Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Article
Volume 13, Issue 3, 2023, 219
https://doi.org/10.33263/BRIAC133.219

Design, Synthesis, and Biological Evaluations of Novel Naphthalene-based Organoselenocyanates

Mohamed Gouda [1], Yasir J. Abbas [2], Hany M. Abd El-Lateef [1,3], Mai M. Khalaf [1,3], Saad Shaaban [1,4,*]

[1] Department of Chemistry, College of Science, King Faisal University, P.O. Box 400 Al-Ahsa 31982, Saudi Arabia; mgoudaam@kfu.edu.sa (M.G.);
[2] College of Dentistry, University of Al-Ameed, Karbala City, P.O No:198 Karbala, Iraq; yyjj73@gmail.com (Y.J.A.);
[3] Chemistry Department, Faculty of Science, Sohag University, Sohag 82524, Egypt; hmahmed@kfu.edu.sa (H.M.A.E.-L.); mmkali@kfu.edu.sa (M.M.K.);
[4] Department of Chemistry, Faculty of Science, Mansoura University, 35516 Mansoura, Egypt; sibrahim@kfu.edu.sa (S.S.);
* Correspondence: sibrahim@kfu.edu.sa; dr_saad_chem@mans.edu.sa (S.S.);

Scopus Author ID 24475680100
Received: 17.02.2022; Accepted: 27.03.2022; Published: 5.06.2022

Abstract: Organoselenocyanates are an interesting category of organoselenium compounds as they usually warrant potential biological activity and give access to other selenium (Se) reactive species, such as selenides diselenides, selenols, and seleninic acids. Twenty-three naphthalene-based organoselenocyanates were synthesized and assessed for their potential anticancer and antimicrobial activities. Among the synthesized compounds, 4,4'-diselanediylbis(naphthalen-1-amine) (**3**), 5-imino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-4,5-dihydro-1H-pyrazol-3-amine (**5a**), 5-amino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-2,4-dihydro-3H-pyrazol-3-one (**5b**) demonstrated pronounced anti-cancer activity against the breast cancer (MCF-7) cells with minimal cytotoxicity to the primary fibroblasts (WI-38). Moreover, 5-imino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-4,5-dihydro-1H-pyrazol-3-amine (**5a**) and 2-(naphthalen-2-yloxy)-N-(4-selenocyanatonaphthalen-1-yl)acetamide (**8)** exhibited a comparable cytotoxicity to adrucil (5-FU) and showed an interesting therapeutic index (TI) (e.g., 15 and 12, respectively). Fortunately, 4,4'-diselanediylbis(naphthalen-1-amine) (**3**), 5-imino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-4,5-dihydro-1H-pyrazol-3-amine (**5a**), 5-amino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-2,4-dihydro-3H-pyrazol-3-one (**5b**) manifested also potential antimicrobial properties against *Escherichia coli* bacteria and *Candida albicans* yeast. Our results point to selective cytotoxicity against MCF-7 cells and good antimicrobial activity for some of the synthesized naphthalene-based organoselenocyanates and therefore considered potential drug candidates.

Keywords: selenocyanates; naphthalene; anticancer; antimicrobial; selectivity.

1. Introduction

Se element is a substantial micronutrient in the core of various key enzymes and proteins, known for their antioxidant activities in the human body [1-3]. Moreover, it is crucial for the proper immune system function and the metabolism of thyroid hormones [1,2,4]. Not surprisingly, the progression of different diseases, such as autoimmune diseases and cancer, have been attributed to Se deficiency [3,5,6]. On the other hand, adequate supplementation of Se is supported in cancer chemoprevention and autoimmune disease management [3,7-9]. Moreover, the regular function of several enzymes (e.g., glutathione peroxidase, thioredoxin

reductases, and iodothyronine deiodinases) relies on the Se redox center [4,10-12]. In general, organoselenium compounds are more bioactive than inorganic Se compounds [1-4,6,13]. This might be due to the superior amphiphilicity and better pharmacokinetics of organoselenium compounds compared to the inorganic Se compounds [2,3,13-17]. Therefore, organoselenium compounds have recently attracted the interest of medicinal chemists due to their unprecedented pharmacological applications [14,18-21]. They manifested antioxidants, chemopreventive, anticancer, and antiviral activities, and there is growing evidence demonstrating the potential of these compounds as chemotherapeutic agents [2,4,15,16,22-24]. Indeed, Se compounds were also used in materials science as potential semiconductors and are therefore implemented in supercapacitors, photocells, sodium-ion batteries, optoelectronics, and H_2evolution catalysts [25].

Organoselenocyanates are among the most investigated organoselenium compounds [26-31]. The selenocyanate group is not only a pharmacophore for the antitumor activity but also a key synthon in the preparation of other organoselenium functional scaffolds such as diselenide, selenate, and selenide [26,27,32-34]. Therefore, scientists' focus has recently been on developing selenocyanates, which encompass good physicochemical properties [25,26,29,30,32,35]. These compounds can metabolize to other bioactive Se metabolites such as selenol, seleninic acid, diselenide, and selenide [27,32,36].

Ebselen (**I**) is among the early discovered Se-based heterocycles with antioxidant and anti-inflammatory properties and recently reached 3 trials for various neurodegenerative disease treatment [31]. p-Xylene selenocyanate (**II**) has shown potential *in vivo* chemopreventive activity against various cancer models such as lung colon and oral tumors (Figure 1) [31,37].

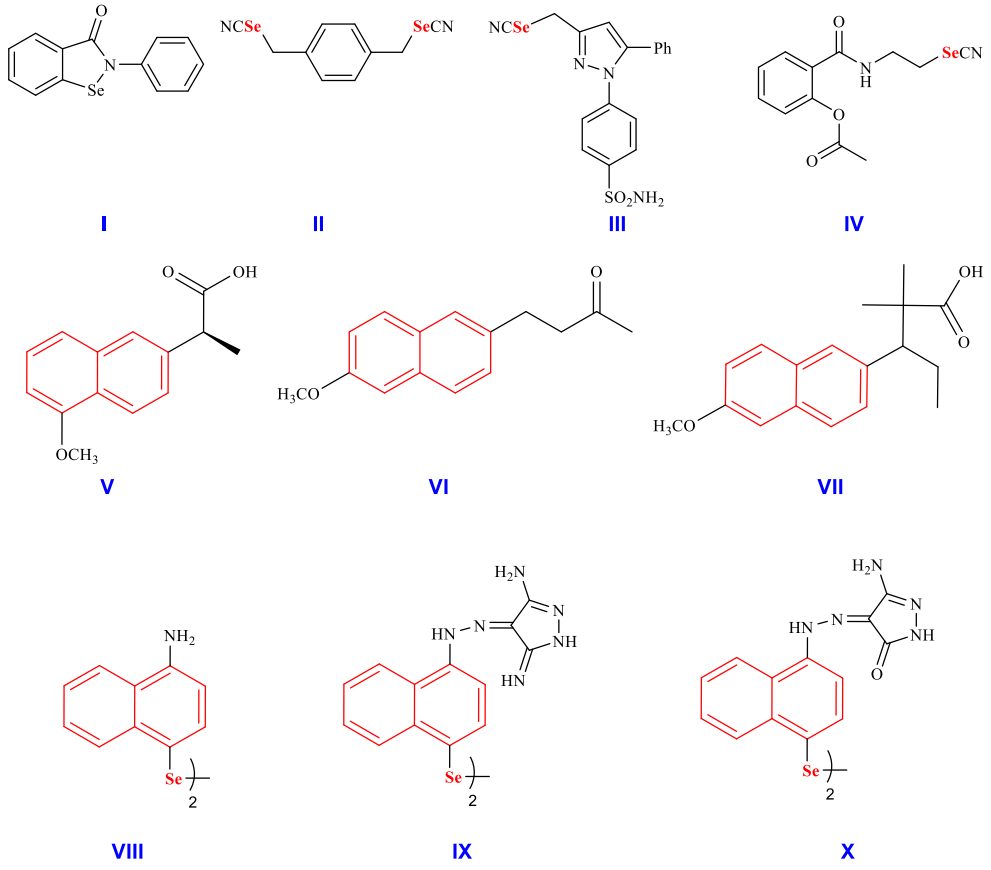


Figure 1. Biologically active selenocyanates and naphthalene-containing drugs.

Additionally, benzyl selenocyanate dietary intake has been associated with small intestinal adenocarcinoma inhibition [31,35]. Furthermore, incorporating selenocyanate moiety into the backbone of several bioactive compounds enhanced the compounds' overall pharmacological activity [38,39]. For example, the selenocyanate-based compound selenocoxib-1 (**III**) has shown potential antiproliferative activity at sub-micromolar concentrations against prostate cancer growth (Figure 1) [38]. Similarly, the aspirin-derived selenocyanate (**IV**) has also shown exciting anticancer activity against colorectal cancer and induced apoptotic cell death by poly (ADP-ribose) polymerase (PARP) cleavage and caspase 3/7 activation [39]. On the other hand, naphthalene scaffolds have attracted our attention since they present in the structure of a vast number of clinical drugs such as naproxen (**V**), nabumetone (**VI**), and methallenestril (**VII**) (Figure 1) [40-45].

Recently, we prepared naphthalene-based diselenides (**VIII-X**) with pronounced anticancer activity against the MCF-7 cancer cells [41]. Furthermore, the parent naphthalene diselenide **VIII** and pyrazoles **IX** and **X** were among the cytotoxic compounds and showed lower toxicity to the normal lung fibroblasts WI-38 with potential TI (≤11) [41]. Furthermore, these compounds manifested interesting antimicrobial activities like ampicillin and clotrimazole drugs [41].

In continuation of our projects directed towards developing novel naphthalene-based anti-HepG2 and anti-MCF-7 potential drugs [41], we are further interested in the synthesis of naphthalene-based selenocyanate analogs. The aim to design and synthesize safer and more potent naphthalene-based candidates will be of substantial interest to pharmaceutical societies. Therefore, we proposed replacing the diselenide functionality with a selenocyanate might improve the overall anticancer activity. Naphthalene-based selenocyanate analogs are unknown, and there is no report regarding their antitumor and antimicrobial properties. Indeed, there is broad proof in the literature that organoselenocyanates have an immense scope of biological applications, as some have already entered clinical trials [27,28,31,32,35]. Therefore, our aim was further extended to develop a naphthalene-based selenocyanate analog to our previously reported naphthalene based-symmetrical diselenides and evaluate their corresponding antitumor and antimicrobial activities following the same protocols to obtain evidence regarding the structural requirements underlying their potential activities.

Since hardly any broad research on aromatic selenocyanates is present in the literature, our attention was directed to synthesizing this chemically stable class of compounds. Herein we report the synthesis of naphthalene-based selenocyanates, estimate their antiproliferative activity against MCF-7, and compare their cytotoxicity in WI-38. Furthermore, the naphthalene-based organoselenocyanates were examined against *Candida albicans* yeast and *Staphylococcus aureus* and *Escherichia coli* bacteria.

2. Materials and Methods

Melting points were measured on the Gallenkamp instrument in degrees centigrade (uncorrected). Elemental analyses were performed at Cairo University. The IR spectra were recorded (KBr, ύ cm^{-1}) at Mansoura University on Mattson 5000 FTIR Spectrophotometer. The Mass spectra were measured at Cairo University on GC-MS-QP-100 EX Shimadzu instrument. The ^{1}H NMR and the ^{13}C NMR (100 MHz) spectra were measured at Cairo University using Varian Spectrophotometer at 300, 400, and 500 MHz, employing the TMS internal reference and $CDCl_3$ or DMSO-d_6 as the solvents. The chemical shifts (δ) in parts per million were recorded to the residual peak of solvents. Biological experiments were carried out at Mansoura.

Compounds number **2** and **3** were prepared according to the known literature procedures [41,46].

2.1. Synthesis and characterization.

2.1.1. Synthesis of 4-selenocyanatonaphthalen-1-amine **(2)**[46].

Selenium dioxide (SeO_2) (0.34 g, 1.5 mmol) was added to solution of malononitrile (0.1 g, 0.75 mmol) in DMSO (1 mL). The solution was stirred for 20 minutes and filtered. Naphthylamine (0.32 g, 1.12 mmol) was added to the filtrate and stirred for 1 h more. The mixture was diluted with 8 ml water, and the solid formed was filtered and recrystallized from methanol.

