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# Novel Podands Containing *N*–Arylthiosemicarbazide Moiety

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*Six novel biological active podands based on N-arylthiosemicarbazide were synthesized from 1,5-bis(2-formylphenoxy)-3-oxapentane or 1,8-bis-(2-formylphenoxy)-3,6-dioxaoctane. All podands have tested cytotoxicity on human cancer cell lines RL, MCF7, RD, and HepG2 and antimicrobial activity.*

**Keyword:** Podands, thiosemicarbazide, polyethers, bioactivity.

# Новые поданды, содержащие фрагмент *N*–арилтиосемикарбазида

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*Шесть новых биологически активных подандов, основанных на N-арилтиосемикарбазиде синтезированы из 1,5-бис(2-формилфенокси)-3-оксапентана или 1,8-бис(2-формилфенокси)-3,6-диоксаоктана. Протестирована цитотоксичность всех подандов на линиях раковых клеток человека RL, MCF7, RD и HepG2, изучена их антибактериальная активность.*

**Ключевые слова:** Поданды, тиосемикарбазид, полиэфиры, биоактивность.

## Introduction

Acyclic analogues of crown ethers (podands) have been received a great attraction by research groups around the world. Studying on synthesis and bioactivities of podands prepared from Shiff reaction of thiosemicarbazides with aldehydes was reported by Russian scientists from 70s–90s of previous century.[1-6] The typical bioactivity of this class is tuberculostatic activity *(in vitro)* which mainly depends on the nature of substituents as well as oxyethylene groups due to theirs ability of making complex.[1,2,5-7] Recently, researches on the antibacterial and cytotoxicity, anticancer (*in vitro*) of podands containing thiosemicarbazides moiety has been reported.[8,9] Studying was carried out on 60 types

of cancer cells from malignant tumors at different tissues: lung cell, breast cell…[9] In addition, this type of podand is also an important part in structures of azacrown ether compounds[10-21] and other crownophane[22] or polycyclic crownophane[23] which are studying hardly by scientists in recent years. Therefore, the development of synthetic methods of compounds containing "privilege" fragments including polyether and *N*-arylthiosemicarbazide derivatives as well as exploration of bioactivities of these podands are interesting targets. This publication has been firstly mentioned on several new podands (**3a-f**) which were successfully prepared from phenylthiosemicacbazide derivatives (**1a-c**). Their structures were ascertained from IR, $^1$H NMR, $^{13}$C NMR and MS analysis. Crystallization solvents, melting points, yields %, and all spectral data of the compounds are given in experimental section.

## Experimental

Melting points were determined by using a Raga melting point apparatus. IR spectra were recorded on Shimadzu FT IR PC (S) 8201 spectrometer by using KBr pellets and the absorption frequencies are expressed in reciprocal centimeters ($cm^{-1}$). NMR spectra were taken on BRUKER 500 MHz spectrometer using TMS as an internal reference. The chemical shifts were expressed in parts per million (ppm). ESI-MS were recorded in LTQ orbitrap XL mass spectrometer, Thermo Scientific Company.

*General method for synthesis of podand* ***3****.* A mixture of 0.5 mmol aldehyde compound, 1 mmol of 4-arylthiosemicarbazide and 10 ml of EtOH was refluxed on water bath in 2 h. After the completion of reaction indicated by TLC spot change, the mixture was filtered, dried and recrystallized in dichloromethane and gave compounds **3**.

