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Synthesis and estrogen receptor binding of (17α,20E)- and (17α,20Z)-21-phenylthio- and 21-phenylseleno-19-norpregna-1,3,5(10),20-tetraene-3,17β-diols

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Previous studies from our laboratory using 17α-E- and 17α-Z-halovinyl estradiols demonstrated a marked enhancement of receptor binding by the Z-isomers. This suggested tolerance at the 17α-position was not previously observed by investigations using 16α and 17α-substituted estradiols. Because of the synthetic access provided by vinyl tin chemistry, we prepared the 17α-E and Z-phenylthiovinyl and phenylselenovinyl estradiols and compared their binding characteristics to those of the previously reported 16α/17α-phenylseleno and methylseleno estradiols. The results, in addition to demonstrating a facile preparation of the target compounds, indicated that significant receptor affinity was retained by these compounds (relative binding affinity = 24.5–117). The highest affinity was demonstrated by the 17α-Z-phenylthiovinyl estradiol **5a,** *which, by molecular modeling, exhibited a significantly different molecular conformation from the corresponding 17α-E-phenylthiovinyl isomer or the 17α-phenyl-thioethynyl analog. The current series possessed better binding characteristics than the phenylseleno and methylseleno estradiols but somewhat poorer binding than the 17α-E/Z-halovinyl series. The observations suggest that some steric limitations exist in a portion of the 17α-region, and that the region is better accessed by compounds possessing Z-vinyl stereochemistry. (Steroids* **61**:384–389, 1996)

Keywords: steroidal derivatives; thio(seleno)vinyl analogs; molecular modeling

Introduction

The conventional wisdom concerning the estrogen receptor has stated that substituents at the 17α-position that are larger than the ethynyl group (–C≡CH) result in a reduction of receptor affinity. This has been based upon numerous studies in which 17α-alkyl, 17α-alkynyl, and substituted allylic derivatives of estradiol were prepared and evaluated for their estrogen potency either by in vivo assays or by in vitro competitive receptor binding assays.[1–6] Invariably, the extension of the 17α-moiety to a substituent containing three or more carbons resulted in a significant decrease in activity or affinity. These observations were apparently further supported by subsequent studies in which heteroatom substituted alkyl and alkynyl groups were introduced at the 17α-position and evaluated.[7–10] The relevance of the structure-activity relationships thus derived was extended to the 16-substituted estrogens prepared and evaluated by Katzenellenbogen and co-workers.[11,12]

We decided to reinvestigate this basic assumption as the result of two observations. We had observed in a previous study that the 17α-halovinyl estradiols, particularly the Z-isomers, displayed relative binding affinities for the estrogen receptor that were equal to or greater than the binding affinity of estradiol itself.[13] For example, the 17α-Z-bromovinyl and iodovinyl estradiols display relative bind-

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ing affinity (RBA) values of 661–776 compared to values of 77 and 78 for the corresponding E-isomers. In addition, the 17α-Z-halovinyl and Z-propenyl progestins display high RBA for the progesterone receptor.[14–16] Based upon the reported homology of the estrogen and progesterone receptor in this region of the ligand-binding domain, stereochemical effects may be present for the 17α-substituted estrogen ligands that are similar to those observed for progestins.[17–21]

Although the synthesis and receptor-binding characteristics of selenium-containing estrogens substituted at the 17α (**1a,b; 3a,b**) or 16a (**2a,b**) positions had been reported previously, data for the 17α-thiovinyl and 17α-selenovinyl analogs (**4a,b; 5a,b**) were not available (Figure 1). Additional information concerning the interaction of these moieties with the receptor would provide an enhanced understanding of the estrogen receptor topography. We report here the synthesis of the 17α-E- and Z-phenylthiovinylestradiols and phenylselenovinylestradiols **4a,b** and **5a,b** and their relative binding affinities to the estrogen receptor of rat uterus. The results suggest that a tolerance of large substituents at the 17α-position exists when a substituted vinyl group is employed. They also identify a site that possesses steric tolerance and allows us to develop new probes for the ligand-binding domain of the estrogen receptor.

Experimental

All melting points were obtained using a Meltemp apparatus and are uncorrected. Proton nuclear magnetic spectra were performed on a multinuclear Varian XL-300 spectrometer.