2.1.2. Synthesis of 4,4'-diselanediylbis(naphthalen-1-amine) **(3)**[41].

Sodium borohydride ($NaBH_4$) (113.4 mg, 3 mmol) was gradually added to aminonapthylselenocynate (**2**) (494.4 mg, 2 mmol) in ethanol (10 ml). The mixture was further stirred for 30 min and then poured into cold water. The resulting yellow precipitate was filtered and recrystallized from methanol.

2.1.3. Synthesis of *2-chloro-N-*(*4-*Selenocyanatonaphthalen-1-yl) acetamide **(6).**

Chloroacetyl chloride (1.8 ml, 4 mmol) was added to solution of 4-selenocyanatonaphthalen-1-amine (**2**) (0.48 g, 2 mmol) and K_2CO_3 (2 g, 2 mmol) in acetone (20 ml). The mixture was heated for 4 hrs and then poured into 8 ml water. The solid obtained was collected, dried, and recrystallized from methanol.

2.1.4. Synthesis of the diazo derivatives **4a** and **4b.**

4-Selenocyanatonaphthalen-1-amine (**2**) (0.12 g, 0.5 mmol) was suspended in 2.5 ml HCl. The resulting solution was cooled to 4 °C, and $NaNO_2$ (0.9 g in 2 ml water, 1.1 mmol) was then added. The solution formed was poured carefully into a 10 ml solution (H_2O: ethanol (1:1)) of sodium acetate (1.0 g) and malononitrile/ ethyl cyanoacetate (0.6 mmol). The solution was stirred for additional 120 minutes and then poured into 22 ml of water. The solid result was washed with water and recrystallized from methanol.

2.1.5. Synthesis of the pyrazoles (**5a, 5b**).

A dioxane solution (5 ml) of the azoic dyes **4a** or **4b** (0.02 mol) and hydrazinium hydroxide (0.02 mol) was heated for 14 hrs. The solid produced was recrystallized from (EtOH/DMF).

2.1.6. The reaction of α-chloroacetamide 6 with different nucleophiles.

Dioxane solution (5 ml) of α-chloroacetamide **6** (0.17 mg, 0.5 mmol), triethylamine (0.5 mmol) and the selected nucleophile (0.5 mmol) was heated for 13 hrs. The solution was then added to ice, and the solid produced was recrystallized from methanol.

2.1.7. The Ugi four-component reaction.

Methanol solution (1 ml) of 4-selenocyanatonaphthalen-1-amine (**2**) (0.5 mmol), aldehyde (0.5 mmol), amine (0.5 mmol) and isonitrile (0.6 mmol) was stirred at 27 ^{0}C for twenty-four hrs. Water (5 ml) was added and extracted with DCM. The DCM layer was dried over sodium sulfate and purified by flash chromatography.

2.1.8. The preparation of maleanilic acid **14** and glutaranilic acid **15.**

Acetone solution (12 mL) of anhydride (0.5 mmol) and 4-selenocyanatonaphthalen-1-amine (**2**) (**2**) (0.12 mg, 0.5 mmol) was heated for 6 hrs. Water was added to the solution, and the solid separated was filtered and recrystallized from methanol.

2.1.9. The preparation of cyclic imides **17**, **19.**

Acids **(32** or **33)** (0.5 mmol) and sodium acetate (50 mg) were heated in acetic anhydride (4 mL) for 4 hrs at 50 ^{0}C. Ice was added, and the solid separated was recrystallized from methanol.

2.2. Anticancer activity.

The breast adenocarcinoma (MCF-7) and normal fibroblast (WI-38) cells were obtained from American Type Culture Collection. Dulbecco's modified Eagle's medium was used as the culture medium for the cells, and the cytotoxicity was evaluated using the reported MTT assay [49]. Fluorouracil (5FU) was used as the positive reference, and the IC_{50} values were obtained from the corresponding dose-response curve.

2.3. Antimicrobial activity.

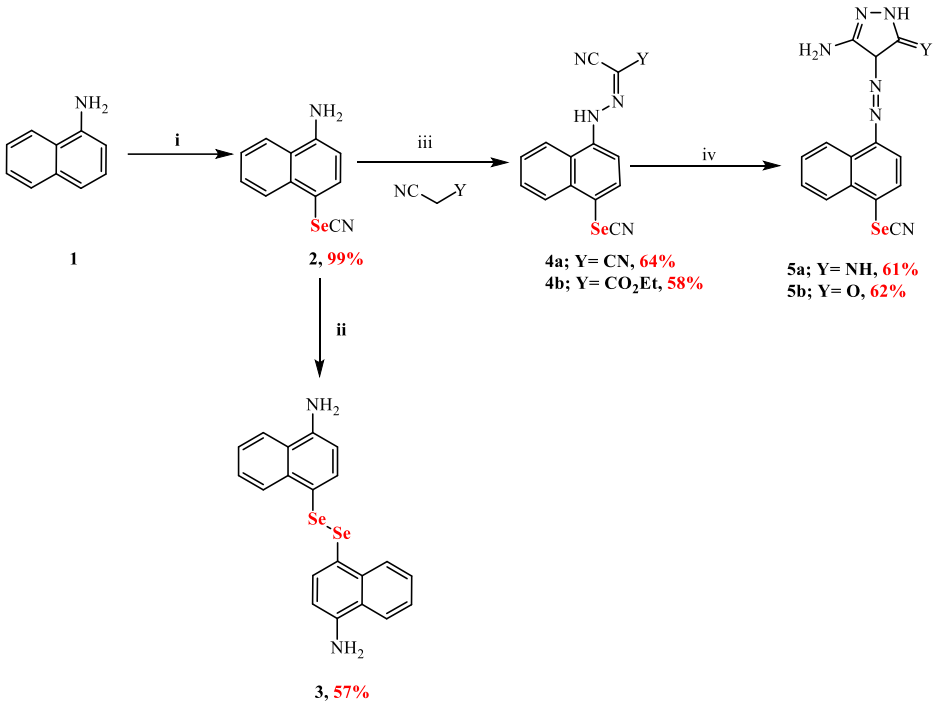
The antimicrobial activity of organoselenocyanates was evaluated against *Candida albicans* yeast and *Escherichia coli* gram-negative and *Staphylococcus aureus* gram-positive bacteria by the agar well diffusion assay. Briefly, 0.1 mL of suspension containing $1x10^4$ spores/mL of *Candida albicans* spread on potato dextrose agar medium, and $1x10^8$ CFU/mL of bacteria spread on nutrient agar. After solidification of the medium, 6 mm diameter paper discs saturated with 20 µl of organoselenocyanates (1mM in DMSO) were added to the agar plates and incubated at 35°C for 48 h, and the inhibition zones were measured. Clotrimazole and ampicillin were chosen as positive references. The relative activity index (%) was estimated as follows:

Activity index%= (organoselenocyanates inhibition zones / inhibition zone of clotrimazole or ampicillin) ×100.

3. Results and Discussion

3.1. Design and synthesis of the naphthalene-based organoselenocyanates.

4-Selenocyanatonaphthalen-1-amine (**2**) was prepared by the reaction of naphthyl amine (**1**) with triselenium dicyanide (TSD), prepared *in situ* from malononitrile and SeO_2, in DMSO. Alkaline hydrolysis of selenocyanate **2** afforded 4,4'-diselanediylbis(naphthalen-1-amine) (**3**). The latter can also be prepared via reduction using $NaBH_4$ in ethanol (Scheme 1).



Scheme 1. Synthesis of 4-selenocyanatonaphthalen-1-amine (**2**), 4-(2-(1-aminonaphthalen-4-yl)diselanyl)naphthalen-1-amine (**3**), and the corresponding azo selenocyanates (**4a-b**,**5a-b**). Conditions and reagents: (**i**) $CH_2(CN)_2/SeO_2$/DMSO; (**ii**) K_2CO_3/H_2O or $NaBH_4$/EtOH; (**iii**) $NaNO_2$/HCl; (**iv**) NH_2NH_2/dioxane.

4-Selenocyanatonaphthalen-1-amine (**2**) is a primary aromatic amine. Therefore the chemical reactivity of its amino group was preliminarily investigated using the azo-coupling reaction using different active methylenes, namely, malononitrile and ethyl cyanoacetate. The respective diazo derivatives **4a** and **4b** were synthesized by diazotization of **1** at 0-5 ^{0}C in HCl (Scheme 1).

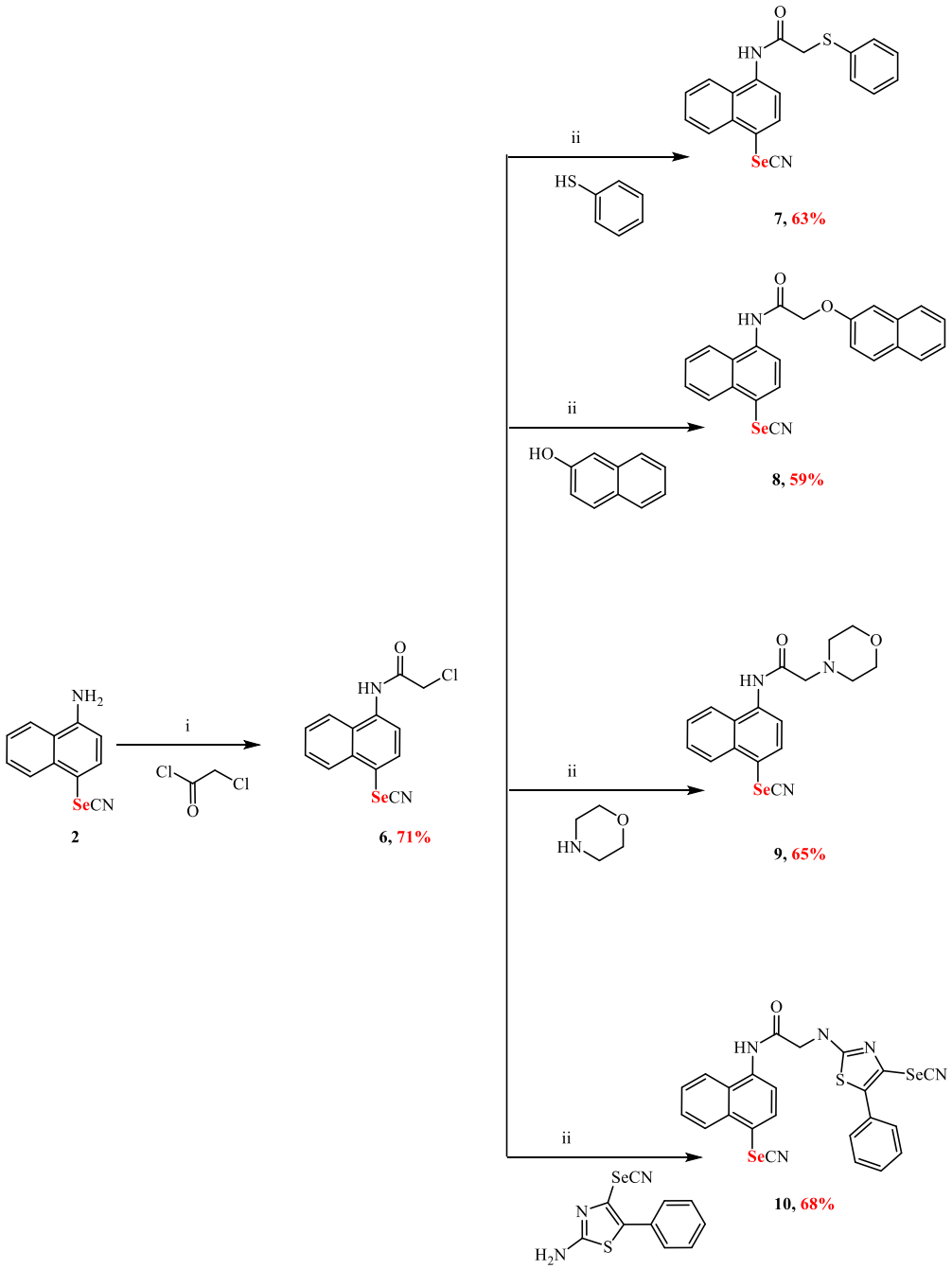
The structure of the diazo derivatives **4a** and **4b** were established using spectral analysis. The IR spectra of compound **4a** showed the distinctive NH absorption band at 3443 cm^{-1}, two characteristic CN bands at 2189 and 2151, and the Se-C band at 512 cm^{-1}. Furthermore, ^{1}H-NMR spectra of compound **4a** manifested the aromatic signals at δ 7.43-7.25 ppm, singlet signal for the NH at 7.06 ppm. The IR spectra of **4b** showed the distinctive NH absorption band at 3443 cm^{-1}, the CN band at 2226 cm^{-1}, the C=O ester band at 1743 cm^{-1}, and the Se-C band at 510 cm^{-1}. The ^{1}H-NMR spectra of compound **4b** manifested the aromatic signals at δ 8.03-7.60 ppm, the singlet signal for NH at 7.19, and the characteristic chemical shift of the ethyl group, i.e., quartet signal at 4.56 ppm for the methylene fragment and triplet signal at1.06 ppm for the methyl fragment.

