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Antiandrogenic Steroidal Sulfonyl Heterocycles. Utility of Electrostatic Complementarity in Defining Bioisosteric Sulfonyl Heterocycles

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Complementarity of electrostatic potential surface maps was utilized in defining bioisosteric steroidal androgen receptor antagonists. Semiempirical and ab initio level calculations performed on a series of methanesulfonyl heterocycles indicated the requirement for a partial negative charge at the heteroatom attached to C-3 of the steroid nucleus to attain androgen receptor affinity. Synthesis and testing of six heterocycle A-ring-fused dihydroethisterone derivatives support this hypothesis, and we have identified two new androgen receptor antagonists of this class.

Introduction

Prostate cancer (PC) and benign prostatic hyperplasia (BPH) are major medical problems in the aging male. PC is the second leading form of cancer in males with approximately 96,000 cases diagnosed and 26,000 deaths annually in the U.S. Although usually not fatal, BPH is the second leading cause of surgery in the U.S. with over 400,000 prostatectomies performed each year, but this only represents 20–25% of men exhibiting symptoms. The worldwide market potential for antiprostatic agents has been estimated at $750–1000 million.[1]

Although surgery presently represents the most accepted treatment for BPH, several pharmacologic approaches are under evaluation. These include inhibition of androgen production by LHRH agonists,[2,3] inhibition of the conversion of testosterone to dihydrotestosterone (DHT) by 5α-reductase inhibitors,[4-6] inhibition of androgen action by androgen receptor antagonists,[7,8] inhibition of the conversion of androgens to estrogens by aromatase inhibitors,[9-11] and relaxation of urogenital smooth muscle by α-adrenergic receptor antagonists.[12-14]

The dihydroethisterone derivative 1 (WIN 49596, Zanoterone, Figure 1) is an androgen receptor antagonist which does not have affinity for other steroid hormone receptors. In vivo preclinical activity of this compound indicates potential utility in proliferative prostatic disease.[15,16] Structure–activity studies in this (pyrazolo steroid) series have identified requirements for androgen receptor affinity and in vivo antiandrogenic activity, revealed several more potent analogues and defined an area

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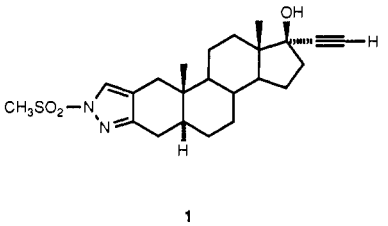

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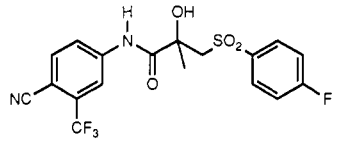

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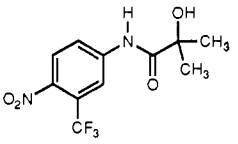
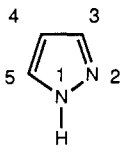


Hydroxyflutamide 3

Figure 1.

Table I



	exptl[a]	MNDO[b]	STO-3G[c]	6-31G*[c]
		bond lengths		
N(1)–N(2)	1.349	1.333	1.384	1.330
N(2)–C(3)	1.331	1.355	1.330	1.302
C(3)–C(4)	1.416	1.440	1.424	1.413
C(4)–C(5)	1.373	1.395	1.354	1.363
C(5)–N(1)	1.359	1.398	1.379	1.341
N(1)–H		1.003	1.023	0.992
		bond angles		
C(5)–N(1)–N(2)	113.1	112.9	112.2	112.9
N(1)–N(2)–C(3)	104.1	106.1	103.2	104.9
N(2)–C(3)–C(4)	111.9	110.2	112.5	111.7
C(3)–C(4)–C(5)	104.5	105.3	105.4	103.9
C(4)–C(5)–N(1)	106.4	105.5	106.6	106.6
dipole (D)	2.209	2.107	2.148	2.433

[a] Data taken from Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press: New York, 1985; p 95. [b] J. J. P. Stewart, MOPAC v5.0, *QCPE* No. 455 (1989). AMPAC *QCPE* No. 506. [c] Gaussian 90. M. J. Frisch, M. Head-Gordon, M. A. Robb, J. S. Binckley, D. J. Defrees, D. J. Fox, R. A. Whiteside, R. Seeger, C. F. Melius, J. Baker, R. L. Martin, L. R. Kahn, J. J. P. Stewart, S. Topiol, and J. A. Pople, Gaussian Inc., Pittsburgh, PA (1990).

of previously unexplored androgen receptor space.[17] Subsequently, we have defined bioisosteres for the sulfonylpyrazole moiety of 1 and report here that the methanesulfonyl-substituted [3,2-*b*] furan **4**, [3,2-*d*] thiazole **6**, and [3,2-*d*] oxazole **7** are isosteres for the methanesulfonyl-substituted [3,2-*c*] pyrazole of compound 1.

