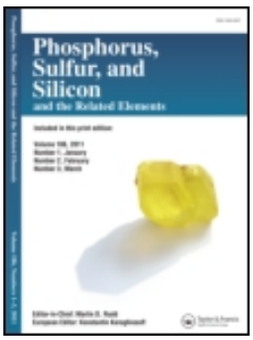

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Novel selenium-containing acenaphtho[1,2-b]pyrrole derivatives: Synthesis and bioactivity

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ABSTRACT

Seven novel selenium-containing acenaphtho[1,2-b]pyrrole derivatives were designed and synthesized and their cytotoxic effects were evaluated by the MTT tetrazolium dye assay. Two compounds presented good anticancer activities.

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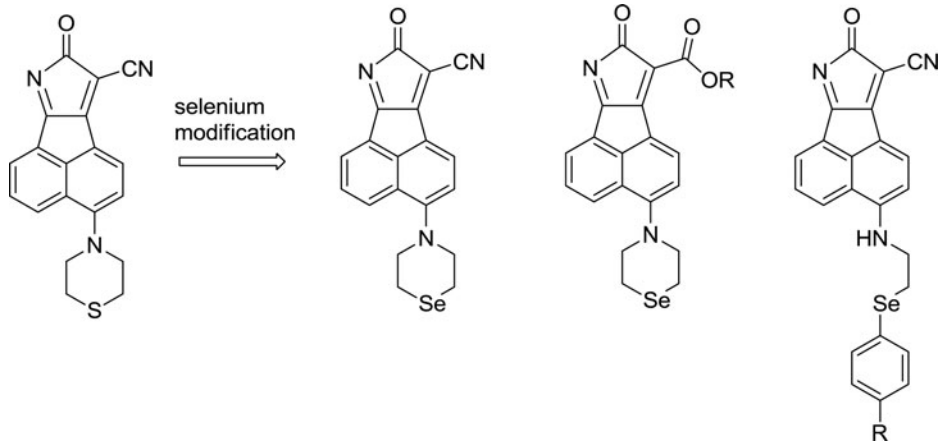
Selenium; acenaphtho[1,2-b]pyrrole; cytotoxicity; cancer

GRAPHICAL ABSTRACT



Introduction

Apoptosis is a physiological cell-death process, and plays an important role during the development and maintenance of tissue homeostasis. Apoptosis induction is arguably the most potent defense against cancer. Recently, 8-Oxo-8H-acenaphtho[1,2-*b*] pyrrolecarbonitrile derivative **1a**[1] was synthesized, which showed high antitumor properties. Later several derivatives[2,3] were designed and synthesized, such as compound **2**[4] exhibited nanomolar IC_{50} against diverse cancer cell lines through the inhibition of anti-apoptotic protein Bcl-2/Mcl-1, and compound **3**[5] was a potent and selective inhibitor of tyrosine kinase fibroblast growth factor receptor 1 (FGRI1) (Figure 1).

Interest in selenium compounds, especially organoselenium compounds, in cancer prevention and treatment is a fascinating field. These compounds have been proven as potent anticarcinogenic agents in different models, such as spontaneous, chemically induced, transplanted tumors or in culture.[6–8] The application of organoselenium compounds, particularly the bioisosteric replacement of oxygen or sulfur atoms in known bioactive compounds with selenium, is promising. Several reports[9–12] and our research[13] have indicated that selenium-containing compounds had higher activity than their sulfur analogues.

Herein we prepared the selenium analogue **4a** of compound **1a** after the successful bioisosteric exchange of thiomorpholine to selenomorpholine; other derivatives **4b–g** were synthesized to improve anticancer activity or selectivity (Figure 2).

Results and discussion

Synthesis

The intermediates 8-Oxo-8H-acenaphtho[1,2-b]pyrrol-9-carbonitrile **7**[14] or its derivates **2** and corresponding amines **8**[15,16] were prepared according to published procedures. Products **4** were prepared in dry CH_3CN; all reactions were monitored by thin-layer chromatography (Scheme 1). The solvent was removed under reduced pressure and the residue