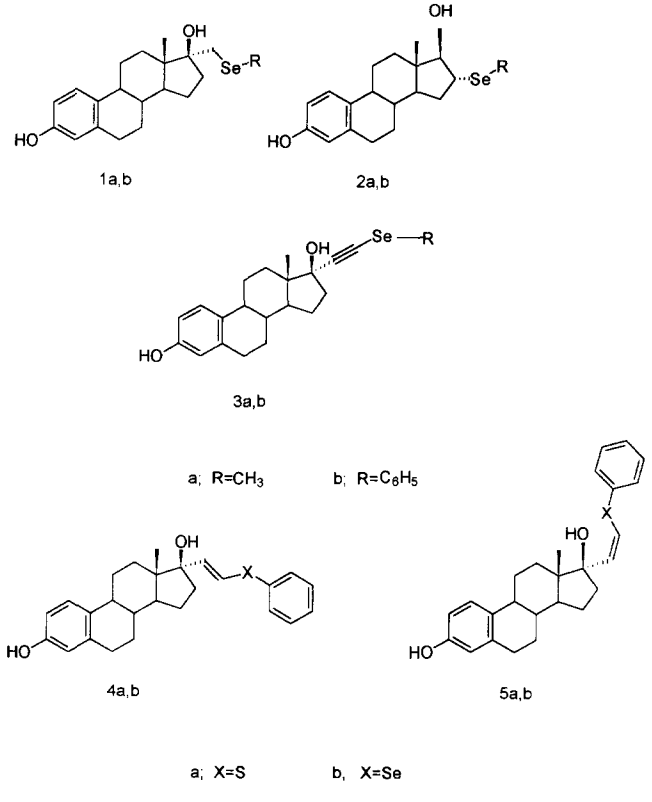


Figure 1 Target phenylthio/phenylselenovinyl estradiols **4a,4b** and **5a,5b,** and previously characterized methylseleno-(**1a,2a,3a**) and phenylseleno- (**1b,2b,3b**) estradiols.

Optical rotations were obtained with a Perkin-Elmer 141 polarimeter. Elemental analyses were performed by Atlantic Microlab (Norcross, GA).

Ethynyl estradiol and other chemical reagents were purchased from Aldrich Chemical Company (Milwaukee, WI). The preparation of 3-acetoxy-17α, 19-norpregna-1,3,5(10)-triene-20-yn-17β-ol **7** was achieved using the procedure of Counsell et al.[2] Solvents were dried prior to use. The silica gel was flash chromatography grade.

Synthetic methods

3-Acetoxy-(17α,20E)-21-(tri-n-butylstannyl)-19-norpregna-1,3,5(10),20-tetraen-17β-ol (**8**)

A solution of **7** (100 mg, 0.31 mmol), tributyltin hydride (0.27 g, 0.25 mol, 0.93 mmol), and tetrahydrofuran (freshly distilled, 1.5 mL) was prepared under nitrogen in a quartz tube. The bottom of the tube containing the solution was immersed just below the surface of a water bath kept at 50–55°C. The solution was magnetically stirred and irradiated from above (= 15 cm) with a sun lamp (275 W; General Electric). Monitoring by TLC (Hexane/EtOAc 4:1) showed the gradual disappearance of **7** (R_f = 0.20) and the temporary formation of **9** (R_f = 0.51), which was converted to **8** (R_f = 0.41) within 1.5–2 h. The solvent was removed by rotary evaporation, and the residue was purified by chromatography, using ethyl acetate/hexane 2:8 to afford **8** (0.170 g, 90%) as an oil that solidified on standing.

8 m.p. 65–67°C; ^{1}H-NMR 0.80–2.32(m,43H), 2.27(s,3H,CH_3CO), 2.85(m,3H), 6.02, 6.09, 6.17, 6.24(AB_g,2H,SnCH=CH), 6.78(d, J = 2.5 Hz, 1H,C(4)(H), 6.83(dd, J = 2.5,8.5 Hz,1H,C(2)H), 7.27 (d, J = 8.5 Hz,1H,C(1)H).