Table II. Experimental Computational Results: Dimethyl Sulfone

	experimental microwave/electron diffraction[28]	MNDO	PM3	STO-3G	6-31G*
		charge			
C		−0.16	−0.57	−0.26	−0.72
S		+1.33	+2.20	+0.56	+1.43
O		−0.67	−0.84	−0.31	−0.68
		angle			
C–S–C	103.3/102.6	105.8	100.5	100.0	104.3
O–S–O	121.0/119.7	115.0	118.2	129.9	120.08
C–S–O			109.1		107.84
		bond length			
C–S	1.777/1.771	1.814	1.795	1.814	1.774
S–O	1.431/1.435	1.533	1.468	1.851	1.437
dipole (D)	4.49	6.16	4.99	4.10	5.10

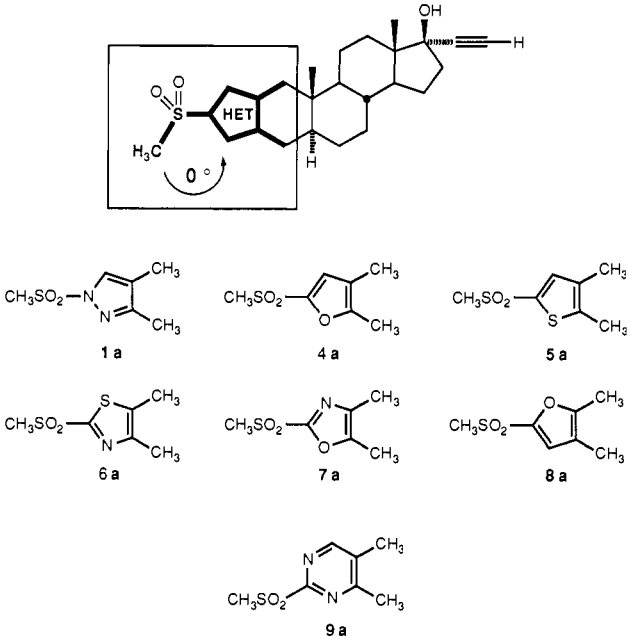


Figure 2.

Computational Chemistry

The techniques available for calculation of atomic charge in small molecules have been recently examined. Kollman and co-workers determined that molecular electrostatic potential, atomic charge and, derived dipole from the