Moreover, the diazo compounds **4a-b** were further used as synthons for the preparation of pyrazole selenoheterocycles. Within this context, pyrazole derivatives **5a-b** were furnished in good yields (65%) by the reaction of the diazo agents **4a-b** with hydrazinium hydroxide in dioxane (Scheme 1). The IR spectra of **5a** showed the distinctive absorption band of NH at 3449 cm^{-1}, the CN band at 2246 cm^{-1}, and the Se-C band at 496 cm^{-1}. The ^{1}H-NMR spectrum of compound **5a** manifested the aromatic signals at δ 7.45-7.23, the NH signal at 6.97 ppm, and its MS spectrum showed molecular ion peaks at 367 (M^{+1}, 0.87), and a base peak at m/z 88. Furthermore, the IR spectra of **5b** showed the distinctive absorption band of NH at 3445 cm^{-1}, the CN band at 2192 cm^{-1}, the C=O band at 1618 cm^{-1}, and the Se-C band at 514 cm^{-1}. The ^{1}H-NMR spectrum of compound **5b** revealed the aromatic signals at δ 7.60-7.32 ppm, the

NH signal at 6.90 ppm, and the ethyl group's characteristic chemical shift, i.e., quartet signal at 4.17 ppm for the methylene fragment and triplet signal at1.35 ppm for the methyl fragment.

Furthermore, 2-chloro-*N*-(4-selenocyanatonaphthalen-1-yl)acetamide (**6**) was obtained from the reaction of 4-selenocyanatonaphthalen-1-amine (**2**) with chloroacetyl chloride (Scheme 2). The former was used to attain another level of diversity via nucleophilic substitution reactions with different nucleophiles such as thiophenol, 2-naphthol, morpholine, and 4-phenyl-5-selenocyanatothiazol-2-amine in refluxing dioxane. The corresponding phenylthio **7**, naphthalenyloxy **8**, morpholino **9**, and thiazol-2-ylamino **10** derivatives were obtained in good-moderate yields (up to 70%) (Scheme 2).

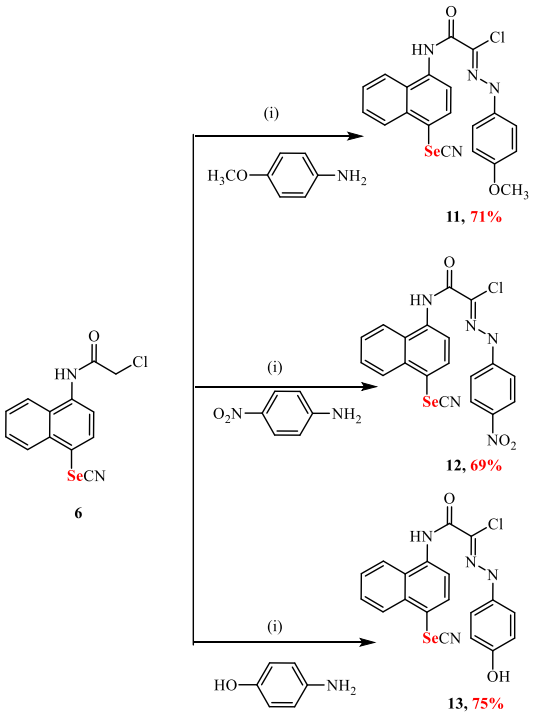
The IR spectra of **7** showed the distinctive absorption band of the NH at 3448 cm^{-1}, CN at 2066 cm^{-1}, C=O at 1685 cm^{-1}, C-S-C at 680 cm^{-1}, and Se-C at 519 cm^{-1}. The ^{1}H-NMR spectrum of compound **7** exhibited a singlet signal at δ 10.42 ppm respective to the NH and the aromatic protons at δ 7.48 -7.28 ppm, and a singlet signal the CH_2 at 3.46 ppm.



Scheme 2. Synthesis of 2-chloro-*N*-(4-selenocyanatonaphthalen-1-yl)acetamide (**6**), and its corresponding nucleophilic substitution reactions. Conditions and reagents: (**i**) K_2CO_3/acetone; (**ii**) dioxane/reflux.

The IR spectra of **8** showed the distinctive absorption band of NH band at 3365 cm^{-1}, CN at 2151 cm^{-1}, C=O at 1665 cm^{-1}, C-N at 1256 cm^{-1}, and Se-C at 515 cm^{-1}. The ^{1}H-NMR spectrum of compound **8** exhibited a singlet signal at δ 10.41 ppm corresponding to NH and the aromatic signals at δ 7.80-7.45 ppm, singlet signal for 2H at 4.49 ppm. The IR spectra of **9** showed the distinctive absorption band of NH at 3460 cm^{-1}, CN at 2145 cm^{-1}, C-H at 2964 cm^{-1}, C=O at 1633 cm^{-1}, C-N at 1286 $cm^{-1,}$ and Se-C 505 cm^{-1}. The ^{1}H-NMR spectrum of compound **9** showed a singlet signal at δ 8.32 ppm corresponding to NH and the aromatic signals at δ 7.52-7.49 ppm, triplet signal for 4H at 3.50 ppm, singlet signal for 2H at 3.35 ppm, triplet signal for 4H at 2.63 ppm. The IR spectra of **10** showed the distinctive absorption band of NH band at 3678 cm^{-1}, cyanide at 2188 cm^{-1}, C=N at 2151 cm^{-1}, C=O at 1648 cm^{-1}, C-S-C at 693 cm^{-1}, and Se-C at 519 cm^{-1}. The ^{1}H-NMR spectrum of compound **10** showed a singlet signal at δ 10.50 ppm corresponding to NH and the aromatic signals at δ 7.64-7.34 ppm, singlet signal for 2H at 4.17 ppm.

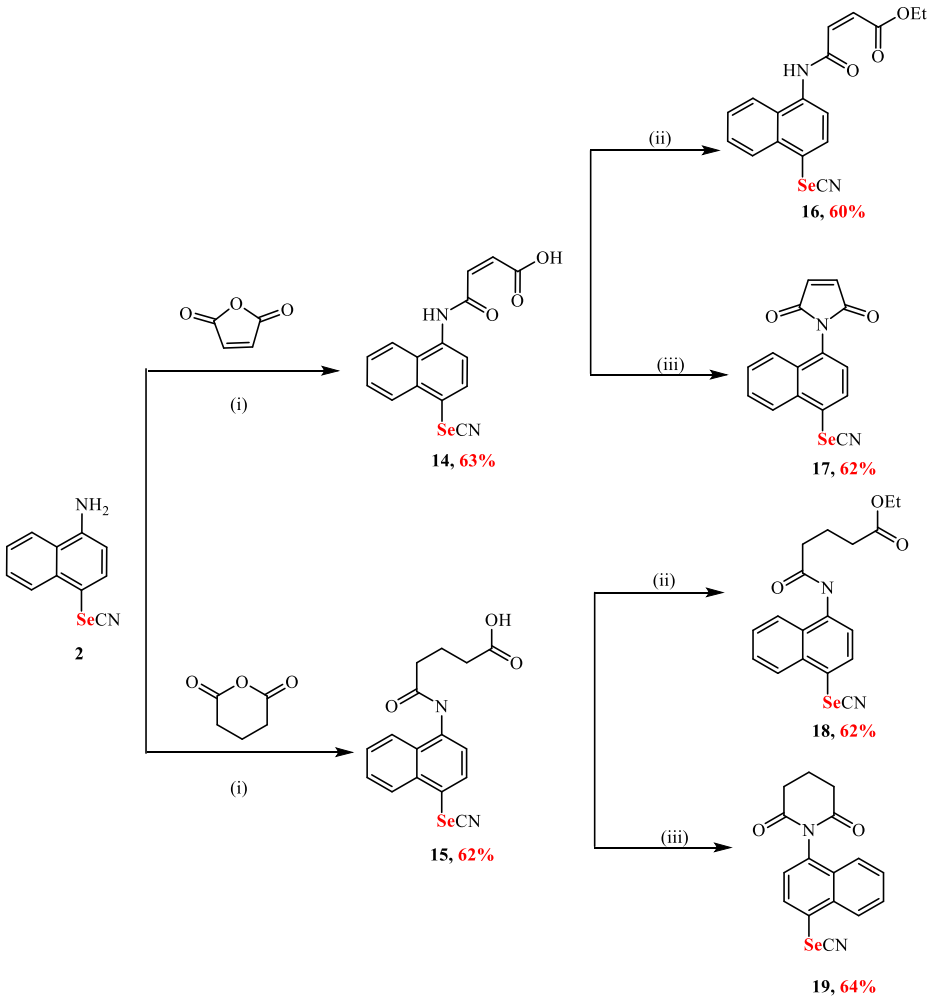
Moreover, 2-chloro-*N*-(4-selenocyanatonaphthalen-1-yl)acetamide (**6**) was subjected to further derivatization via azo-coupling with different aromatic amines, namely: *p*-anisidine, *p*-nitroaniline, and *p*-hydroxyaniline (Scheme 3). The IR spectra of **11** showed the distinctive absorption band of NH at 3447 cm^{-1}, CN at 2151 cm^{-1}, C-N at 1247 $cm^{-1,}$ and Se-C at 514 cm^{-1}. The ^{1}H-NMR spectrum of compound **11** exhibited a singlet signal for NH at 10.56 ppm, a singlet signal for NH at 9.80 ppm, and the aromatic signals appear at δ 8.33-7.21 ppm, singlet signals for 3H at 4.10 ppm. The IR spectra of **12** showed the distinctive absorption band of NH at 3448 cm^{-1}, CN at 2150 cm^{-1}, C-N at 1263 $cm^{-1,}$ and Se-C at 518 cm^{-1}. The ^{1}H-NMR spectrum of compound **12** showed a singlet signal for NH at 11.03 ppm, a singlet signal for NH at 10.08 ppm, and the aromatic signals appear at δ 8.15-7.05 ppm. The IR spectra of **13** showed the distinctive absorption band of OH at 3444 cm^{-1}, NH at 3231 cm^{-1}, CN at 2149 cm^{-1}, C-N at 1258 $cm^{-1,}$ and Se-C at 513 cm^{-1}. The ^{1}H-NMR spectrum of compound **13** showed a singlet signal for NH at 10.40 ppm, a singlet signal for NH at 10.04 ppm, and a singlet signal for OH at 9.64 ppm; the aromatic signals appear at δ 8.06-7.61 ppm.



Scheme 3. Azo-coupling reactions of 2-chloro-*N*-(4-selenocyanatonaphthalen-1-yl)acetamide (**6**). Conditions and reagents: **(i)** $NaNO_2$/HCl/EtOH.