*1,5-Bis-[2-(N-phenylthiosemicarbazono)methylphenoxy]-3-oxapentane (**3a**).* Yield 60 %. $T_{mp}$=197–199 °C. $R_f$=0.45 (*n*-hexane:ethylacetate=1:1). HRMS (ESI) *m/z*: 613.2057 $[M+H]^+$. Calc. for $C_{32}H_{33}N_6O_3S_2$ *m/z*: 613.2050. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3310, 3158, 2919, 1595, 1550, 1255, 1189, 1067, 741. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ ppm: 9.17 (2H, s, -CS-N*H*-N=C), 9.15 (2H, s, -CS-N*H*-Ar), 8.25 (2H, s, *H*C=N), 7.87 (2H, d.d $^3J$=8.0 Hz, $^5J$=1.5 Hz), 7.61 (4H, d $^3J$=8.0 Hz), 7.32–7.38 (6H, m), 7.19 (2H, t $^3J$=7.5), 6.99 (2H, t $^3J$=7.5), 6.92 (2H, d $^3J$=8.5), 4.19 (4H, m, Ar-OC$H_2$-), 3,91 (4H, m, -C$H_2$O-). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta_C$ ppm: 68.33 (Ar-O*C*H$_2$-), 70.07 (-*C*H$_2$O-), 112.92, 121.48, 124.43, 125.98, 126.57, 128.67, 132.09, 139.11 (16$C_{aromatic}$), 157.6 (C=N); 176 (C=S).

*1,5-Bis-[2-(N-toluenylthiosemicarbazono)methylphenoxy]-3-oxapentane (**3b**).* Yield 71 %. $T_{mp}$=200–202 °C. $R_f$=0.58 (*n*-hexane:ethylacetate=1:1). HRMS (ESI) *m/z*: 641.2260 $[M+H]^+$. Calc. for $C_{34}H_{36}N_6O_3S_2$ *m/z*: 641.2363. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3321, 3161, 1597, 1551, 1261, 1072, 746. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ ppm: 9.17 (2H, s, -CS-N*H*-N=C), 9.15 (2H, s, -CS-N*H*-Ar), 8.21 (2H, s, *H*C=N), 7.89 (2H, d $^3J$=6.5 Hz), 7.46 (4H, d $^3J$=8.0 Hz), 7.36 (2H, t.d. $^3J$=8.5 Hz, $^4J$=1.5 Hz), 7.16 (4H, d $^3J$=8.0 Hz), 7.01 (2H, t $^3J$=8.5 Hz), 6.93 (2H, d $^3J$=8.5 Hz), 4.21 (4H, m, Ar-OC$H_2$-), 3.92 (4H, m, -C$H_2$O-). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta_C$ ppm: 21.05 (*C*H$_3$), 68.33 (ArO*C*H$_2$), 69.77 (-*C*H$_2$O-), 89.66, 112.94, 121.26, 121.53, 122.02, 124.69, 126.64, 129.29, 132.06, 135.39, 135.92, 138.93 (16$C_{aromatic}$), 157.61 (*C*=N), 176.02 (*C*=S).

*1,5-Bis-{2-[N-(p-chlorophenyl)thiosemicarbazono]methylphenoxy}-3-oxapentane (**3c**).* Yield 55 %. $T_{mp}$=216–218 °C. $R_f$=0.48 (*n*-hexane:ethylacetate = 1:1). HRMS (ESI) *m/z*: 681.1237 $[M+H]^+$. Calc. for $C_{32}H_{30}Cl_2N_6O_3S_2$ *m/z*: 681.1276. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3274, 3157, 2988, 1591, 1542, 1252, 1066, 746. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ ppm: 9.7 (2H, s, -CS-N*H*-N=C), 9.16 (2H, s, -CS-N*H*-Ar), 8.33 (2H, s, *H*C=N), 7.88 (2H, d.d $^3J$=7.5 Hz, $^5J$=1.5 Hz), 7.57 (4H, d $^3J$=8.5 Hz), 7.36 (2H, t.d. $^3J$=7.0 Hz, $^5J$=1.5 Hz), 7.24 (4H, d $^3J$=8.5 Hz), 7.00 (2H, t $^3J$=7.5 Hz), 6.93 (2H, d $^3J$=8.0 Hz), 4.21 (4H, m, Ar-OC$H_2$-), 3.95 (4H, m, -C$H_2$O-). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta_C$ ppm: 68.13 (Ar-O*C*H$_2$), 69.88 (-*C*H$_2$O-), 112.79, 121.50, 122.17, 125.91, 126.06, 126.68, 128.77, 131.29, 132.21, 136.69, 140.15 (16$C_{aromatic}$), 157.77 (*C*=N), 175.61 (*C*=S).

