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Original article

Antimicrobial activity of imidazo[1,5-*a*]quinoxaline derivatives with pyridinium moiety☆

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ABSTRACT

3-Phenyl(methyl)-5-alkyl-1-(pyridin-3-yl)imidazo[1,5-*a*]quinoxalin-4-ones (**2a**–**f**) and their *N*-alkylpyridinium salts (**3a**–**o**), including 1,*n*-bis{3-(3-phenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-on-1-yl)pyridinium}alkane dibromides (**4a**–**d**, **5**, **6**) have been synthesized. It has been established that the antimicrobial properties of imidazo[1,5-*a*]quinoxaline derivatives are connected with the presence of various alkyl substituents in the position 1 of the pyridine ring and in the position 5 of the imidazo[1,5-*a*]quinoxaline system. Chlorides and iodides are more active towards bacteria than fungi. Compounds **3d**, **3e**, **3m** and **3n** showed an effective bacteriostatic activity. Compound showed not only well defined bacteriostatic activities but also good fungistatic activities, with the MIC values comparable with the reference drugs.

Toxicity of more effective (imidazo[1,5-*a*]quinoxalin-4-on-1-yl)-1-pyridinium halides was examined in mice.

1. Introduction

Heterocyclic systems containing quinoxaline moiety exhibit important biological activities. Many of them possess anticancer [1,2], antiviral [3], antibacterial [4], antiinflammatory [5] properties and serve as inhibitor of enzymes by catalyzing the transport of the phosphate group from ATP (kinase inhibitor) [6]. Quinoxalines are used as antibiotics [7,8], DNA-binding agents [9], building blocks in the synthesis of anion receptors [10], etc. Imidazoquinoxaline is one of the important classes of heterocycles that are often found in biologically active and pharmacologically useful agents such as Dazoquinast (antiallergic), FG 10571, NNC 14-0571, Panadiplon, U-78875 anxiolytic (benzodiazepine receptor partial agonist), U-8044 (antidepressant, anxiolytic), U-97775 (anxiolytic ($GABA_A$ receptor ligand)) and LU 73068 (anticonvulsant glycine/NMDA) but not in the NMDA receptor antagonist (Fig. 1) [11].

Some of the derivatives of imidazoquinoxalines are used in the treatment of central nervous system ailments [12,13] such as anticonvulsant, anxiolytic, hypnotic, and sedative/hypnotic properties [13–15]. Imidazoquinoxalines are proved to be useful as GABAa receptor ligands or prodrugs and selective GABA agonists, antagonists or inverse agonists of GABA receptors [16–20]. They are also used for the treatment of anxiety, sleep disorders, seizure disorders or for memory enhancement [20]. Many of these compounds contain substituents in various positions of 1,2,4-oxadiazol-3-yl [3,8,9,11,12,15], 1,2,4-oxadiazol-5-yl [14], 1,2-oxazol-3-yl [13], 2-oxazol-5-yl [13], imidazol-1-yl [21–23], pyrrolidin-1-yl [15,23] and morpholin-4-yl [21,23] moieties. This affects the manifestation of one or the other kind of properties. There is only one patent with the imidazo[1,5-*a*]quinoxaline derivatives containing a pyridinyl moiety in their structure as useful in treatment of central nervous system diseases such as psychosis and also in treatment of obesity, type 2 diabetes, metabolic syndrome, glucose intolerance, and pain [24].

The introduction of a pyridyl moiety with the free nitrogen atom into imidazoquinoxalines is assumed to greatly enhance their possibilities in synthesis and also in searching for physiologically active compounds. We assumed that due to the additional binding with the biotarget the efficiency of a specific moiety connected with imidazo[1,5-*a*]quinoxaline and pyridyl units would dramatically increase. The latter can be caused by the more rigid framework of the bis-heterocyclic systems with two quaternized nitrogen atoms in comparison with their mono counterparts. The bis-heterocyclic system involves complementary with the biotarget,

☆ Dedicated to the 75th anniversary of Professor Vladimir Savich Reznik.

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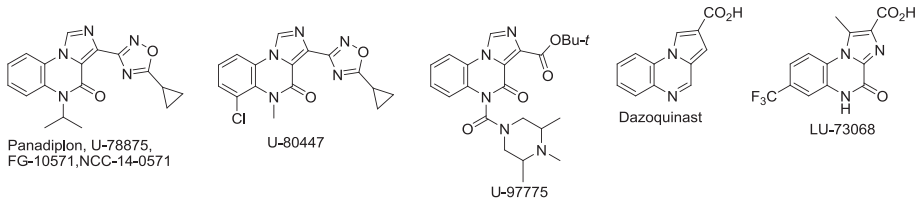


Fig. 1. Some quinoxaline derivatives of pharmacolical interest.

particularly with the bis-heterocyclic systems with two pyridyl moieties and can exhibit activity due to the macrocyclic framework as a specific target.