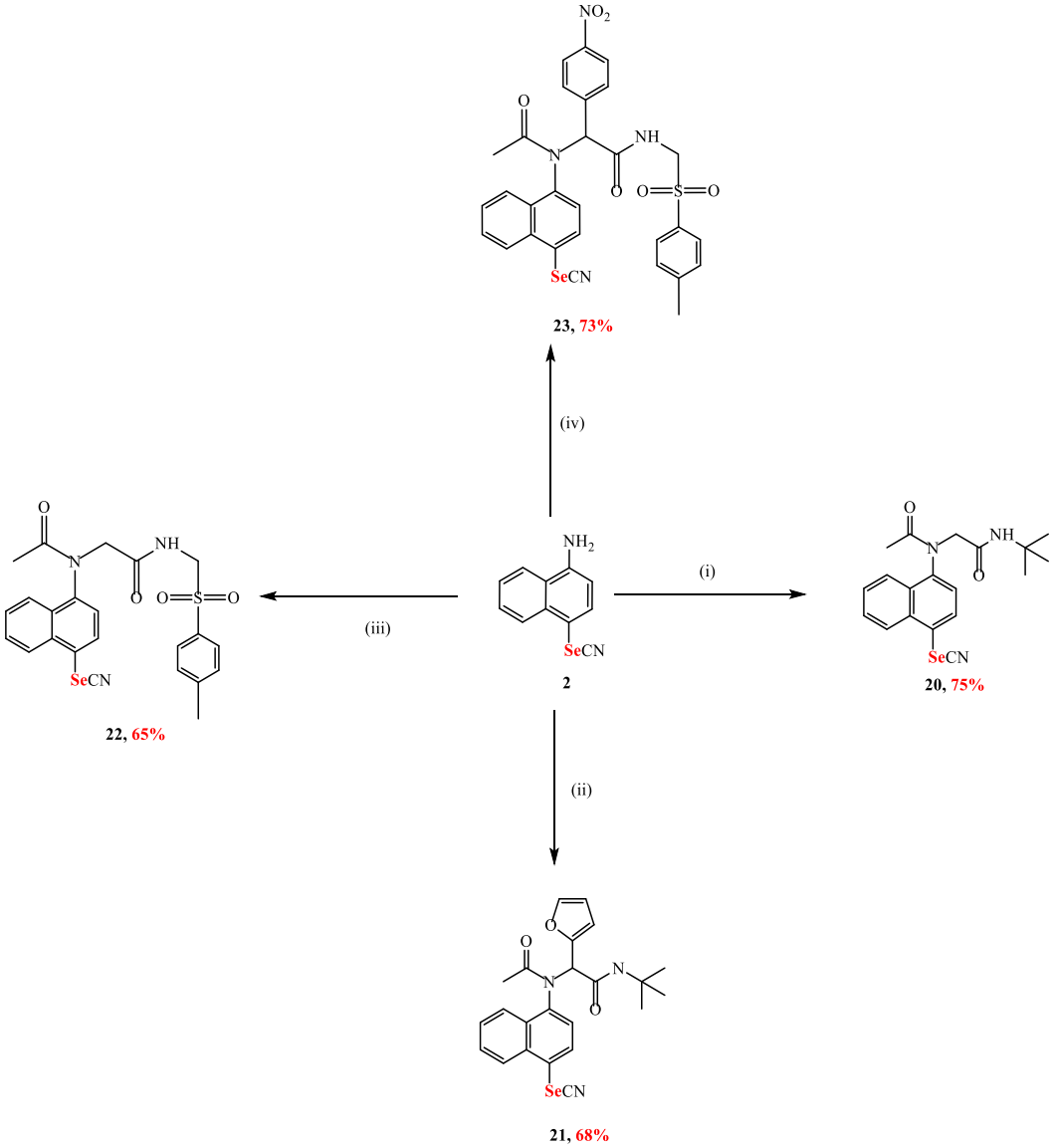
Our attention was then oriented to preparing naphthalene-based cyclic imides, which have drawn much interest in chemotherapy [47,48]. They form an integral part of various alkaloids such chlorophthalim, rebeccamycin, and isogranulatimide [48]. Indeed, they exhibited various pharmacological activities (e.g., antioxidant, antidepressant, neuroprotective, and antinociceptive) owing to their lipophilic nature, which in turn enabled their smooth absorption by cells [47]. The reactions of 4-selenocyanatonaphthalen-1-amine (**2**) with maleic and glutaric anhydrides in refluxing acetone furnished *N*-substituted maleanilic **14** and glutaranilic **15** acids in good yields (Scheme 4).

The IR spectra of **14** showed the distinctive absorption band of OH band at 3487 cm^{-1}, NH at 3450 cm^{-1}, C-H at 2998 cm^{-1}, CN at 2267 cm^{-1}, and C=O at 1708 cm^{-1}, C-N at 1263 $cm^{-1,}$ and Se-C at 497 cm^{-1}. The ^{1}H-NMR spectrum of compound **14** showed a singlet signal at δ 10.53 and 8.29 ppm corresponding to COOH and NH, respectively. The aromatic signals appear at δ 7.94-7.82 ppm, doublet of doublet signals for 2H at 6.75 (dd, 2H, 2CH) ppm. The IR spectra of **15** showed the distinctive absorption of the OH band at 3564 cm^{-1}, NH at 3448 cm^{-1}, C-H at 2932 cm^{-1}, CN at 2196 cm^{-1}, C=O at 1649 cm^{-1}, C-N at 1254 $cm^{-1,}$ and Se-C at 459 cm^{-1}. The ^{1}H-NMR spectrum of compound **15** showed a singlet signal at δ10.66, and 8.42 ppm corresponding to COOH and NH, respectively. The aromatic signals appear at δ 7.74-7.52 ppm, singlet signal for 6H at 2.45 ppm.



Scheme 4. Synthesis of *N*-substituted maleanilic**14** and glutaranilic **15** acids and their acid-catalyzed esterification and dehydration. Conditions and reagents: (**i**) acetone/55 °C; (**ii**) ethanol/H_2SO_4; (**iii**) Ac_2O/NaOAc.

Furthermore, the acid-catalyzed esterification of the monoamidic acids **14** and **15** afforded the corresponding ethyl esters **16** and **18**, respectively (Scheme 4). The IR spectra of **14** showed the distinctive absorption band of NH band at 3447 cm^{-1}, CN at 2198 cm^{-1}, C=O at 1774 cm^{-1}, C=O amid at 1623 cm^{-1}, C-N at 1256 cm^{-1}, C-O at 1020 $cm^{-1,}$ and Se-C at 459 cm^{-1}. The ^{1}H-NMR spectrum of compound **14** showed a singlet signal at δ 8.30 ppm corresponding to NH, and the aromatic signals appear at δ 7.76-7.43 ppm, doublet of doublet signals for H 6.61ppm, doublet of doublet signals for H 6.59 ppm, quartet signals for 2H at 3.40 ppm, quartet signal for 2H 1.26 ppm. The IR spectra of **15** showed the distinctive absorption band of NH band at 3448 cm^{-1}, C-H at 2933 cm^{-1}, CN at 2196 cm^{-1}, C=O at 1706 cm^{-1}, and C=O amid at 1649 cm^{-1}, C-N at 1260 cm^{-1}, C-O at 1027 cm^{-1} and Se-C at 451 cm^{-1}. The ^{1}H-NMR spectrum of compound **15** showed a singlet signal at δ 9.99 ppm corresponding to NH, and the aromatic signals appear at δ 7.56-7.96 ppm, quartet signals for 2H at 4.09 ppm, triplet signals for 4H at 2.36ppm, multiplet signals for 2H at 2.41 ppm, quartet signals for 3H at 2.60 ppm.



Scheme 5. The U-4C reaction of 4-selenocyanatonaphthalen-1-amine (**2**). Conditions and reagents: (**i**) 4-selenocyanatonaphthalen-1-amine (**2**) (1 mmol), paraformaldehyde (1 mmol), acetic acid (1 mmol), and Me_3CNC (1.1 mmol)/MeOH; (**ii**) 4-selenocyanatonaphthalen-1-amine (**2**) (1 mmol), furfuraldehyde (1 mmol), acetic acid (1 mmol), and Me_3CNC (1.1 mmol)/MeOH; (**iii**) 4-selenocyanatonaphthalen-1-amine (**2**) (1 mmol), 4-nitrobenzaldehyde (1 mmol), acetic acid (1 mmol), and (**iv**) toluenesulfonylmethyl isocyanide (1.1 mmol)/MeOH.

On the other hand, cyclic imides **17** and **19** were also achieved by dehydration followed by ring-closure of the *N*-substituted maleanilic **14** and glutaranilic **15** acids upon heating with acetic anhydride (Scheme 4).

The IR spectra of **17** showed the distinctive absorption band of the cyano group at 2196 cm^{-1}, C=O at 1653 cm^{-1}, C-N at 1261 $cm^{-1,}$ and Se-C at 454 cm^{-1}. The ^{1}H-NMR spectrum of compound **17** showed the aromatic signals appear at δ 7.73-7.23 ppm, double of doublet signals for 2H 6.67 ppm.

The IR spectra of **19** showed the distinctive absorption band of the cyano group at 2199 cm^{-1}, C=O at 1670 cm^{-1}, C-N at 1257 $cm^{-1,}$ and Se-C at 502 cm^{-1}. The ^{1}H-NMR spectrum of compound **19** showed the aromatic signals appear at δ 7.27-7.13 ppm, triplet signals for 4H at 2.50 ppm, multiplet signals for 2H at 2.25 ppm.

To this end, our preliminary studies disclosed that 4-selenocyanatonaphthalen-1-amine (**2**) possesses an active aromatic amino group. Therefore, the reactivity of **2** was further investigated in the Ugi four-component reaction (U-4C), which gives access to peptidomimetic compounds (Scheme 5) [49-53]. Commercially available aldehydes (e.g., furfuraldehyde, 4-nitrobenzaldehyde, and paraformaldehyde) were employed as the carbonyl building block. For the library validation, the high reactivity and commercially available *tert*-butyl isocyanide (Me_3CNC) and toluenesulfonylmethyl isocyanide were also incorporated, whereas acetic acid was used as the acid component [6,54].

The U-4CR one-pot sequence was started by reacting aldehyde methanolic solution with the amine, followed by adding the isocyanide and then carboxylic acid. Naphthalene selenocyanate-based peptidomimetic compounds **20**, **21**, **22**, and **23** were obtained in good yields (Scheme 5). In this context, the IR spectra of **20** showed the distinctive absorption band of NH band at 3401 cm^{-1}, CN at 2200 cm^{-1}, C=O at 1652 cm^{-1}, C-N at 1253 $cm^{-1}$and Se-C at 457cm^{-1}. The ^{1}H-NMR spectrum of compound **20** showed a singlet signal at δ 10.02 ppm corresponding to NH, and the aromatic signals appear at δ 8.01-7.89 ppm, singlet signal for 2H at4.67 ppm, singlet signal for 3H at 2.50 ppm, singlet signal for 9H at 1.22 (s, 9H, $3CH_3$) ppm. The IR spectra of **21** showed the distinctive absorption bands of the 2NH at 3388 cm^{-1}, CN at 2199 cm^{-1}, C=O at 1660 cm^{-1}, C-N at 1259 $cm^{-1}$and Se-C at 513 cm^{-1}. The ^{1}H-NMR spectrum of compound **21 s**howed a singlet signal at δ 9.62 ppm corresponding to NH, and the aromatic signals appear at δ 8.65 – 8.28 ppm. As multiplet for 3H at6.86 ppm, singlet signal for H at 5.91 ppm, singlet signal for 3H at 1.93 ppm, singlet signal for 9H at 1.29 ppm.

The structure of **22** was established based on its elemental analysis and spectral data. The IR spectra of **22** showed the distinctive absorption band of NH band at 3378 cm^{-1}, CN at 2199 cm^{-1}, C=O at 1625 cm^{-1}, C-N at 1285 cm^{-1}, C-S-C at 672 $cm^{-1}$and Se-C at 512 cm^{-1}. The ^{1}H-NMR spectrum of compound **22** showed a singlet signal at δ 9.05 ppm corresponding to NH, and the aromatic signals appear at δ 7.34-7.54 ppm, singlet signal for 2H at 4.60 ppm, singlet signal for 2Hat4.28 ppm, singlet signal for 3Hat 2.50 ppm, singlet signal for 3H at 2.32ppm. The IR spectra of **23** showed the distinctive absorption band of NH band at 3447 cm^{-1}, CN at 2150 cm^{-1}, C=O at 1626 cm^{-1}, C-N at 1286 cm^{-1}, C-S-C at 688 $cm^{-1,}$ and Se-C at 487 cm^{-1}. The ^{1}H-NMR spectrum of compound **23** showed a singlet signal at δ8.92 ppm corresponding to NH, and the aromatic signals appear at δ 8.30-7.19 ppm, singlet signal for 2H at 4.84 ppm, singlet signal for 3H at 2.39-2.36ppm, singlet signal for 3H at 2.36ppm.

3.2. Organoselenocyanates cytotoxicity evaluation against MCF-7 and normal WI-38.

As far as chemistry is concerned, it is now worth further investigating the possible pharmacological applications of the newly synthesized compounds. Therefore, our efforts were directed to evaluate their cytotoxicity against MCF-7 and compare it with their respective cytotoxicity in healthy WI-38 using the MTT assay. The positive control used is 5-FU, and the IC_{50}s were deduced from their respective dose-response curves. Furthermore, the therapeutic indices (TI) provide a basic index for estimating the efficacy and safety of a drug and are calculated according to the following equation: TI = IC_{50} for the WI-38 cells/IC_{50} for the MCF-7 cells (Table 1).

