Journal of Medicinal Chemistry

Article

pubs.acs.org/jmc

Ferrocenylselenoamides: Synthesis, Characterization and Cytotoxic Properties

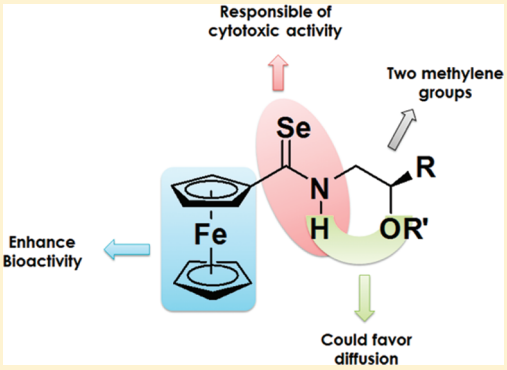
Alejandro I. Gutiérrez-Hernández,[†] José G. López-Cortés,*[,†] M. Carmen Ortega-Alfaro,[‡] M. Teresa Ramírez-Apan,[†] José de Jesús Cázares-Marinero,[†] and Rubén A. Toscano[†]

[†]Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán, C.P. 04360 México D.F., México

[‡]Instituto de Ciencias Nucleares, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán, C.P. 04360 México D.F., México

Supporting Information

ABSTRACT: A new series of ferrocenyl selenoamides **7**−**11** (FcSeNH-$(CH_2)_nCH_2(R)OH$, n = 1, 2, 3, R = H, Me, Ph) were prepared in good yields by selenative demetalation of Fischer aminocarbene complexes. The crystal structures of **7** [$FcSeNH(CH_2)_2OH$] and **19** [$PhSeNH(CH_2)_2OH$] reveal their capability to form intermolecular hydrogen bonding in solid state. Results of SRB assays show that these new selenium compounds have a good anticancer potency superior to tamoxifen and cisplatin, with IC_{50} values ranging from 4.5 to 13.32 μM against human breast cancer cell lines. A preliminary model to explain the structure−cytotoxic activity relation is proposed where different structural parameters such as the alkyl chain length, the presence of bulky groups in the same chain, the effect of hydroxyl group, and also the role of ferrocene moiety are included as being responsible for the cytotoxic response.



INTRODUCTION

Considerable efforts have been devoted to the development of new transition metal-based drugs and have gained great importance in cancer chemotherapy and other diseases.[1,2] In 1985, the concept "bioorganometallic chemistry" was introduced by Gérard Jaouen to describe any compound with a metal−carbon bond with a biological function whether naturally occurring or synthetic.[3] This kind of compounds is generally known as organometallic compounds, and due to the metal−ligand bonds with strong covalent character, are often more stable than inorganic metal coordination complexes.[4] For instance, the use of ferrocene in bioorganometallic chemistry has been growing rapidly in recent years. Ferrocenyl derivatives usually are not toxic compounds and are robust, lipophilic, and have good redox properties.[5] Several ferrocenyl compounds display interesting antitumor,[6] antimalarial,[7] antifungal,[8] and DNA-cleaving activities.[9] To improve the biological response of some organic bioactive compounds, several ferrocene derivatives have been prepared (Figure 1). Following this approach, Edwards synthesized ferrocenyl-antibiotics against penicillin resistant bacteria (I, II).[10] Then, in 1997, a ferrocenyl analogue of chloroquine called ferroquine (III) was produced, resulting in a more active compound not only against chloroquine-sensitive bacteria but also against a chloroquine resistant strain.[11] Another successful example is the well-known ferrocenyl tamoxifen analogue, ferrocifen (IV), which exhibits great activity against both hormone-dependent and hormone-independent breast cancer cells.[1a,b,2a,4b,6a,b,d]

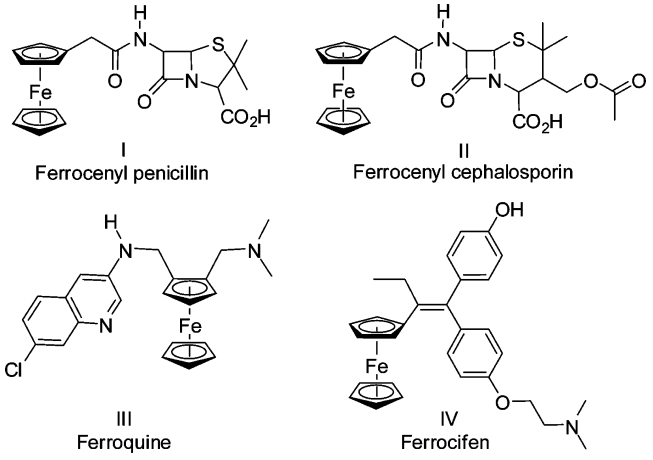
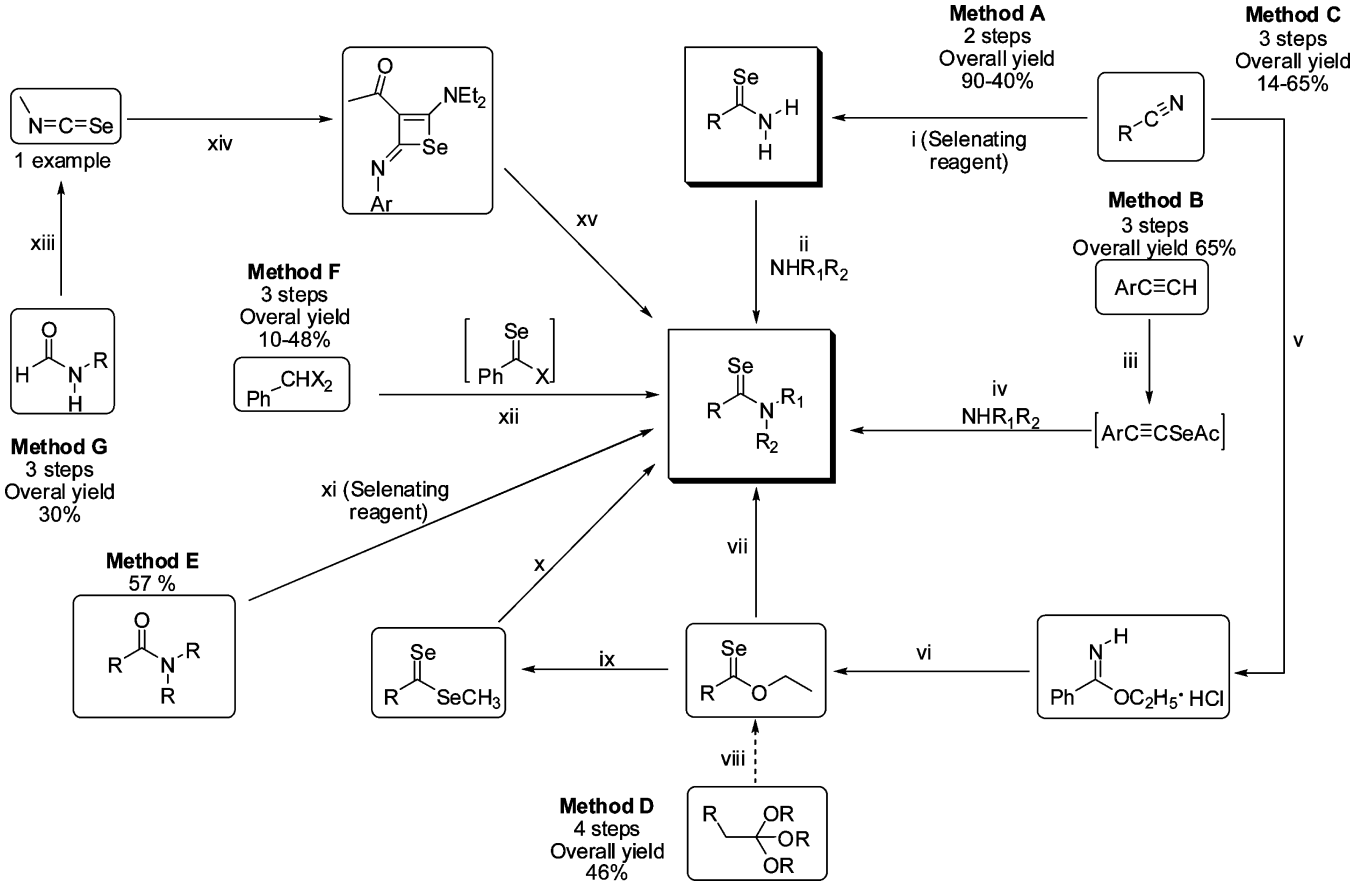


Figure 1. Some representative bioactive ferrocenyl compounds.

In the same context, during the past decade selenium compounds have attracted considerable attention in organic synthesis[12] as well as in industry.[13] Nevertheless, one of the most prolific areas of research in selenium chemistry is by the potential biological activities observed in selenoderivatives[14] such as antiviral,[15] antihypertensive,[16] antimicrobial,[17] and especially anticancer properties.[18] Moreover, many reports

Received: February 2, 2012
Published: April 23, 2012

Scheme 1. General Procedures for the Preparation of Selenoamides[a]



[a]Method A: (i) Woollins' reagent, P_2Se_5, H_2Se, Al_2Se_3, NaSeH, potassium selenobenzoate; (ii) NHR_1R_2, EtOH, HCl, 100 °C, 5h; NHR_1R_2, DMF, HCl, 100 °C, 3 h. Method B: (iii) ether, BuLi, Se, AcCl, 0 °C; (iv) NHR_1R_2, ether, 20 °C, 3 h. Method C: (v) ROH, HCl, ether, 0 °C; (vi) ethyl acetimidate, pyridine, triethylamine, H_2Se, −30 °C; (vii) Mg, EtBr, NH_2R, ether, 1 h. Method D: (viii) $(Me_2Al)_2Se$, toluene−dioxane, 50 °C, 3h; (ix) $(CH_3)_2AlSeCH_3$, toluene; (x) NHR_1R_2, THF, 0°C. Method E: (xi) $(Bu^iAlSe)_n$, $Me_2AlSeAlMe_2$, Se, $HSiCl_3$, Et_4WSe_4, LiAlHSeH, Woollins' reagent, bis-(1,5-cyclooctanediylboryl)selenide. Method F: (xii) NaH, Se, NHR_1R_2, HMPA, 120 °C. Method G: (xiii) *N*-arylformamide, Et_3N, Se, toluene reflux, 10 h; (xiv) 4-diethylamino-3-butyn-2-one, THF reflux; (xv) NHR_1R_2, THF reflux.

described the identification of various selenoproteins involved in the modulation of redox balance such as glutathione peroxidase enzyme (GPx), among others.[19] Epidemiologic evidence suggests an inverse relationship between serum selenium levels and cancer risk; Bhattachariyya suggests that 200 μg per day of selenium supplements could reduce the incidence of prostate cancer by 49%, and previous in vivo studies confirmed that selenium compounds inhibit tumor development and growth in a variety of prostate cancer models.[20]

In this context, we report an efficient synthesis for a new class of compounds with potential anticancer properties, linking as key fragments a ferrocene skeleton and a functional group containing selenium, as a strategy designed to have a positive synergic effect on anticancer properties. A synthetic strategy based on the oxidative demetalation using $NaBH_4$ and elemental selenium of Fischer aminocarbene complexes was used to synthesize ferrocenyl selenoamides as bioactive compounds. The cytotoxic activity of a series of selenoamides was determined using IC_{50} values obtained against different human cancer cell lines.

