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Original article

Synthesis and antiproliferative evaluation of some new amidino-substituted bis-benzothiazolyl-pyridines and pyrazine

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ABSTRACT

Novel diamidino substituted conformationally restricted derivatives of bis-benzothiazolyl-pyridines and pyrazine were synthesized and their antiproliferative activity against several human cancer cell lines were determinated. The synthetic approach used for preparation of isomeric amidinobenzotiazolyl disubstituted pyridines **3a**–**3k** and pyrazine **3l** was achieved by condenzation reaction of commercially available pyridine and pyrazine dicarboxylic acids with amidino- **2a** and 2-imidazolinyl-substituted 2-aminothiophenol **2b** in polyphosphoric acid in moderate to good yield. The condenzation reaction was greatly optimized. The targeted compounds were converted in the desired water soluble dihydrochloride salts by reaction of appropriate free base with concd HCl in ethanol or acetic acid. Antiproliferative assays revealed significant differences in antiproliferative activities of diamidino- and diimidazolinyl-derivatives, the latter exerting stronger concentration-dependent antiproliferative effects on tested tumor cell lines and thus being a prominent compound class for further chemical optimization and biological studies. Biological studies on SW620 cell line and BJ fibroblasts performed for the diimidazolinyl-derivative **3b** revealed oxidative stress as a possible mechanism of antiproliferative action and predicted antineoplastic properties for this class of compounds.

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1. Introduction

Heterocyclic compounds from the series of benzothiazoles have been investigated due to their biological and pharmacological activity. These compounds have interesting biological properties including antiallergic [1], anti-inflammatory [1,2], antitumor [3–7] and analgesic [8,9] activities. Considering their mechanism of action as antitumor agents, it was shown that benzothiazole derivatives act as tyrosine kinase [10–13] and topoisomerase I and II inhibitors [14,15]. Therefore, various benzothiazole compounds are considerably interesting due to their potential for diverse pharmaceutical uses.

Although a variety of novel benzothiazole derivatives with antitumor activity were described so far, these are structurally different from compounds presented in this paper [16–18]. A group however, of similar compounds has been reported in the recent literature and describes the synthesis and cytotoxic evaluation of thiourea and *N*-bis-benzothiazole derivatives. This novel class of cytotoxic benzothiazolyl thiocarbamides has been achieved using a catalytic amount of 4-dimethylaminopyridine (DMAP) followed by its chemoselective oxidative cyclization with 1,3-di-*n*-butylimidazolium tribromide [bbim][Br_3] to afford the *N*-bis-benzothiazole derivatives. Synthesized compounds had significant antiproliferative activity on human monocytic cell lines U 937 and a mouse melanoma cell line B16-F10 cells [19].

Our previously published data showed accentuated antiproliferative effects for this class of compounds as well. We found that antiproliferative activity of amidino [20,21] and amino [22] substituted 2-phenylbenzothiazole derivatives strongly depends on the position of the substituent on 2-phenylbenzothiazole skeleton, as well as on the type of attached amidino substituent. We found that, in a series of unsubstituted, *N*-isopropyl substituted, as