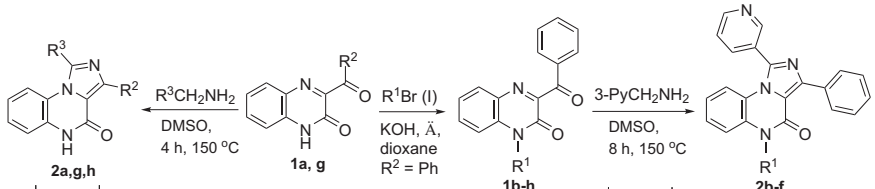
To our knowledge, in spite of advances in imidazo[1,5-*a*]quinoxalines chemistry, the biological activity for these compounds have so far not been investigated. The possible explanation might be due to the insolubility of almost all the known imidazo[1,5-*a*] quinoxalines in water, which prevents testing their biological properties. A wide screening of various kinds of biological activity is possible for imidazoquinoxalines of this type.

It is known that quaternary ammonium salts in combination with lipophilic residues display nonspecific activity through interaction with cell walls and cell membranes of microorganisms. The use of organic cations as disinfectants in agriculture, food processing industry and clinics is particularly important because they possess a high antibacterial activity and a broad spectrum of antimicrobial activity. Taking into account of the above points and considering the imidazoquinoxaline framework as a specific target to interfere with the main biochemical pathways (cell wall synthesis, DNA and RNA synthesis, protein formation) we have prepared a series of 1-(pyridin-3-yl)imidazo[1,5-*a*]quinoxalin-4-ones, and quaternized them by benzyl and alkyl halides. This preliminary communication demonstrates the *in vitro* antibacterial and antifungal activities of the imidazo[1,5-*a*]quinoxalinones and their toxicity, which have so far not been studied. We have also synthesized and tested a new type of imidazo[1,5-*a*]quinoxalinaphane with two 1-(pyridin-3-yl)imidazo[1,5-*a*]quinoxalin-4-one units and two spacers. One of them is the decamethylene fragment which connects the N4 and N4′ of the carbamoyl function of pyrazinone ring systems, and another one is the *m*-xylylene fragment which connects N and N′ of the pyrimidine rings. Besides, we tested the 1-(pyridin-3-yl)imidazo[1,5-*a*]quinoxalin-4-ones with the structural features of the examined bis-compounds and imidazo [1,5-*a*]quinoxalinaphane. The imidazo[1,5-*a*]quinoxalin-4-ones are subjected to screening in an attempt to determine the units responsible for antimicrobial activity and to evaluate the importance of ring-closure for efficiency. The objective of our study is to generate novel bioactive compounds and to optimize the structure to display the potency. As new infectious diseases appear time to time, it has become especially important to search for absolutely new agents for their remedy.

2. Chemistry

We have recently reported the synthesis of imidazo[1,5-*a*] quinoxalines by the reaction of 3-aroylquinoxalin-2(1*H*)-ones and their *N*-alkyl analogues with benzylamines in DMSO. The reaction proceeds through an intermediate formation of *N*-(α-quinoxalinylbenzylydene)benzylamine, which when subjected to oxidative cyclocondensation gives imidazo[1,5-*a*]quinoxalines [25]. The same synthetic protocol was used for the preparation of pyridyl containing imidazo[1,5-*a*]quinoxalin-4-ones. The use of 3-acylquinoxalin-2(1*H*)-ones **1a**, **g** and *N*-alkyl derivatives **1b**–**h**, and aminomethylpyridines make it possible to develop fundamentally new methods of imidazoannulation and lead to 1-pyridylimidazo[1,5-*a*]quinoxalin-4(5*H*)-ones **2g**, **h** and their *N*-alkylated derivatives **2b**–**f** (Scheme 1). The 1-pyridylimidazo[1,5-*a*]quinoxalin-4(5*H*)-ones **2a**, **g**, **h** were synthesised from ketones **1a**, **b**, **g** and picolylamines under heating conditions in DMSO in good yields [25]. In the cases of **c**–**f** a modified procedure involving alkylation of compound **1a** with alkylbromide was used with subsequent imidazoannulation of the crude *N*-bromalkyl derivatives **1b**–**f** with the 3-picolylamine. The products **2b**–**f** were readily isolated in pure form by filtration and the overall yield of the two-stage process **1a** → **1b**–**f** → **2b**–**f** is 44–57% (Scheme 1).

The reaction of 1-(pyridin-3-yl)imidazo[1,5-*a*]quinoxalin-4(5*H*)-ones with various types of alkyl halides gave rise to water-soluble derivatives **3**, **4**, **6** with a quaternized nitrogen atom in the pyridine ring system. Reaction conditions were optimised to obtain compounds **4** in which they were precipitated in their pure form from the reaction mixture. The synthesis of compounds **4a**, **b**, containing the NH group, were carried out in DMF, whereas synthesis of compounds **4c**, **d** with *N*-alkylated fragment in acetonitrile (Table 1).



2	R^2	R^3
a	Ph	3-Py
g	Me	3-Py
h	Ph	2-Py

1, 2	R^1	Yield[b],
b	Me	76 (65)[a]
c	Pr	51 (32)[a]
d	C_6H_{13}	57 (42)[a]
e	C_9H_{19}	51 (35)[a]
f	$C_{18}H_{37}$	44 (30)[a]

[a] drop out of the reaction mixture in analytically pure form
[b] in case **c-f** for 2 steps (alkylation and annulation)

Scheme 1. The synthesis of imidazo[1,5-*a*]quinoxalin-4-ones **2a**–**h**.