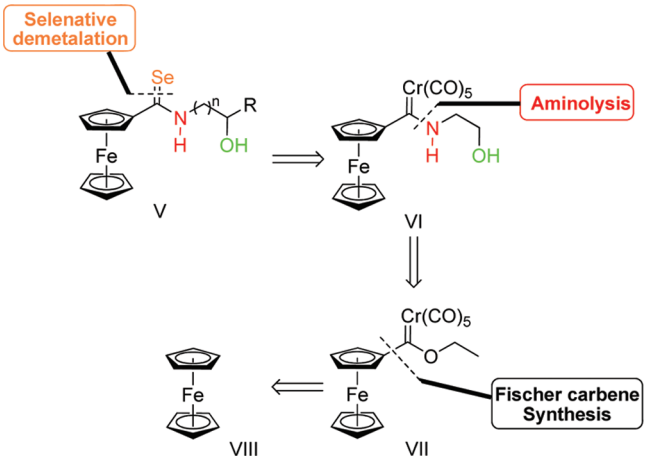
RESULTS AND DISCUSSION

Synthesis. As described above, our goal is to prepare a new family of ferrocenyl selenoamides, which combines two fragments with potential biological properties. Although several methods have been recently reported for the conversion of carbonyl groups to the corresponding selenocarbonyl compounds through treatment with various selenating reagents possessing reactive metal−selenium bonds,[21] the syntheses of the selenocarbonyl compounds have often been impeded by the difficulty of preparing and treating such selenating reagents. Current interest has thus concentrated on the use of elemental selenium in combination with an appropriate reducing agent as the reagent to introduce the selenium functionalities into organic compounds.[22] Despite the efforts in this area, there are no methodologies to prepare ferrocenyl selenoamides and much less if they contain sensitive functional groups (Scheme 1). Thus, a good alternative for accessing ferrocenyl selenoamides could be via an extended methodology based on the oxidative demetalation of Fischer carbene complexes using elemental selenium/$NaBH_4$.[23]

The retrosynthetic analysis of target ferrocenyl selenoamide **V** is outlined in Scheme 2. Ferrocenyl selenoamide **V** has functional groups capable of forming hydrogen bond interactions. We envisaged that the selenium carbonyl group

dx.doi.org/10.1021/jm300150t | J. Med. Chem. 2012, 55, 4652−4663

Scheme 2. Retrosynthetic Planning for Obtaining of New Ferrocenyl Selenoamides



might be introduced through selenative removal of the metallic fragment in **VI**. The fragment containing the functional groups **N−H** and **O−H** could be introduced via aminolysis of ethoxyferrocenyl Fischer carbene complex **VII**, which could be easily prepared from ferrocene. The introduction of functional groups in the side chain of the amine will allow selenoamides to have good solubility properties and the talent to promote specific interactions with biomolecular targets by hydrogen bond interaction.

The ethoxyferrocenyl Fischer carbene complex **1** was prepared through improved methods already described in the literature[24] and was used in aminolysis reaction using different amino alcohols leading the complexes **2−6** (Scheme 3). These reactions are nearly quantitative and proceed with a short reaction time (Table 1).

The new Fischer aminocarbene complexes **4−6** exhibit on their infrared spectra bands around 2000 cm^{-1} characteristic of Cr-CO. In all cases, the molecular ion is observed in the mass spectra (FAB^+). In the ^{13}C NMR spectra, a signal for carbenic carbon around δ = 270 ppm is observed, as well as signals around δ = 200−225 ppm for Cr-*CO*.

With aminocarbenes **2−6** in hand, we then proceed with the selenative removal of the metal fragment. As shown in Scheme 3, a 10-fold excess of the selenating reagent ($Se/NaBH_4$) in ethanol at room temperature is required to complete these reactions (Scheme 3).

The new ferrocenyl selenoamides **7−11** were obtained as red solids in excellent yields. Table 2 summarizes the ideal conditions for the reaction of selenative demetalation of complexes **2−6** to afford the new ferrocenyl selenoamides **7−11**. The ferrocenyl selenoamides were characterized by

Table 1. Yields of Fischer Aminocarbene Complexes 2−6, 12, 14, and 15

entry	compd	time (min)	yield (%)[a]
1	**2**[b]	15	91
2	**3**[b]	30	90
3	**4**	60	97
4	**5**	15	97
5	**6**[c]	30	99
6	**12**[b]	20	99
7	**14**	20	99
8	**15**[d]	48 h	37

[a]Yields are for pure isolated materials. [b]Already described in the ref 23b. [c]The reaction proceeds with addition of NaH (10 mol). [d]The reaction proceeds with addition of NaH (10 mol) and stirring of 48 h.

Table 2. Yields of Ferrocenyl Selenoamides 7−11, 13, 16, and 17

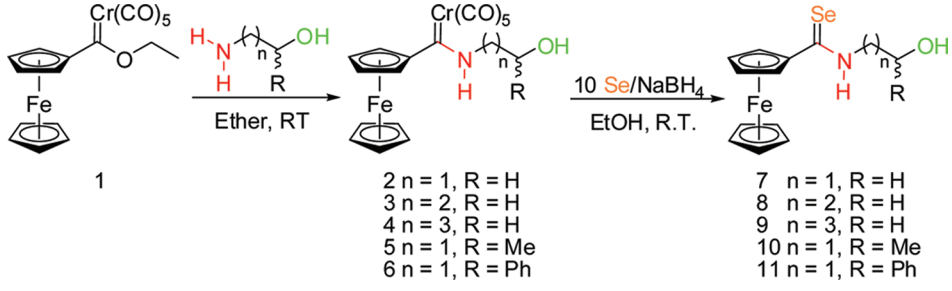
entry	compd	time (min)	yield (%)[a]
1	**7**	45	98
2	**8**	60	81
3	**9**	60	88
4	**10**	30	92
5	**11**	30	91
6	**13**	30	80
7	**16**	30	97
8	**17**	30	46

[a]Yields are for pure isolated materials.

conventional spectroscopic techniques. They exhibit in infrared spectra a characteristic band between 1500 and 1400 cm^{-1} assigned to the fragment N−C═Se. The mass spectrum (EI) of each compound agrees with the molecular formula of the expected selenocarbonyl compound and confirms the loss of the metallic fragment [$Cr(CO_5)$] in all cases. The ^{13}C NMR spectrum exhibits a signal around δ = 203 ppm assigned to *C*═Se.

The structural arrangement for **7** was fully established by a single-crystal X-ray diffraction analysis (Figure 2). The selenocarbonyl moiety is directly bonded to ferrocene; the sum of bond angles around C11 ($\sum$ = 359.94°) indicates that this group has a trigonal geometry. The bond distance C═Se [Se(1)−C(11) 1.838 (2)] is quite similar to other reported selenoamides, whereas the bond distance N(1)−C(11) 1.318(3) is relatively longest.[25] The structure presents disorder in one of Cp ring generating two orientations in 71:29 ratio. Only the major contributor is shown in Figure 2. Intermolecular hydrogen bonds N−H···O are an important feature in the solid state packing, providing evidence of the

Scheme 3. Selenative Demetalation of Fischer Aminocarbene Complexes



dx.doi.org/10.1021/jm300150t | J. Med. Chem. 2012, 55, 4652−4663

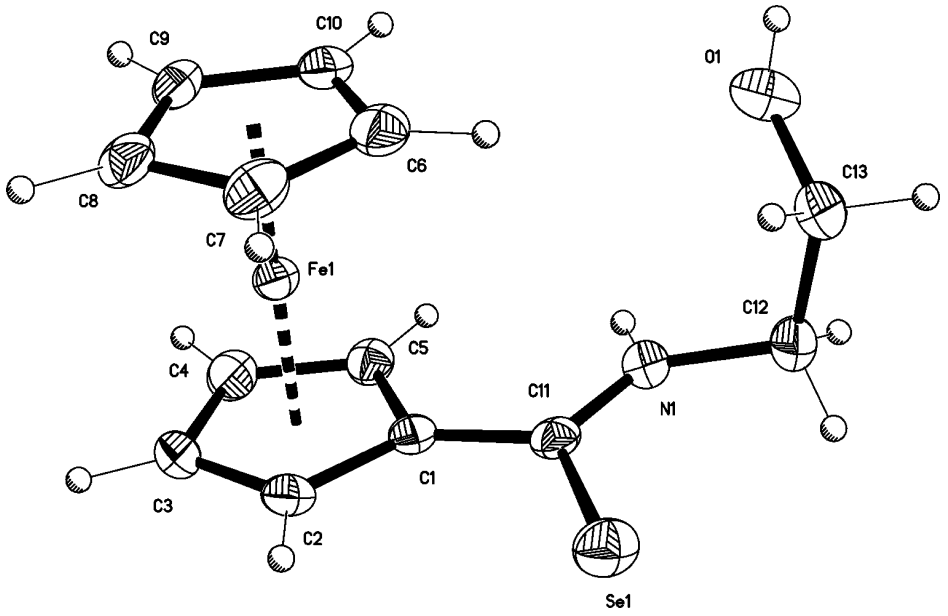


Figure 2. ORTEP representation of ferrocenyl selenoamide **7**. Ellipsoids are shown at 30% probability level. Selected bond lengths [Å] and angles [deg]: Se(1)−C(11) 1.838 (2), N(1)−C(11) 1.318 (3), C(1)−C(11) 1.463 (3); N(1)−C(11)−Se(1) 122.38(17), C(1)−C(11)−Se(1) 120.66(16), N(1)−C(12)−C(13) 111.23(19).

Table 3. Inhibition of the Growth (%) of Human Tumor Cell Lines for 7−11, 7S, and 13 at 50 μM in EtOH

		cell lines					
entry	compd	U251	PC-3	K562	HCT-15	MCF-7	SKLU-1
1	**7**	98.27	88.64	62.68	98.51	>100	95.7
2	**8**	>100	88.51	21.80	98.01	>100	98.04
3	**9**	92.46	75.47	41.01	96.19	>100	95.37
4	**10**	88.85	76.24	33.22	97.28	>100	95.38
5	**11**	68.76	51.46	12.4	47.72	67.75	48.17
6	**7S**	<0	<0	<0	<0	41.32	<0
7	**13**	<0	40.85	63.17	<0	81.96	84.49

capability of the hydroxyl groups on the side chain to favor the formation of dimers and may be a significant influence in biological systems.

Cytotoxicity of the Selenoamides 7−11. The cytotoxicities of the selenocarbonyl compounds toward different cancer cell lines, including human glioblastoma (CNS U251), human prostatic adenocarcinoma (PC-3), human chronic myelogenous leukemia (K562), human colorectal adenocarcinoma (HCT-15), human mammary adenocarcinoma (MCF-7), and non-small cell lung cancer (SKLU) were determined by using the protein-binding dye sulforhodamine B (SRB) assay in microculture to determine cell growth.[26] The initial cytotoxic screening data listed in Table 3 show excellent activities specifically toward U251, HCT-15, and MCF-7 tumor cell lines.

From those data, we observe good values of cell growth inhibition, **7** being the most active compound. To assess the influence of the chalcogen moiety in the cytotoxic activity shown by the new family of ferrocenyl selenoamides (**7**−**11**), we synthesized the sulfur analogue (**7S**) (Figure 3) of compound **7**. The synthesis of compound **7S** was achieved using the same protocol already described by us in the literature.[23b]

Once this analogue **7S** had been prepared, it was submitted to the same biological tests. The results of the cytotoxic screening (Figure 4) demonstrate that the presence of the selenium atom is absolutely necessary, given that if this atom is

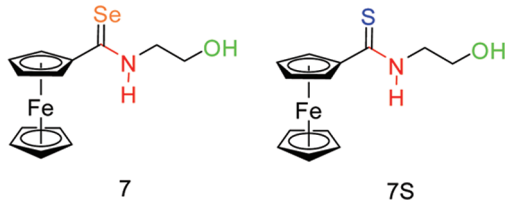


Figure 3. Influence of chalcogen moiety.

replaced by sulfur, the cytotoxic activity disappears, obtaining only a minimum of activity against MCF-7 cancer cell line with 41.32% of inhibition of the cell grown (Table 3 entry 6).