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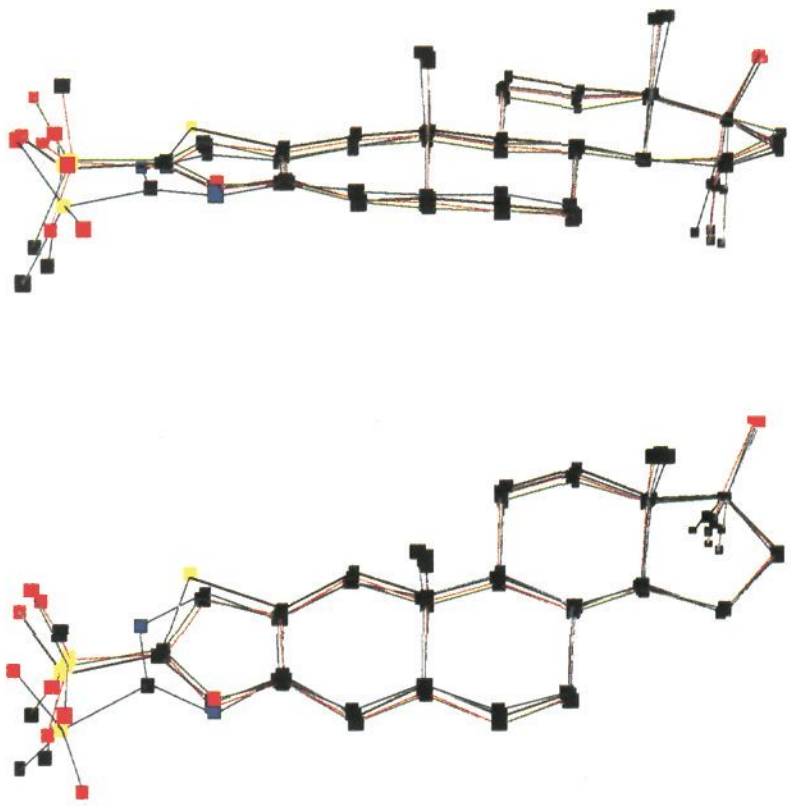
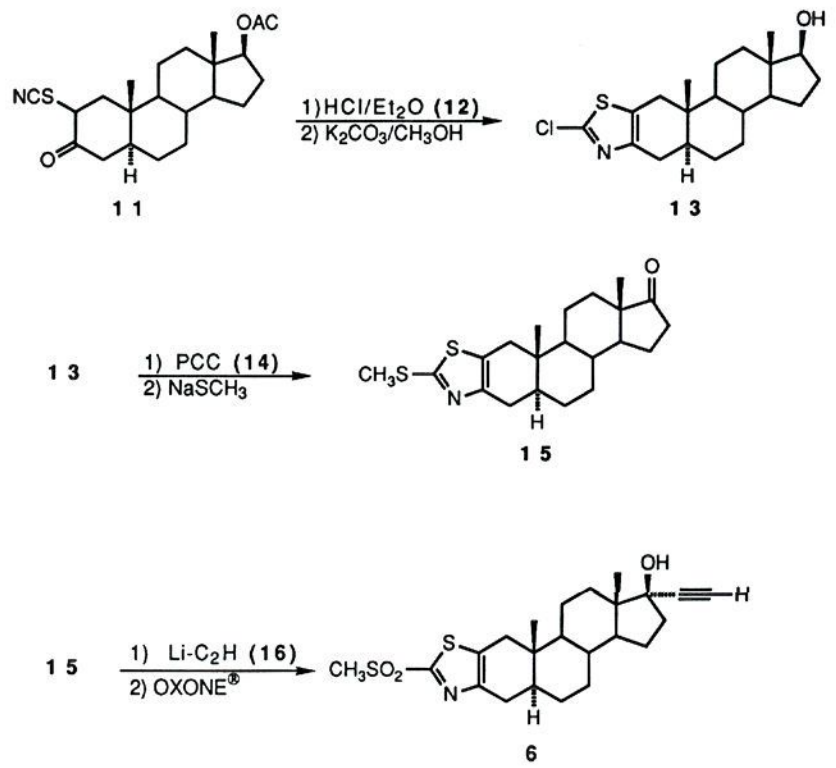


Figure 3. Representations of X-ray crystallographic structure determinations for compounds **1**, **4**, **6**, and **9**, red, green, black, and, blue, respectively. Skeletal conformations are nearly identical with rotational variation noted at the sulfone–heterocycle bond. Compound **6** had two molecules per asymmetric unit, differing in rotation about this bond. The preferred rotational isomer is unknown.

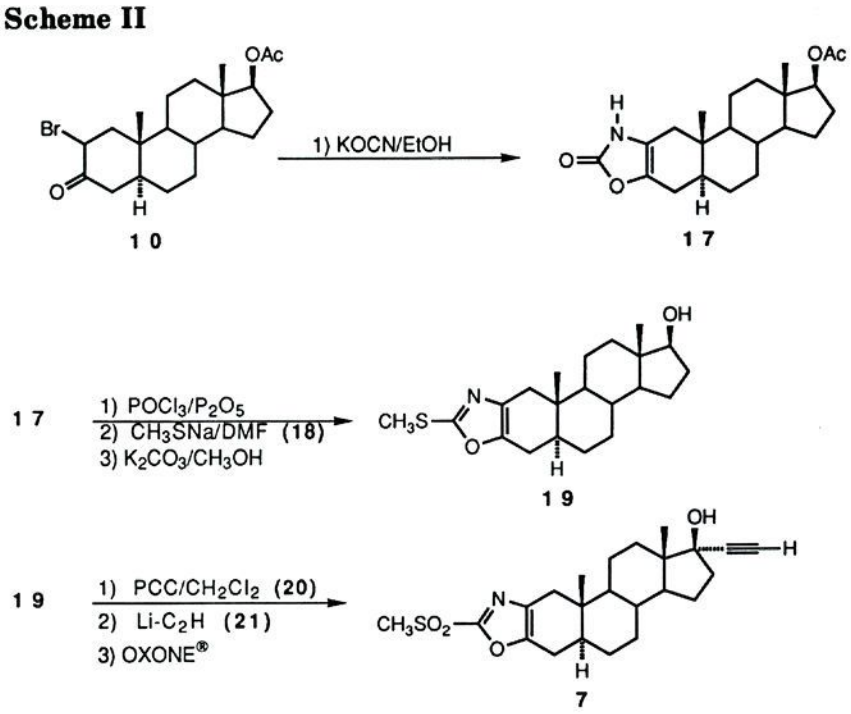
MNDO semiempirical method are in reasonable agreement with both experimentally determined dipole and charge and dipole derived from 6-31g* calculations.[18] We have conducted a study of point-charge generation and resulting geometries with the methanesulfonyl heterocycles described in this paper and arrive at a similar conclusion regarding these techniques. An example of this study is given in Table I.[19] The computational results for dimethyl sulfone are shown in Table II.