3-Acetoxy(17α,20Z)-21-(tri-n-butylstannyl)-19-norpregna-1,3,5(10),20-tetraen-17β-ol(**9**)

A solution of **7** (100 mg, 0.31 mmol) and tributyltin hydride (0.27 g, 0.25 mL, 0.93 mmol) in tetrahydrofuran (1.5 mL) was sealed in an ampule and heated for 2 h at 60°C. The solvent was then evaporated and the residue triturated with hexane; unreacted **7** (35 mg) was separated as a solid, which was removed by filtration. The filtrate was charged on a chromatographic column and eluted with ethyl acetate/hexane 1:9 to afford **9** (87 mg, 46%) and **8** (13 mg, 5%). Further elution with ethyl acetate/hexane 1:1 gave additional **7** (12 mg).

9 m.p. 84–86°C; ^{1}H-NMR 0.75–2.05(m,38H),2.14–2.35(m,5H), 2.28(s,3H,CH_3CO), 2.82–2.90(m,3H), 5.87(d J = 13.0 Hz,1H,SnCH=CH), 6.77(d, J = 13.0 Hz,1H, SnCH=CH), 6.79(d, J = 2.5 Hz,1H,C(4)H, 6.83 (dd, J = 2.5,8.5 Hz,1H,C(2)H), 7.28(d,8.5Hz,C(1)H).

Conditions for preparation of E-Z/phenylthio (**4a,b**) and phenylseleno (**5a/5b**) vinyl derivatives

To a solution of **8/9** (0.2 mmol) in CCl_4 (10 ml), stirred at −18°C, was added dropwise a solution of phenylsulfenyl chloride (30 mg, 0.2 mmol) or phenylselenyl chloride (38 mg, 0.2 mL) in CCl_4 (5 mL). The solution was warmed to ambient temperature, added to a column of silica gel, and

eluted with ethyl acetate/hexane 1:4 (flash chromatography). The major product was dissolved in methanol (10 mL) containing 0.2 mL of 10N NaOH. After 5 min, the reaction mixture was acidified by the addition of acetic acid and partitioned between ethyl acetate and water. The organic phase was washed with aqueous Na_2CO_3 (10%) and dried over Na_2SO_4 (anhydrous). Flash chromatography gave the products in 85–95% overall yield for the two steps.

4a m.p. 160–168°C$[\alpha]_{D^{25}}$ = +38.10 (c = 1.08, ethyl acetate), ^{1}H-NMR($CDCl_3$) 0.95(s,3H,C(18)H), 1.22–2.38(m,13H), 2.83(m,3H), 4.60(s,1H), 6,57(d, J = 2.5 Hz, C(4)H), 6.63(dd, J = 2.5,8.5 Hz,C(2)H), 7.15(d, J = 8.5 Hz,1H,C(1)H), 7.16–7.40(m,5H,S-C_6H_5) R_f = 0.29 (ethyl acetate/hexane 1:2). Analysis calculated for $C_{26}H_{30}S$-1 H_2O C = 73.60; H = 7.60. Found: C = 74.04; H = 7.27.

5a m.p. 138–140°C$[\alpha]_{D^{25}}$ = +11.36 (c = 0.53, ethyl acetate), ^{1}H-NMR($CDCl_3$) 0.96(s,3H,C(18)H), 1.22–2.38(m,16H), 2.62(s,1H), 2.82(m,3H), 4.60(s,1H), 5.92(d, J = 10.5 Hz, S-CH=CH), 6.34(d, J = 10.5 Hz, 1H,SCH–=CH), 6.56(d, J = 2.5 Hz,1H,C(4)H), 6.63(dd, J = 2.5,8.5 Hz,1H,C(2)H), 7.16(d), J = 8.5 Hz,1H,C(1)H,), 7.22–7.45(m,5H,S-C_6H_5) R_f = 0.34 (ethyl acetate/hexane 1:2). Analysis calculated for $C_{26}H_{30}O_2S$·0.5H_2O:C = 75.14; H = 7.52. Found: C = 75.66; H = 7.38.