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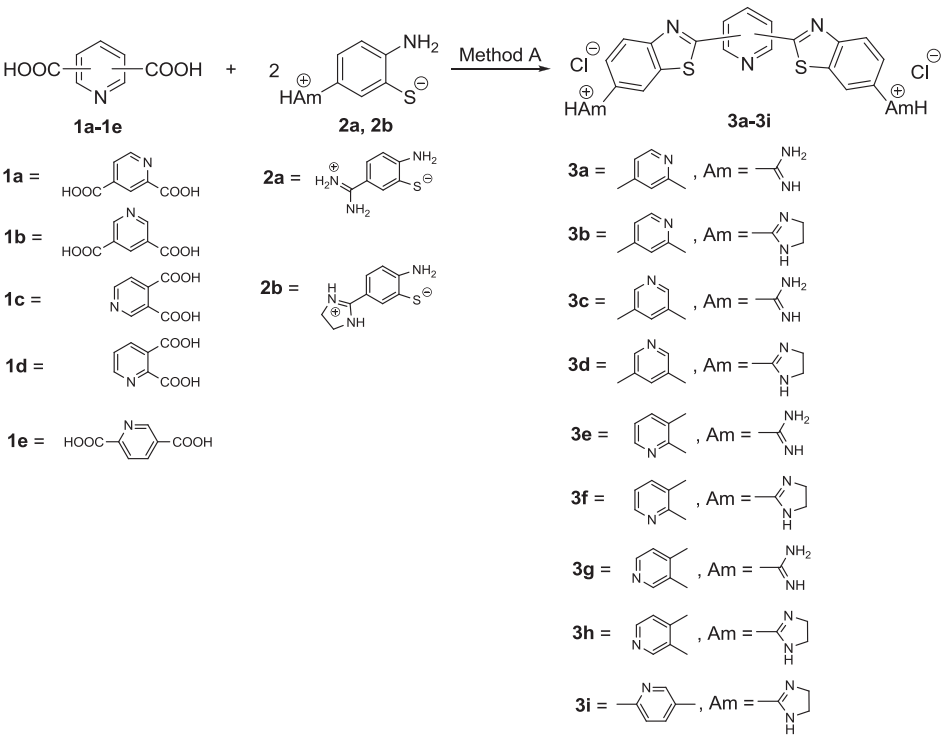


Method A 1.) PPA 120-140°C, 1h then 160-180°C, 2h; 2.) 2M NaOH; 3.) CH_3COOH/HCl or EtOH/HCl

Scheme 1.

well as 2-imidazolinyl mono- and bis-amidino derivatives of 2-phenylbenzothiazole, *N*-isopropyl substituted amidine possess less pronounced antiproliferative activity on tested tumor cell lines.

In relation with the above considerations, we designed and efficiently synthesized new diamidino-, diisopropylamidino- and diimidazolinyl-substituted derivatives of phenyl-benzothiazolyl- and bisbenzothiazolyl-furans and -thiophenes and evaluated their antiproliferative activity on tumor cell lines *in vitro*, DNA binding propensity and sequence-selectivity as well as cellular distribution. In addition, two compounds were chosen according to their differential effect for further biological studies including the cell cycle analysis and apoptosis induction in order to reveal a more detailed picture on the possible antiproliferative mechanisms and/or targets [23]. On the other hand, novel amidino substituted conformationally restricted derivatives of pentamidine were synthesized and their antiproliferative activity against several human cancer cell lines has been determined. It was found that introduction of furan-2,5-dicarboxamide core moiety increases antiproliferative activity as well as selectivity against certain tumor cell lines in comparison with amidino-substituted furan-mono-carboxamide. Unlike the furan series where isopropyl substituted amidine exhibits more potent overall antiproliferative activity and selectivity toward certain cell lines, the same was found for unsubstituted amidines in pyridine series [24].

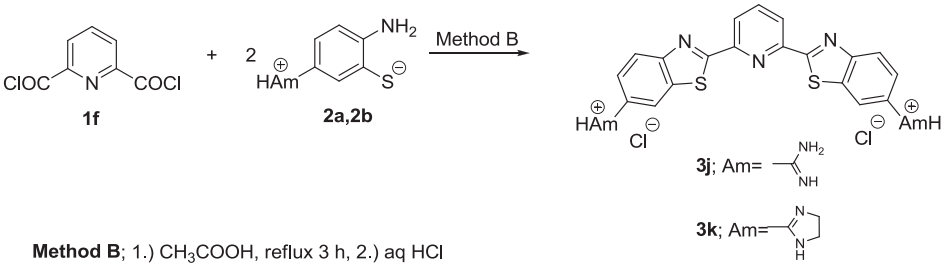
As a continuation of these previous studies, we present the synthesis and biological evaluation of newly synthesized amidino substituted conformationally restricted derivatives of bisbenzothiazolyl-pyridines and pyrimidine.

2. Results and discussion

2.1. Chemistry

The synthetic approach used to prepare isomeric amidinobenzotiazolyl disubstituted pyridines **3a**–**3k** is outlined in Schemes 1 and 2.

Recently, we found a convenient and efficient method for the synthesis of amidino substituted benzothiazolyl compounds by condensation reaction of carboxylic acids or acyl chlorides and



Method B; 1.) CH_3COOH, reflux 3 h, 2.) aq HCl

Scheme 2.

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