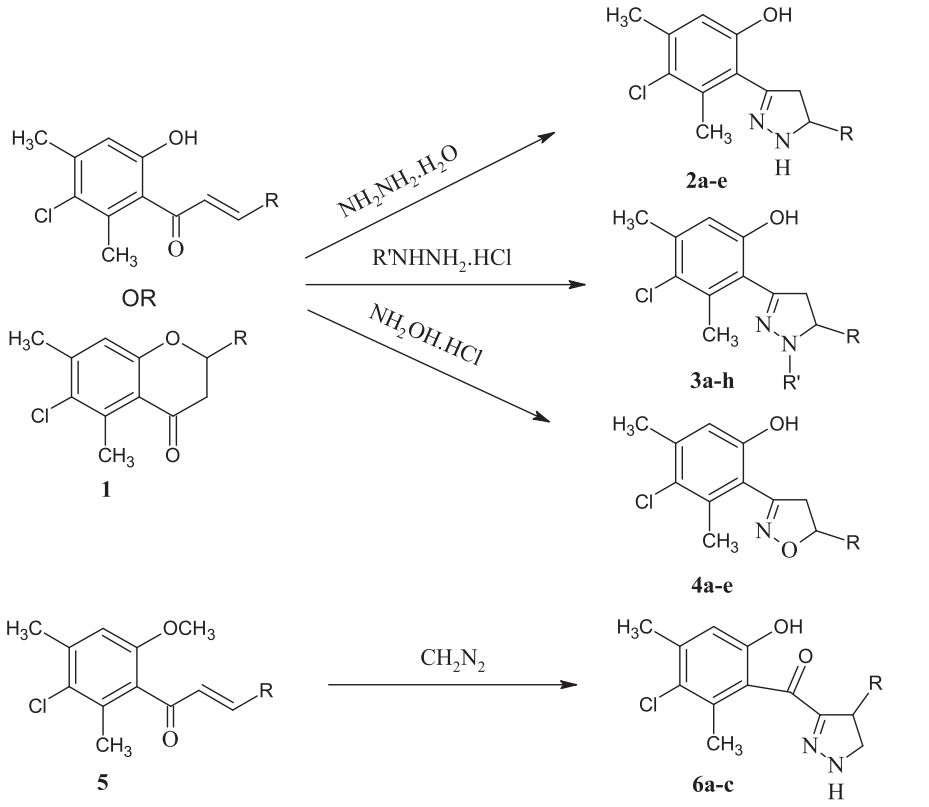
Keeping in view the therapeutic importance of heterocyclic compounds and in continuation of our work on synthesis of biologically active heterocycles [10–12] we hereby report the synthesis, molecular docking and biological studies of pyrazolines and isoxazolines derivatives. The new substituted pyrazolines and isoxazolines in addition to eight previously reported pyrazolines bearing benzenesulfonamide moiety [11] were screened for their antibacterial and antifungal activities. Our group has earlier reported the anti-inflammatory and anti-cancer profile of pyrazolines bearing benzenesulfonamide moiety [11]. The molecular docking study of all the compounds has been done for the better understanding of the drug-receptor interaction.

## 2. Chemistry

The reactions involved in the synthesis of title compounds are given in Scheme 1. The chalcones/flavanones were prepared by reacting acetophenone with appropriate aldehydes in the presence of a base by conventional reactions. Five novel 3,5-diaryl-2-pyrazoline (**2a**–**e**) as well as five 3,5-diaryl-2-isoxazoline (**4a**–**e**) were synthesized by the condensation of chalcones/flavanones with hydrazine hydrate and hydroxylamine hydrochloride respectively. Three novel 3-aroyl-4-aryl-2-pyrazolines **6a**–**c** were synthesized by treatment of appropriate chalcones with freshly prepared diazomethane gas dissolved in ether at 0 °C. Reaction between synthesized chalcones/flavanones and 4-hydrazinobenzenesulfonamide hydrochloride in ethanol led to synthesis of pyrazolines bearing sulphonamide moiety (**3a**–**h**) as reported earlier [11]. All the synthesized compounds were characterized by IR, $^{1}$H NMR, $^{13}$C NMR, mass and elemental analysis.

## 3. Results and discussion

The IR spectra of all the compounds showed absorption bands in the regions 1517–1614 cm$^{-1}$ corresponding to C=N stretching because of ring closure. The infrared spectra of (**6a**–**c**) also revealed CO band at 1642–1600 cm$^{-1}$. In the $^{1}$H NMR spectra of all compounds the three hydrogen atoms attached to the C-4 and C-5 carbon atoms of the heterocyclic ring gave an ABX spin system. The pyrazoline/isoxazoline structures were unambigously proved by the measured chemical shifts. In compounds (**2a**–**e**) and (**4a**–**e**), H-4 (*trans*) and H-4 (*cis*) appeared as double doublets and H-5 either appeared as multiplets or double doublets. In **4a** and **4e** the peak for H-4 (*cis*) of pyrazolines could not be picked out because of its merger with solvent peak. In compounds (**6a**-**c**) H-5 (*cis*) appeared as multiplets and H-4 appeared either as multiplets or double doublets. The peak for H-5 (*trans*) could not be identified because of merging with solvent peak. The methyl and aromatic protons were observed at expected ppm. All structures were further supported by $^{13}$C NMR spectra which showed the chemical shift values of




R = Phenyl, 2-Methoxyphenyl, 4-Methoxyphenyl, 2-Chlorophenyl, 4-Chlorophenyl, 2-Hydrohyphenyl, 3-Hydrohyphenyl, 2-Nitrohyphenyl, 3,4-Dimethoxyphenyl, 3,4,5-Trimethoxyphenyl

R' = p-Sulfamylphenyl

**Scheme 1.** Synthesis of pyrazolines and isoxazolines derivatives.