Antibacterial and antiproliferative activity of novel 2-benzimidazolyl and 2-benzothiazolyl substitued benzo[*b*]thieno-2-carboxamides

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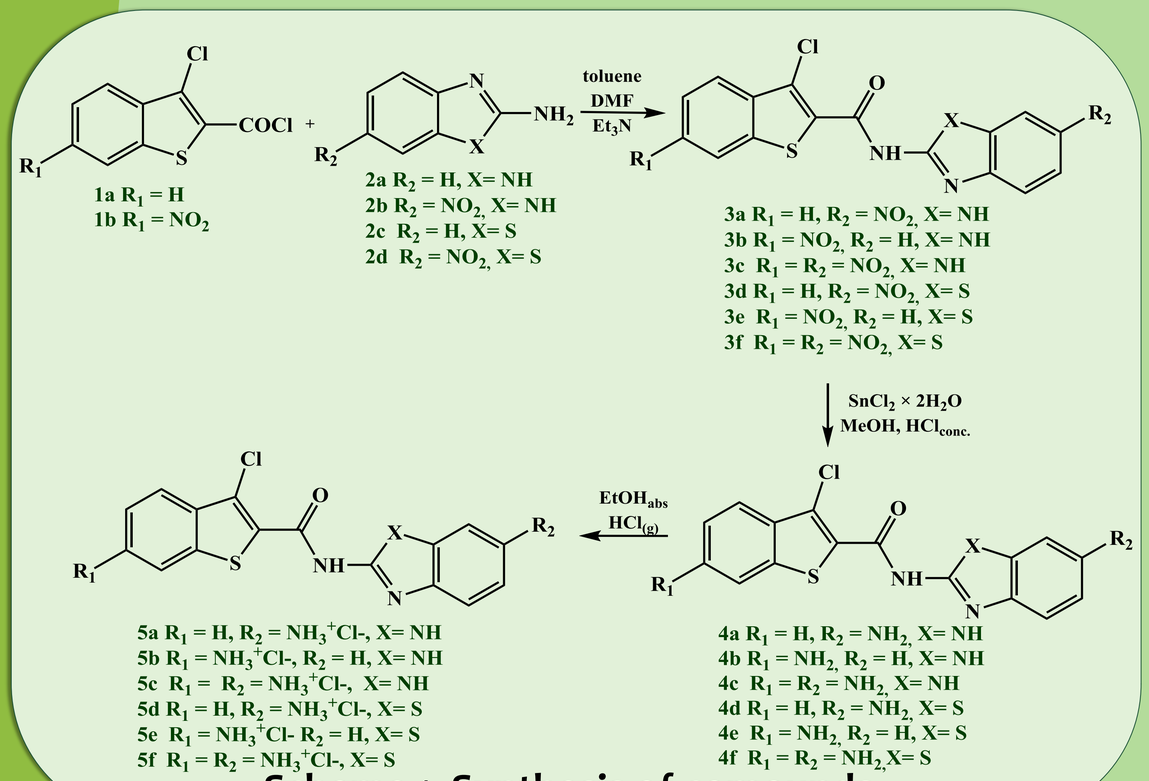
Small heteroaromatic molecules, like nitrogen and sulphur-containing heterocycles play an extremely important role in medicinal chemistry due to variety of their possible chemical, pharmacological and industrial applications. Benzimidazoles and benzothiazoles are one of the privileged sub-structures and an important bioactive heterocyclic building block in medicinal chemistry, while benzothiophene skeleton is incorporated in the structure of numerous therapeutic agents. Herein, we present the synthesis and biological evaluation of novel nitro and amino substituted 2-benzimidazolyl and 2-benzothiazolyl benzo[*b*]thieno-2-carboxamides synthesized according to the Scheme 1.



Scheme 1. Synthesis of comounds

Additionally, the tested compounds not displaying promising antibacterial activity were further tested for the antiproliferative activity *in vitro* against three human cancer cell lines. The most pronounced and selective antiproliferative activity against MCF-7 cell line was demonstrated by amino substituted hydrochloride salt of benzothiazole derivative with an IC_{50} of 0.04 μM.

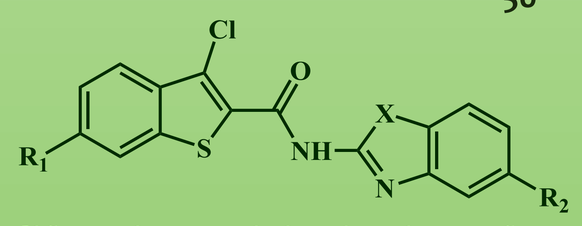


Table 2. Antiproliferative activity *in vitro* of tested comounds

Comp	R_1	R_2	X	IC_{50}[a] (μM)		
				HCT116	MCF-7	H460
3a	H	NO_2	NH	>10	4±0.8	>10
3b	NO_2	H	NH	5±2	2±0.1	>10
3d	H	NO_2	S	7±1	3±1	2±0.03
4d	H	NH_2	S	47±10	7±0.4	>10
5d	H	$NH_3^+Cl^-$	S	4±3	0.04±0.03	>10
5e	$NH_3^+Cl^-$	H	S	>10	≥10	>10
5f	$NH_3^+Cl^-$	$NH_3^+Cl^-$	S	>10	>10	>10
Etoposide	-			5±2	1±0.7	0.1±0.04

Antibacterial activity was assessed against Gram-positive and Gram-negative bacteria and the highest antibacterial activity was observed for the nitro and amino substituted benzimidazole derivatives with MICs in the range of 2-8 μg/mL.

Table 1. Antibacterial activity of tested compounds

Comp	R_1	R_2	X	MIC (μg/ml)			
				S. aureus	*M. catarrhalis*	*E. faecalis*	*E. coli*
3a	H	NO_2	NH	>128	>128	16	>128
3b	NO_2	H	NH	>128	128	16	>128
3c	NO_2	NO_2	NH	>128	4	16	>128
3d	H	NO_2	S	>128	128	16	>128
3e	NO_2	H	S	>128	8	64	>128
4a	H	NH_2	NH	>128	4	16	>128
4d	H	NH_2	S	>128	>128	8	>128
5a	H	$NH_3^+Cl^-$	NH	>128	4	8	32
5b	$NH_3^+Cl^-$	H	NH	>128	2	8	64
5c	$NH_3^+Cl^-$	$NH_3^+Cl^-$	NH	>128	16	8	>128
5d	H	$NH_3^+Cl^-$	S	>128	>128	16	>128
5e	$NH_3^+Cl^-$	H	S	>128	>128	8	>128
5f	$NH_3^+Cl^-$	$NH_3^+Cl^-$	S	>128	>128	16	>128
Azithromycin	-	-	-	4	0.25	16	0.5

Within this scientific study we have additionally confirmed the promising biological potential of benzo[*b*]thiophene nuclei bearing benzimidazole or benzothiazole heterocyclic skeleton. The obtained results suggest that here presented benzimidazole and benzothiazole series of derivatives represents a solid starting point for further optimization of the chemical space around this scaffold towards more active and selective antibacterial and antitumor agents (Fig. 1).

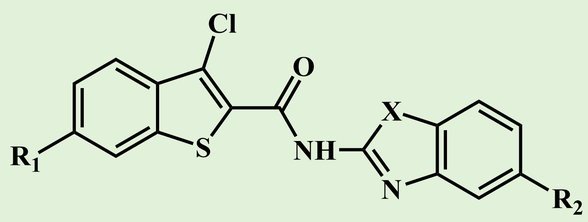


Figure 1. SAR of tested comounds

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