The tested compounds could be classified according to their cytotoxicity into three categories: (a) cytotoxic compounds (e.g., **3**, **5a**, **5b**, and **8**); (b) compounds with moderate cytotoxicity (e.g., **4a**, **7**, **9**, **11**, **12**, **13**, and **18**); and (c) non-cytotoxic compounds (e.g., **6**, **10**, **17**, **19**, **20**, **21**, **22**, and **23**) (Table 1).

Table 1. Organoselenocyanates cytotoxicity against MCF-7 and WI-38 cells and their respective TI values.[a]

Compounds	IC_{50} (µM)		
	MCF-7	WI-38	TI[b]
5-FU	7.82±0.13	4.11±0.63	4
3	11.8±0.18	[c]-	8
4a	42.4±2.34	62.4±4.06	2
5a	13.6±1.20	[c]-	7
5b	6.5±0.16	[c]-	15
6	[c]-	[c]-	[d]-
7	24.8±1.30	81.4±4.38	4
8	8.2±0.38	>100	12
9	38.7±1.86	74.8±3.45	3
10	[c]-	[c]-	[d]-
11	41.2±1.99	81.4±5.15	3
12	34.5±1.34	86.5±4.42	4
13	23.4±1.05	[c]-	4
14	18.5±0.98	[c]-	5
16	28.9±1.43	80.5±5.42	5
17	[c]-	[c]-	[d]-
18	36.1±2.04	76.3±3.08	2
19	[c]-	[c]-	[d]-
20	[c]-	[c]-	[d]-
21	[c]-	[c]-	[d]-
22	[c]-	[c]-	[d]-
23	[c]-	[c]-	[d]-

[a] The antiproliferative activity of MCF-7 and WI-38 cells was estimated after forty-eight hrs of incubation with serial concentrations of organoselenocyanates by MTT assay. [b]TI is calculated by dividing the respective IC_{50}s of WI-38 over the IC_{50}s of MCF-7 for each compound; [c]No growth inhibition was observed at the tested concentration ranges (IC_{50} >100 µM); [d]TI values were not significant.

Furthermore, candidates with high TI are often preferred as they can selectively kill cancer cells at lower doses without affecting normal cells. Within this context, significant selective toxicity zones were observed in the case of high and moderate cytotoxic compounds (e.g., **3**, **4a**, **5a**, **5b**, **7**, **8**, **9**, **11**, **12**, **13**, **14**, **16,** and **18**). The TI values varied from two to fifteen-fold in the magnitude of MCF-7 cells killing compared to the healthy WI-38 cells. Interestingly, most of the TI values were higher than that of 5-FU proposing their selective and effective antitumor activities. A preliminary relationship between the compounds' structure and their corresponding cytotoxic/selective activities revealed that the pyrazole- **5b** and **8** naphthalen-2-yloxy-based were among the potent compounds and exhibited comparable cytotoxicity to 5-FU as well as TI values 15 and 12, respectively. Despite our exciting results, these data are

preliminary in nature and require more in-depth studies using additional tumor and primary cells.

3.2.1. Organoselenocyanates antimicrobial activities

The interesting cytotoxic activity of organoselenocyanates encouraged us to further study their activity beyond the mammalian cells; we also, i.e., against lower organisms (e.g., bacteria and fungi). Therefore, the organoselenocyanates antimicrobial activities were estimated against *Candida albicans* yeast and *Escherichia coli* gram-negative and *Staphylococcus aureus* gram-positive bacteria using the agar diffusion assay (Table 2). Clotrimazole and ampicillin were used as the antifungal and antibacterial references, respectively. The relative activity indices were calculated as follows: activity index= 100 *(organoselenocyanates inhibition zones/reference drugs inhibition zones) and inhibition zone diameters are outlined in Table 2.

Table 2. Organoselenocyanates antimicrobial inhibition zones diameters (in mm) and their activity index.[a]

	E. coli		***S. aureus***		***C. Albicans***	
Compound	**Inhibition zone diameter (mm)**	**% Activity index**	**Inhibition zone diameter (mm)**	**% Activity index**	**Inhibition zone diameter (mm)**	**% Activity index**
3	20	83	15	68	23	82
4a	8	33	5	23	2	7
5a	19	79	15	68	20	71
5b	21	88	18	82	24	86
6	3	13	2	9	[b]-	[b]-
7	16	67	17	77	13	46
8	17	71	13	59	11	39
9	9	38	7	32	5	18
10	2	8	[b]-	[b]-	[b]-	[b]-
11	8	33	6	27	10	36
12	10	42	10	45	14	50
13	10	42	11	50	8	29
14	15	63	10	45	7	25
16	13	54	11	50	9	32
17	[b]-	[b]-	[b]-	[b]-	[b]-	[b]-
19	2	8	2	9	[b]-	[b]-
20	[b]-	[b]-	2	9	[b]-	[b]-
21	2	8	[b]-	[b]-	[b]-	[b]-
22	4	17	2	9	[b]-	[b]-
23	7	29	3	14	[b]-	[b]-
Ampicillin	24	100	22	100	[b]-	[b]-
Colitrimazole	[b]-	[b]-	[b]-	[b]-	28	100

[a] Inhibition zone diameters are in millimeters and recorded after forty-eight hrs.[b] Antimicrobial values below six mm are worthless and refer to inactive compounds.

Generally, most of the organoselenocyanates manifested enhanced antibacterial activity against the gram-negative *Escherichia coli* bacteria compared to the *Staphylococcus aureus* gram-positive bacteria. Within this regard, compounds **3**, **5a**, **5b**, **7**, and **8** were among the potent compounds against *Escherichia coli* with 67-88 activity indices.

The same activity was observed in the case of *Candida albicans*, where organoselenocyanates **3**, **5a**, and **5b** manifested 71-86 activity indices concerning Colitrimazole. These potential results were in line with that obtained from the anticancer screening and point toward interesting properties of some organoselenocyanates, which require further studies using a wider number of human pathogens.

4. Conclusions

Twenty-three naphthalene-based organoselenocyanates were synthesized in good-moderate yields, and their anticancer and antimicrobial properties were also evaluated. 4,4'-Diselanediylbis(naphthalen-1-amine) (**3**), 5-imino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-4,5-dihydro-1H-pyrazol-3-amine (**5a**), 5-amino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-2,4-dihydro-3H-pyrazol-3-one (**5b**) exhibited potential anti-MCF-7 activity and showed TI values up to fifteen folds which were higher than that of the 5-FU proposing their interesting anti-cancer activity.

Furthermore, the naphthalene-based organoselenocyanates pharmacological potential was studied beyond the cancer cells to lower organisms (e.g., *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*). Coincidentally, 4,4'-diselanediylbis(naphthalen-1-amine) (**3**), 5-imino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-4,5-dihydro-1H-pyrazol-3-amine (**5a**), 5-amino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-2,4-dihydro-3H-pyrazol-3-one (**5b**) exhibited also good antimicrobial activities compared to the reference drugs. Herein there is proof that these agents play a role in the antitumor mechanism and the antimicrobial process. However, it is still too early to conclude. A reliable structure-activity relationship requires more diverse naphthalene-based organoselenocyanate scaffolds within this context. While it might show that naphthalene-based organoselenocyanate has not a great activity, there is enough proof s to ensure further experiments and additional studies to investigate their possible mode(s) of action. Ultimately, these results boost more questions, such as their possible pharmacokinetic profiles and pharmacological applications.

Funding

This research was funded by King Faisal University, Al-Ahsa, Saudi Arabia, under the research group project track (Grant No. 1811004).

Acknowledgments

The authors acknowledge the Deanship of Scientific Research at King Faisal University, Saudi Arabia, for financial support under the research group project track (Grant No. 1811004).

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Nogueira, C.W.; Barbosa, N.V.; Rocha, J.B. Toxicology and Pharmacology of Synthetic Organoselenium Compounds: An Update. *Arch. Toxicol.* **2021**, *95*, 1179-1226, https://doi.org/10.1007/s00204-021-03003-5.
2. Makhal, P.N.; Nandi, A.; Kaki, V.R. Insights into the Recent Synthetic Advances of Organoselenium Compounds. *ChemistrySelect* **2021**, *6*, 663-679, https://doi.org/10.1002/slct.202004029.
3. Ma, Y.; Liu, M.; Zhou, Y.; Wu, H. Synthesis of Organoselenium Compounds with Elemental Selenium. *Advanced Synthesis & Catalysis* **2021**, *363*, 5386-5406, https://doi.org/10.1002/adsc.202101227.
4. Liao, L.; Zhao, X. Modern Organoselenium Catalysis: Opportunities and Challenges. *Synlett* **2021**, *32*, 1262-1268, https://doi.org/10.1055/a-1506-5532.
5. Metanis, N.; Hilvert, D. Natural and Synthetic Selenoproteins. *Curr. Opin. Chem. Biol.* **2014**, *22*, 27-34, https://doi.org/10.1016/j.cbpa.2014.09.010.

6. El-Senduny, F.F.; Shabana, S.M.; Rösel, D.; Brabek, J.; Althagafi, I.; Angeloni, G.; Manolikakes, G.; Shaaban, S. Urea-Functionalized Organoselenium Compounds as Promising Anti-HepG2 and Apoptosis-Inducing Agents. *Future Medicinal Chemistry* **2021**, *13*, 1655-1677, https://doi.org/10.4155/fmc-2021-0114.
7. Radomska, D.; Czarnomysy, R.; Radomski, D.; Bielawska, A.; Bielawski, K. Selenium as a Bioactive Micronutrient in the Human Diet and its Cancer Chemopreventive Activity. *Nutrients* **2021**, *13*, 1649, https://doi.org/10.3390/nu13051649.
8. Bevinakoppamath, S.; Ahmed, A.M.S.; Ramachandra, S.C.; Vishwanath, P.; Prashant, A. Chemopreventive and Anticancer Property of Selenoproteins in Obese Breast Cancer. *Frontiers in Pharmacology* **2021**, *12*, 618172, https://doi.org/10.3389/fphar.2021.618172.
9. Radomska, D.; Czarnomysy, R.; Radomski, D.; Bielawski, K. Selenium Compounds as Novel Potential Anticancer Agents. *International Journal of Molecular Sciences* **2021**, *22*, 1009, https://doi.org/10.3390/ijms22031009.
10. Han, L.; Pang, K.; Fu, T.; Phillips, C.J.; Gao, T. Nano-Selenium Supplementation Increases Selenoprotein (Sel) Gene Expression Profiles and Milk Selenium Concentration in Lactating Dairy Cows. *Biol. Trace Elem. Res.* **2021**, *199*, 113-119, https://doi.org/10.1007/s12011-020-02139-2.
11. Ringuet, M.T.; Hunne, B.; Lenz, M.; Bravo, D.M.; Furness, J.B. Analysis of Bioavailability and Induction of Glutathione Peroxidase by Dietary Nanoelemental, Organic and Inorganic Selenium. *Nutrients* **2021**, *13*, 1073, https://doi.org/10.3390/nu13041073.
12. Kalimuthu, K.; Keerthana, C.K.; Mohan, M.; Arivalagan, J.; Christyraj, Johnson Retnaraj Samuel Selvan; Firer, M.A.; Choudry, M.H.A.; Anto, R.J.; Lee, Y.J. The Emerging Role of Selenium Metabolic Pathways in Cancer: New Therapeutic Targets for Cancer. *J. Cell. Biochem.* **2021**, *123*, 532-542, https://doi.org/10.1002/jcb.30196.
13. Shaaban, S.; Zarrouk, A.; Vervandier-Fasseur, D.; Al-Faiyz, Y.S.; El-Sawy, H.; Althagafi, I.; Andreoletti, P.; Cherkaoui-Malki, M. Cytoprotective Organoselenium Compounds for Oligodendrocytes. *Arabian Journal of Chemistry* **2021**, *14*, 103051, https://doi.org/10.1016/j.arabjc.2021.103051.
14. Lenardão, E.J.; Santi, C.; Sancineto, L. *New Frontiers in Organoselenium Compounds*.; Springer, 2018. Volume 6330, https://doi.org/10.1007/978-3-319-92405-2.
15. Jain, V.K. An Overview of Organoselenium Chemistry: From Fundamentals to Synthesis. In *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments*, **2017**, 1-33, https://doi.org/10.1039/9781788011907-00001.
16. Barbosa, N.V.; Nogueira, C.W.; Nogara, P.A.; de Bem, A.F.; Aschner, M.; Rocha, J.B. Organoselenium Compounds as Mimics of Selenoproteins and Thiol Modifier Agents. *Metallomics* **2017**, *9*, 1703-1734, https://doi.org/10.1039/c7mt00083a.
17. Azeredo, J.B., Penteado, F., Nascimento, V., Sancineto, L., Braga, A.L., Lenardao, E.J., Santi, C. "Green Is the Color": An Update on Ecofriendly Aspects of Organoselenium Chemistry. *Molecules* **2022**, *27*, 1597, https://doi.org/10.3390/molecules27051597.
18. Kumar, S.; Engman, L.; Valgimigli, L.; Amorati, R.; Fumo, M.G.; Pedulli, G.F. Antioxidant Profile of Ethoxyquin and some of its S, Se, and Te Analogues. *J. Org. Chem.* **2007**, *72*, 6046-6055, https://doi.org/10.1021/jo0705465.
19. Martinez, E.E.; Darke, A.K.; Tangen, C.M.; Goodman, P.J.; Fowke, J.H.; Klein, E.A.; Abdulkadir, S.A. A Functional Variant in NKX3.1 Associated with Prostate Cancer Risk in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *Cancer. Prev. Res. (Phila)* **2014**, *7*, 950-957, https://doi.org/10.1158/1940-6207.CAPR-14-0075.
20. Back, T.G.; Moussa, Z. Diselenides and Allyl Selenides as Glutathione Peroxidase Mimetics. Remarkable Activity of Cyclic Seleninates Produced in Situ by the Oxidation of Allyl Ω-Hydroxyalkyl Selenides. *J. Am. Chem. Soc.* **2003**, *125*, 13455-13460, https://doi.org/10.1021/ja0357588.
21. Rahman El-Zayadi, A.; Abaza, H.; Shawky, S.; Mohamed, M.K.; Selim, O.E.; Badran, H.M. Prevalence and Epidemiological Features of Hepatocellular Carcinoma in Egypt-a Single Center Experience. *Hepatol. Res.* **2001**, *19*, 170-179, https://doi.org/10.1016/s1386-6346(00)00105-4.
22. Li, B.; Li, W.; Tian, Y.; Guo, S.; Qian, L.; Xu, D.; Cao, N. Selenium-Alleviated Hepatocyte Necrosis and DNA Damage in Cyclophosphamide-Treated Geese by Mitigating Oxidative Stress. *Biol. Trace Elem. Res.* **2020**, *193*, 508-516, https://doi.org/10.1007/s12011-019-01717-3.
23. Schomburg, L. The Other View: The Trace Element Selenium as a Micronutrient in Thyroid Disease, Diabetes, and Beyond. *Hormones* **2020**, *19*, 15-24, https://doi.org/10.1007/s42000-019-00150-4.