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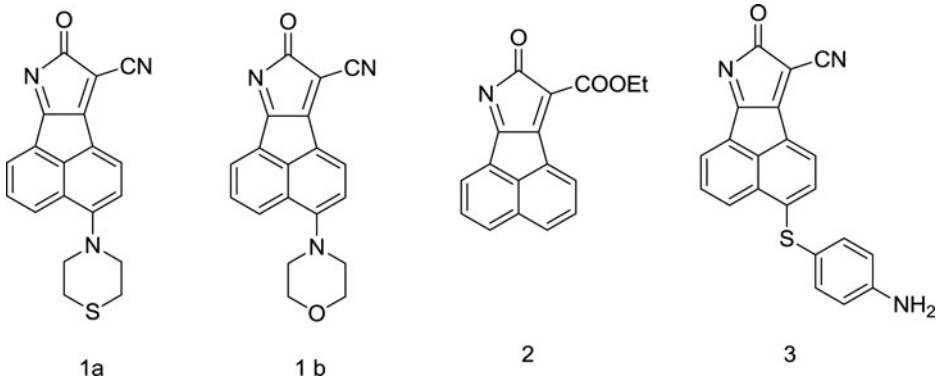


Figure 1. Structural formulas of 8-Oxo-8H-acenaphtho[1,2-b] pyrrolecarbonitrile derivatives **1–3.**

was subjected to column chromatography on silica gel. Products were separated with CH_2Cl_2/EtOH 50:1 (v/v) as a dark purple powder.

Cytotoxic evaluation in vitro

The in vitro antitumor activities of the target compounds were evaluated by examining their cytotoxic effects using the MTT tetrazolium dye assay against Hela (human cervical carcinoma cell line), HCT116 (human colon cancer cell line), K562 (chronic myelogenous leukemia cell line), A549 (human lung cancer cell line), and MCF-7 (human Caucasian breast adenocarcinoma cell line). The IC_{50} values representing the drug concentration (μM) required to inhibit cell growth by 50% are summarized in Table S1 (available online in Supplemental Materials).

The selenium analogue **4a** showed better cytotoxicity than **1a**, especially against MCF-7 cell lines. But the functional group modification of esters to nitrile was not successful. Interestingly, among compounds containing 2-aryl-selanyl-ethylamino group, only **4d** presented bioactivity against K562 and MCF-7 cell lines, and the IC_{50} value was 12.4 μM and 6.2 μM respectively.

Conclusions

Herein we prepared seven novel seleninm-containing acenaphtho[1,2-b]pyrrole derivatives, and evaluated their cytotoxic effects. Compound **4a** had better cytotoxic effects than its sulfur analogue **1a**, and compound **4d** presented good cytotoxic activity against K562 and MCF-7 cell lines.

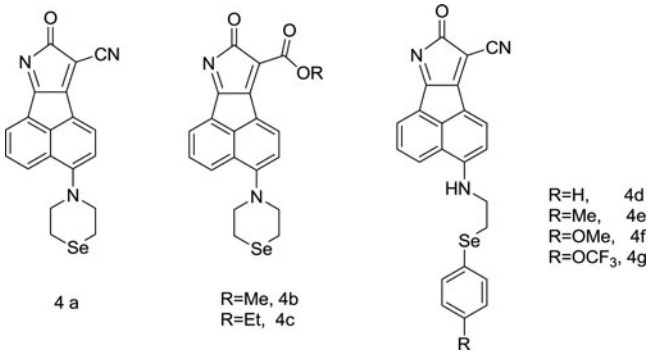


Figure 2. Selenium bioisosteric exchange and modification of sulfur.

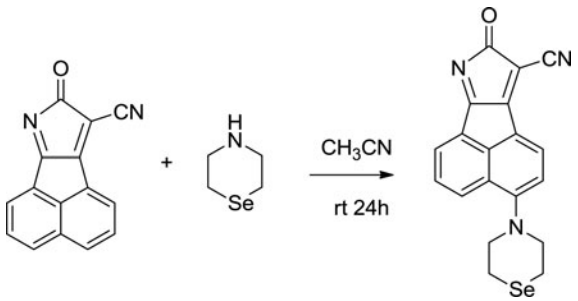
Experimental

Synthesis

All chemical reagents and solvents were purchased from commercial sources and used without further purification. Thin layer chromatography (TLC) was performed on silica gel plate. Column chromatography was performed using silica gel 300–400 mesh. ^{1}H NMR was obtained with a Bruker AV-400 spectrometer with chemical shifts reported as ppm (in dimethyl sulfoxide (DMSO), tetramethylsilane (TMS) as internal standard). IR spectra were obtained using a Perkin–Elmer 2000 FT-IR instrument. High-resolution mass spectra (HRMS) were obtained on an HPLC-Q-Tof MS (micro) spectrometer. Melting points were determined using a Büchi melting point B-540 apparatus, and were uncorrected.