4b m.p. 90°C (dec.) $[\alpha]_{D^{25}}$ = +32.49 (c = 0.95, ethyl acetate), ^{1}H-NMR($CDCl_3$) 0.93(s,3H,C(18)H, 1.22–2.33(m,13H), 3.82(m,3H), 4.80(s,1H), 6.29(d, J = 15.5 Me,SeCH=CH), 6.54–6.68(m,2H,C(2)H,C(4)H, SeCH=CH), 7.14(d, J = 8.5 Hz,1H,C(1)H), 7.22–7.34(m,3H), 7.45–7.55(m,2H). R_f = 0.32 (ethyl acetate/hexane 1:2). Analysis calculated for $C_{26}H_{30}O_2Se$·H_2O): C = 66.23; H = 6.84. Found: C = 66.69; H = 6.87.

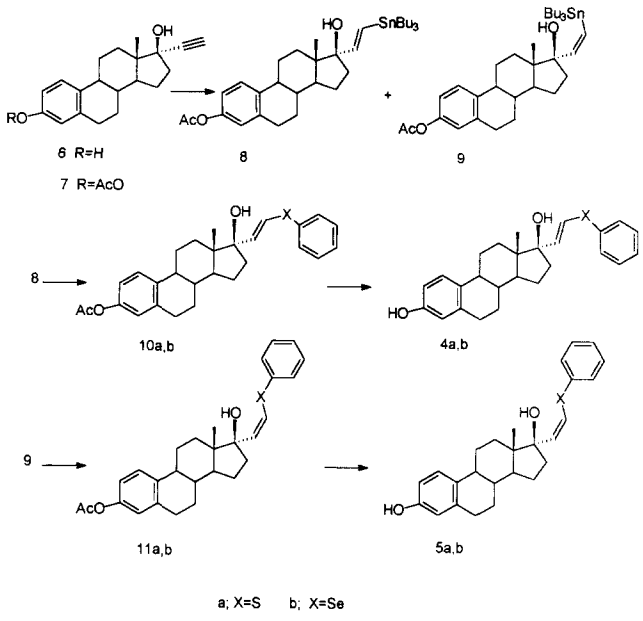
5b m.p. 108–110°C $[\alpha]_{D^{25}}$ = +19.48 (c = 1.08, ethyl acetate), ^{1}H-NMR($CDCl_3$) 0.96(s,3H,C(18)H), 1.22–2.38(m,13H), 2.83(m,3H), 4.80(m,1H), 6.19(d, J = 10.0 Hz,1H,SeCH=CH), 6.55–6.70(m,3H,C(2)H, C(4)H,SeCH=CH), 7.15(d, J = 8.5 1H, C(1)H), 7.24–7.36(m,3H), 7.42–7.52(m,2H). R_f = 0.36 (ethyl acetate/hexane 1:2). Analysis calculated for $C_{26}H_{30}O_2Se$·H_2O): C = 66.23; H = 6.84. Found: C = 66.27; H = 6.94.

Competitive receptor binding assay

All cytosol for the estrogen receptor was prepared and stored in TEA buffer (0.01 M Tris-HCl:0.0015 M EDTA: 0.02% sodium azide, pH 7.4 at 25°C. Rat uterine cytosol was prepared from Holtzman rats (21–25-day-old females) and stored in liquid nitrogen. The competitive receptor binding assays were performed as previously described by Katzenellenbogen et al.,[22,23] and the results were tabulated as RBAs relative to estradiol (RBA = 100).

Results and Discussion

In this study we prepared stereospecifically the 17α-E- and 17α-Z-phenylthiovinyl and phenylselenovinyl estradiols via the route described in Scheme 1. These syntheses utilized the facile preparation of the corresponding E- and Z-tri-n-butylstannylvinyl derivatives **8** and **9.** The subsequent electrophilic destannylation with the phenylsulfenyl or

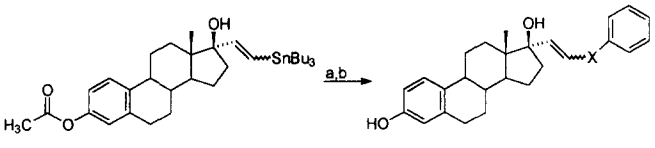


Scheme 1

phenylselenyl chloride in carbon tetrachloride gave, after hydrolysis, the desired E- and Z-phenylthio and phenylseleno vinyl products in 85–95% isolated yields (Table 1). The destannylation reaction proceeded stereospecifically, as was evidenced by the coupling constant of the products, **4a, 5a,** J = 15.2–15.5 Hz (E) and **4b, 5b,** J = 10.5 Hz (Z). The products were stable for several months when stored in the dark at 4°C.

