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Original article

The synthesis and activities of novel mononuclear or dinuclear cyclen complexes bearing azole pendants as antibacterial and antifungal agents

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ABSTRACT

A series of novel compounds containing 1,4,7,10-tetraazacyclododecane and azoles were synthesized and characterized by ^{1}H NMR, MS and elemental analysis. Bioactive assay manifested that some target compounds, such as **11a**, **11b** and **11d**, displayed good and broad spectrum antimicrobial activities with relative low MIC values against most of tested strains. These dinuclear complexes gave comparable or even better antimicrobial efficiencies than the reference drugs *Fluconazole* and *Chloromycin*. The result showed that the metal ions were the key factors to enhance the antimicrobial activities for mononuclear or dinuclear complexed in varying degrees. The interaction evaluation of compound **11b** with bovine serum albumin (BSA) as an example was tested by fluorescence method. The thermodynamic parameters indicated that the hydrogen bonds and van der waals forces played the major roles in the strong association between dinuclear compound and BSA. The CCK-8 tests also confirmed the safeties of these dinuclear compounds *in vitro*.

1. Introduction

The increasing emergence of pathogenic bacterial strains and concerns about multidrug-resistance, especially the explosion of New Delhi metallo-β-lactamase 1 (NDM-1) superbugs very recently, had made most of the first-line clinical antibiotics ineffective [1]. This situation has stimulated an urgent need to develop more effective antimicrobial agents with novel chemical structures which are helpful for overcoming drug-resistance and improving the antimicrobial potency.

As we know, heterocyclic compounds such as imidazole, benzimidazole, pyrazole and triazole have been frequently found to display a variety of biological activities such as antihelmintic [2], antihistaminic [3], anticancer [4], antiviral [5], antiinflammatory [6], antiproliferative [7], antioxidant [8], anticoagulant properties [9], antitubercular [10], anticonvulsant [11]. Particularly, many benzimidazole drugs like antiparasitic thiabendazole, mebendazole, albendazole, antihistaminic norastemizole and mizolastine, as well as antihypertensive telmisartan etc. have been successfully developed and extensively used in clinic. This has attracted increasing interest to investigate the possible applications of azole-based derivatives in medicinal aspects. What's more important is that numerous azole supermolecules as chemical drugs are under actively ongoing researches and developments, and have shown enormous potential [12]. It is undoubted that this research area will become a new direction for the exploitation of azole complex as antimicrobial drugs [13], and azole derivatives coordinating with metal cation to form complexes always showed enhanced antimicrobial properties [14]. Besides these azole derivatives, macrocyclic compounds are already extensively exploited for their medical applications as MRI agents [15], antibacterial and anticancer agents [16]. As a well-known macrocyclic polyamine, 1,4,7,10-tetraazacyclododecane (cyclen) has been widely studied for its strong coordination ability towards a wide range of cations, and the safeties of some macrocyclic compounds used *in vivo* have been confirmed. Recently, the increasing prevalence strategy to develope new classes of antimicrobial agents with novel mechanism of