*1,8-Bis-[2-(N-phenylthiosemicarbazono)methylphenoxy]-3,6-dioxaoctane (**3d**).* Yield 53 %. $T_{mp}$=218–220 °C. $R_f$=0.39 (*n*-hexan:ethylacetate = 1:1). HRMS (ESI) *m/z*: 657.2320 $[M+H]^+$. Calc. for $C_{34}H_{36}N_6O_4S_2$ *m/z*: 657.2317. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3297, 3170, 1594, 1546, 1254, 1068, 745. $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ ppm: 10.02 (2H, s, -CS-N*H*-N=C), 9.03 (2H, s, -CS-N*H*-Ar), 8.48 (2H, s, *H*C=N), 7.74 (2H, d $^3J$=8.0 Hz), 7.63 (4H, d $^3J$=7.5 Hz), 7.38 (4H, t $^3J$=8.0 Hz), 7.33 (2H, t $^3J$=7.5 Hz), 7.20 (2H, t $^3J$=7.5 Hz), 7.13 (2H, t $^3J$=8.0 Hz), 6.99 (2H, t $^3J$=7.5 Hz), 4.44 (4H, m, Ar-OC$H_2$-), 3.92 (4H, m, Ar-OCH$_2$C$H_2$-), 3.84 (4H, br.s, Ar-O(CH$_2$)$_2$O-C$H_2$-). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta_C$ ppm: 69.29 (Ar-OC$H_2$-), 70.03 (Ar-OCH$_2$C$H_2$-), 70.21 (Ar-O(CH$_2$)$_2$OC$H_2$-), 116.02, 122.25, 123.67, 124.17, 125.67, 125.83, 128.70, 131.99, 138.10, 139.44 (18$C_{aromatic}$), 157.56 (C=N), 175.64 (C=S).

*1,8-Bis-[2-(N-toluenylthiosemicarbazono)methylphenoxy]-3,6-dioxaoctane (**3e**).* Yield 57 %. $T_{mp}$=206–208 °C. $R_f$=0.54 (*n*-hexane:ethylacetate = 1:1). HRMS (ESI) *m/z*: 685.2612 $[M+H]^+$. Calc. for $C_{36}H_{40}N_6O_4S_2$ *m/z*: 685.2630. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3294, 3155, 1597, 1554, 1257, 1070, 750. $^1$H NMR ($CDCl_3$, 500MHz) $\delta_H$ ppm: 9.97 (2H, s, -CS-N*H*-N=C), 8.95 (2H, s, -CS-N*H*-Ar), 8.47 (2H, s, *H*C=N), 7.74 (2H, dd $^3J$=8.0 Hz, $^5J$=1.5 Hz), 7.50 (2H, d $^3J$=8.5 Hz), 7.46 (4H, d $^3J$=8.5 Hz), 7.31 (2H, td $^3J$=8.5 Hz, $^5J$=2.0 Hz), 7.18 (4H, d $^3J$=8.5 Hz), 7.12 (2H, d $^3J$=8.5 Hz), 6.99 (4H, m), 4.43 (4H, m), 3.91 (4H, m), 3.83 (4H, br.s). $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta_C$ ppm: 21.05 (*C*H$_3$), 69.29 (Ar-OC$H_2$-), 70.03 (Ar-OCH$_2$C$H_2$-), 70.22 (Ar-O(CH$_2$)$_2$OC$H_2$-), 116.05, 122.23, 123.73, 124.51, 125.67, 129.29, 129.35, 131.93, 135.49, 135.75, 139.33 (18$C_{aromatic}$), 157.54 (C=N), 175.92 (C=S).