Among nearly isosteric ligands, complementarity of electrostatic surfaces may be a determinant of molecular associations.[20] In an attempt to better understand the factors governing androgen receptor affinity we examined the complementarity of electrostatic potential surfaces for representative heterocycles. The substructure methanesulfonyl heterocycles **1a**, and **4a–9a** were constructed using standard facilities of the molecular modeling software package CHEMX.[21] The substructure depicted in Figure 2 was utilized in order to reduce the total number of heavy atoms submitted to calculation; this is supported by the minimal conformational variation observed in X-ray crystal structures for compounds **1**, **4**, **6**, and **9**, Figure 3.[22] After optimization using default settings within CHEMX, the individual substructures were submitted to AMPAC specifying the MNDO method. Full geometry optimizatioin with "precise" convergence criteria were also specified as recommended by Dewar.[23,24] The results were then imported into CHEMX, and electrostatic potential surfaces were generated with the SET SURF facility at 1 VDW radii. The three-color surface is coded according to the electrostatic potential (in kcal/mol) experienced at each point

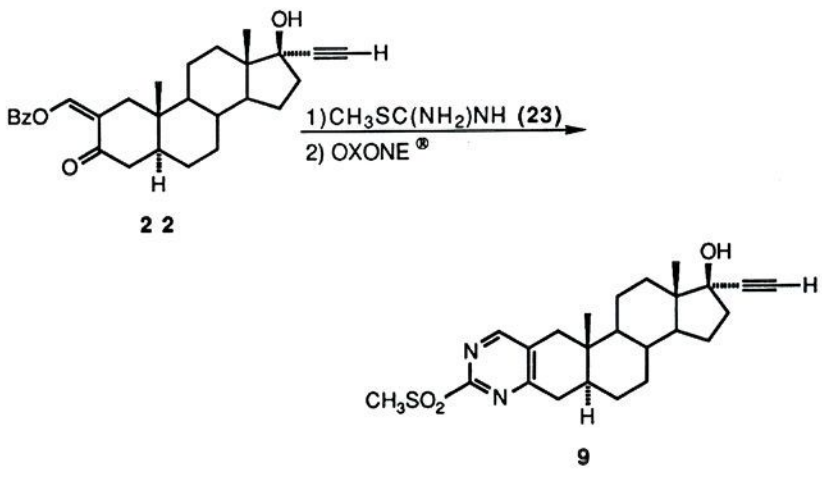
Scheme I



Scheme II



Scheme III



(18) Besler, B. H.; Merz, K. M., Jr.; Kollman, P. A. Atomic Charges Derived from Semiempirical Methods. *J. Comput. Chem.* **1990**, *11*, 431–439.
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(20) Naray-Szabo, G. Electrostatic Complementarity in Molecular Associations. *J. Mol. Graphics* **1989**, *7*, 76–81.
(21) CHEMX, Chemical Design Ltd., January 1989.
(22) X-ray coordinates were imported into CHEMX and standard facilities were used unmodified. Overlay of the structures shown in Figure 3 was performed in the CHEMX "FLY" facility in a rigid manner; the crystal-derived geometry was not altered.

(23) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: A New General Purpose Quantum Mechanical Molecular Model. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909. (see also: Dewar, M. J. S.; Reynolds, C. H. *J. Comput. Chem.* **1986**, *7*, 140.)
(24) Dewar, M. J. S. *J. Phys. Chem.* **1985**, *89*, 2145–2151.