The competitive receptor binding assays for the compounds were determined, with rat uterine cytosol as the receptor source. The incubations were conducted at 0°C and 25°C with [^{3}H]estradiol as the radioligand. The two temperatures for the cytosol inventions were chosen based on the observations of Raynaud and co-workers[5] that the differing conditions provided evidence of the relative dissociation rate of the competitor compared to the radioligand. Compounds that tend to dissociate slowly would form more stable complexes and therefore demonstrate substantial RBA values at long incubation times. This tends to be im-

Table 1 Yields of electrophilic destannylation and saponification



X	Reagent	E Yield (J)	Z Yield (J)
S	PhSCl	90% (15.2 Hz)	94% (10.5 Hz)
Se	PhSeCl	85% (15.5 Hz)	90% (10.5 Hz)

a, Reaction performed in CCl_4 at −15°C.
b, Reaction performed in MeOH with 4-fold excess of 10 M aqueous NaOH, followed by acidification with AcOH, dilution with water extraction and chromatography.

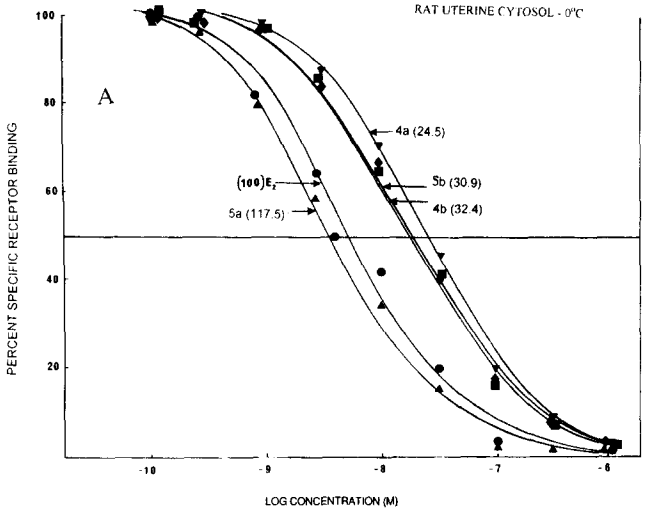


Figure 2 Relative binding affinity assay. Various concentrations of competitor (E_2 (estradiol), **4a,4b,5a,** or **5b**) were incubated with [^{3}H]estradiol in rat uterine cytosol at 0°C **(A)** or 25°C **(B)**. Dextran-coated charcoal was used to adsorb unbound steroid. Relative binding affinity (RBA) values are given in parentheses.

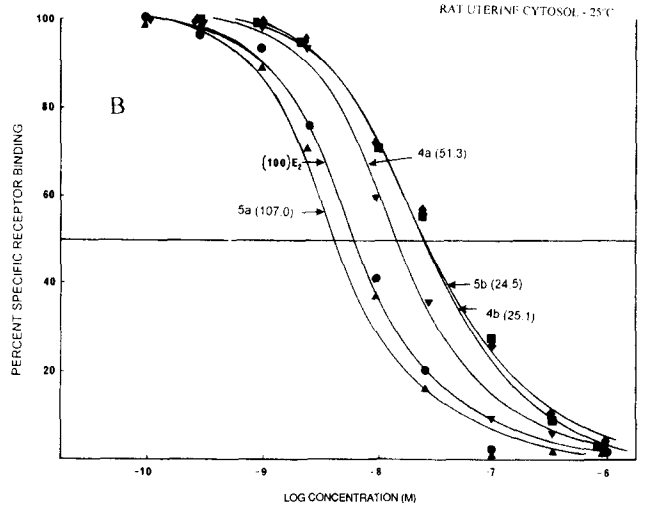


Figure 3 Comparison of the conformation for 17α-phenylselenoethynyl estradiol **3b,** 17α-E-phenylthiovinyl estradiol **4a,** and 17α-Z-phenylthiovinyl estradiol **5a** using superimposed CHARMM low-energy conformers.