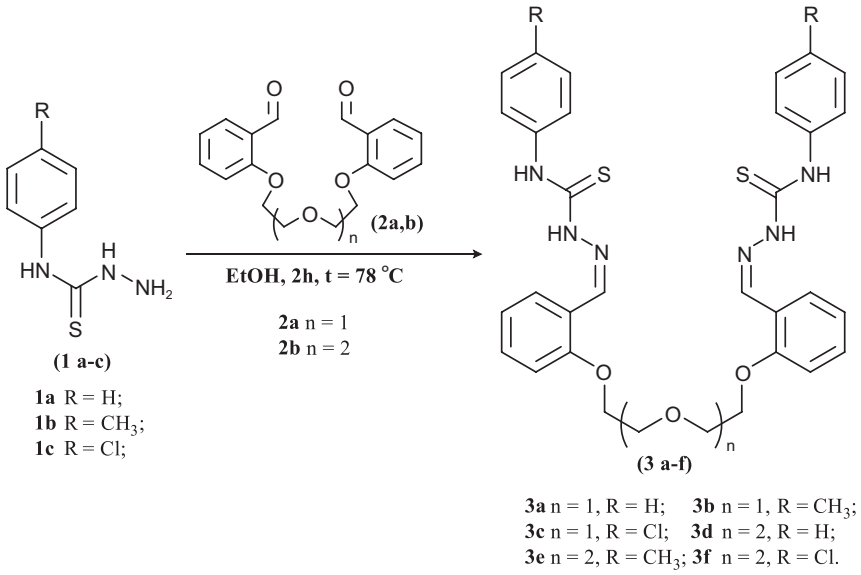
*1,8-Bis-{2-[N-(p-chlorophenyl)thiosemicarbazono]methylphenoxy}-3,6-dioxaoctane (**3f**).* Yield 45 %. $T_{mp}$=196–198 °C. $R_f$=0.40 (*n*-hexane:ethylacetate = 1:1). HRMS (ESI) *m/z*: 723.1389 $[M+H]^+$. Calc. for $C_{34}H_{34}Cl_2N_6O_4S_2$ *m/z*: 723.1381. IR (KBr) $\nu_{max}$ $cm^{-1}$: 3277, 3176 (NH), 1683 (C=N), 1254 (C=S), 1070 (N-N), 745 (δ(C=S)). $^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ ppm: 10.10 (2H, s, -CS-N*H*-N=C), 8.99 (2H, s, CS-N*H*-Ar), 8.49 (2H, s, *H*C=N), 7.74 (2H, d $^3J$=7.5 Hz), 7.58 (4H, d $^3J$=8.5 Hz), 7.32 (4H, d $^3J$=9.0 Hz), 7.12 (2H, d $^3J$=8.0 Hz), 6.99 (2H, d $^3J$=7.5 Hz), 4.44 (4H, br.s), 3.92 (4H, br. s), 3.84 (4H, br.s).

The bioactivities of synthesized podands was evaluated based on previously published methods (antimicrobial activity[24,25] and cytotoxic activity[26,27]).

## Results and Discussion

The synthesis of podands (**3a-f**) was carried out in the same manner (Scheme 1), in which *N*-arylthiosemicarbazide (**1a-c**) and polyether (**2a-b**) reacted at boiling point of ethanol.

In general, it took 2 hours to complete this reaction with high yield after purification. The synthesized compounds appeared as colorless or light-yellowish crystalline substances, soluble in polar solvents such as DCM, DMF, DMSO. This type of podand in numerous publications was normally made with the free $NH_2$-terminal residues. It looked simpler than our case with podand containing *N*-aryl as terminal group. As a consequence, changing the R substituents attached in benzene ring leaded to the different compounds of (**1a-c**) and (**3a-f**) so on. The proposed structures of substances (**3a-f**) were confirmed by spectroscopic techniques.




**Scheme 1**. General method for synthesis of podands containing *N*-arylthiosemicarbazide moiety.

The IR spectrum of podand **3a** showed bands around 1250 $cm^{-1}$ and 1070 $cm^{-1}$ due to the ν(C=S) and δ(C=S), respectively. The bands observed at 3100–3200 $cm^{-1}$ were assigned to two groups of ν(N–H) vibrations. The $^1$H NMR spectra of the podand in $CDCl_3$ solutions with assignments are described in experimental part. The presence of secondary amine protons appeared at δ=9.17 ppm (1H) and δ=9.15 ppm (1H) as singlet in which proton of NH attached with aryl ring has lower shift compared with the last. The azomethine proton resonated at δ=8.25 ppm (s, 1H). The methylene protons appeared at δ=4.19 ppm (t, 2H) and δ=3.91 ppm (t, 2H) toward podands **3a-c** containing three oxygen atoms (**3a**, for example). With the last podands **3d-f** containing four oxygen atoms, the methylene protons resonated at δ=4.43 ppm (m, 4H), δ=3.91 ppm (m, 4H), 3.83 ppm (br.s, 4H), respectively (**3e**, for example). The spectrum of $^{13}$C NMR and HRMS also indicated the suitable structures of proposed podands (see experimental part).