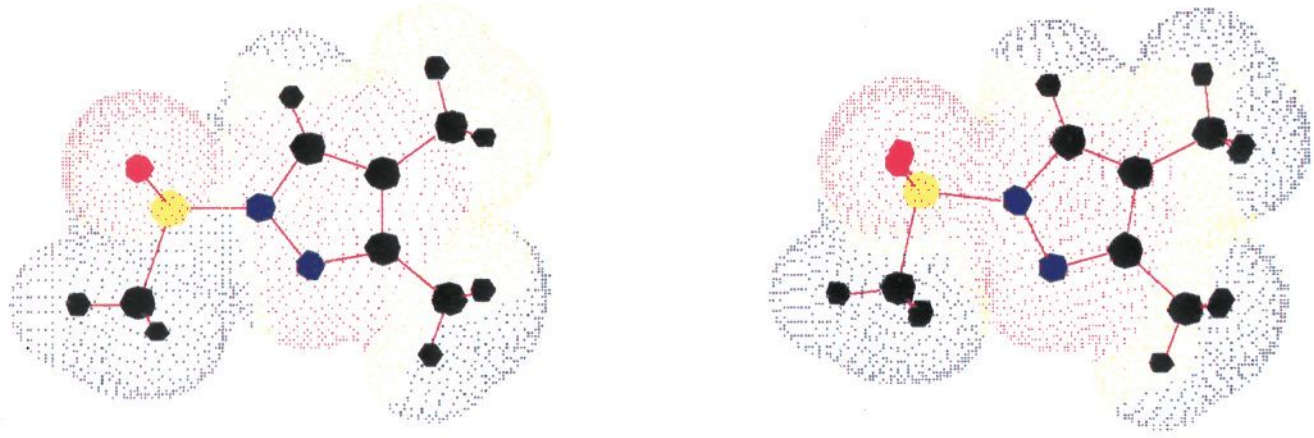


Figure 4. Graphical comparison of electrostatic potential surfaces derived from two levels of point charge calculation for substructure **1a**. A potential of >5 kcal/mol is shown as blue (positive), <5 and >−5 is white (neutral), and <−5 kcal/mol is red (negative).