To gain more information about the key fragments responsible for cytotoxicity, we evaluated the role of the hydroxyl group in the inhibition of cell growth. The strategy was to synthesize an analogue of compound **7** without the hydroxyl group in its structure (Scheme 4). The synthesis of compound **13** involves the preparation of the Fischer aminocarbene complex **12** using improved methods already described in the literature (Table 1, entry 6).[24] Once complex **12** had been prepared, the selenium derivative **13** was synthesized using the selenative demetalation reaction under the conditions previously described (Table 2, entry 7).

The results of cytotoxic screening of compound **13** (Figure 4) compared with the selenoamide **7** reveal that the hydroxyl

dx.doi.org/10.1021/jm300150t | J. Med. Chem. 2012, 55, 4652−4663

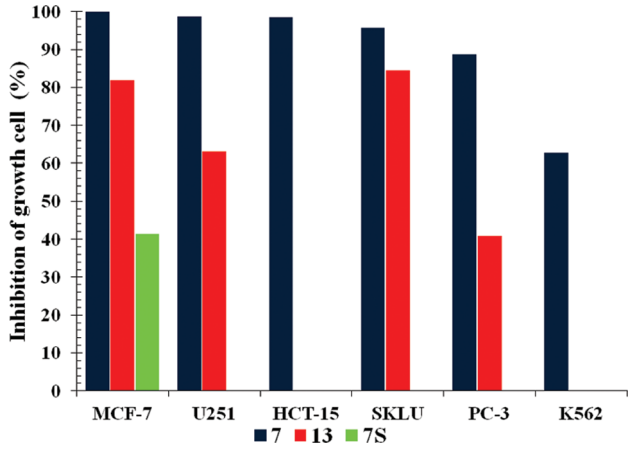


Figure 4. Effect of chalcogen atom and acceptor group on the bioactivity.

group is very important in the cytotoxic activity, so if this group is not included a significant loss of the cytotoxic activity is observed, which means that the hydroxyl group could participate by allowing a specific interaction with its probable biomolecular target.

With the aim of effectively rationalizing the influence of the length of the side chain and the possible steric hindrance produced by an alkyl or aryl group over the side chain, we have included the compounds **8**, **9**, **10**, and **11** (Figure 5). We determined the IC_{50} over MCF-7, U251, and HCT-15 cancer cell lines, where the compounds **7**−**11** were more active (Table 4). Analyzing these results, we observe that the most active compound is **7**, with IC_{50} values around 4.5 μM toward MCF-7 and HCT-15 cancer cell lines. A comparison between the compounds **7**, **8**, and **9**, including different lengths in the alkyl side chain, indicates that if the chain length increases, biological activity decreases (Figure 6). On the other hand, the bulky groups on the alkyl chain dramatically decrease the cytotoxic activity (Compounds **10** and **11**, Table 4, entry 4 and 5). These results imply that the selenoamide **7** could be considered as the leader compound in this study.

As we suggested above, the molecular design of these bioactive compounds was envisioned, considering that these systems could form a weak hydrogen bond interaction,[27] because this interaction could provide an equilibrium between a closed conformation, enhancing their lipophilic properties, and increasing their permeability through the membrane, and an open conformation, where the polar groups could be solvated, and therefore be more water-soluble (Scheme 5).[28] Nevertheless, as was described in the X-ray structure analysis of lead **7**, the hydrogen bond in solid state is intermolecular rather than intramolecular; however, the cytotoxic screenings and IC_{50} determinations were obtained in solution.

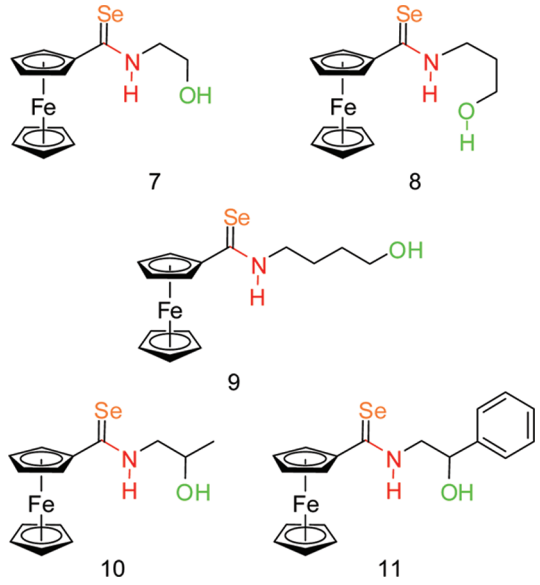


Figure 5. Variations in the structure of ferrocenylselenoamides.

Table 4. IC_{50} (μM) of Human Tumor Cell Lines for 7−11, 16, 17, 19, Tamoxifen, and Cisplatin at 48 h in EtOH

entry	compd	U251	HCT-15	MCF-7
1	**7**	7.24 ± 0.5	4.48 ± 0.09	4.58 ± 0.4
2	**8**	7.78 ± 0.4	11.65 ± 1.0	13.62 ± 1.2
3	**9**	7.52 ± 0.3	10.99 ± 1.0	12.69 ± 0.9
4	**10**	7.15 ± 0.5	11.26 ± 1.1	9.87 ± 0.6
5	**11**	38.47 ± 1.6	32.58 ± 3.0	37.28 ± 2.8
6	**16**	6.80 ± 0.2	9.14 ± 0.44	9.44 ± 0.29
7	**17**	25.17 ± 0.88	35.62 ± 1.5	40.64 ± 3.5
8	**19**	15 ± 0.5	16.6 ± 1.4	17.01 ± 0.9
9	tamoxifen	13.63 ± 1.3	13.3 ± 1.1	12.78 ± 1.1
10	cisplatin	9.5 ± 0.7	13.5 ± 0.7	25.8 ± 2.3

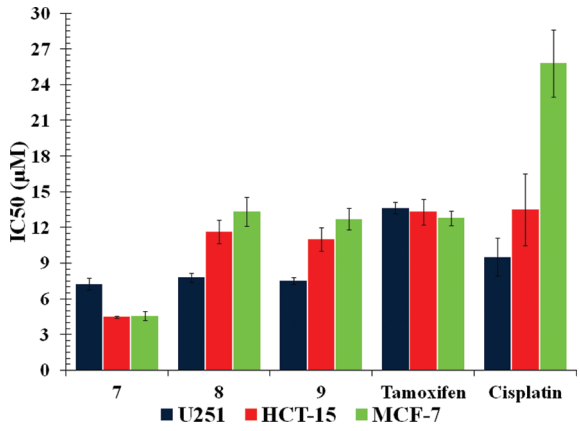
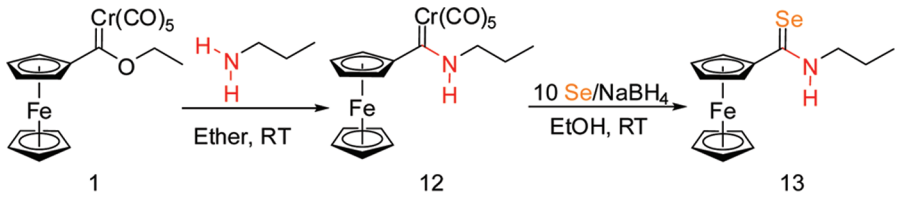


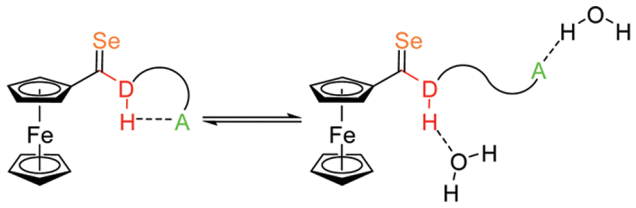
Figure 6. IC_{50} (μM) of compounds **7**−**9** in selected cancer cell lines.

Scheme 4. Synthesis of Ferrocenyl Selenoamide 13



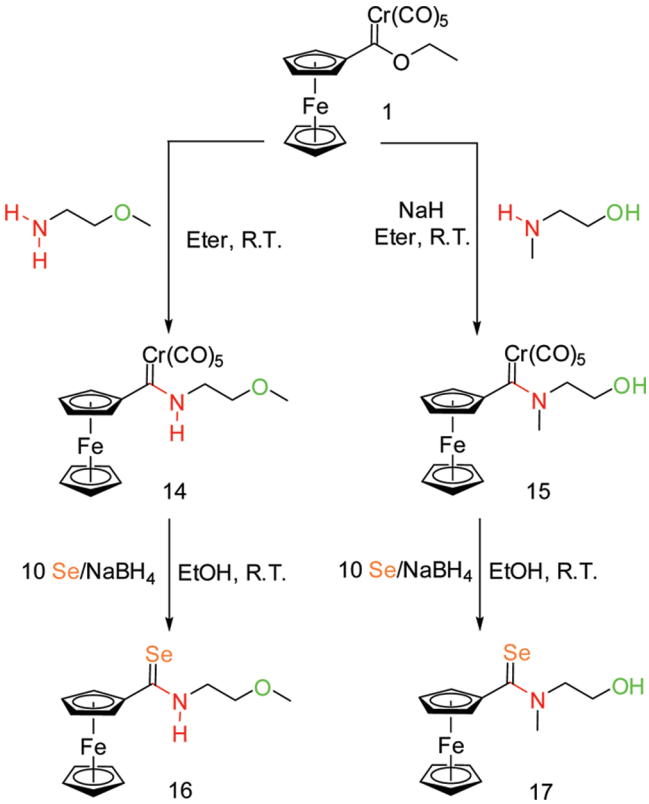
dx.doi.org/10.1021/jm300150t | J. Med. Chem. 2012, 55, 4652−4663

Scheme 5. Ferrocenyl Selenoamides with Hydrogen Bond Donor (D−H) and Acceptor (A) Functionalities in Proximity Often Occur in a Thermodynamic Equilibrium between Closed (left) and Open (right) Conformations



Nevertheless, the leader compound (**7**) contains two different groups (NH and OH) that could participate in a hydrogen bond interaction. Taking into account this possibility, we decided to synthesize separately the corresponding methylated derivatives of each functional group (**16** and **17**) (Scheme 6).

Scheme 6. Synthetic Route for the Synthesis of Ferrocenyl Selenoamides 16 and 17



The selenoamides **16** and **17** (Table 2, entries 7 and 8) were prepared by a selenative demetalation of the corresponding aminocarbene complexes **14** and **15**, respectively (Table 1, entries 7 and 8) (Scheme 6). The synthesis of complex **14** occurs without complication, obtaining the expected product as a red solid in almost quantitative yield (99%). Common spectroscopic characterization denotes signals according to those observed for all previously described aminocarbenes. Compound **16** was obtained from **14** after a subsequent selenative demetalation as a red solid in 97% yield. Characterization of **16** shows spectroscopic data similar to those observed in selenoamides described here.

The synthesis of complex **15** was a little tricky due to the nature of the amine used in the aminolysis reaction. The use of secondary amines in this kind of reaction often involves longer reaction times, which causes decomposition of the starting carbene, side-products, or in fact does not even carry on. To favor this transformation, NaH was added to the reaction mixture to afford the complex **15** after 48 h of reaction in 37% yield. Ferrocenyl selenoamide **17** was obtained using the selenative demetalation protocol previously described from **17** in moderate yields (46%) and a short period time of reaction (30 min). Common spectroscopic characterization techniques allowed the structural determination of both compounds **15** and **17**, respectively.