All the synthesized podands were assessed the antimicrobial activity such as: *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 25923), *Bacillus subtillis* (ATCC 11774), *Staphylococcus aureus* subsp. *aureus* (ATCC 11632), *Aspergillus niger* (439), *Fusarium oxysporum* (M42), *Candida albicans* (ATCC 7754) and *Saccharomyces cerevisiae* (SH 20). The starting concentration of 50 μg/ml for each compound was prepared and diluted step by step until there wasn't any positive signal of antimicrobial activity. The obtained result showed that most of new podands, excepted compound **3c**, have antimicrobial activity on the fungi *Aspergillus niger* (439) with the MIC 25 μg/ml (Table 1).

Besides, the new podands (**3b**, **3d–f**) were evaluated *in vitro* for their cytotoxic activity against several human cancer cell lines as Hep-G2 (*Human hepatocellular carcinoma*), LU-1 (*Human lung adenocarcinoma*), RD (*Human rhabdomyosarcoma*) and FL (*Human cervix carcinoma*) and the results are summarized in Table 2.

**Table 1.** Antimicrobial activity of new podands **3a-f** with the MIC 25 μg/ml.

| Comp. | Conc. (μg/ml) | Minimum Inhibitory Concentration (MIC: μg/ml) | | | | | | | | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Gram-negative bacteria | | Gram-positive bacteria | | Filamentous fungi | | Yeast fungi | | |
| | | *E. coli* | *P. aeruginosa* | *B. subtillis* | *S. aureus* | *A. niger* | *F. oxysporum* | *S. cerevisiae* | *C. albicans* | |
| **3a** | 50 | (–) | (–) | (–) | (–) | 25 | (–) | (–) | (–) | Positive with 01 fungi line |
| **3b** | 50 | (–) | (–) | (–) | (–) | 25 | (–) | (–) | (–) | Positive with 01 fungi line |
| **3c** | 50 | (–) | (–) | (–) | (–) | (–) | (–) | (–) | (–) | Negative |
| **3d** | 50 | (–) | (–) | (–) | (–) | 25 | (–) | (–) | (–) | Positive with 01 fungi line |
| **3e** | 50 | (–) | (–) | (–) | (–) | 25 | (–) | (–) | (–) | Positive with 01 fungi line |
| **3f** | 50 | (–) | (–) | (–) | (–) | 25 | (–) | (–) | (–) | Positive with 01 fungi line |

**Table 2.** Results of cytotoxicity tests performed on compounds **(3b, 3d–f)** in four human cancer cell lines: Hep-G2; LU-1; RD; FL.

| Comp. | Conc. (μg/ml) | Cell survival, % | | | | Conclusion |
|---|---|---|---|---|---|---|
| | | Hep-G2 | LU-1 | RD | FL | |
| DMSO | – | 100 | 100 | 100 | 100 | |
| Vinblastine (+) | 5 | 1.3±0.8 | 3.7±0.9 | 0.7±0.3 | 3.9±1.1 | Positive |
| **3b** | 10 | 88.6±1.8 | 90.5±1.9 | 98.3±0.5 | 99.6±0.4 | Negative |
| **3d** | 10 | 90.8±2.4 | 95.4±2.2 | 93.7±1.1 | 92.1±1.5 | Negative |
| **3e** | 10 | 97.2±2.6 | 85.4±1.5 | 98.1±1.0 | 88.4±1.8 | Negative |
| **3f** | 10 | 96.4±2.5 | 90.35±0.70 | 98.8±0.8 | 97.6±1.2 | Negative |

## Conclusion

In this study, we successfully synthesized various derivatives of podand **3** which may attract interest in the viewpoint of search for novel azacrown ethers or azacrownophane. We also showed the results of bioactivities test performed on these new podands.

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