Synthesis and biological capacity of *N*-substituted alkyl benzisoselenazolones and diselenides

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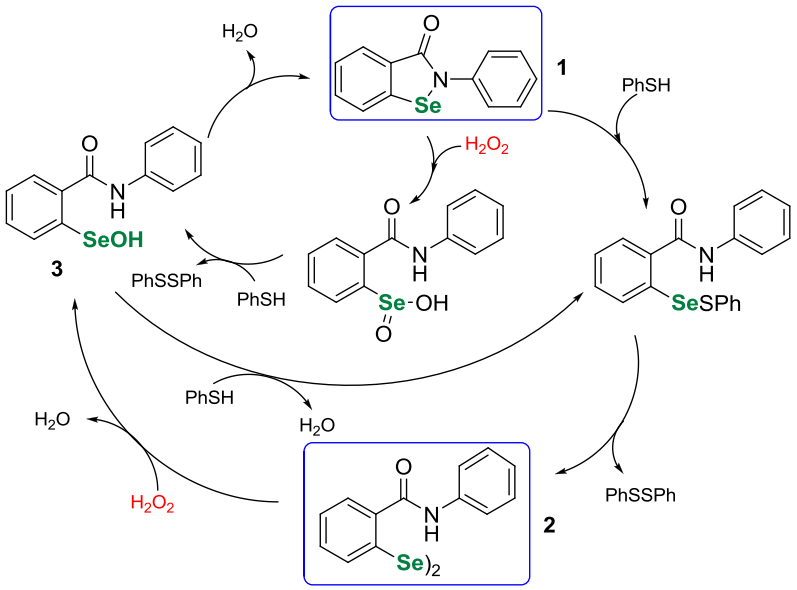
Abstract: *N*-Substituted benzisoselenazol-3(2*H*)-ones are well known for their ability to mimic the activity of an important antioxidant enzyme glutathione peroxidase. They eliminate the excess of reactive oxygen and nitrogen species and restore the cells redox homeostasis. In the catalytic cycle they can be easily transformed to diselenides, which also exhibit these unique properties. In this work, we have synthetized a series of *N*-alkyl benzisoselenazolones and corresponding diselenides. The antioxidant activity of all obtained compounds was evaluated and compared. The connection between the antioxidant properties and the ability to inhibit cancer cells proliferation was evaluated by a cytotoxic activity assay using PC-3 and DU145 cell lines.

Keywords: benzisoselenazolones, diselenides, antioxidant and anticancer activity

Introduction

The pharmacological potential of benzisoselenazolones is mainly associated with their antioxidant properties. This feature is based on the ability of organoselenium compounds to mimic the activity of glutathione peroxidase, an enzyme responsible for maintaining the redox balance in the human body. First discovery, in the early 80's, that ebselen (*N*-phenylbenzisoselenazol-3(2*H*)-one) inhibits generation of reactive oxygen species, cleared the way for a broader research elucidating the application of organoselenium compounds in oxidative stress induced diseases. This includes cancer prevention, anti-Alzheimer and anti-Parkinson therapeutics and also cardiovascular drugs and therapy [1-3]. In the catalytic cycle hydrogen peroxide can be eliminated, in the presence of endogenous thiols, by ebselen **1** or by the corresponding diselenide **2** which are further transformed to selenenic acid **3** and regenerated by the elimination of a water molecule (Scheme 1)[4].

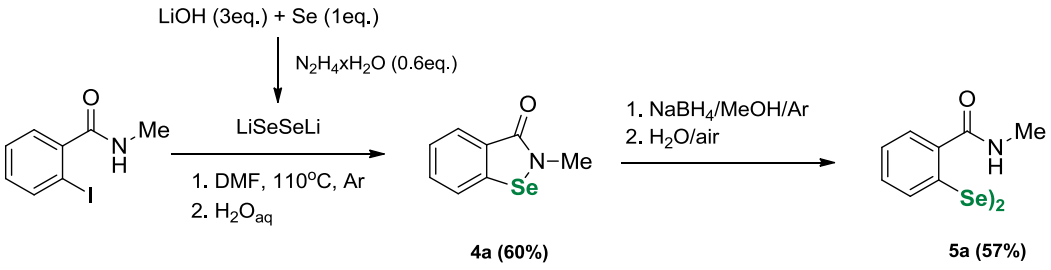


Scheme 1. Catalytic elimination of peroxides by ebselen **1** and diselenide **2**

In this communication we present the evaluation of the antioxidant capacity of a series of newly synthetized *N*-alkyl benzisoselenazol-3(2*H*)-ones and corresponding diselenides. As oxidative stress is highly connected with carcinogenesis the anticancer activity of selected, most potent derivative is also presented.