To establish the importance of the hydrogen atom on cytotoxic activity, that either belong to hydroxyl group or the selenoamide moiety, the compounds **16** and **17** were the subject of IC_{50} determination against MCF-7, HCT-15, and U251 cancer cell lines and their values were compared with those obtained for lead compound **7** (Table 4, entries 6 and 7). The IC_{50} values obtained for selenoamide **16** are close to those observed in the selenoamide **7** for U251 cancer cell line, whereas the cytotoxic activity of **16** is lower than **7** toward MCF-7 and HCT-15 cancer cell lines. However, the IC_{50} values shown by selenoamide **17** are lower than those of **7** and **16** in every cancer cell line (Figure 7). From these data, we could say

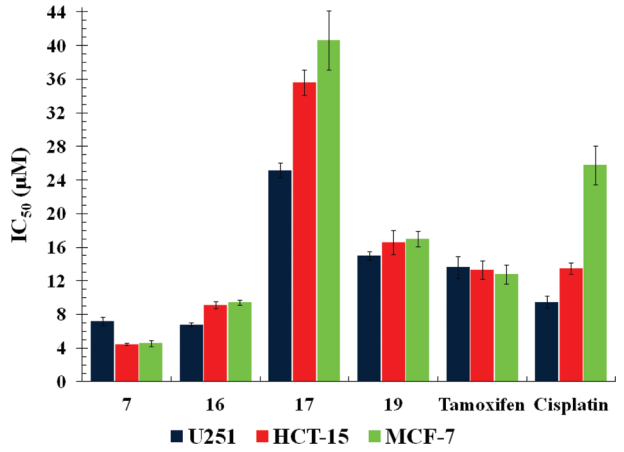
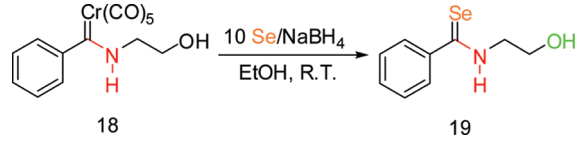


Figure 7. Comparison of the IC_{50} values (μM) of compounds **7**, **16**, **17**, and **19**.

that the presence of the hydrogen atom bonded to selenoamide function is an important structural requirement for achieving a good cytotoxic activity; moreover, modifications over the possible donor H-group could change the biological response of these compounds.

Finally, with the aim of understanding the role of ferrocene moiety in cytotoxicity, we carried out the synthesis of benzene analogue (**19**) of lead compound (**7**), using the methodology already described (Scheme 7). The Fischer aminocarbene **18** was prepared using the method reported by Wulf.[29] A

Scheme 7. Proposed Synthesis for Obtaining 19



dx.doi.org/10.1021/jm300150t | J. Med. Chem. 2012, 55, 4652−4663

selenative demetalation of **18** gives the corresponding selenoamide **19** as a bright-yellow solid in excellent yield (94%). Spectroscopic characterization of compound **19** reveals the characteristic signal pattern already expected.

Additionally, the structural arrangement for **19** was fully established by a single-crystal X-ray diffraction analysis (Figure 8). Similar to the structure of selenoamide **7**, compound **19**

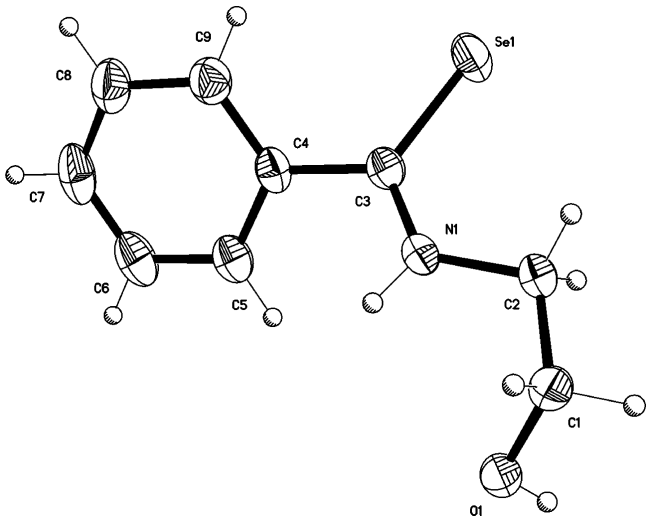


Figure 8. ORTEP representation of ferrocenylselenoamide **19**. Ellipsoids are shown at 30% probability level. Selected bond lengths [Å] and angles [deg]: Se(1)−C(3) 1.830 (2), N(1)−C(3) 1.305 (3), C(3)−C(4) 1.490 (3); N(1)−C(3)−Se(1) 122.77(18), C(4)−C(3)−Se(1) 121.46(17), N(1)−C(3)−C(4) 115.82(19).

shows the selenocarbonyl moiety directly bonded to benzene ring; the sum of bond angles around C3 ($\sum$ = 360.05°) indicates that this group has a trigonal geometry. As in structure **7**, the double bond length C═Se [Se(1)−C(3) 1.830(2)] is quite similar to that of other aryl selenoamides This compound also shows intermolecular hydrogen bonds forming dimers through the N−H···O interaction, with a N−H bond distance slightly longer than **7** (**7**, N−H 0.76(2); **19**, N−H 0.87(2)).[25]

The structural features related to solid packing of **7** and **19** are quite similar, showing small differences related to the coplanarity of the selenoamide group in both compounds. Bearing this in mind and in order to compare the effect of aryl group bonded to selenoamide functionality, we proceeded to determine the IC_{50} values of **19** against the family of cancer cell lines. The results obtained were compared to those obtained for **7** and are shown in Figure 7. In general, the results indicate that **7** is more active than **19**, indicating that the ferrocenyl group increases the cytotoxic activity, being even more active than the reference drugs (tamoxifen and cisplatin). Importantly, the most relevant results were obtained against HCT-15 and MCF-7.

All the data collected during the course of this study allowed us to establish the mean structure requirements for selenoamide compounds to exert quite cytotoxic activity toward different cancer cell lines (Figure 9). These requirements include the selenoamide function as mean feature, a ferrocenyl moiety, and two methylene groups in the alkyl chain, no bulky substituent along this chain, and one functional group capable of interacting through a hydrogen bond.

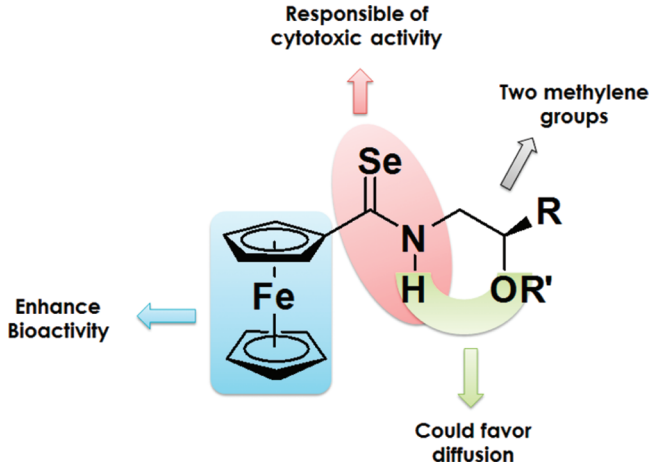


Figure 9. Principal structural features for explaining the cytotoxic activity.

CONCLUSION

A new route to easily access a diversity of new cytotoxic potential ferrocenyl selenoamides in good yields, using Fischer amino ferrocenyl carbene complexes as key substrates has been developed.

The cytotoxic properties toward different cancer cell lines of interest were evidenced by cytotoxic screenings and the determination of IC_{50} values. The results show that selenoamide **7** is the most active compound in the series (4.5 μM), including tamoxifen and cisplatin as reference drugs. The cytotoxic activities obtained and in particular those related to the breast cancer cell line (4.5−13.32 μM) indicate that these compounds are good prospects for further studies related to the mechanisms of action. The recognition of primary structural aspects related to the biological response led us to propose a model for the explanation of these results.

EXPERIMENTAL SECTION

Materials and Instruments. THF and diethyl ether were distilled from sodium/benzophenone under a nitrogen atmosphere. All reagents and solvents were obtained from commercial suppliers and used without further purification. All compounds were characterized by IR spectra, recorded on a Bruker Tensor 27 spectrophotometer, by KBr or film techniques, and all data are expressed in wave numbers (cm^{-1}). Melting points were obtained on a Melt-Temp II apparatus and are uncorrected. NMR spectra were measured with a JEOL Eclipse +300, using $CDCl_3$ and CD_3CN as solvents. Chemical shifts are in ppm (δ), relative to TMS. The MS-EI were obtained JEOL JMS-AX505 HA using 70 eV as ionization energy and for MS-FAB a JEOL JMS-SX102A using nitrobenzyl alcohol and polyethyleneglycol as matrix. All tested compounds synthesized are more than 95% pure, analyzed using HPLC HP 1100 with diode array detector.

*Synthesis of Fischer Ethoxyferrocenylcarbene Chromium 0 (**1**).* The preparation of this Fischer-type carbene complex was carried out using the methodology previously described elsewhere.[24]

*Synthesis of Fischer Hydroxyl Alkylamino Ferrocenyl Carbene Complexes (**2**−**6**), **12**, **14**, and **15**.* To a solution of **1** (23 mmol, 1 g) in 20 mL of anhydrous diethyl ether under nitrogen atmosphere was added the corresponding hydroxyl alkylamine (49 mmol). The reaction mixture was stirred at room temperature for 20−60 min and then diluted with 20 mL of water. The organic phase was separated and dried with anhydrous Na_2SO_4, and the solvent was evaporated in vacuum. The crude product was purified by flash column chromatography using alumina and hexane−CH_2Cl_2 mixture as eluent.

[(Ferrocenyl)(4-hydroxybutylamino)methylidene]-pentacarbonyl Chromium (0) (4). Yield 97%. ^{1}H NMR (300 MHz,

dx.doi.org/10.1021/jm300150t | J. Med. Chem. 2012, 55, 4652−4663

$CDCl_3$, TMS): δ = 9.55 (s, 1 H, NH), 4.49 (d, 4 H, C_5H_4), 4.18 (s, 5 H, Cp), 4.07 (s, 2 H, OCH_2), 3.79 (s, 2 H, NCH_2), 2.20 (s, 1 H, OH), 1.87 ppm (m, 4H, 2 CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 267.0 (CCr), 224.0 ($CrCO_{ax}$), 218.3 ($CrCO_{eq}$), 91.0 (C, C_5H_4), 70.6, 68.9 (4 CH, C_5H_4), 69.3 (5 CH, Cp), 62.2 (OCH_2), 52.8 (NCH_2), 29.6, 26.8 ppm (2 CH_2). IR (film): ν = 3318 (NH), 2050, 1908 cm^{-1} (CO). MS (FAB^+) *m/z* (%): 477 (5) [M^+], 449 (2.5) [M^+-CO], 421 (16) [M^+-2CO], 393 (5) [M^+-3CO], 365 (32.5) [M^+-4CO], 337 (100) [M^+-5CO]. HRMS (FAB^+) *m/z*: calcd for $C_{20}H_{19}CrFeNO_6$, 476.9967 [M^+]; found, 476.9958.

[(Ferrocenyl)(2-hydroxypropylamino)methylidene]-pentacarbonyl Chromium (0) (5). Yield 97%; mp 84−86 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.99 (s, 1 H, NH), 4.47 (d, 5 H, C_5H_4 + OCH), 4.24 (s, 7 H, Cp + NCH_2), 3.81 (s, 1 H, OH), 1.43 ppm (d, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 271.0 (CCr), 223.7 ($CrCO_{ax}$), 218.0 ($CrCO_{eq}$), 99.1 (C, C_5H_4), 70.1, 68.6 (4 CH, C_5H_4), 69.6 (5 CH, Cp), 67.1 (OCH), 58.9 (NCH_2), 21.5 ppm (CH_3). IR (KBr): ν = 3264 (NH), 2051, 1982, 1883 cm^{-1} (CO). MS (FAB^+) *m/z* (%): 463 (23) [M^+], 435 (19) [M^+-CO], 407 (30) [M^+-2CO], 379 (36) [M^+-3CO], 351 (79) [M^+-4CO], 323 (100) [M^+-5CO]. HRMS (FAB^+) *m/z*: calcd for $C_{19}H_{17}CrFeNO_6$, 462.9810 [M^+]; found, 462.9810.