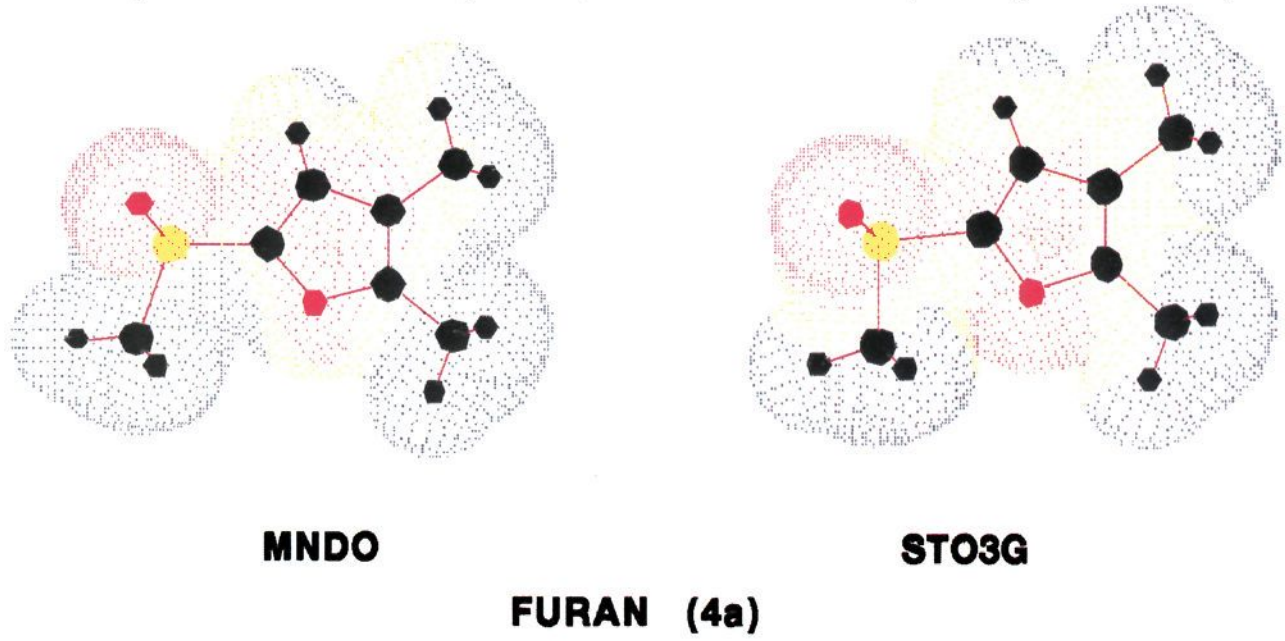


Figure 5. Graphical comparison of electrostatic potential surfaces derived from two levels of point charge calculation for substructure **4a**. A potential of >5 kcal/mol is shown as blue (positive), <5 and >−5 is white (neutral), and <−5 kcal/mol is red (negative).

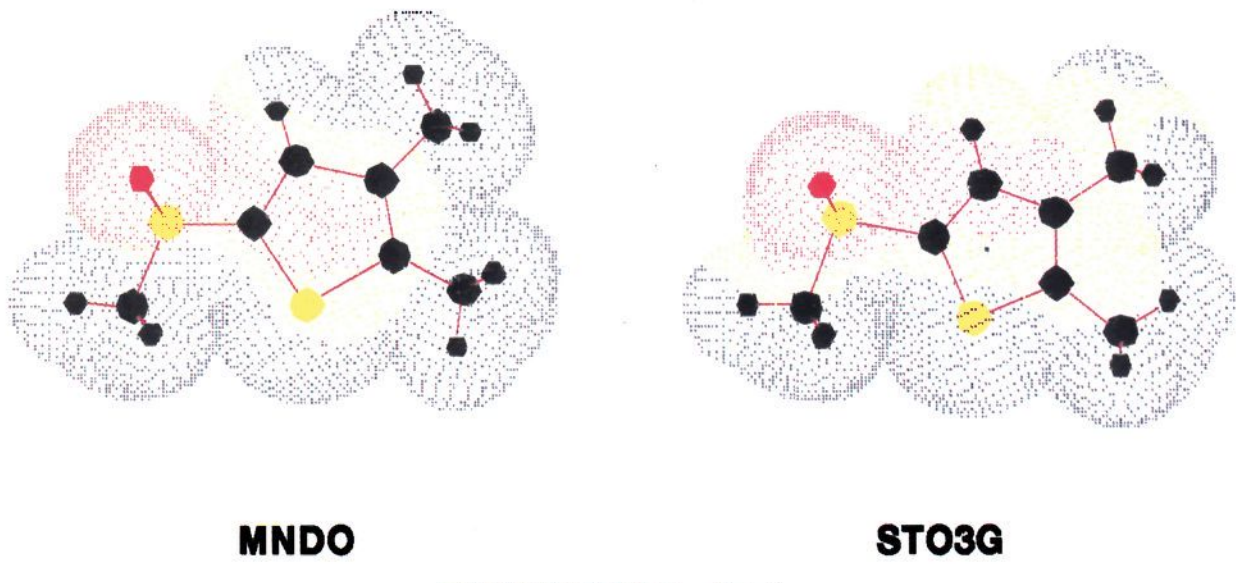


Figure 6. Graphical comparison of electrostatic potential surfaces derived from two levels of point charge calculation for substructure **5a**. A potential of >5 kcal/mol is shown as blue (positive), <5 and >−5 is white (neutral), and <−5 kcal/mol is red (negative).

on the surface. A potential of >5 kcal/mol is shown as blue (positive) <5 and >−5 is white (neutral), and <−5 kcal/mol is red (negative). For comparison, color-coded electrostatic potential surfaces, derived from MNDO and STO3G calculations for the methanesulfonyl pyrazole, furan, and thiophene substructures **1a**, **4a**, and **5a** are shown in Figures 4–6. Only slight differences between the semiempirical and ab initio results are apparent at this level of inspection for each heterocycle. We conclude the MNDO method to be sufficient for this study.

Synthetic Chemistry

Compounds **4**, **5**, and **8** were prepared as previously described.[25] Heterocyclic steroids (17α-ethynyl) con-

(25) Kumar, V.; Daum, S. J.; Bell, M. R.; Alexander, M. A.; Christiansen, R. G.; Ackerman, J. H.; Krolski, M. E.; Pilling, G. M.; Herrmann, J. L., Jr.; Winneker, R. C.; Wagner, M. M. Synthesis and Androgen Receptor Affinity of Steroidal Methylsulfonylfurans and a Methylsulfonylthiophene. *Tetrahedron* **1991**, *47*, 5099–5110.

