AZINE DERIVATIVES WITH ANTIMICROBIAL PROPERTIES

DERIVAȚI AZINEI CU PROPRIETĂȚI ANTIMICROBIENE

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Summary. *Azine derivatives, especially pyridine, quinoline and their fused derivatives, are invaluable scaffolds in medicinal chemistry having a large variety of biological activities, antimicrobials including. In this work we present some recent results that we obtained in the field of azine with antibacterial, antifungal and antituberculosis activity. Some of the obtained results are very promising, the antimicrobial activity of some azine derivatives being spectacular.*
Keywords. *azine; antibacterial; antifungal; fused derivatives*

INTRODUCTION

Azine derivatives are six member ring azaheterocycles with one nitrogen atoms, the most representative compounds being pyridine, quinoline and their fused derivatives. Azine heterocycles are invaluable scaffolds in medicinal chemistry, being reported to have many biological and pharmacological activities such as antibacterial, antifungal, antituberculosis, antiviral, anti-inflammatory, anticancer, antihypertensive, anticonvulsant, analgesic, antihistaminic, antiulcer, etc. [1-5]. On the other hand, infectious diseases caused by microorganisms represent nowadays a major threat to human health and society, especially because of the abuse and misuse of antimicrobial drugs which conduct to emergence of drug resistance, multi-drug resistance and extensively-drug-resistance phenomena. As a result, obtaining of new drugs with antimicrobial properties remains a very challenging and important task in medicinal chemistry.

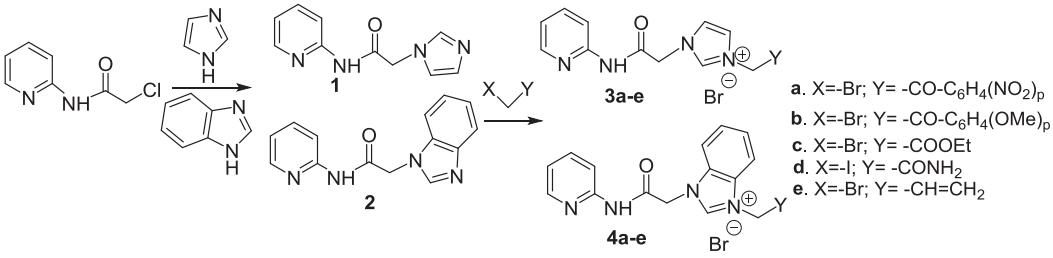
In continuation of our concern in the field of six member ring azaheterocycles with antimicrobial activity, we will present to the conference some selective core results of obtained by our group in the last five years related to antimicrobial activity of some pyridine, quinoline and their fused derivatives.

MATERIAL AND METHOD

Reagents and solvents were purchased from TCI and Sigma Aldrich. The NMR spectra were acquired with a Bruker Avance III 500 MHz spectrometer operating at 500 MHz for 1H and 125 MHz for 13C. Infrared (IR) data were obtained using a FT-IR VERTEX 70 Bruker spectrophotometer (ATR module). The X-ray structures of the compounds were analyzed by X-ray diffraction on single-crystals, by using a Rigaku Supernova dual Cu/Mo micro-focused source diffractometer. Ultrasound assisted reactions were accomplished using Sonics (Sonics VCX-130, USA), with a nominal power of 130W and a frequency of 20 kHz. General procedures to obtain the desired compounds were previously described in the literature by us [6-11].

RESULTS AND DISCUSSIONS

In order to achieve our goal, we synthesized and tested for their antimicrobial several classes of hybrid azine derivatives. Thus, Diaconu, Mantu et al. [6,7] synthesized a library of pyridine mono-salts with imidazole (**3a-e**) and benzimidazole (**4a-e**) moiety following the reaction scheme described bellow: an N-alkylation reaction of the -NH- amino group from imidazole or benzimidazole heterocycle is followed by a quaternization reaction of the second N-imidazole atom (with activated halogenated compounds), Scheme 1.