24. Chen, Z.; Lai, H.; Hou, L.; Chen, T. Rational Design and Action Mechanisms of Chemically Innovative Organoselenium in Cancer Therapy. *Chemical Communications* **2020**, *56*, 179-196, https://doi.org/10.1039/C9CC07683B.
25. Phadnis, PP. Synthesis strategies for organoselenium compounds and their potential applications in human life. In: *Handbook on Synthesis Strategies for Advanced Materials*. Springer; 2021, 537-641.
26. Shaaban, S.; Negm, A.; Sobh, M.A.; Wessjohann, L.A. Organoselenocyanates and Symmetrical Diselenides Redox Modulators: Design, Synthesis and Biological Evaluation. *Eur. J. Med. Chem*. **2015**, *97*, 190-201, https://doi.org/10.1016/j.ejmech.2015.05.002.
27. Shaaban, S.; Arafat, M.A.; Gaffer, H.E.; Hamama, W.S. Synthesis and Anti-Tumor Evaluation of Novel Organoselenocyanates and Symmetrical Diselenides Dyestuffs. *Der Pharma Chemica* **2014**, *6*, 186-193.
28. Sk, U.H.; Sharma, A.K.; Ghosh, S.; Bhattacharya, S. Synthesis and Biological Evaluation of Novel Spiro 6-Methoxytetralin-1,3'-Pyrrolidine Based Organoselenocyanates Against Cadmium-Induced Oxidative and Hepatic Damage in Mice. *Eur. J. Med. Chem*. **2010**, *45*, 3265-3273, https://doi.org/10.1016/j.ejmech.2010.04.001.
29. Shaaban, S.; Arafat, M.A.; Hamama, W.S. Vistas in the Domain of Organo Selenocyanates. *Arkivoc* **2014**, 470-505, https://doi.org/10.3998/ark.5550190.p008.763.
30. Garud, D.R.; Koketsu, M.; Ishihara, H. Isoselenocyanates: A Powerful Tool for the Synthesis of Selenium-Containing Heterocycles. *Molecules* **2007**, *12*, 504-535, https://doi.org/10.3390/12030504.
31. Ali, W.; Álvarez-Pérez, M.; Marć, M.A.; Salardón-Jiménez, N.; Handzlik, J.; Domínguez-Álvarez, E. The Anticancer and Chemopreventive Activity of Selenocyanate-Containing Compounds. *Current Pharmacology Reports* **2018**, *4*, 468-481, https://doi.org/10.1007/s40495-018-0160-3.
32. Chakraborty, P.; Singha Roy, S.; Bhattacharya, S. Molecular Mechanism Behind the Synergistic Activity of Diphenylmethyl Selenocyanate and Cisplatin Against Murine Tumor Model. *Anticancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents)* **2015**, *15*, 501-510, https://doi.org/10.2174/1871520615666150113123401.
33. Roy, S.S.; Chakraborty, P.; Biswas, J.; Bhattacharya, S. 2-[5-Selenocyanato-Pentyl]-6-Amino-Benzo [De] Isoquinoline-1, 3-Dione Inhibits Angiogenesis, Induces p53 Dependent Mitochondrial Apoptosis and Enhances Therapeutic Efficacy of Cyclophosphamide. *Biochimie* **2014**, *105*, 137-148, https://doi.org/10.1016/j.biochi.2014.07.010.
34. Mugesh, G.; Singh, H.B. Synthetic Organoselenium Compounds as Antioxidants: Glutathione Peroxidase Activity. *Chemical Society Reviews* **2000**, *29*, 347-357, https://doi.org/10.1039/A908114C.
35. Plano, D.; Baquedano, Y.; Moreno-Mateos, D.; Font, M.; Jiménez-Ruiz, A.; Palop, J.A.; Sanmartín, C. Selenocyanates and Diselenides: A New Class of Potent Antileishmanial Agents. *Eur. J. Med. Chem.* **2011**, *46*, 3315-3323, https://doi.org/10.1016/j.ejmech.2011.04.054.
36. Ninomiya, M.; Garud, D.R.; Koketsu, M. Biologically Significant Selenium-Containing Heterocycles. *Coord. Chem. Rev.* **2011**, *255*, 2968-2990, https://doi.org/10.1016/j.ccr.2011.07.009.
37. Alcolea, V.; Moreno, E.; Etxebeste-Mitxeltorena, M.; Navarro-Blasco, I.; González-Peñas, E.; Jiménez-Ruiz, A.; Irache, J.M.; Sanmartín, C.; Espuelas, S. 3, 5-Dimethyl-4-Isoxazoyl Selenocyanate as Promising Agent for the Treatment of Leishmania Infantum-Infected Mice. *Acta Trop.* **2021**, *215*, 105801, https://doi.org/10.1016/j.actatropica.2020.105801.
38. Desai, D.; Sinha, I.; Null, K.; Wolter, W.; Suckow, M.A.; King, T.; Amin, S.; Sinha, R. Synthesis and Antitumor Properties of Selenocoxib-1 Against Rat Prostate Adenocarcinoma Cells. *International journal of cancer* **2010**, *127*, 230-238, https://doi.org/10.1002/ijc.25033.
39. He, X.; Nie, Y.; Zhong, M.; Li, S.; Li, X.; Guo, Y.; Liu, Z.; Gao, Y.; Ding, F.; Wen, D. New Organoselenides (NSAIDs-Se Derivatives) as Potential Anticancer Agents: Synthesis, Biological Evaluation and in Silico Calculations. *Eur. J. Med. Chem*. **2021**, *218*, 113384, https://doi.org/10.1016/j.ejmech.2021.113384.
40. Shaabana, S.; Negm, A.; Ibrahim, E.E.; Elrazak, A.A Chemotherapeutic Agents for the Treatment of Hepatocellular Carcinoma: Efficacy and Mode of Action. *Onc Rev* **2014**, *8*, 25-35, https://doi.org/10.4081/oncol.2014.246.
41. Shaaban, S.; Gaffer, E.H.; Jabar, Y.; Elmorsy, S.S. Cytotoxic Naphthalene Based-Symmetrical Diselenides with Increased Selectivity Against MCF-7 Breast Cancer Cells. *International Journal of Pharmacy* **2015**, *5*, 738-746.
42. Tandon, V.K.; Maurya, H.K.; Mishra, N.N.; Shukla, P.K. Design, Synthesis and Biological Evaluation of Novel Nitrogen and Sulfur Containing Hetero-1,4-Naphthoquinones as Potent Antifungal and Antibacterial Agents. *Eur. J. Med. Chem*. **2009**, *44*, 3130-3137, https://doi.org/10.1016/j.ejmech.2009.03.006.

43. Rokade, Y.B.; Sayyed, R.Z. Naphthalene Derivatives: A New Range of Antimicrobials with High Therapeutic Value. *Rasayan J.Chem* **2009**, *2*, 972-980.
44. Bhati, S. Structure-Based Drug Designing of Naphthalene Based SARS-CoV PLpro Inhibitors for the Treatment of COVID-19. *Heliyon* **2020**, *6*, e05558, https://doi.org/10.1016/j.heliyon.2020.e05558.
45. Makar, S.; Saha, T.; Singh, S.K. Naphthalene, a Versatile Platform in Medicinal Chemistry: Sky-High Perspective. *Eur. J. Med. Chem*. **2019**, *161*, 252-276, https://doi.org/10.1016/j.ejmech.2018.10.018.
46. Kachanov, V.A.; Slabko, Y.O.; Baranova, V.O.; Shilova, V.E.; Kaminskii, A.V. Triselenium Dicyanide from Malononitrile and Selenium Dioxide. One-Pot Synthesis of Selenocyanates. *Tetrahedron Lett*. **2004**, *45*, 4461-4463, https://doi.org/10.1016/j.tetlet.2004.04.071.
47. Zhang, L.; Hao, G.F.; Tan, Y.; Xi, Z.; Huang, M.Z.; Yang, G.F. Bioactive Conformation Analysis of Cyclic Imides as Protoporphyrinogen Oxidase Inhibitor by Combining DFT Calculations, QSAR and Molecular Dynamic Simulations. *Bioorg. Med. Chem.* **2009**, *17*, 4935-4942, https://doi.org/10.1016/j.bmc.2009.06.003.
48. Smith, G.; Wermuth, U.D. Cyclic Imides and an Open-Chain Amide Carboxylic Acid from the Facile Reaction of Cis-Cyclohexane-1,2-Carboxylic Anhydride with the Isomeric Monofluoroanilines. *Acta Crystallographica Section C: Crystal Structure Communications* **2012**, *68*, 253-256, https://doi.org/10.1107/S010827011202447X.
49. Shaaban, S.; Negm, A.; Sobh, M.A.; Wessjohann, L.A. Expeditious Entry to Functionalized Pseudo-Peptidic Organoselenide Redox Modulators Via Sequential Ugi/SN Methodology. *Anticancer Agents Med. Chem.* **2016**, *16*, 621-632, https://doi.org/10.2174/1871520615666150916092035.
50. Shaaban, S.; Negm, A.; Ashmawy, A.M.; Ahmed, D.M.; Wessjohann, L.A. Combinatorial Synthesis, in Silico, Molecular and Biochemical Studies of Tetrazole-Derived Organic Selenides with Increased Selectivity Against Hepatocellular Carcinoma. *European Journal of Medicinal Chemistry* **2016**, *122*, 55-71, https://doi.org/10.1016/j.ejmech.2016.06.005.
51. Shaaban, S.; Sasse, F.; Burkholz, T.; Jacob, C. Sulfur, Selenium and Tellurium Pseudopeptides: Synthesis and Biological Evaluation. *Bioorg. Med. Chem.* **2014**, *22*, 3610-3619, https://doi.org/10.1016/j.bmc.2014.05.019.
52. Shabaan, S.; Ba, L.A.; Abbas, M.; Burkholz, T.; Denkert, A.; Gohr, A.; Wessjohann, L.A.; Sasse, F.; Weber, W.; Jacob, C. Multicomponent Reactions for the Synthesis of Multifunctional Agents with Activity Against Cancer Cells. *Chem. Commun. (Camb)* **2009**, *31*, 4702-4704, https://doi.org/10.1039/B823149D.
53. Ugi, I.; Lohberger, S.; Karl, R. The Passerini and Ugi Reactions. In *Comprehensive Organic Synthesis.*; Barry M. Trost and Ian Fleming, Eds.; Pergamon: Oxford, **1991**, 1083-1109.
54. Shaaban, S.; Shabana, S.M.; Al-Faiyz, Y.S.; Manolikakes, G.; El-Senduny, F.F. Enhancing the Chemosensitivity of HepG2 Cells Towards Cisplatin by Organoselenium Pseudopeptides. *Bioorg. Chem.* **2021**, *109*, 104713, https://doi.org/10.1016/j.bioorg.2021.104713.