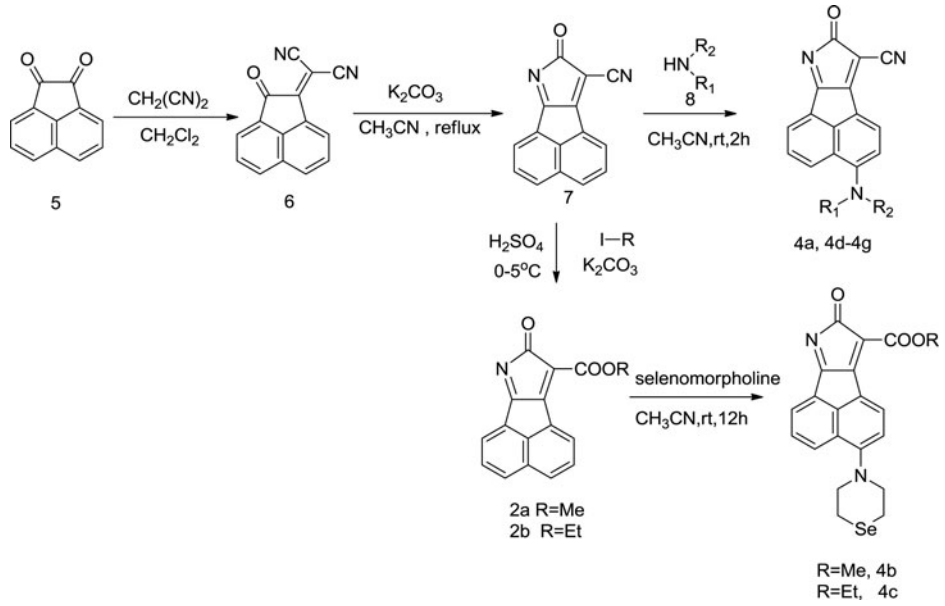
Characterization

8-oxo-3-selenomorpholino-8H-acenaphtho[1,2-b]pyrrole-9-carbonitrile (**4a**)

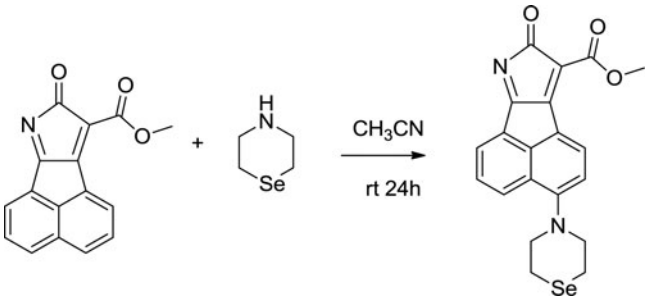


Yield 41%, dark purple powder, mp > 300°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.68–8.65 (m, 2H), 8.17 (d, 1H, J = 8.8 Hz), 7.97 (t, 1H, J = 7.9 Hz), 7.43 (d, 1H, J = 8.8 Hz), 4.07 (t, 4H, J = 4.2 Hz, $N(CH_2CH_2)_2Se$), 3.02 (t, 4H, J = 4.2 Hz, $N(CH_2CH_2)_2Se$) ppm; HRMS (EI) m/z $[M]^+$ calcd for $C_{19}H_{13}N_3O^{80}Se$ 379.0224, found 379.0234; IR (KBr): ν 2219, 1624, 1572, 1499 cm^{-1}.

Methyl 8-oxo-3-selenomorpholino-8H-acenaphtho[1,2-b]pyrrole-9-carboxylate (**4b**)

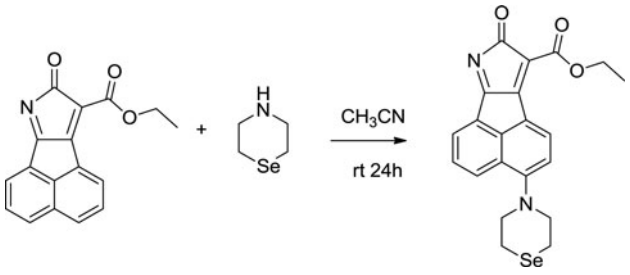


Scheme 1. Synthesis of **4a–g**.