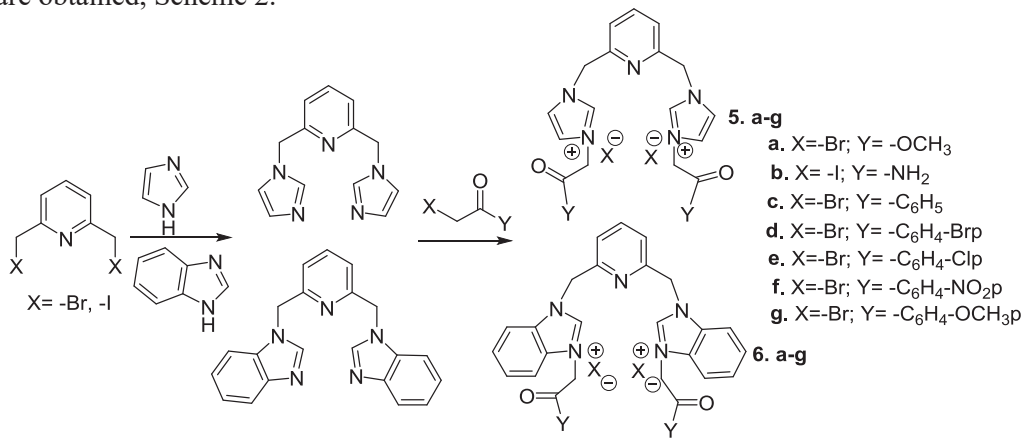


Scheme 1. Reaction pathway to obtain the pyridine mono-salts **3a-e** and **4a-e**.

The obtained compounds were tested for their antimicrobial activity against germs *Staphylococcus aureus* and *Escherichia coli*, fungus *Candida albicans* and for their antituberculosis activities against *Mycobacterium tuberculosis H37Rv* under aerobic conditions. The pyridine imidazole mono-salts **3a,b** and pyridine benzimidazole mono-salts **4a,b** manifest promising antibacterial properties, one compound (the pyridine benzimidazole salt **4a**) having a powerful antibacterial activity against *S. aureus* and *E. coli* (with

a diameter of inhibition zone (DIZ) of 30 mm), superior to control drug *Gentamicin* (DIZ = 18 mm). The antimycobacterial assay reveals that our hybrids have a modest activity against *Mtb* strains.

Antoci et al. [8] obtained a new class of pyridine bis-salts with imidazole and benzimidazole skeleton and studied their antituberculosis activity. The reaction pathway was direct and efficient, involving an N-alkylation reaction of the -NH- amino group from imidazole / benzimidazole heterocycle, followed by a quaternization reaction of N-imidazole atom (with activated halogenated compounds), when the corresponding pyridine - bis(imidazole) salts **5a-g** respectively pyridine - bis(benzimidazole) **6a-g** salts, are obtained, Scheme 2.

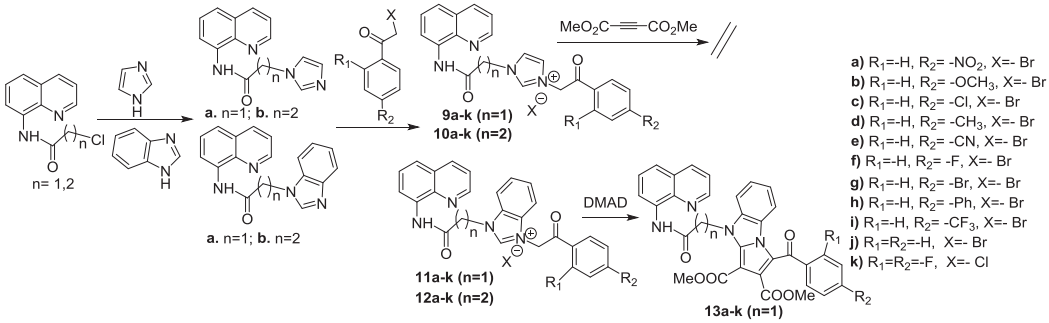


Scheme 2. Reaction pathway to obtain the pyridine - bis(imidazole) and pyridine - bis(benzimidazole)- salts **5a-g** and **6a-g.**

The obtained compounds were tested in a primary screening for their antituberculosis activities against *Mycobacterium tuberculosis H37Rv* under aerobic conditions, some compounds (**5e,f** and **6c,e,f,g**) having an excellent antituberculosis activity, with a Minimum Inhibitory Concentration (MIC) in the range of 17-92 μM. The most active compounds (namely **5f**, **6c** and **6f)** were subjected to the secondary antituberculosis assay. The obtained results of second stage assay show that our pyridine - bis(imidazole) and pyridine - bis(benzimidazole)- salts exhibited an excellent activity against both replicating and non-replicating *Mtb* (superior to control *Metronidazole*), have an excellent intracellular activity, are very active against drug-resistant *Mtb* strains, have no cytotoxicity and, very important, have a bactericidal mechanism of action. These results together with those one of the ADMET pharmacokinetic studies (low clearance rate, a great half-time in vivo, a low potential for drug–drug interactions with a high duration of action and lack of cytotoxicity), reveal that compound **6f** is a suitable candidate for a future drug.