[(Ferrocenyl)(2-hydroxy-2-phenylethylamino)methylidene]-pentacarbonyl Chromium (0) (6). In the case of this complex, was necessary the use of NaH (9.2 mmol) to complete the reaction. Yield 99%; mp 105−108 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.96 (s, 1 H, NH), 7.49 (s, 5 H, CH_{Arom}), 5.15 (s, 1 H, OCH), 4.44 (s, 4 H, C_5H_4), 4.21 (s, 7 H, Cp + NCH_2), 2.43 ppm (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 271.9 (CCr), 223.5 ($CrCO_{ax}$), 217.9 ($CrCO_{eq}$), 140.2 (C_{Arom}), 129.2, 125.9 (CH, C_5H_4), 98.8 (C, C_5H_4), 73.2 (OCH), 71.8, 68.6 (4 CH, C_5H_4), 70.0 (5CH, Cp), 58.9 ppm (NCH_2). IR (KBr): ν = 3247 (NH), 2049, 1972, 1893 cm^{-1} (CO). MS (FAB^+) *m/z* (%): 525 (4) [M^+], 497 (4) [M^+-CO], 469 (4) [M^+-2CO], 441 (13) [M^+-3CO], 413 (39) [M^+-4CO], 385 (100) [M^+-5CO]. HRMS (FAB^+) *m/z*: calcd for $C_{24}H_{19}CrFeNO_6$, 524.9967 [M^+]; found, 524.9661.

[(Ferrocenyl)(2-methoxyethylamino)methylidene]-pentacarbonyl Chromium (0) (14). Yield 99%; mp 80−84 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 9.96 (s, 1 H, NH), 4.43 (s, 4 H, C_5H_4), 4.21 (s, 7 H, Cp + OCH_2), 3.81 (s, 2 H, NCH_2), 3.53 ppm (s, 3 H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 271.8 (CCr), 223.5 ($CrCO_{ax}$), 217.9 ($CrCO_{eq}$), 99.9 (C, C_5H_4), 70.8, 68.5 (4 CH, C_5H_4), 70.0 (OCH_2), 69.5 (5CH, Cp), 59.3 (OCH_3), 52.1 ppm (NCH_2). IR (KBr): ν = 3292 (NH), 2051, 1982, 1894 cm^{-1} (CO). MS (FAB^+) *m/z* (%): 463 (4) [M^+], 435 (5) [M^+-CO], 407 (9) [M^+-2CO], 379 (13) [M^+-3CO], 351 (48) [M^+-4CO], 323 (100) [M^+-5CO]. HRMS (FAB^+) *m/z*: calcd for $C_{19}H_{17}CrFeNO_6$, 462.9810 [M^+]; found, 462.9815.

{(Ferrocenyl)[(*N*-(2-hydroxyethyl)-*N*-methyl)amino]-methylidene}pentacarbonyl Chromium (0) (15). Yield 37%; mp 76−74 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 4.53 (s, 4 H, C_5H_4), 4.25 (s, 7 H, Cp + OCH_2), 3.73 (s, 2 H, NCH_2), 3.34 (s, 3 H, NCH_3), 2.01 ppm (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 268.7 (CCr), 221.5 ($CrCO_{ax}$), 216.9 ($CrCO_{eq}$), 97.7 (C, C_5H_4), 70.5, 67.8 (4 CH, C_5H_4), 69.9 (OCH_2), 69.5 (5CH, Cp), 55.3 (NCH_3), 52.1 ppm (NCH_2). IR (KBr): ν = 2055, 1991, 1905 cm^{-1} (CO). MS (FAB^+) *m/z* (%): 463 (3) [M^+], 435 (6) [M^+-CO], 407 (7) [M^+-2CO], 379 (16) [M^+-3CO], 351 (52) [M^+-4CO], 323 (100) [M^+-5CO]. HRMS (FAB^+) *m/z*: calcd for $C_{19}H_{17}CrFeNO_6$, 462.9810 [M^+]; found, 462.9815.

Synthesis of Selenoamides (7−11), 13, 16, 17, and 19. *Preparation of Selenating Agent.* To a solution of 0.01 mol of $NaBH_4$ in 10 mL of ethanol was added 0.01 mol of powdered selenium, and the mixture was vigorously stirred at room temperature for 30 min under nitrogen atmosphere.

The selenating agent was then added to a solution of **1** (0.001 mol) in 5 mL of ethanol under nitrogen atmosphere; the reaction was monitored by TLC on silica gel. After the reaction was completed, the solvent was evaporated under vacuum, the residual mixture was dissolved in distilled water, and the product was extracted with CH_2Cl_2 and then dried with anhydrous Na_2SO_4. After the evaporation of the solvent, the resultant mixture was purified by silica gel column using hexane as eluent.

*N-(2-Hydroxyethyl)ferroceneselenoamide (**7**).* Yield 98%; mp 140−143 °C (d). ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.24 (s, 1 H, NH), 4.91 (t, 2 H, C_5H_4), 4.50 (t, 2 H, C_5H_4), 4.21 (s, 5 H, Cp), 4.00 (m, 4 H, 2 CH_2), 2.04 ppm (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 203.0 (CSe), 86.8 (C, C_5H_4), 71.7, 69.6 (4 CH, C_5H_4), 71.2 (5 CH, Cp), 60.7 (OCH_2), 50.7 ppm (NCH_2). IR (KBr): ν = 3282 (NH), 1540 cm^{-1} (C═Se). MS (EI, 70 eV) *m/z* (%): 337 (100) [M^+], 319 (7) [M^+-H_2O], 256 (49) [M^+-H_2Se], 212 (66) [$FcCNH^+$], 121 (34) [$CpFe^+$]. HRMS (FAB^+) *m/z*: calcd for $C_{13}H_{15}FeNOSe$, 336.9668 [M^+]; found, 336.9665. Elemental Analysis Calcd (%) for $C_{13}H_{15}FeNOSe$: C 46.46, H 4.50, N 4.17. Found: C 45.89, H 4.51, N 4.16.

*N-(3-Hydroxypropyl)ferroceneselenoamide (**8**).* Yield 81%; mp 104−106 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.85 (s, 1 H, NH), 4.90 (t, 2 H, C_5H_4), 4.48 (t, 2 H, C_5H_4), 4.20 (s, 5 H, Cp), 3.99 (q, 2 H, OCH_2), 3.88 (t, 2 H, NCH_2), 2.80 (s, 1 H, OH), 1.97 ppm (q, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 203.0 (CSe), 86.8 (C, C_5H_4), 71.6, 69.5 (4 CH, C_5H_4), 71.1 (5 CH, Cp), 61.6 (OCH_2), 48.1 (NCH_2), 30.4 ppm (CH_2). IR (KBr): ν = 3227 (NH), 1541 cm^{-1} (C═Se). MS (EI, 70 eV) *m/z* (%): 351 (100) [M^+], 333 (3) [M^+-H_2O], 270 (45) [M^+-H_2Se], 212 (73) [$FcCNH^+$], 121 (23) [$CpFe^+$]. HRMS (FAB^+) *m/z*: calcd for $C_{14}H_{17}FeNOSe$, 350.9825 [M^+]; found, 350.9825.

*N-(4-Hydroxybutyl)ferroceneselenoamide (**9**).* Yield 88%; mp 80−82 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.97 (s, 1 H, NH), 4.98 (t, 2 H, C_5H_4), 4.46 (t, 2 H, C_5H_4), 4.19 (s, 5 H, Cp), 3.79 (m, 4 H, 2 CH_2), 3.09 (s, 1 H, OH), 1.90 (q, 2 H, CH_2), 1.72 ppm (q, 2 H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 202.0 (CSe), 86.0 (C, C_5H_4), 71.6, 69.7 (4 CH, C_5H_4), 71.1 (5 CH, Cp), 62.0 (OCH_2), 49.2 (NCH_2), 29.7, 24.8 ppm (2 CH_2). IR (KBr): ν = 3239 (NH), 1534 cm^{-1} (C═Se). MS (EI, 70 eV) *m/z* (%): 365 (63) [M^+], 347 (1) [M^+-H_2O], 283 (5) [M^+-H_2Se], 212 (100) [$FcCNH^+$], 121 (17) [$CpFe^+$]. HRMS (FAB^+) *m/z*: calcd for $C_{15}H_{19}FeNOSe$, 364.9981 [M^+]; found, 364.9977.

*N-(2-Hydroxypropyl)ferroceneselenoamide (**10**).* Yield 92%; mp 151−152 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.26 (s, 1 H, NH), 4.91 (t, 2 H, C_5H_4), 4.50 (t, 2 H, C_5H_4), 4.21 (s, 7 H, Cp + NCH_2), 3.58 (m, 1 H, OCH), 2.07 (s, 1 H, OH), 1.34 ppm (d, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 203.9 (CSe), 86.3 (C, C_5H_4), 71.7, 69.5 (4 CH, C_5H_4), 71.1 (5 CH, Cp), 66.5 (OCH), 55.3 (NCH_2), 21.7 ppm (CH_3). IR (KBr): ν = 3296 (NH), 1445 cm^{-1} (C═Se). MS (EI, 70 eV) *m/z* (%): 351 (95) [M^+], 333 (4) [M^+-H_2O], 269 (48) [M^+-H_2Se], 212 (100) [$FcCNH^+$], 121 (55) [$CpFe^+$]. HRMS (FAB^+) *m/z*: calcd for $C_{14}H_{17}FeNOSe$, 350.9825 [M^+]; found, 350.9830.

*N-(2-Phenyl-2-hydroxyethyl)ferroceneselenoamide (**11**).* Yield 91%; mp 143−144 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.21 (s, 1 H, NH), 7.42 (m, 5 H, CH_{Arom}), 5.19 (m, 1 H, CH), 4.87 (t, 2 H, C_5H_4), 4.48 (t, 2 H, C_5H_4), 4.17 (s, 5 H, Cp), 3.80 (m, 2 H, NCH_2), 2.81 ppm (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 203.9 (CSe), 141.2 (C_{Arom}), 128.9, 128.4, 125.8, (5 CH_{Arom}), 86.2 (C, C_5H_4), 72.3 (OCH), 71.8, 69.5 (4 CH, C_5H_4), 71.2 (5 CH, Cp), 55.3 ppm (NCH_2). IR (KBr): ν = 3285 (NH), 1400 cm^{-1} (C═Se). MS (EI, 70 eV) *m/z* (%): 413 (43) [M^+], 396 (3) [M^+-H_2O], 331 (53) [M^+-H_2Se], 212 (100) [$FcCNH^+$], 121 (34) [$CpFe^+$], 103 (34) [$PhCH{=}CH^+$], 77 (74) [Ph^+]. HRMS (FAB^+) *m/z*: calcd for $C_{19}H_{19}FeNOSe$, 412.9981 [M^+]; found, 412.9981.