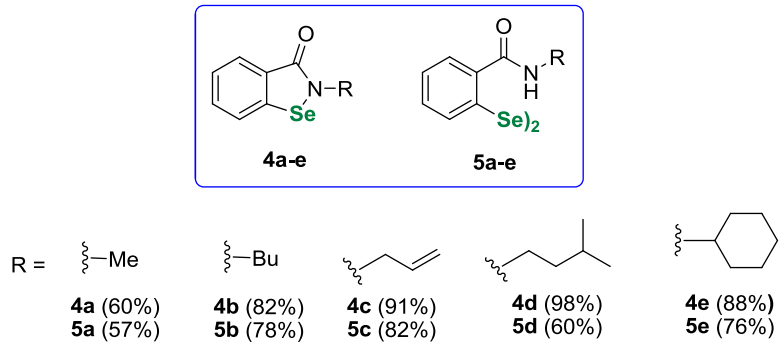
Results and discussion

In the methodology developed in our research group benzisoselenazolone **4** was synthesized from appropriate *o*-iodobenzamide in the reaction with lithium diselenide formed *in situ* from lithium hydroxide and selenium in the presence of hydrazine hydride. Compound **4** was then transformed to the corresponding diselenide **5** by reduction with sodium borohydride, then oxidation (Scheme 2) [5].



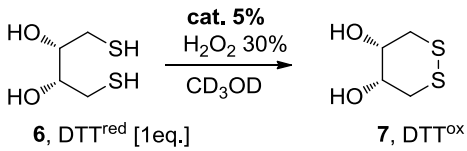
Scheme 2. Synthesis of ebselen derivatives and corresponding diselenides

By applying this method we were able to synthesis a series of *N*-alkyl benzisoselenazol-3(2H)-ones and diselenides in moderate to high yields (57-98%) (Scheme 3).



Scheme 3. Synthesized *N*-alkyl derivatives

The ability to eliminate peroxides was tested by a NMR assay were dithiol **6** is transformed by a selenocatalyst, in the presence of hydrogen peroxide, to a disulphide **7**. The rate of the reaction is measured from the changes in the ^{1}H NMR spectrum (Table 1) [6].



	Substrate concentration [%]				
Catalyst [0.1 equiv.]	**3 min**	**5 min**	**15 min**	**30 min**	**60 min**
4a	78	65	35	11	0
5a	96	94	90	85	77
4b	81	59	41	32	29
5b	93	88	82	77	73
4c	76	69	58	53	41
5c	59	36	12	0	0
4d	77	58	42	28	13
5d	65	49	38	31	21
4e	75	69	62	55	44
5e	92	85	75	65	54
Ebselen	84	75	64	58	52

Table 1. Activity of the tested catalysts

Benzisoselenazolones exhibited higher activity than corresponding diselenides, only in the case of *N*-allyl derivatives better result was obtained for the diselenide **5c** which was additionally the most active compound. To analyze if the high antioxidant potential can be related to anticancer properties compound **5c** was also tested as a cytotoxic agent using prostate cancer cell lines with genetic background (PC-3, DU145). The cytotoxicity and inhibition of cell proliferation were identified by Sulforhodamine B assay (SRB), 24h treatment with different concentrations of compound **5c** (** $p < 0{,}001$, * $p < 0{,}01$ significant differences versus control) (Figure 1).

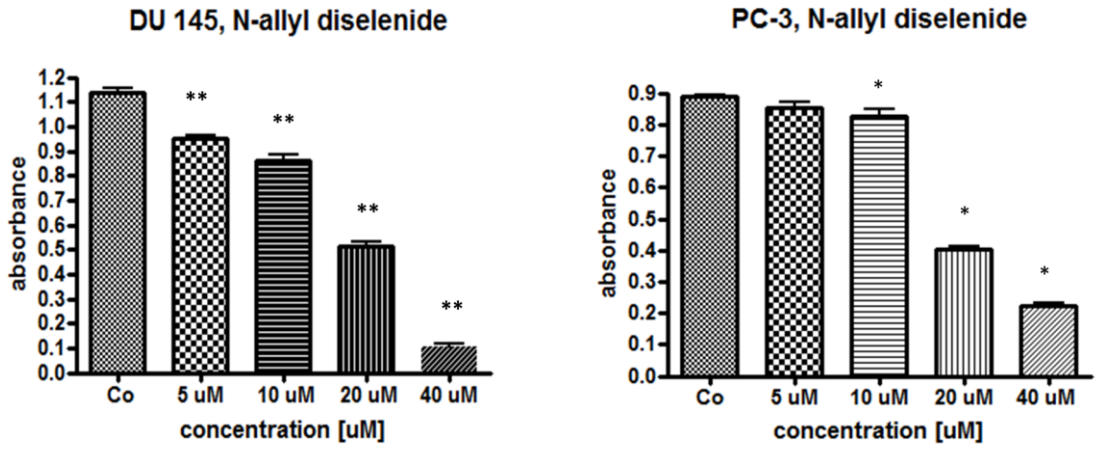


Figure 1. Effect of *N*-allyl diselenide on DU 145 and PC-3 cancer cells, determined by SRB assay

Conclusion

A series of *N*-alkyl benzisoselenazolones have been synthetized and further easily transformed into corresponding diselenides. On the basis of the high peroxide-scavenging properties of ebselen evaluation of the antioxidant activity of all synthetized compounds has been performed. Best results were obtained for *N*-allyl diselenide **5c**. Compound **5c** was also tested as an anticancer agent and resulted to possess high antioxidant and antiproliferative activity against prostate cancer cell lines.

References

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