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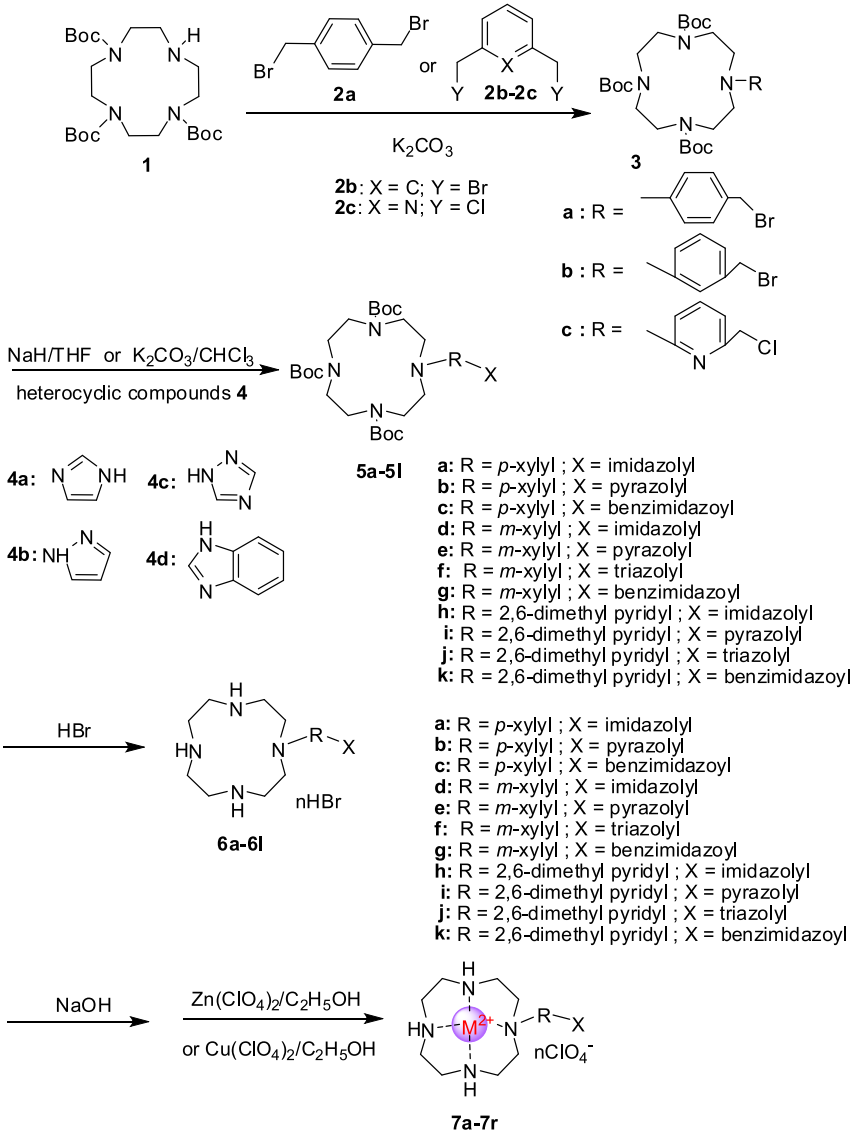
action was to employ combination of two different active fragments into one molecule [17]. So that, in view of above observation, it is reasonable for us with great interest to prepare cyclen complexes having azoles pendants, and to evaluate their antibacterial and antifungal behaviours. Herein a series of novel compounds were prepared for the first time (Schemes 1 and 2). Their antibacterial and antifungal activities were evaluated, and the structure–activity relationships were also investigated.

Serum albumins as the most important and abundant macromolecule proteins in the circulatory system have received much attention for that they could deliver drugs or other bioactive small molecules to the binding sites [18]. A thorough binding analysis between drugs or bioactive small molecules and serum albumin may beneficially provide useful information for the absorption, transportation, distribution, metabolism and excretion properties of drugs. It might also be significant for design, modification and screening of drug molecules. So that there were many important reasons for us to further investigate the interaction behaviour between the highly active compound and bovine serum albumin (BSA) which was used as study model to preliminarily evaluate their transportation and pharmacokinetic properties by fluorescence spectroscopy on molecular level. Further more, the safety or toxicity of those dinuclear complexes were tested by CCK-8 method.



a: R = *p*-xylyl ; X = imidazolyl ; M = Zn; n = 2;
b: R = *p*-xylyl ; X = imidazolyl ; M = Cu; n = 2;
c: R = *p*-xylyl ; X = pyrazolyl ; M = Zn ; n = 2;
d: R = *p*-xylyl ; X = benzimidazoyl ; M = Zn; n = 3;
e: R = *p*-xylyl ; X = benzimidazoyl ; M = Cu; n = 2;
f: R = *m*-xylyl ; X = imidazolyl ; M = Zn; n = 2;
g: R = *m*-xylyl ; X = imidazolyl ; M = Cu; n = 2;
h: R = *m*-xylyl ; X = pyrazolyl ; M = Zn; n = 4;
i: R = *m*-xylyl ; X = pyrazolyl ; M = Cu; n = 2;
j: R = *m*-xylyl ; X = triazolyl ; M = Zn; n = 2;
k: R = *m*-xylyl ; X = benzimidazoyl ; M = Zn; n = 2;
l: R = *m*-xylyl ; X = benzimidazoyl ; M = Cu; n = 2;
m: R = 2,6-dimethyl pyridyl ; X = imidazolyl ; M = Zn; n = 2;
n: R = 2,6-dimethyl pyridyl ; X = pyrazolyl ; M = Zn; n = 2;
o: R = 2,6-dimethyl pyridyl ; X = triazolyl ; M = Zn; n = 3;
p: R = 2,6-dimethyl pyridyl ; X = triazolyl ; M = Cu; n = 3;
q: R = 2,6-dimethyl pyridyl ; X = benzimidazoyl ; M = Zn; n = 3;
r: R = 2,6-dimethyl pyridyl ; X = benzimidazoyl ; M = Cu; n = 3;

Scheme 1. Synthetic route of target compounds **7a**–**r**.