*N-Propylferroceneselenoamide (**13**).* Yield 80%; mp 68−70 °C. ^1H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.82 (s, 1 H, NH), 4.90 (s, 2 H, C_5H_4), 4.48 (s, 2 H, C_5H_4), 4.19 (s, 5 H, Cp), 3.80 (q, 2 H, NCH_2), 1.81 (dt, 2 H, CH_2), 1.06 ppm (t, 3 H; CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 203.0 (CSe), 86.1 (C, C_5H_4), 71.6, 69.3 (4 CH, C_5H_4), 71.1 (5 CH, Cp), 50.7 (NCH_2), 21.7 (CH_2), 11.6 ppm (CH_3). IR (KBr): ν = 3204 (NH), 1438 cm^{-1} (C═Se). MS (EI, 70 eV) *m/z* (%): 335 (64) [M^+], 254 (17) [M^+-H_2Se], 211 (100) [$FcCN^+$], 121 (32) [$CpFe^+$]. HRMS (FAB^+) *m/z*: calcd for $C_{14}H_{17}FeNSe$, 334.9876 [M^+]; found, 334.9875.

dx.doi.org/10.1021/jm300150t | *J. Med. Chem.* 2012, 55, 4652−4663

*N-(2-Methoxyethyl)ferrocenoselenoamide (**16**).* Yield 97%; mp 100−101 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 8.18 (s, 1 H, NH), 4.90 (s, 2 H, C_5H_4), 4.48 (s, 2 H, C_5H_4), 4.15 (s, 5 H, Cp), 4.05 (q, 2 H, OCH_2), 3.70 (t, 2 H, NCH_2), 3.44 ppm (s, 3 H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 203.2 (CSe), 86.3 (C, C_5H_4), 71.6, 69.5 (4 CH, C_5H_4), 71.1 (5 CH, Cp), 69.9 (OCH_2), 59.1 (OCH_3), 48.2 ppm (NCH_2). IR (KBr): ν = 3293 (NH), 1533 cm^{-1} (C═Se). MS (EI, 70 eV) *m*/*z* (%): 351 (98) [M^+], 270 (27) [M^+-H_2Se], 212 (68) [FcCNH$^+$], 121 (24) [CpFe$^+$]. HRMS (FAB$^+$) *m*/*z*: calcd for $C_{14}H_{17}FeNOSe$, 350.9825 [M^+]; found, 350.9830. Elemental Analysis Calcd (%) for $C_{14}H_{17}FeNOSe$: C 48.03, H 4.89, N 4.00. Found: C 48.02, H 4.90, N 4.92.

*N-(2-Hydroxyethyl)-N-methylferroceneselenoamide (**17**).* Yield 46%; mp 80 °C. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 4.95 (t, 2 H, C_5H_4), 4.46 (t, 2 H, C_5H_4), 4.19 (s, 5 H, Cp), 3.79 (m, 4 H, 2 CH_2), 3.65 (m, 3 H, NCH_3), 3.09 ppm (s, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$, TMS): δ = 202.0 (CSe), 86.0 (C, C_5H_4), 71.6, 69.7 (4 CH, C_5H_4), 71.3 (5 CH, Cp), 67.0 (OCH_2), 56.7 (NCH_3), 49.2 ppm (NCH_2). IR (KBr): ν = 1534 cm^{-1} (C═Se). MS (EI, 70 eV) *m*/*z* (%): 351 (43) [M^+], 333 (3) [M^+-H_2O], 270 (12) [M^+-H_2Se], 212 (100) [FcCNH$^+$], 121 (14) [CpFe$^+$]. HRMS (FAB$^+$) *m*/*z*: calcd for $C_{14}H_{17}FeNOSe$, 350.9825 [M^+]; found, 350.9821. Elemental Analysis Calcd (%) for $C_{14}H_{17}FeNOSe$: C 48.03, H 4.89, N 4.00. Found: C 48.13, H 4.92, N 4.27.

*N-(2-Hydroxyethyl)benzoselenoamide (**19**).* Yield 94%; mp 78−81 °C. ^{1}H NMR (300 MHz, CD_3CN, TMS): δ = 9.27 (s, 1 H, NH), 4.98 (t, 2 H, C_5H_4), 7.73 (m, 2 H, C_6H_5), 7.41 (m, 1 H, C_6H_5), 7.38 (m, 2 H, C_6H_5), 3.88 (m, 4 H, OCH_2, NCH_2), 3.13 ppm (m, 1 H, OH). ^{13}C NMR (75 MHz, CD_3CN, TMS): δ = 204.6 (CSe), 144.5 (C, C_6H_5), 131.4, 128.8, 127.6 (5 CH, C_6H_5), 59.3 (OCH_2), 53.0 ppm (NCH_2). IR (KBr): ν = 3173 (NH), 1550 cm^{-1} (C═Se). MS (EI, 70 eV) *m*/*z* (%): 229 (63) [M^+], 211 (7.03) [M^+-H_2O], 147 (60) [M^+-H_2Se], 104 (100) [FcCNH$^+$]. HRMS (FAB$^+$) *m*/*z*: calcd for $C_9H_{12}NOSe$, 229.0084 [M^+]; found, 229.0083.

Determination of Purity. The purity of the final products (≥95%) were determined using 60:40 and 40:60 (hexane:ammonium acetate) as the mobile phase with a flow rate of 0.2 mL/min on a Zorbax Bonus RP column (3.5 μm, 2.1 mm × 100 mm, Agilent).

X-ray Crystallography. Suitable X-ray quality crystal s of **7** and **19** were grown by slow evaporation of *n*-hexane/benzene mixture at −5 °C and chloroform at room temperature, respectively. The crystals of each compound were mounted on a glass fiber at room temperature and then placed on a Bruker Smart Apex CCD diffractometer, equipped with Mo KR radiation; decay was negligible in both cases. Details of crystallographic data collected on compounds **7** and **19** are provided in Table 5. Systematic absences and intensity statistics were used in space group determination. The structure was solved using direct methods.[30] Anisotropic structure refinements were achieved using full matrix, least-squares technique on all non-hydrogen atoms. All hydrogen atoms were placed in idealized positions, based on hybridization, with isotropic thermal parameters fixed at 1.2 times the value of the attached atom. Structure solutions and refinements were performed using SHELXTL V6.10.[31] CCDC-8494413 (**7**) and CCDC-8494414 (**19**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.ac.uk/data_request/cif.

Cytotoxicity Assay. The compounds were screened in vitro against three human cancer cell lines: U251 (human glioblastoma), HCT-15 (human colorectal adenocarcinoma), and SKLU-1 (human lung adenocarcinoma) cell lines were supplied by National Cancer Insitute (USA). The human tumor cytotoxicity was determined using the protein-binding dye sulforhodamine B (SRB) in microculture assay to measure cell growth, as described in the protocols established by the NCI. The cell lines were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10000 units/mL penicillin G sodium, 10000 μg/mL streptomycin sulfate, and 25 μg/mL amphotericin B (Gibco) and 1% nonessential aminoacids (Gibco). They were maintained at 37° in humidified atmosphere with 5% CO_2. The viability of the cells used in the experiments exceeds 95% as determined with trypan blue.

The cells were removed from the tissue culture flask and diluted with fresh media. Of this cell suspension, 100 μL containing 5000 or 10000 cells per well, were pipetted into 96-well microtiter plates (Costar) and the material was incubated at 37 °C for 24 h in a 5% CO_2 atmosphere. Subsequently, 100 μL of a solution of the test compounds obtained by diluting the stocks were added to each well. The cultures were exposed for 48 h to the drug at concentrations ranging from 1.0 to 50 μM.

After the incubation period, cells were fixed to the plastic substratum by the addition of 50 μL of cold 50% aqueous trichloroacetic acid. The plates were incubated at 4 °C for 1 h. Washed with tap H_2O, and air-dried. The trichloroacetic-acid-fixed cells were stained by the addition of 0.4% SRB. Free SRB solution was removed by washing with 1% aqueous acetic acid. The plates were air-dried, and the bound dye was solubilized by the addition of 10 mM unbuffered tris based (100 μL). The plates were placed on a shacked for 5 min, and the absorption was determinate at 515 nM using an ELISA plates reader (Bio-Tex Instruments).

Table 5. Crystal Data and Structure Refinement for 7 and 19

	7	19
empirical formula	$C_{13}H_{15}FeNOSe$	$C_9H_{11}NOSe$
formula wt (g mol^{-1})	336.07	228.15
crystal size (mm^3)	0.28 × 0.18 × 0.09	0.46 × 0.31 × 0.10
color	red	orange
crystal system	monoclinic	monoclinic
space group	*C*2/c	$P2_1/n$
a (Å)	17.983(2)	9.598(3)
b (Å)	7.410(2)	8.166(2)
c (Å)	19.235(2)	12.750(4)
α (deg)	90	90
β (deg)	93.649(2)	103.190(4)
γ (deg)	90	90
V (Å^3)	2558.0(5)	973.1(5)
Z	8	4
D_{calc} (g cm^3)	1.745	1.557
no. of collected reflections	10155	5126
no. of independent reflections (R_{int})	2337, R_{int}= 0.0268	1775, R_{int}= 0.0236
absorption correction method	semiempirical from equivalents	semiempirical from equivalents
maximum and minimum transmission	0.7048 and 0.4250	0.6888 and 0.2190
data/parameters	2337/206	1775/115
final *R* indices [$I > 2\sigma(I)$]	*R* = 0.0254, *wR2* = 0.0603	*R* = 0.0283, *wR2* = 0.0696
R indices (all data)	*R* = 0.0315, *wR2* = 0.0629	*R* = 0.0367, *wR2* = 0.0736
goodness-of-fit on F^2	1.059	1.036

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectrum for compounds **4**−**6**, **8**−**11**, **13**−**15**, and **19**. Crystallographic information files for compounds **7** and **19** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +52-55-56224513. Fax: +52-55-56162203. E-mail: jglcvdw@unam.mx.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We appreciate the technical assistance of Rocío Patiño, Ma. Isabel Chávez, Antonio Nieto-Camacho, Luis Velasco, and Javier Pérez. We also thank the DGAPA-PAPIIT IN-201411 and CONACYT 153310 projects and CONACYT for the Ph.D. grant extended to A.I.G.-H.

■ REFERENCES

(1) (a) Jaouen, G.; Metzler-Nolte, N. Medicinal Organometallic Chemistry. In *Topics in Organometallic Chemistry 32*; Springer: Berlin, 2010; (b) Alesio, E. *Bioinorganic Medicinal Chemistry*; Wiley-VCH: Weinheim, 2011.

(2) (a) Fish, R. H.; Jaouen, G. Bioorganometallic Chemistry: Structural Diversity of Organometallic Complexes with Bioligands and Molecular Recognition Studies of Several Supramolecular Hosts with Biomolecules, Alkali-Metal Ions, and Organometallic Pharmaceuticals. *Organometallics* **2003**, *22*, 2166−2177. (b) Schatzschneider, U.; Metzler-Nolte, N. New Principles in Medicinal Organometallic Chemistry. *Angew. Chem., Int. Ed.* **2006**, *45*, 1504−1507. (c) Patra, M.; Gasser, G.; Pinto, A.; Merz, K.; Ott, I.; Bandow, J. E.; Metzler-Nolte, N. Synthesis and Biological Evaluation of Chromium Bioorganometallics Based on the Antibiotic Platensimycin Lead Structure. *ChemMedChem* **2009**, *4*, 1930−1938. (d) Bergamo, A.; Sava, G. Ruthenium Anticancer Compounds: Myths and Realities of the Emerging Metal-Based Drugs. *Dalton Trans.* **2011**, 7817−7823. (e) Smith, G. S.; Therrien, B. Targeted and Multifunctional Arene Ruthenium Chemotherapeutics. *Dalton Trans.* **2011**, *40*, 10793−10800.

(3) (a) Top, S.; Jaouen, G.; Vessières, A.; Abjean, J.-P.; Davoust, D.; Rodger, C. A.; Sayer, B. G.; McGlinchey, M. J. Chromium Tricarbonyl Complexes of Estradiol Derivatives: Differentiation of α- and β-Diasteromers Using One- and Two-Dimensional NMR Spectroscopy at 500 MHz. *Organometallics* **1985**, *4*, 2143−2150.

(4) (a) Abeysinghe, P. M.; Harding, M. M. Antitumor Bis-(cyclopentadienyl) Metal Complexes: Titanocene and Molybdocene Dichloride and Derivatives. *Dalton Trans.* **2007**, 3474−3482. (b) Nguyen, A.; Vessières, A.; Hillard, E. A.; Top, S.; Pigeon, P.; Jaouen, G. Ferrocifens and Ferrocifenols as New Potential Weapons Against Breast Cancer. *Chimia* **2007**, *61*, 716−724.