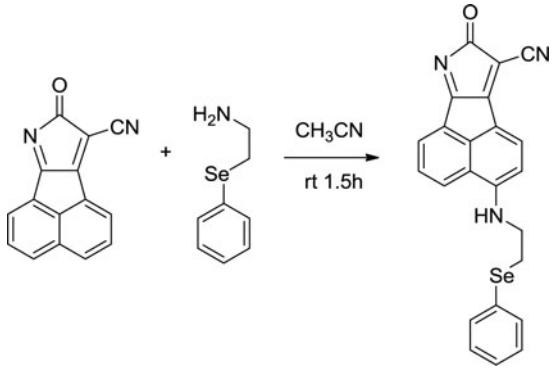
Yield 32%, dark purple powder, mp: 238.2–237.6°C. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.04$ (d, 1H, $J = 8.3$ Hz), 8.79 (d, 1H, $J = 7.4$ Hz), 8.52 (d, 1H, $J = 7.3$ Hz), 7.75 (t, 1H, $J = 7.8$ Hz), 7.23 (d, 1H, $J = 8.3$ Hz), 3.87–3.84(m, 4H), 3.20 (s, 3H), 3.05–3.03 (m, 4H) ppm; HRMS (EI) m/z $[M+H]^+$ calcd for $C_{20}H_{17}N_2O_3{}^{80}Se$ 413.0404, found 413.0406; IR(KBr): ν 2916, 1786,1785, 1653, 1607, 1511 cm^{-1}.

Ethyl 8-oxo-3-selenomorpholino-8H-acenaphtho[1,2-b]pyrrole-9-carboxylate (**4c**)



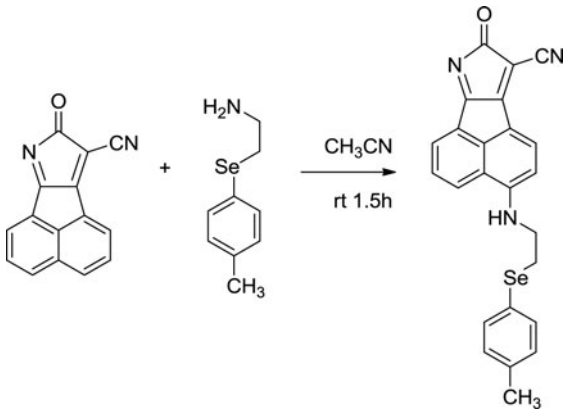
Yield 33%, dark purple powder, mp: 245.2–246.9°C, ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.03$ (d, 1H, $J = 8.3$ Hz), 8.77 (d, 1H, $J = 7.4$ Hz), 8.46 (d, 1H, $J = 8.2$ Hz), 7.82 (t, 1H, $J = 7.8$ Hz), 7.22 (d, 1H, $J = 8.3$ Hz), 3.84 (m, 4H), 3.76 (q, 2H, $J = 7.1$ Hz), 3.04 (m, 4H), 1.31 (t, 3H, $J = 7.2$ Hz) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta =$ 178.18, 169.20, 166.97, 165.48, 160.02, 144.57, 142.51, 135.34, 132.31, 132.15, 131.13, 127.66, 126.66, 116.34, 115.45, 56.67, 32.86, 18.16, 13.63 ppm; HRMS (EI) m/z $[M]^+$ calcd for $C_{21}H_{18}N_2O_3{}^{80}Se$ 426.0483, found 426.0485; IR: ν 2922, 1816,1779, 1658, 1627, 1501 cm^{-1}.

8-oxo-3-((2-(phenylselanyl)ethyl)amino)-8H-acenaphtho[1,2-b]pyrrole-9-carbonitrile (**4d**)



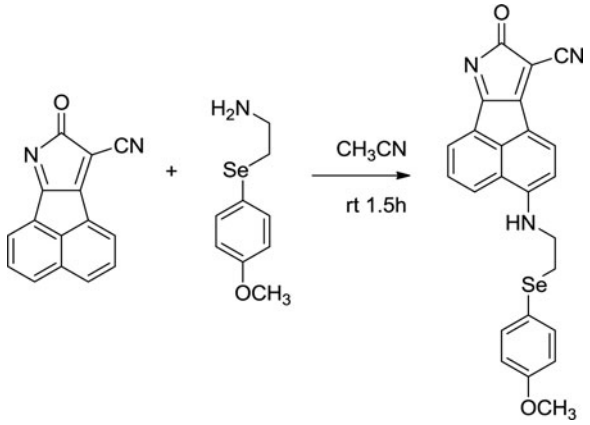
Yield 27%, dark purple powder, mp > 300°C, ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.64$ (s, 1H), 8.85 (d, 1H, $J = 7.9$ Hz), 8.65 (d, 1H, $J = 7.4$ Hz), 8.01 (d, 1H, $J = 9.1$ Hz), 7.93 (t, 1H, $J = 7.9$ Hz), 7.53 (dd, 2H, $J_1 = 1.1$ Hz, $J_2 = 8.1$ Hz), 7.26–7.17(m, 3H), 7.02 (d, 1H, $J = 9.1$ Hz), 3.92 (t, 2H, $J = 6.9$ Hz), 3.36–3.35 (m, 2H) ppm; HRMS (EI) m/z $[M]^+$ calcd for $C_{23}H_{15}N_3O^{80}Se$ 429.0380, found 429.0425; IR(KBr): ν 3284, 2217, 1619, 1562, 1529 cm^{-1}.