portant biologically, since the response depends upon both the number of binding sites occupied and the average duration of occupation. The concentration of the labeled competitive ligand, estradiol, ranged from 10^{-10} M to 10^{-5} M, and the specifically bound activity was determined using standard methods. The results of the competitive binding assays are illustrated in Figure 2A–B. At 0°C, the 17α-substituted vinyl estradiols competed well for the estrogen receptor, with RBAs of 25–118%, the highest value being that obtained with 17α-Z-phenylthiovinyl estradiol **5a.** At 25°C, the RBA values for the four estradiol derivatives ranged from 25 to 107%, the highest value again being associated with the 17α-Z-phenylthiovinyl estradiol **5a.**

The values obtained from the competitive binding assay were compared with the results previously reported by Sadek et al.[7,8] and Caspi et al.[9,10] for a series of 16α/17α-phenylseleno- and methylseleno-substituted estradiols (Table 2). The RBA values obtained in the present study were equal to or greater than those previously reported for the selenium-containing analogs. In the earlier studies the only selenium-containing derivatives that had RBA values comparable to estradiol were those in which the heteroatom was part of a small substituent, e.g., 16α-methylseleno, 17α-methylselenomethyl, or 17α-methylselenoethynyl. Replacement of the methylseleno by a phenylseleno group in these cases produced a substantial decrease in receptor affinity, from 18.7–31% to 1.3–5%. In our series, the phenylseleno and analogous phenylthio derivatives retained high receptor affinity, one to two orders of magnitude greater than the previously reported compounds. The Z-phenylthio compound, in fact, had a receptor RBA slightly better than that of estradiol (117.5% vs. 100%). Therefore, based upon our data, the assertion that the receptor pocket into which the 16α/17α-substituents fit is sterically limited is not entirely justified.

To visualize the disposition of the 17α-substituent, we undertook a preliminary molecular modeling study of three of the estradiol derivatives. Molecular mechanics calculations were performed on the *cis* and *trans* phenylthiovinyl estrogens, as well as the phenylselenoethynyl-estrogen, using the CHARMM force field as implemented for Quanta 3.2.1. Sulfur parameters were estimated according to the method of Allinger et al.[24] from values derived for the MM2 force field. The three structures were superimposed by

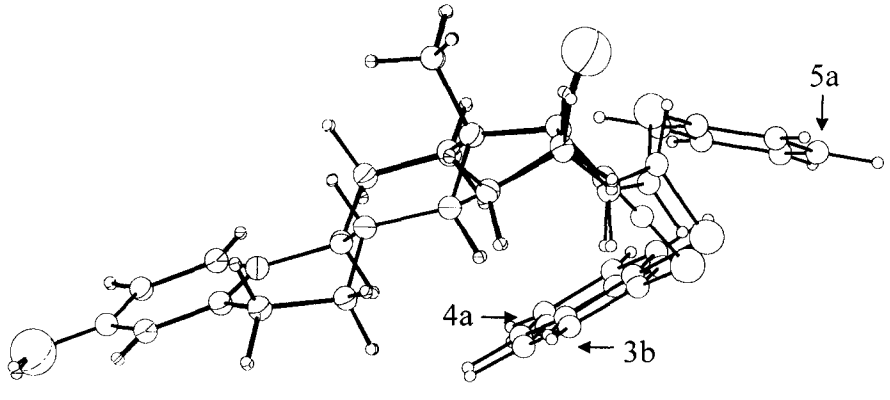


Figure 4

Table 2 Comparison of estrogen receptor binding phenylthiovinyl and phenylselenovinyl estradiols **(4a,b; 5a,b)** with other phenyl seleno and methylseleno substituted estradiols **(1a,b;2a,b;3a,b)**

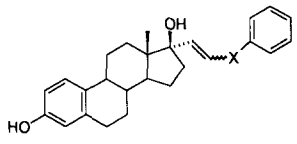
Compound	RBA (0°C)	Reference
Estradiol	100	
1a 17α-methylselenomethyl	31, 5.1	8,10
1b 17α-phenylselenomethyl	5, <1.0	8,10
2a 16α-methylseleno	27	10
2b 16α-phenylseleno	1.3	8
3a 17α-methylselenoethynyl	18.7	8
3b 17α-phenylselenoethynyl	2.0	9
4a 17α-E-phenylthio	24.5	
5a 17α-Z-phenylthio	117.5	
4b 17α-E-phenylseleno	32.5	
5b 17α-Z-phenylseleno	30.9	

For structures see Figure 1.