(5) (a) van Staveren, D. R.; Metzler-Nolte, N. Bioorganometallic Chemistry of Ferrocene. *Chem. Rev.* **2004**, *104*, 5931−5985. (b) Metzler-Nolte, N. Medicinal Applications of Metal−Peptide Bioconjugates. *Chimia* **2007**, *61*, 736. (c) Fouda, M. F. R.; Abd-Elzaher, M. M.; Abdelsamaia, R. A.; Labib, A. A. On the Medicinal Chemistry of Ferrocene. *Appl. Organomet. Chem.* **2007**, *21*, 613−625. (d) Wu, C.; Xu, B.; Zhao, J.; Jiang, Q.; Wei, F.; Jiang, H.; Wang, X.; Yan, H. Ferrocene-Substituted Dithio-*o*-Carborane Isomers: Influence on the Native Conformation of Myoglobin Protein. *Chem.—Eur. J.* **2010**, *16*, 8914−8922. (e) Martić, S.; Labib, M.; Shipman, P. O.; Kraatz, H.-B. Ferrocene−peptido Conjugates: From Synthesis to Sensory Applications. *Dalton Trans* **2011**, *40*, 7264−7290. (f) Ornelas, C. Application of Ferrocene and its Derivatives in Cancer Research. *New J. Chem.* **2011**, *35*, 1973−1985. (g) Gasser, G.; Ott, I.; Metzler-Nolte, N. Organometallic Anticancer Compounds. *J. Med. Chem.* **2011**, *54*, 3−25.

(6) (a) Buriez, O.; Heldt, J. M.; Labbé, E.; Vessières, A.; Jaouen, G.; Amatore, C. Reactivity and Antiproliferative Activity of Ferrocenyl−Tamoxifen Adducts with Cyclodextrins Against Hormone-Independent Breast-Cancer Cell Lines. *Chem.—Eur. J.* **2008**, *14*, 8195−8203. (b) Hamels, D.; Dansette, P. M.; Hillard, E. A.; Top, S.; Vessières, A.; Herson, P.; Jaouen, G.; Mansuy, D. Ferrocenyl Quinone Methides as Strong Antiproliferative Agents: Formation by Metabolic and Chemical Oxidation of Ferrocenyl Phenols. *Angew. Chem., Int. Ed.* **2009**, *48*, 9124−9126. (c) Mooney, A.; Corry, A. J.; Ruairc, N.; Mahgoub, T.; O'Sullivan, D.; O'Donovan, N.; Crown, J.; Varughese, S.; Draper, S. M.; Rai, D. K.; Kenny, P. T. M. Synthesis, Characterisation and Biological Evaluation of *N*-(ferrocenyl)naphthoyl Amino Acid Esters as Anticancer Agents. *Dalton Trans.* **2010**, *39*, 8228−8239. (d) Hillard, E. A.; Jaouen, G. Bioorganometallics: Future Trends in Drug Discovery, Analytical Chemistry, and Catalysis. *Organometallics* **2011**, *30*, 20−27. (g) Schobert, R.; Seibt, S.; Mahal, K.; Ahmad, A.; Biersack, B.; Effenberger-Neidnicht, K.; Padhye, S.; Sarkar, F. H.; Mueller, T. Cancer Selective Metallocenedicarboxylates of the Fungal Cytotoxin Illudin M. *J. Med. Chem.* **2011**, *54*, 6177−6182.

(7) (a) Wu, X.; Tiekink, E. R. T.; Kostetski, I.; Kocherginski, N.; Tan, A. L. C.; Khoo, S. B.; Wilairat, P.; Go, M.-L. Antiplasmodial Activity of Ferrocene Chalcones: Investigations into the Role of Ferrocene. *Eur. J. Pharm. Sci.* **2006**, *27*, 175−187. (b) Biot, C.; Pradines, B.; Sergeant, M.-H.; Gut, J.; Rosenthal, P. J.; Chibale, K. Design, Synthesis, and Antimalarial Activity of Structural Chimeras of Thiosemicarbazone and Ferroquine Analogues. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6434−6438. (c) Dive, D.; Biot, C. Ferrocene Conjugates of Chloroquine and other Antimalarials: the Development of Ferroquine, a New Antimalarial. *ChemMedChem* **2008**, *3*, 383−391. (d) Payen, O.; Top, S.; Vessières, A.; Brulé, E.; Lauzier, A.; Plamont, M.-A.; McGlinchey, M. J.; Müller-Bunz, H.; Jaouen, G. J. Synthesis and Biological Activity of Ferrocenyl Derivatives of the Non-steroidal Antiandrogens Flutamide and Bicalutamide. *J. Organomet. Chem.* **2011**, *696*, 1049−1056.

(8) (a) Cohan, Z. H. Antibacterial and Antifungal Ferrocene Incorporated Dithiothione and Dithioketone Compounds. *Appl. Organomet. Chem.* **2006**, *20*, 112−116. (b) Patra, M.; Gasser, G.; Wenzel, M.; Merz, K.; Bandow, J. E.; Metzler-Nolte, N. Synthesis and Biological Evaluation of Ferrocene-Containing Bioorganometallics Inspired by the Antibiotic Platensimycin Lead Structure. *Organometallics* **2010**, *29*, 4312−4219. (c) Zaheer, M.; Shah, A.; Akhter, Z.; Qureshi, R.; Mirza, B.; Tauseef, M.; Bolte, M. Synthesis, Characterization, Electrochemistry and Evaluation of Biological Activities of Some Ferrocenyl Schiff Bases. *Appl. Organomet. Chem.* **2011**, *25*, 61−69. (d) Patra, M.; Gasser, G.; Wenzel, M.; Merz, K.; Bandow, J. E.; Metzler-Nolte, N. Synthesis of Optically Active Ferrocene-Containing Platensimycin Derivatives with a C6-C7 Substitution Pattern. *Eur. J. Inorg. Chem.* **2011**, 3295−3302.

(9) (a) Maity, B.; Roy, M.; Chakravarty, A. R. Ferrocene-Conjugated Copper(II) Dipyridophenazine Complex as a Multifunctional Model Nuclease Showing DNA Cleavage in Red Light. *J. Organomet. Chem.* **2008**, *693*, 1395−1399. (b) Gellet, A. M.; Huber, P. W.; Higgins, P. J. Synthesis of the Unnatural Amino Acid N^{α}-N^{ε}-(ferrocene-1-acetyl)-L-lysine: A Novel Organometallic Nuclease. *J. Organomet. Chem.* **2008**, *693*, 2959−2962. (c) Maity, B.; Chakravarthi, V. S. K.; Roy, M.; Karande, A. A.; Chakravarty, A. R. DNA Photocleavage and Cytotoxic Properties of Ferrocene Conjugates. *Eur. J. Inorg. Chem.* **2011**, 1379−1386.

(10) (a) Edwards, E. I.; Epton, R.; Marr, G. The Synthesis and Reactions of Homonuclear Ferrocene Acid Anhydrides and Their Use in the Preparation of Ferrocenylpenicillins and Cephalosporins. *J. Organomet. Chem.* **1979**, *168*, 259−272.

(11) (a) Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S. Synthesis and Antimalarial Activity in Vitro and in Vivo of a New Ferrocene-Chloroquine Analogue. *J. Med. Chem.* **1997**, *40*, 3715−3718. (b) Bellot, F.; Coslédan, F.; Vendier, L.; Brocard, J.; Meunier, B.; Robert, A. Trioxaferroquines as New Hybrid Antimalarial Drugs. *J. Med. Chem.* **2010**, *53*, 4103−4109.

(12) (a) Liotta, D.; Monahan, R. Selenium in Organic Synthesis. *Science* **1986**, *231*, 356−361. (b) Wirth, T. Organoselenium Chemistry in Stereoselective Reactions. *Angew. Chem., Int. Ed.* **2000**, *39*, 3740−3749. (c) Hua, G.; Woollins, J. D. Formation and Reactivity of Phosphorus Selenium Rings. *Angew. Chem., Int. Ed.* **2009**, *48*, 1368−1377. (d) Rhoden, C. R. B.; Zeni, G. New Development of Synthesis and Reactivity of Seleno- and Tellurophenes. *Org. Biomol. Chem.* **2011**, *9*, 1301−1313. (e) Levason, W.; Reid, G.; Zhang, W. The Chemistry of the p-Block Elements with Thioether, Selenoether and Telluroether Ligands. *Dalton Trans.* **2011**, *40*, 8491−8506.

(13) (a) Krief, A.; Hevesi, L.; *Organoselenium Chemistry*; Springer: Berlin, 1988; (b) Krief, A. *Comprehensive Organometallic Chemistry*; Pergamon Press: Oxford, 1991; p 85; (c) Swapna, K.; Narayana-Murthy, S.; Durga-Nageswar, Y. V. Magnetically Separable and

Reusable Copper Ferrite Nanoparticles for Cross-Coupling of Aryl Halides with Diphenyl Diselenide. *Eur. J. Org. Chem.* **2011**, 1940−1946.

(14) (a) Mugesh, G.; du Mont, W. W.; Sies, H. Chemistry of Biologically Important Synthetic Organoselenium Compounds. *Chem. Rev.* **2001**, *101*, 2125−2179. (b) Nogueira, C. W.; Zeni, G.; Rocha, T. B. T. Organoselenium and Organotellurium Compounds: Toxicology and Pharmacology. *Chem. Rev.* **2004**, *104*, 6255−6285. (c) Jamier, V.; Ba, L. A.; Jacob, C. Selenium- and Tellurium-Containing Multifunctional Redox Agents as Biochemical Redox Modulators with Selective Cytotoxicity. *Chem.—Eur. J.* **2010**, *16*, 10920−10928. (d) Mobli, M.; Morgenstern, D.; King, G. F.; Alewood, P. F.; Mutenthaler, M. Site-Specific pK_a Determination of Selenocysteine Residues in Selenovasopressin by Using ^{77}Se NMR Spectroscopy. *Angew. Chem., Int. Ed.* **2011**, *50*, 1−5.

(15) (a) Goldstein, B. M.; Takusagawa, F.; Berman, H. M; Srivastava, P. C.; Robins, R. K. Structural Studies of a New Antitumor Antiviral Agent: Selenazofurin and Its α Anomer. *J. Am. Chem. Soc.* **1985**, *107*, 1394−1400.

(16) Grange, R. L.; Ziogas, J.; Angus, J. A.; Schiesser, C. H. Selenofonsartan Analogues: Novel Selenium-Containing Antihypertensive Compounds. *Tetrahedron. Lett.* **2007**, *48*, 6301−6303.

(17) (a) Mehta, S.; Andrews, J. S.; Johnston, B. D.; Svensson, B.; Pinto, B. M. Synthesis and Enzyme Inhibitory Activity of Novel Glycosidase Inhibitors Containing Sulfur and Selenium. *J. Am. Chem. Soc.* **1995**, *117*, 9783−9790. (b) Garud, D. R.; Koketsu, M. Synthesis of 3-Selena-1-dethiacephems and Selenazepines via Iodocyclization. *Org. Lett.* **2008**, *10*, 3319−3322. (c) Wiles, J. A.; Phadke, A. S.; Bradbury, B. J.; Pucci, M. J.; Thanassi, J. A.; Deshpande, M. Selenophene-Containing Inhibitors of Type IIA Bacterial Topoisomerases. *J. Med. Chem.* **2011**, *54*, 3418−3425.