Diaconu et al. [9] synthesized and tested for their antimicrobial properties three new class of quinoline derivatives: quinoline salts with imidazole skeleton (**9a-k**, **10a-k**),

quinoline salts with benzimidazole skeleton (**11a-k**, **12a-k**) and quinoline with pyrrolo-benzimidazole skeleton (**13a-k**). The reaction pathway to obtain the quinoline compounds was straight and efficient, involving an N-alkylation reaction of the -NH- amino group from imidazole / benzimidazole moiety, followed by a quaternization reaction of the second N-imidazole atom and, finally, a Huisgen 3+2 dipolar cycloaddition of imidazolium and benzimidazolium ylides (generated in situ from the corresponding salts) with dimethyl acetylenedicarboxylate (DMAD), Scheme 3.

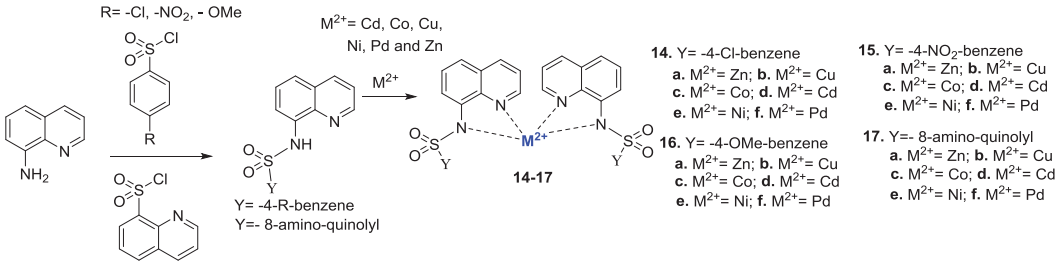


Scheme 3. Reaction pathway to obtain quinoline salts with imidazole skeleton (**9a-k**, **10a-k**), quinoline salts with benzimidazole skeleton (**11a-k**, **12a-k**) and quinoline with pyrrolo-benzimidazole skeleton (**13a-k**).

The obtained quinolione derivatives **9-13** were tested for their antimicrobial activity against germs *Staphylococcus aureus* and *Escherichia coli*, and fungus *Candida albicans*. Some of the quinolione derivatives **9-13** manifest promising antimicrobial properties as follow:

- the quinoline salts with benzimidazole skeleton (**11a-k**, **12a-k**) are very active compounds active in the range of nano-molar, five compounds (namely 12c, 12d, 12f, 12h, 11h) having an excellent activity against Gram-negative bacteria *E. coli* (DIZ = 20-24 mm), superior to control gentamicin (DIZ = 12 mm); the others compounds are moderate to active;
- one compound (the quinoline salts with imidazole skeleton **10i**) have an excellent activity against Gram-positive bacteria *S. aureus* (DIZ = 20 mm), superior to control gentamicin (DIZ = 14 mm); the others compounds are moderate to active;
- the fused quinoline with pyrrolo-benzimidazole skeleton (**13a-k**) are moderate to active against the tested bacterial strains;
- all compounds have moderate to week antifungal activity.

Diaconu et al. [10,11] obtained a new class of quinoline-sulfonamide complexes **14-17** and studied their antimicrobial activity. The reaction pathway was straight and efficient, involving an N-acylation reaction of 8-aminoquinoline followed by complexation with different M^{2+} metals: Cd^{2+}, Co^{2+}, Cu^{2+}, Ni^{2+}, Pd^{2+} and Zn^{2+}, Scheme 4.



Scheme 4. Reaction pathway to obtain quinoline-sulfonamide complexes **14-17**.

These reactions were performed both by conventional thermal heating (TH) and ultrasound (US) irradiations. Comparative with conventional TH under US irradiations the reactions became environmentally friendly, having some certain advantages: higher yields, lower reaction time (with about 150 folds for complexation), a decrease of the amount of used solvents.

The synthesized quinoline-sulfonamide complexes **14-17** were evaluated for their antimicrobial activity, some of them having a very good antibacterial (*Staphylococcus aureus*, *Escherichia coli*) and antifungal (*Candida albicans*) activity. The most active compound have proved to be the hybrid N-(quinolin-8-yl)-4-chloro-benzenesulfonamide cadmium **14d**, with a DIZ of 21 mm and a MIC of 19.04×10^{-5} μg/mL against *S. aureus*, respectively a DIZ of 19 mm and a MIC of 609×10^{-5} μg/mL against *E. coli*. The quinoline cadmium complex **14d** have also an excellent antifungal activity against fungus *C. albicans*, with a DIZ of 25 mm and a MIC of 19.04×10^{-5} μg/mL.

CONCLUSIONS

In conclusion we present herein a thoroughly study concerning synthesis and antimicrobial activity of some pyridine, quinoline and fused azine derivatives. The synthesis were straight and efficient, being realized usually under both conventional thermal heating (TH) and ultrasound irradiations. The antibacterial, antifungal and antituberculosis activity was determined, some of the compounds having an excellent activity and, so far, being suitable candidate for a future drug.

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