Supplementary Data

Melting points were measured on Gallenkamp instrument in degree centigrade (uncorrected). Elemental analyses were performed at Cairo University. The IR spectra were recorded (KBr, ύ cm^{-1}) at Mansoura University on Mattson 5000 FTIR Spectrophotometer. The Mass spectra were measured at Cairo University on GC-MS-QP-100 EX Schimadzu instrument. The ^{1}H NMR and the ^{13}C NMR (100 MHz) spectra were measured at Cairo University using Varian Spectrophotometer at 300, 400 and 500 MHz, employing the TMS internal reference and $CDCl_3$ or DMSO-d_6 as the solvents. The chemical shifts (δ) in parts per million were recorded with respect to the residual peak of solvents. Biological experiments were carried out at Mansoura University, Faculty of Pharmacy.

Synthesis and characterization

Synthesis of 4-selenocyanatonaphthalen-1-amine (2) [46]

SeO_2 (0.34 g, 1.5 mmol) was added to solution of malononitrile (0.1 g, 0.75 mmol) in DMSO (1 mL). The solution was stirred for 20 minutes and filtered. Naphthylamine (0.32 g, 1.12 mmol) was added to the filtrate and stirred for 1 h more. The mixture was diluted with 8 ml water and the solid formed was filtered and recrystallized from methanol (Melting point = 165 ^{0}C; literature melting point 160–170 dec).

Synthesis of 4,4'-diselanediylbis(naphthalen-1-amine) (3) [41]

Sodium borohydride (113.4 mg, 3 mmol) was gradually added to aminonapthylselenocynate (**2**) (494.4 mg, 2 mmol) in ethanol (10 ml). The mixture was further stirred for 30 min and then poured on cold water. The resulting yellow precipitate was filtered and recrystallized from methanol.

Yellow crystals; yield 759.1 mg (57%); mp 192-194 ^{o}C (ethanol); R_f = 0.14 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υ_{max}. cm^{-1}: 3363 (NH_2), 2292 (C-H),1229 (C-N), 757 (Se-Se), 493 (Se-C); EIMS *m/z* (%) 443 (M^+, 14.3), 444 (M^++1, 27).

General procedure for the synthesis of diazo derivatives 4a and 4b

4-Selenocyanatonaphthalen-1-amine (**2**) (0.12 g, 0.5 mmol) was suspended in 2.5 ml HCl. The resulting solution was cooled to 4 °C, and $NaNO_2$ (0.9 g in 2 ml water, 1.1 mmol) was then added. The solution formed was poured carefully to 10 ml solution (H_2O: ethanol (1:1)) of sodium acetate (1.0 g) and malononitrile/ ethyl cyanoacetate (0.6 mmol). Solution was stirred for additional 120 minutes and then poured into 22 ml water. The solid resulted was washed with water and recrystallized from methanol.

N-(4-Selenocyanatonaphthalen-1-yl)carbonohydrazonoyl dicyanide (4a)

Brown crystals; yield 104 mg (64%); mp 173-175 ^{o}C (methanol); R_f = 0.11 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3443 (NH), 2189 (CN), 1254 (C-N), 512 (Se-C); EIMS m/z (%) 325 (M^+, 0.49); ^{1}H NMR (300 MHz, DMSO-d6) δ 8.02-7.70 (m, 4H, Ar-H), 7.43-7.25 (m, 2H, Ar-H), 7.06 (s, H, NH) ppm.

Ethyl-2-cyano-2-(2-(4-selenocyanatonaphthalen-1-yl)hydrazono)acetate (4b)

Brown-black crystals; yield 108 mg (58%); mp 177-179 ^{o}C (methanol); R_f = 0.13 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3443 (NH), 2932 (C-H), 2226 (CN), 1743 (C=O), 1251 (C-N), 510 (Se-C); EIMS m/z (%) 372 (M^+, 2.78); ^{1}H NMR (300 MHz, DMSO-d6) δ 8.03-7.60 (m, 4H, Ar-H), 7.41-7.36 (m, 2H, Ar-H), 7.19 (s, H, NH), 4.56 (q, J = 7.22 Hz, 2H, CH_2), 1.06 (t, J = 7.02 Hz, 3H, CH_3).

General procedure for the synthesis of pyrazoles (5a, 5b) *via* cyclo-condensation of 4a and 4b with hydrazine hydrate.

A dioxane solution (5 ml) of the azoic dyes **4a** or **4b** (0.02 mol) and hydrazinium hydroxide (0.02 mol) was heated for 14 hrs. The solid produced was recrystallized from (EtOH/DMF).

4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-4H-pyrazole-3,5-diamine (5a)

Brown crystals; yield 436 mg (61%); mp 183-185 ^{o}C (ethanol); R_f = 0.10 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3449 (NH_2), 2772 (C-H), 1251 (C-N), 496 (Se-C); EIMS m/z (%) 357 (M^+, 0.69); ^{1}H NMR (300 MHz, DMSO-d6) δ 8.06-7.75 (m, 4H, Ar-H), 7.45-7.23 (m, 2H, Ar-H), 6.97 (s, H, NH), 2.50 (s, H, CH).

5-amino-4-((4-selenocyanatonaphthalen-1-yl)diazenyl)-2,4-dihydro-3H-pyrazol-3-one (5b)

Brown crystals; yield 443 mg (62%); mp 186-188 ^{o}C (ethanol); R_f = 0.11 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3445 (NH), 2928 (C-H), 1618 (C=O), 1253 (C-N), 514 (Se-C); EIMS m/z (%) 358 (M^+, 0.14); ^{1}H NMR (300 MHz, DMSO-d6) δ 8.73-7.94 (m, 2H, Ar-H), 7.60-7.32 (m, 4H, Ar-H), 6.90 (s, H, NH), 2.35 (s, H, CH).

2-Chloro-N-(4-Selenocyanatonaphthalen-1-yl) acetamide (6)

Chloroacetyl chloride (1.8 ml, 4 mmol) was added to solution of 4-selenocyanatonaphthalen-1-amine (**2**) (0.48 g, 2 mmol) and K_2CO_3 (2 g, 2 mmol) in acetone (20 ml). The mixture was heated for 4 hrs and then poured into 8 ml water. The solid obtained was collected, dried and recrystallized from methanol.

Light green crystals; yield 460 mg (71%); mp 170-172 ^{o}C (methanol); R_f = 0.1 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3443 (NH), 2952 (C-H), 2150 (CN), 1663 (C=O), 1261 (C-N), 670 (C-Cl), 512 (Se-C); EIMS m/z (%) 324 (M^+, 19.08); ^{1}H NMR (300 MHz, DMSO-d6) δ 10.5 (s, H, NH), 7.80(m, 4H, Ar-H), 7.72 (m, 2H, Ar-H), 4.48 (s, 2H, CH_2).

General procedure for the reaction of α-chloroacetamide 6 with different nucleophiles (4-phenyl-5-selenocyanatothiazol-2-amine, thiophenol, α-naphthol, and morpholine)

Dioxane solution (5 ml) of α-chloroacetamide **6** (0.17 mg, 0.5 mmol), triethylamine (0.5 mmol) and the selected nucleophile (0.5 mmol) was heated for 13 hrs. The solution was then added to ice and the solid produced was recrystallized from methanol.

2-(Phenylthio)-N-(4-selenocyanatonaphthalen-1-yl)acetamide (7)

Brown crystals; yield 125 mg (63%); mp 186-188 ºC (methanol); R_f =0.2 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3448 (NH), 2929 (C-H), 2066 (CN), 1685 (C=O),1271 (C-N), 680 (C-S-C), 519(Se-C); EIMS m/z (%) 398 (M^+, 0.26); ^{1}H NMR (300 MHz, DMSO-d6) δ 10.42 (s, H, NH), 7.48-7.42 (m, 5H, Ar-H), 7.31-7.28 (m, 6H, Ar-H), 3.46 (s, 2H, CH_2).

2-(Naphthalen-2-yloxy)-N-(4-selenocyanatonaphthalen-1-yl)acetamide (8)

Brown crystals; yield 127 mg (59 %); mp 193-195 ºC (methanol); R_f = 0.21 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3365 (NH), 2855 (C-H), 2151 (CN), 1665 (C=O),1256 (C-N), 515 (Se-C); EIMS m/z (%) 432 (M^+, 0.16); ^{1}H NMR (300 MHz, DMSO-d6) δ 10.51 (s, H, NH), 8.15-8.11 (m, 6H, Ar-H), 7.80-7.45 (m, 2H, Ar-H), 7.45-7.08 (m, 5H, Ar-H), 4.49(s, 2H, CH_2).

2-Morpholino-N-(4-Selenocyanatonaphthalen-1-yl)acetamide (9)

Yellow brown crystals; yield 122 mg (65%); mp 183-185 ºC (methanol); R_f = 0.30 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3460 (NH), 2964 (C-H), 2145 (CN), 1633 (C=O),1286 (C-N), 505(Se-C); EIMS m/z (%) 375 (M^+, 8.00); ^{1}H NMR (300 MHz, DMSO-d6) δ 8.32 (s, H, NH), 8.13 -7.74 (m, 4H, Ar-H) ,7.52-7.49 (m, 2H, Ar-H), 3.44 (s, 2H, CH_2), 3.50-3.40 (m, 8H, $4CH_2$).

2-(4-phenyl-5-selenocyanatothiazol-2-ylamino)-N-(1-elenocyanatonaphthalen-4-yl)acetamide (10)

Green crystals; yield 194 mg (68%); mp 190-192 ºC (methanol); R_f = 0.09 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3447 (NH), 2151 (CN),1650 (C=O), 1266 (C-N), 693 (C-S-C), 519(Se-C); EIMS m/z (%) 569 (M^+, 1.17); ^{1}H NMR (300 MHz, DMSO-d6) δ 10.50 (s, H, NH), 8.10 -7.88 (m, 4H, Ar-H), 7.83-7.77 (m, 2H, Ar-H), 7.64-7.34 (m, 5H, Ar-H), 4.47 (s, 2H, CH_2); ^{13}C NMR (75 MHz, DMSO) δ 169.72, 165.75, 135.84, 133.53, 128.92, 128.50, 128.20, 128.12, 127.94, 127.73, 127.59, 126.83, 125.45, 124.61, 123.48, 121.48, 109.22, 104.89, 103.32, 103.13, 56.22.

N-(4-Methoxyphenyl)-2-((4-Selenocyanatonaphthalen-1-yl)amino)acetohydrazonoyl chloride (11)

To a cooled solution of 4-methoxyaniline (0.12 g, 0.5 mmol) in HCl (2 ml) was added $NaNO_2$ (0.7 g in 2 ml water, 1.1 mmol) at 4 °C. To this solution, sodium acetate (1 g) and α-chloroacetamide **6** (0.5 mmol) in (20 ml of ethanol: water (1:1)) was added and mixture was stirred for 120 minutes. The solid was recrystallized from methanol.

N-(4-Methoxyphenyl)-2-((4-Selenocyanatonaphthalen-1-yl)amino)acetohydrazonoyl chloride (11)

Brown black crystals; yield 163 mg (71%); mp 183-185 ºC (methanol); R_f = 0.11 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3447 (NH) , 2151 (CN), 1247 (C-N), 514 (Se-C); EIMS m/z (%) 473 (M^+, 0.49); ^{1}H NMR (300 MHz, DMSO-d6) δ 10.56 (s, H, NH), 8.33-8.21 (m, 4H, Ar-H), 8.09-7.82 (m, 2H, Ar-H), 7.80 (s, H, NH), 7.71-7.59 (m, 4H, Ar-H) ppm.