(18) (a) Koketsu, M.; Ishihara, H. Synthesis of 1,3-Selenazine and 1,3-Selenazole and Their Biological Activities. *Curr. Org. Chem.* **2003**, *7*, 175−185. (b) Tsukagoshi, H.; Koketsu, M.; Kato, M.; Kurabayashi, M.; Nishina, A.; Kimura, H. Superoxide Radical-Scavenging Effects From Polymorphonuclear Leukocytes and Toxicity in Human Cell Lines of Newly Synthesized Organic Selenium Compounds. *FEBS J.* **2007**, *274*, 6046−6054. (c) Lee, Y. K.; Park, S. Y.; Kim, Y.-M.; Kim, D. C.; Lee, W. S.; Surh, Y.-J.; Park, O. J. Suppression of mTOR via Akt-dependent and -Independent Mechanisms in Selenium-Treated Colon Cancer Cells: Involvement of AMPKα_1. *Carcinogenesis* **2010**, *31*, 1092−1099. (d) Doering, M.; Ba, L. A.; Lilienthal, N.; Nicco, C.; Scherer, C.; Abbas, M.; Zada, A. A. P.; Coriat, R.; Burkhholz, T.; Wessjohann, L.; Diederich, M.; Batteux, F.; Herling, M.; Jacob, C. Synthesis and Selective Anticancer Activity of Organochalcogen Based Redox Catalysts. *J. Med. Chem.* **2010**, *53*, 6954−6963. (e) Amouri, H. J.; Moussa, J.; Renfrew, A. K.; Dyson, P. J.; Rager, M. N.; Chamoreau, L.-M. Discovery, Structure, and Anticancer Activity of an Iridium Complex of Diselenobenzoquinone. *Angew. Chem., Int. Ed.* **2010**, *49*, 7530−7533. (f) Ninomiya, M.; Garud, D. R.; Koketsu, M. Biologically Significant Selenium-Containing Heterocycles. *Coord. Chem. Rev.* **2011**, *255*, 2968−2990.

(19) (a) Takahashi, H.; Nishina, A.; Kimura, H.; Motoki, K.; Koketsu, M.; Ishihara, H. Tertiary Selenoamide Compounds are Useful Superoxide Radical Scavengers in Vitro. *Eur. J. Pharm. Sci.* **2004**, *23*, 207−211. (b) Baliga, M. S.; Wang, H.; Zhuo, P.; Schwartz, J. L.; Diamond, A. M. Selenium and GPx-1 Overexpression Protect Mammalian Cells Against UV-Induced DNA Damage. *Biol. Trace Elem. Res.* **2007**, *115*, 227−242. (c) Bhabak, K. P.; Mugesh, G. Functional Mimics of Glutathione Peroxidase: Bioinspired Synthetic Antioxidants. *Acc. Chem. Res.* **2010**, *43*, 1408−19. (d) Huang, X.; Liu, X.; Luo, Q.; Liu, J.; Shen, J. Artificial Selenoenzymes: Designed and Redesigned. *Chem. Soc. Rev.* **2011**, *40*, 1171−1184. (e) Satheeshkumar, K.; Mugesh, G. Synthesis and Antioxidant Activity of Peptide-Based Ebselen Analogues. *Chem.—Eur. J.* **2011**, *17*, 4849−4857. (f) Selvakumar, K.; Shah, P.; Singh, H. B.; Butcher, R. J. Synthesis, Structure, and Glutathione Peroxidase-Like Activity of Amino Acid Containing Ebselen Analogues and Diaryl Diselenides. *Chem.—Eur. J.* **2011**, *17*, 12741−12755. (g) Yoshida, S.; Kumakura, F.; Komatsu, I.; Arai, K.; Onuma, Y.; Hojo, H.; Singh, B. G.; Priyadarsini, K. I.; Iwaoka, M. Antioxidative Glutathione Peroxidase Activity of Selenoglutathione. *Angew. Chem., Int. Ed.* **2011**, *50*, 2125−2128.

(20) (a) Peters, U.; Takata, Y. Selenium and the Prevention of Prostate and Colorectal Cancer. *Mol. Nutr. Food. Res.* **2008**, *52*, 1261−1272. (b) Bhattacharyya, R. S.; Husbeck, B.; Feldman, D.; Knox, S. J. Selenite Treatment Inhibits LAPC-4 Tumor Growth and Prostate-Specific Antigen Secretion in a Xenograft Model of Human Prostate Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* **2008**, *72*, 935−940.

(21) Selected references: (a) Shimada, K.; Jin, N.; Kawaguchi, M.; Dobashi, K.; Nagano, Y.; Fujimura, M.; Kudoh, E.; Kai, T.; Saito, N.; Masuada, J.; Iwaya, M.; Fujisawa, H.; Aoyagi, S.; Takikawa, Y. Efficient Synthesis of Selenocarbonyl Compounds by Treating Carbonyl Compounds with Bis(1,5-cyclooctanediylboryl) Selenide. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 197−206. (b) Ming-Li, G.; Zingaro, R. A.; Segi, M.; Reibenspies, J. H.; Nakajima, T. Synthesis and Structure of Telluroamides and Selenoamides. The First Crystallographic Study of Telluroamides. *Organometallics* **1997**, *16*, 756−762. (c) Ming, G.; Zingaro, R. A. Reaction of Diisobutylaluminium Hydride with Selenium and Tellurium: New Reagents for the Synthesis of Seleno- and Telluro-Amides. *J. Chem. Soc., Perkin. Trans. 1* **1998**, *1*, 647−650. (d) Ishihara, H.; Koketsu, M.; Fukata, Y.; Nada, F. Reaction of Lithium Aluminum Hydride with Elemental Selenium: Its Application as a Selenating Reagent into Organic Molecules. *J. Am. Chem. Soc.* **2001**, *123*, 8408−8409. (e) Koketsu, M.; Okayama, Y.; Aoki, H.; Ishihara, H. Facile Synthesis of *N*,*N*-dialkylselenoamides from amides. *Heteroatom. Chem.* **2002**, *13*, 195−198. (f) Saravanan, V.; Mukherjee, C.; Das, S.; Chandrasekaran, S. Facile Conversion of Amides and Lactams to Selenoamides and Selenolactams Using Tetraethylammonium Tetraselenotungstate. *Tetrahedron Lett.* **2004**, *45*, 681−683. (g) Shibahara, F.; Sugiura, R.; Murai, T. Direct Thionation and Selenation of Amides Using Elemental Sulfur and Selenium and Hydrochlorosilanes in the Presence of Amines. *Org. Lett.* **2009**, *11*, 3064−3067.

(22) Selected references (a) Ishihara, H.; Yoshimi, M.; Hara, N.; Ando, H.; Kato, S. A Facile Preparation of *O*-Alkyl Selenocarboxylates and Selenoamides via Se-Alkynyl Selenocarboxylates. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 835−841. (b) Takikawa, Y.; Yamaguchi, M.; Sasaki, T.; Ohnishi, K.; Shimada, K. Convenient Syntheses of *N*,*N*-Dialkylselenoamides and *N*,*N*,*N*′,*N*′- Tetraalkylselenoureas by Treating Terminal *gem*-Dihaloalkanes, Chloroform, or Sodium Trichloroacetate with a Base, Elemental Selenium, and Amines. *Chem. Lett.* **1994**, 2105−2108. (c) Shimada, K.; Yamaguchi, M.; Sasaki, T.; Ohnishi, K.; Takikawa, Y. A Willgerodt−Kindler Type Selenation of Dihalomethane Derivatives, Chloroform, and Sodium Trichloroacetate by Treating with a Base, Elemental Selenium, and an Amine. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2235−2242. (d) Murai, T.; Ezaka, T.; Kanda, T.; Kato, S. Highly Efficient One-Pot Synthesis of α,α-Disubstituted Selenoamides and their First Reduction to Amines. *Chem. Commun.* **1996**, 1809−1810. (e) Murai, T.; Ezaka, T.; Niwa, N.; Kanda, T.; Kato, S. An Efficient Synthetic Method of Aliphatic Selenoamides via Selenoketene Intermediates. *Synlett* **1996**, 865−866. (f) Murai, T.; Fujishima, A.; Iwamoto, C.; Kato, S. Highly Efficient Peterson Olefination Leading to Unsaturated Selenoamides and Their Characterization. *J. Org. Chem.* **2003**, *68*, 7979−7982.

(23) (a) Zheng, Z.; Chen, J.; Yu, Z.; Han, X. Oxidative Demetalation of Fischer Alkoxy Carbene Complexes with Stoichiometric Pyridine *N*-Oxide and $NaBH_4$-Promoted Demetalation of Fischer Iminocarbene Complexes with Sulfur and Selenium. *J. Organomet. Chem.* **2006**, *691*, 3679−3692. (b) Sandoval-Chávez, C.; López-Cortés, J. G.; Gutiérrez-Hernández, A. I.; Ortega-Alfaro, M. C.; Toscano, A.; Alvarez-Toledano, C. An Expedient Approach to Ferrocenyl Thioamides via Fischer Carbenes. *J. Organomet. Chem.* **2009**, *694*, 3692−3700.

(24) (a) López-Cortés, J. G.; Contreras de la Cruz, L. F.; Ortega-Alfaro, M. C.; Toscano, R. A.; Alvarez-Toledano, C.; Rudler, H. Improved Approaches and Structures of New Ferrocenyl Carbene Complexes of Chromium, Tungsten, and Molybdenum. *J. Organomet. Chem.* **2005**, *690*, 2229−2237. (b) López-Cortés, J. G.; Samano-Galindo, A.; Ortega-Alfaro, M. C.; Toscano, A.; Rudler, H.; Parlier, A.; Alvarez-Toledano, C. Synthesis and X-ray Structure of an Unexpected

Bidentate Allene−Aminocarbene Complex of Tungsten. *J. Organomet. Chem.* **2005**, *690*, 3664−3668.
(25) (a) Murai, T.; Mizutani, T.; Kanda, T.; Kato, S. Reactions of Diselenoic Acid Esters with Amines and X-ray Crystal Structure Analyses of Aromatic Selenoamides. *Heteroatom. Chem.* **1995**, *6*, 241−246. (b) Li, Y.; Hua, G. X.; Slawin, A. M. Z.; Woollins, J. D. The X-Ray Crystal Structures of Primary Aryl Substituted Selenoamides. *Molecules* **2009**, *14*, 884−892 and references cited therein..
(26) Monks, A.; Scudeiro, D.; Skehan, P.; Shoemaker, R.; Paull, K.; Vistica, D.; Hose, C.; Langley, J.; Cronise, P.; Vaigro-Wolff, A.; Gray-Goodrich, M.; Campbell, H.; Mayo, J.; Boyd, M. Feasibility of a High-Flux Anticancer Drug Screen Using a Diverse Panel of Cultured Human Tumor Cell Lines. *J. Natl. Cancer Inst.* **1991**, *83*, 757−766.
(27) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford University Press: Oxford, 1997.
(28) (a) Steiner, T. The Hydrogen Bond in the Solid State. *Angew. Chem., Int. Ed.* **2002**, *41*, 48−76. (b) Ju, J.; Park, M.; Suk, J.; Lah, M. S.; Jeong, K.-S. An Anion Receptor with NH and OH Groups for Hydrogen Bonds. *Chem. Commun.* **2008**, 3546−3548. (c) Kuhn, B.; Mohr, P. Stahl, Intramolecular Hydrogen Bonding in Medicinal Chemistry. M. *J. Med. Chem.* **2010**, *53*, 2601−2611.
(29) Powers, T. S.; Wulff, W. D.; Quinn, J.; Shi, Y.; Jiang, W.; Hsung, R.; Parisi, M.; Rahm, A.; Jiang, X. W.; Yap, G. P. A.; Rheingold, A. L. The Preparation of Imidazolidinone and Oxazolidinone Chelated Carbene Complexes. *J. Organomet. Chem.* **2001**, *617*−*618*, 182−208.
(30) Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Canalli, M. SIRPOW.92—A Program for Automatic Solution of Crystal Structures by Direct Methods Optimized for Power Data. *J. Appl. Crystallogr.* **1994**, *27*, 435−436.
(31) Sheldrick, G. M. A Short History of SHELX. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *A64*, 112−122.