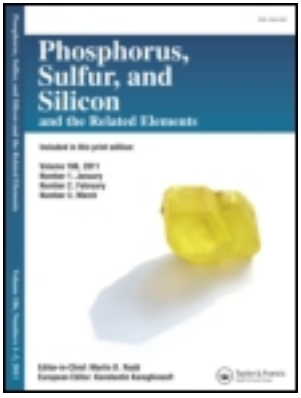

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Bis(2-aminophenyl) Diselenide Derivatives with Amino Acids Moieties as Potential Antivirals and Antimicrobials

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Bis(2-aminophenyl) Diselenide Derivatives with Amino Acids Moieties as Potential Antivirals and Antimicrobials

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*The seleno-organic compounds based on bis(2-aminophenyl) diselenide-**1** are potential antiviral, antibacterial and antifungal agents.[1] In this work, we reported synthesis of bis(2-aminophenyl) diselenide derivatives **2**, **3** having amino acid and dipeptide moieties. This process was realized by acylation of amine groups in **1** with N-blocked amino acids, using the active esters method (with DCC and HOBT). After removing protective groups successive N-blocked amino acids were added the same way as previously.*

All compounds have been tested against broad spectrum of pathogenic microorganisms (Staphylococcus aureus, Staphylococcus simulans, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Candida albicans, Aspergillus niger) and viruses (HSV-1, EMCV, VSV), in vitro. Most of them exhibited high activity against EMCV. Some of tested compounds were active against gram-positive bacteria species (Staphylococcus aureus, Staphylococcus simulans) and yeast Candida albicans.

Keywords Antimicrobial activity; bis(2-aminophenyl) diselenide derivatives; seleno-amino acids; seleno-dipeptides; antivirals

INTRODUCTION

Many organoselenium compounds have a very interesting spectrum of chemical or biological activities.[1] Among them are natural and synthetic seleno derivatives of aminoacids, peptides, or enzymes.[2] Some of them have been tested as a kidney-selective pro-drugs,[3] glutathion peroxidase (GPx) mimetics,[4] or play an important role in elucidation of both the local and global structures of many enzymes and proteins.[5]

Recently it has been described that bis(2-aminophenyl) diselenide **1** and its simple derivatives were potential antiviral, antibacterial and antifungal agents.[6] In this work, we report synthesis of

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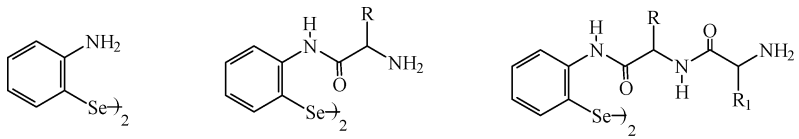


1 **2** **3**

R = H, CH_3, CH_2Ph, $(CH_3)_2SCH_3$, $CH_2CH(CH_3)_2$, $CH(CH_2CH_3)CH_3$

R_1= H, CH_2Ph, $(CH_2)_2SCH_3$, $CH_2CH(CH_3)_2$

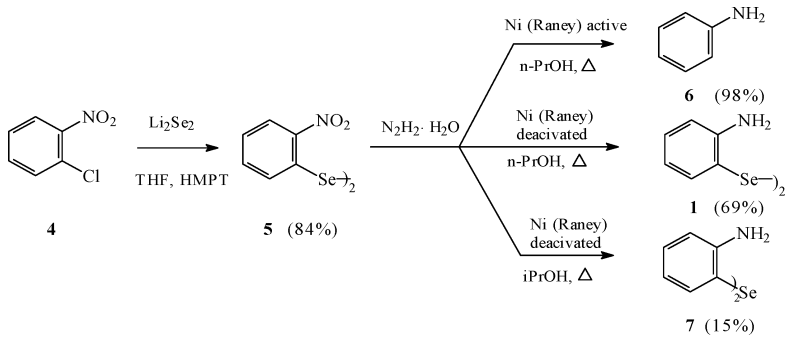
FIGURE 1 Diselenide derivatives of aminoacids and peptides.

bis(2-aminophenyl) diselenide derivatives **2**, **3** having amino acid and dipeptide moieties (Figure 1). This process was realized by acylation of amine groups in **1** with N-blocked amino acids, using the active esters method (with DCC and HOBT). After removing protective groups, subsequent N-blocked amino acids were added in the same manner as previously. All compounds have been tested against broad spectrum of pathogenic microorganisms (Staphylococcus aureus, Staphylococcus simulans, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Candida albicans, Aspergillus niger) and viruses (HSV-1, EMCV, VSV), in vitro.