N-(4-Nitrophenyl)-2-((4-Selenocyanatonaphthalen-1-yl)amino)acetohydrazonoyl chloride (12)

To a cooled solution of 4-nitroaniline (0.12 g, 0.5 mmol) in HCl (2 ml) was added $NaNO_2$ (0.7 g in 2 ml water, 1.1 mmol) at 4 °C. To this solution, sodium acetate (1 g) and α-chloroacetamide **6** (0.5 mmol) in (20 ml of ethanol: water (1:1)) was added and mixture was stirred for 120 minutes. The solid was recrystallized from methanol.

N-(4-Nitrophenyl)-2-((4-selenocyanatonaphthalen-1-yl)amino)acetohydrazonoyl chloride (12)

Red black crystals; yield 163 mg (69%); mp 187-189 ºC (ethanol); R_f = 0.13 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3448 (NH), 2151 (CN), 1263 (C-N), 518 (Se-C); EIMS m/z (%) 473 (M^+, 0.09); ^{1}H NMR (300 MHz, DMSO-d6) δ 10.56 (s, H, NH), 8.33-8.21 (m, 4H, Ar-H), 8.09-7.82 (m, 2H, Ar-H), 7.80 (s, H, NH), 7.71-7.59 (m, 4H, Ar-H) ppm.

N-(4-Hydroxyphenyl)-2-((4-Selenocyanatonaphthalen-1-yl)amino)acetohydrazonoyl chloride (13)

To a cooled solution of 4-aminophenol (0.12 g, 0.5 mmol) in HCl (2 ml) was added $NaNO_2$ (0.7 g in 2 ml water, 1.1 mmol) at 4 °C. To this solution, sodium acetate (1 g) and α-chloroacetamide **6** (0.5 mmol) in (20 ml of ethanol: water (1:1)) was added and mixture was stirred for 120 minutes. The solid was recrystallized from methanol.

Red brown crystals; yield 167 mg (75%); mp 189-191 ºC (ethanol); R_f = 0.12 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. cm^{-1}: 3444 (OH), 3231 (NH), 2149 (CN), 1258 (C-N), 513 (Se-C); EIMS m/z (%) 445 (M^+ +1, 0.11); ^{1}H NMR (300 MHz, DMSO-d6) δ 10.40 (s, H, NH), 8.12-8.08 (m, 4H, Ar-H), 7.82-7.80 (m, 2H, Ar-H), 7.76-7.61 (m, 4H, Ar-H) ppm.

General procedure for the Ugi four component reaction with using compound (2)

Methanol solution (1 ml) of 4-selenocyanatonaphthalen-1-amine (**2**) (0.5 mmol), aldehyde (0.5 mmol), amine (0.5 mmol) and isonitrile (0.6 mmol) was stirred at 27 ^{0}C for twenty-four hrs. Water (5 ml) was added and extracted with DCM. The DCM layer was dried over sodium sulfate and purified by flash chromatography.

General procedure for the preparation of maleanilic acid 14 and glutaranilic acid 15

Acetone solution (12 mL) of anhydride (0.5 mmol) and 4-selenocyanatonaphthalen-1-amine (**2**) (0.12 mg, 0.5 mmol) was heated for 6 hrs. Water was added to the solution and the solid separated was filtered and recrystallized from methanol.

4-oxo-4-((4-Selenocyanatonaphthalen-1-yl)amino)but-2-enoic acid (14)

Brown yellow crystals; yield 109 mg (63%); mp 176-178 ºC (methanol); R_f = 0.45 [CH_2Cl_2/MeOH (5:2)]; IR (KBr): υmax. cm^{-1}: 3487 (O-H), 3450 (NH), 2998 (CH), 2267 (CN), 1708 (C=O), 1263 (C-N), 497(Se-C); EIMS m/z (%) 347 (M^++1, 0.11); ^{1}HNMR (300 MHz, DMSO-d6) δ 10.53 (s, H, CO_2H), δ 8.29 (s, H, NH), 7.94-7.82 (m, 4H, Ar-H), 7.24-6.90 (m, 2H, Ar-H), 6.75 (d, J= 12 Hz, 2H, 2CH).

5-oxo-5-((4-Selenocyanatonaphthalen-1-yl) amino) pentanoic acid (15)

Brown crystals; yield 122 mg (62%); mp 169-171 ^{o}C (methanol); R_f = 0.42 [CH_2Cl_2/MeOH (5:2)]; IR (KBr): υmax. cm^{-1}: 3564 (O-H), 3448 (NH), 2932 (C-H), 2196 (CN), 1774 (C=O), 1254 (C-N), 45 (Se-C); EIMS m/z (%) 362 (M^+, 0.42); ^{1}H NMR (300 MHz, DMSO-d6) δ 10.66 (s, H, COOH), 8.42 (s, H, NH), 8.16-7.80 (m, 4H, Ar-H), 7.46-6.56 (m, 2H, Ar-H), 2.57-2.36 (m, 6H, 3CH_2), 2.08-1.92 (m, 2H, CH_2).

General procedure for the preparation of ethyl ester derivatives 16 and 18

Ethanolic (15 ml) solution of acids (**32** or **33**) (0.5 mmol) and conc. H_2SO_4 (100 µl) was stirred at 28 ^{0}C for 8 hrs. Water was added to the solution and the solid separated was recrystallized from diethyl ether.

Ethyl 4-oxo-4-((4-selenocyanatonaphthalen-1-yl)amino)but-2-enoate (16)

Brown crystals; yield 224 mg (60%); mp 167-169 ^{o}C (diethyl ether); R_f = 0.14 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υmax. Cm^{-1}: 3447 (NH), 2928 (C-H), 2198 (CN), 1774 (C=), 1623 (C=O),1256 (C-N), 1020 (C-O), 459 (Se-C); EIMS m/z (%) 374 (M^+, 0.20); ^{1}H NMR (300 MHz, DMSO-d6) δ 7.76-7.43 (m, 6H, Ar-H), 7.33-7.18 (m, 2H, Ar-H) in ^{1}HNMR 6.61-6.59 (d, J = 12.01 Hz, 2H, 2CH), 4.10 (q, 2H, CH_2), 1.21 (t, J = 7.3, 0.8 Hz, 3H, CH_3).

Ethyl 5-oxo-5-((4-selenocyanatonaphthalen-1-yl) amino) pentanoate (18)

Brown crystals; yield 121 mg (62%); mp 172-174 ^{o}C (diethyl ether); R_f = 0.12 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υ max. Cm $^{-1}$: 3448 (NH), 2933 (C-H), 2196 (CN), 1706 (C=O), 1649 (C=O), 1260 (C-N), 1027 (C-O), 451 (Se-C); EIMS m/z (%) 390 (M^+, 4.12) ; ^{1}H NMR (300 MHz, DMSO-d6) δ 9.99 (s, 1H, NH), 7.56-7.96 (m, 4H, Ar-H), 7.48-6.98 (m, 2H, Ar-H), 4.09 (q, J = 7.3, 0.78 Hz, 2H, CH_2), 2.54-2.36 (t, 6H, 3CH_2), 1.26 (q, 3H, CH_3).

General procedure for the preparation of cyclic imides 17, 19

Acids **(32** or **33)** (0.5 mmol) and sodium acetate (50 mg) were heated in acetic anhydride (4 mL) for 4 hrs at 50 ^{0}C. Ice was added and the solid separated was recrystallized from methanol.

1-(4-Selenocyanatonaphthalen-1-yl)-1H-pyrrole-2,5-dione (17)

Red crystals; yield 102 mg (62%); mp 175-177 ^{o}C (methanol); R_f = 0.12 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υ_{max}. cm^{-1}:, 2928 (C-H), 2196 (CN), 1653 (C=O), 1261 (C-N), 454 (Se-C); EIMS *m/z* (%) 328 (M^+, 5.99); ^{1}H NMR (300 MHz, DMSO-d_6) 7.73-7.23 (m, 4H, Ar-H), 7.25 (d, *J* = 12.9 Hz, 2H, Ar-H), 6.67 (d, *J* = 11.4 Hz, 2H, 2CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.33, 170.24, 134.95, 133.37, 130.37, 130.17, 129.66, 129.26, 128.02, 127.03, 126.49, 125.51, 123.78, 123.55.

1-(4-Selenocyanatonaphthalen-1-yl)piperidine-2,6-dione (19)

Red crystals; yield 110 mg (64%); mp 173-175 ^{o}C (methanol); R_f = 0.10 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υ_{max}. cm^{-1}: 3061 (C-H), 2199 (CN), 1670 (C=O), 1257 (C-N),

502 (Se-C); EIMS *m/z* (%) 344 (M^++1, 1.04); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.27-7.13 (m, 4H, Ar-H), 7.65 (d, *J* = 7.7 Hz, 2H, Ar-H), 2.50-2.25 (m, 6H, 3CH_2).

N-(tert-Butyl)-2-(N-(4-Selenocyanatonaphthalen-1-yl)acetamido)acetamide (20)

Yellow crystals; yield 121 mg (75%); m p 186-188 °C (ethanol); R_f = 0.12 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υ_{max}. cm^{-1}: 3401 (NH), 2927 (C-H), 2199 (CN), 1663 (C=O), 1253 (C-N), 457(Se-C); EIMS *m/z* (%) 403 (M^+, 1.26); ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.02 (s, H, NH), 8.01-7.89 (m, 4H, Ar-H), 7.32 – 6.78 (m, 2H, Ar-H), 4.67 (s, 2H, CH_2), 2.50 (s, 3H, CH_3), 1.22 (s, 9H, 3CH_3).

N-(tert-Butyl)-2-(furan-2-yl)-2-(N-(4-Selenocyanatonaphthalen-1-yl)acetamido)acetamide (21)

Yellow crystals; yield 160 mg (68%); m p 190-192 °C (ethanol); R_f = 0.14 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υ_{max}. cm^{-1}: 3388 (NH), 2929 (C-H), 2199 (CN), 1650 (C=O), 1259 (C-N), 513(Se-C); EIMS *m/z* (%) 469 (M^+, 1.97); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.62 (s, H,NH), 8.65-8.28 (m, 4H, Ar-H), 8.09 (d, *J* = 23.7 Hz, 2H, Ar-H), 6.86-6.34 (m, 3H, Furyl-H), 5.91 (s, H, CH), 1.93 (s, 3H, CH_3), 1.29 (s, 9H, 3CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.34, 146.40, 144.07, 137.35, 133.89, 128.09, 127.61, 125.24, 124.50, 122.88, 117.03, 112.85, 110.97, 109.55, 106.03, 104.84, 75.34, 59.77, 29.59, 22.36.

N-(2-oxo-2-((Tosylmethyl)amino)ethyl)-N-(4-Selenocyanatonaphthalen-1-yl)acetamide (22)

Brown crystals; yield 167 mg (65%); m p 187-189 °C (ethanol); R_f = 0.13 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υ_{max}. cm^{-1}: 3378 (NH), 2979 (C-H), 2199 (CN), 1625 (C=O), 1285 (C-N), 672 (C-S-C), 512(Se-C); EIMS *m/z* (%) 515 (M^+, 0.32); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.97-8.67 (m, 4H, Ar-H), 8.50-7.94 (m, 2H, Ar-H), 7.34-7.54 (m, 4H, Ar-H), 4.60 (s, 2H, CH_2), 4.28 (s, 2H, CH_2), 2.50 (s, 3H, CH_3), 2.32 (s, 3H, CH_3).

2-(4-Nitrophenyl)-2-(N-(4-Selenocyanatonaphthalen-1-yl)acetamido)-N-(tosylmethyl)acetamide (23)

Orange crystals; yield 232 mg (73%); m p 193-195 °C (ethanol); R_f = 0.13 [pet. ether /ethyl acetate (4:2)]; IR (KBr): υ_{max}. cm^{-1}: 3447 (NH), 2936(C-H), 2150 (CN), 1626 (C=O), 1286 (C-N), 688 (C-S-C), 487(Se-C); EIMS *m/z* (%) 636 (M^+, 1.62) ; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, H, NH), 8.30-7.87 (d, *J* = 12.9 Hz, 4H, Ar-H), 7.85-7.70 (m, 4H, Ar-H), 7.61-7.51 (m, 4H, Ar-H), 7.33-7.19 (m, 2H, Ar-H), 5.95 (s, H, CH), 4.84 (s, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.36 (s, 3H, CH_3).