8-oxo-3-((2-(p-tolylselanyl)ethyl)amino)-8H-acenaphtho[1,2-b]pyrrole-9-carbonitrile (**4e**)



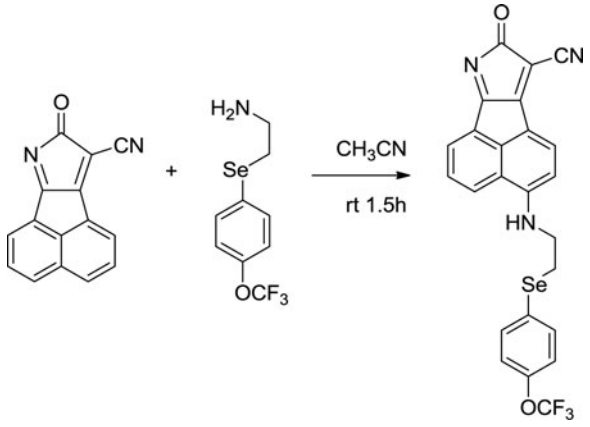
Yield 31%, dark purple powder, mp > 300°C,^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.62$ (s, 1H), 8.82 (d, 1H, $J = 8.0$ Hz), 8.64 (d, 1H, $J = 7.6$ Hz), 7.98 (d, 1H, $J = 9.0$ Hz), 7.92 (t, 1H, $J =$ 7.9 Hz), 7.39 (d, 2H, $J = 8.0$ Hz), 7.00–6.97 (m, 3H), 3.90 (s, br, 2H), 3.31–3.28 (m, 2H), 2.15 (s, 3H) ppm; HRMS (EI) m/z $[M]^+$ calcd for $C_{24}H_{17}N_3O^{80}Se$ 443.0537, found 443.0541; IR(KBr): ν 3328, 2217, 1629, 1580, 1545 cm^{-1}.

3-((2-((4-methoxyphenyl)selanyl)ethyl)amino)-8-oxo-8H-acenaphtho[1,2-b]pyrrole-9-carbonitrile (**4f**)



Yield 40%, dark purple powder, mp > 300°C,^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.62$ (s, 1H), 8.82 (d, 1H, $J = 8.0$ Hz), 8.64 (d, 1H, $J = 7.6$ Hz), 7.97 (d, 1H, $J = 8.9$ Hz), 7.91 (t, 1H, J = 7.9 Hz), 7.45 (d, 2H, $J = 8.6$ Hz), 6.95 (d, 1H, $J = 9.2$ Hz), 6.75 (d, 2H, $J = 8.6$ Hz), 5.76 (s, 3H), 3.89 (t, 2H, $J = 6.9$ Hz), 3.65 (s, 3H), 3.24 (t, 2H, $J = 6.9$ Hz) ppm; HRMS (EI) m/z $[M]^+$ calcd for $C_{24}H_{17}N_3O_2{}^{80}Se$ 459.0486, found 459.0492; IR(KBr): ν 3321, 2209, 1601, 1549 cm^{-1}.

8-oxo-3-((2-((4-(trifluoromethoxy)phenyl)selanyl)ethyl) amino)-8H-acenaphtho[1,2-b]pyrrole-9-carbonitrile (**4g**)



Yield 35%, dark purple powder, mp > 300°C, ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.61$ (s, 1H), 8.82 (d, 1H, $J = 8.1$ Hz), 8.63 (d, 1H, $J = 7.6$ Hz), 7.98 (d, 1H, $J = 9.1$ Hz), 7.91 (t, 1H, $J =$ 7.9 Hz), 7.62 (d, 2H, $J = 8.4$ Hz), 7.18 (d, 2H, $J = 8.3$ Hz), 7.01 (d, 1H, $J = 9.1$ Hz), 3.92–3.94 (m, 2H), 3.39 (t, 2H, $J = 6.8$ Hz) ppm; HRMS (EI) m/z $[M]^+$ calcd for $C_{24}H_{14}F_3N_3O_2{}^{80}Se$ 513.0203, found 513.0208; IR(KBr): ν 3317, 2258, 1637, 1526 cm^{-1}.

Evaluation of in vitro cell proliferation by MTT colorimetric assay

Growth inhibitory effects on the cell lines (Hela, HCT116, K562, A549, and MCF-7) were measured by using MTT assay.

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