EXPERIMENTAL

Synthesis of Bis(2-aminophenyl) Diselenide 1

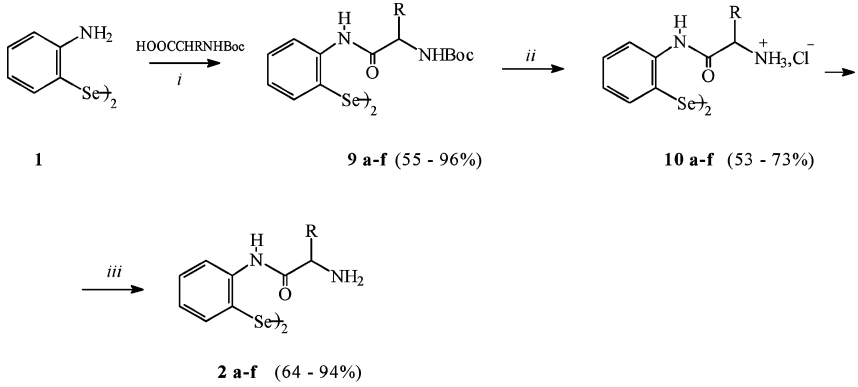
The key substrate, bis(2-aminophenyl) diselenide **1** has been obtained in a two steps synthesis, starting from 2-chloronitrobezene **4**, same way as reported.[6] Its selenylation using lithium diselenide in hexamethylphosphoramide-tetrahydrofurane solution produced bis (2-nitrophenyl) diselenide **5** in 84% yield (ref.[6] 86%). In the next step, dinitro compound was transformed into amine **1** by reduction using hydrazine monohydrate in the presence of Raney nickel as a catalyst (Scheme 1). We observed that yield and products of this reaction were strongly dependent on activity of used catalyst and solvent. When fresh, commercially available catalyst in boiling n-propanol mixture was used, aniline **6** as a product of deselenylation was obtained in high yield. Amine **1** was obtained in the same conditions in yields up to 69% (lit.[6] 71%) when catalyst dried overnight on air was used. At the same time in case of using isopropanol as a solvent, bis(2-aminophenyl) selenide **7** was produced in 15% yield.



SCHEME 1

Synthesis of Amino Acid Derivatives 2

Active esters method (with hydroxybenzotriazole (HOBT) and dicycloheksyl carbodiimide (DCC)) as a route of coupling carboxylic group of N-Boc-protected natural amino acids **8 a–f** and both amino group in diselenide **1** was used. Reactions were carried out in dichloromethane in temperature −14°C and N-Boc protected diselenides **9a–f** with 55 to 96% yield were produced. Free amines **2a–f** were obtained by removing protective groups by saturation of 1,4-dioxane solution of **9a–f** with gaseous hydrochloride and then by neutralization obtained this way hydrochlorides **10a–f** in reaction with N-methylmorpholine in dichlorometane solution. Yields of these both procedures were 56–73% and 64–94%, respectively (Scheme 2).



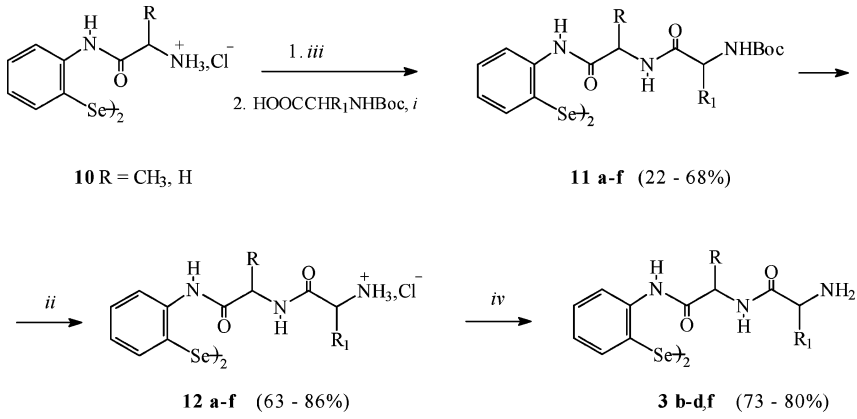
a: R = CH_3; **b**: R = H; **c**: R = CH_2Ph; **d**: R = $(CH_2)_2SCH_3$; **e**: $CH_2CH(CH_3)_2$; **f**: $CH(CH_3)CH_2CH_3$

i: HOBT, DCC, CH_2Cl_2;
ii: HCl (gaseus), 1,4-dioxane;
iii: N-methylmorpholine

SCHEME 2

Synthesis of Dipeptide Derivatives 3

Active esters method was also used to preparation of dipeptide derivatives **3a–f**. Hydrochlorides **10a, b** were converted in situ to amines **2a**,**b** in presence of N-methylmorpholine and then it was coupled with N-Boc protected L-amino acids **8a**,**c**, **d**, **f** in presence of HOBT and DCC. Reactions were carried out in dichlorometane-dimethylformamide solution in temperature −14°C and N-Boc protected diselenides **11a-f** with 22–68% yield were produced. Hydrochlorides **12a–f** were prepared the same way as it was described for compounds **10** with 63–86% yield. Free amine **3b**,**c**,**d**,**f** were involved in reaction with propylene oxide in anhydrous ethanol with 73–80% yield (Scheme 3).



10 R = CH_3, H

11 a-f (22 - 68%)

12 a-f (63 - 86%)

3 b-d,**f** (73 - 80%)

a: R = CH_3, R_1 = CH_2Ph; **b**: R = CH_3, R_1 = CH_2Ph; **c**: R = CH_3, R_1 = $(CH_2)_2SCH_3$;
d: R = CH_3, R_1 = $CH_2CH(CH_3)_2$; **e**: R = H, R_1 = CH_3; **f**: R = H, R_1 = CH_2Ph

iv : propylene oxide, EtOH

SCHEME 3

CONCLUSIONS

New derivatives of bis(2-aminophenyl)diselenide **1** with aminoacids and dipeptides moieties has been designed and synthesized using the active esters method (with DCC and HOBT). All compound were tested against selected viruses and microbes. The majority of tested compounds exhibited high activity against EMCV. However, high cytotoxicity of these compounds resulted in undesirable low I values. Some of tested compounds were weakly active Staphylococcus aureus,

Staphylococcus simulans, Escherichia coli, Candida albicans and *Aspergillus niger*.

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