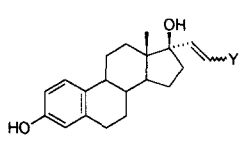
matching five points selected at random on the estrogen backbone. The *trans*-E-vinyl and -ethynyl compounds, which have similar in vitro estrogen receptor binding, show remarkably close superimposition, whereas the *cis*-Z-vinyl compound, which exhibits much higher receptor binding, allows a unique conformation for the phenylthio group. Systematic conformational searching reveals that this conformation, which is one of the lower energy conformers possible, is energetically inaccessible for the other two compounds. It is possible that the enhanced receptor binding is due to nonpolar interactions of the aromatic ring, rather than via lone pair interactions of the sulfur atom. It appears that for the Z-isomers, which display enhanced receptor binding relative to the E-isomers, the phenylthio or phenylseleno group may project into a different region of the receptor, where the steric bulk is apparently better tolerated. The presence of such a region could not have been predicted based upon the other alkyl- or alkynyl-seleno ethers. Experiments with high-field NMR spectrometry such as those recently reported by Dionne and Poirier[25] could assist in supporting the proposed conformational model or in identifying more reasonable confirmers. Future studies with these and newer ligands will employ such COSY experiments.

That the steric tolerance in that region of the receptor may be limited can be demonstrated by comparing the 17α-E- and Z-phentlthio and phenylseleno vinyl estradiols with their 17α-E- and Z-halovinyl counterparts. As Table 3 indicates, the RBA values for the present series of estrogens are lower by at least a factor of 3 (25–118% vs. 77–776%) compared to the halovinyl estradiols. For the phenylthiovinyl estradiols **4a** and **5a,** one observes the relationship where Z > E, previously seen with the halogenated estrogens. This effect is apparently lost with the phenylselenovinyl estradiols. Furthermore, one does not see the enhancement of RBA values upon raising the incubation temperatures to 25°C. Only the 17α-E-phenylthiovinyl estradiol **4a** exhibits this increase. Therefore, this substitution pattern illustrates that although the receptor can accommodate the 17α-phenylthiovinyl or phenylselenovinyl moiety, this steric tolerance is less than that for the halovinyl group. Furthermore, the interaction with the receptor does not appear to produce a significant increase in the ligand-receptor complex stabilization, which is observed with the slowly dissociation estrogens.

Table 3 Comparison of 17α-E/Z-phenylthiovinyl- and 17a-E/Z-phenylselenovinyl estradiols **(4a,b; 5a,b)** with 17β-E/Z-halovinyl estradiols



X= S, Se



Y= Cl, Br, I

Compound	RBA 0°C	RBA 25°C
Estradiol	100	100
17α-E-phenylthio **4a**	24.5	51.3
17α-Z-phenylthio **5a**	117.5	107.0
17α-E-phenylseleno **4b**	32.4	25.1
17α-Z-phenylseleno **5b**	30.9	24.5
17α-E-chlorovinyl	102	80
17α-Z-chlorovinyl	126	199
17α-E-bromovinyl	78	56
17α-Z-bromovinyl	195	661
17α-E-iodovinyl	77	62
17α-Z-iodovinyl	202	776

The results of our study demonstrated that the steric tolerance of the estrogen receptors for substituents at the 17α-position of estradiol is greater than previously reported and supports the finding that we initially reported for the 17α-halovinyl estradiols. Because the selenium-containing estrogens may possess potential diagnostic or chemotherapeutic effects,[7–10] the introduction of other substituents onto the estradiol nucleus that are known to enhance receptor binding may improve the interaction of these derivatives with the estrogen receptor. Studies to demonstrate these aspects are currently in progress and will be reported in subsequent publications. The observation that aromatic substituents can be incorporated at the 17α-position without a significant loss of affinity provides the opportunity to generate new probes to investigate that domain of the estrogen receptor.

Acknowledgments

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