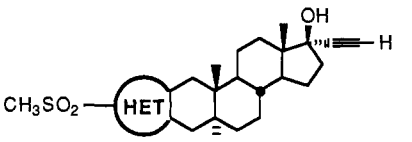
taining the substructures **6a**, **7a**, and **9a** were prepared as shown in Schemes I–III. Treatment of the known thiocyanato androstane **11**[30] with anhydrous $HCl_{(g)}$ gave the cyclized product, 2′-chloro [3,2-*d*] thiazole **12** in 83% isolated yield. Hydrolysis of the 17-acetate and oxidation of the resulting alcohol **13** with pyridinium chlorochromate (PCC) afforded the key intermediate **14** in 90% yield over two steps. Treatment of **14** with methanethiolate anion results in nucleophilic displacement of the 2′-chloro substituent in 92% isolated yield. Conversion of this material to the target compound **6** was performed as described for the thiophene and furans. A similar sequence was attempted for the oxazole **7**; however, treatment of known 2-bromoandrostane **10** with potassium cyanate did not produce the expected 2-cyanatoandrostane. Instead the cyclized 2′-oxo [2,3-*d*] oxazole **17** was isolated in modest yield. Conversion of oxazolone **17** to the required 2′-methylthio intermediate proved problematic. Isolation of the 2′-chlorooxazole intermediate resulted in rapid conversion back to oxazolone **17** in addition to other unidentified decomposition products. Treatment of the reactive 2′-chlorooxazole intermediate directly with methanethiolate anion in DMF followed by hydrolysis of the 17-acetate gave useful amounts of 2′-methylthio [2,3-*d*] oxazole **19**. Compound **19** was then converted into **7** using standard procedures described above. The pyrimidine **9** was prepared in two steps from the known intermediate **22**[17] by treatment with 2-methyl-2-thiopseudourea in refluxing ethanol which produced 2′-methylthio [3,2-*d*] pyrimidine **23** in good yield. Oxidation of the sulfide with Oxone as described by Trost and Curran[34] afforded the sulfone **9** in 60% isolated yield over two steps.

Results and Discussion

In a previous paper[17] the effects of various 17-α substituents on androgen receptor (AR) affinity and in vivo antiandrogenic activity for **1** were reported. The generalizations reported hold true for the series described here as well: maximal AR affinity is achieved with hydrogen (and methyl); the 17α-ethynyl substituent is preferred for in vivo activity. In accord with these observations and preferences, we report here on the activity of structures bearing this preferred substituent.

The approach to defining bioisosteres of the sulfonyl pyrazole of compound **1** was based upon the contrasting androgen receptor affinity observed for furan **4** and thiophene **5**.[25] Furan **4** had high AR affinity (and improved in vivo potency) compared with pyrazole **1**, while thiophene **5** lacked AR affinity at the highest concentration tested. Electrostatic potential surfaces of substructures **4a** and **5a** show a striking difference at all levels of calculation. The heteroatom attached to C-3 of the steroid nucleus, the position occupied by the carbonyl oxygen of the natural agonist dihydrotestosterone, carries a partial negative charge in pyrazole **1a** and furan **4a** but not in thiophene **5a**. It was postulated that it may be this potential that distinguishes these nearly isosteric heterocycles at the AR. Electrostatic potential surfaces for heterocyclic substructures **6a** through **9a** are shown in Figure 7. Qualitative assessment of this characteristic leads to the anticipation of AR affinity for steroids **6** and **7**. According to the hypothesis presented, compound **8** should have reduced AR affinity as it presents characteristics similar to the thiophene **5** at this position.

Table III



HET	compd	androgen receptor RBA[a]	androgen receptor K_i (μM) ± SD[26]	AA ED_{50} (mg/kg)[27]
[3,2-*c*] pyrazole	1	2.2/0.05	2.0 ± 0.85	15[b]
[3,2-*b*] furan	4	1.9/0.2	0.52**[c]	8
[3,2-*b*] thiophene	5	<.01/<.01	>29*	>100
[3,2-*d*] thiazole	6	1.4/0.16	0.86 ± 0.16	17
[2,3-*d*] oxazole	7	1.2/0.05	1.65 ± 0.17	22
[2,3-*b*] furan	8	<.01/<.01	>29*	>100
[3,2-*d*] pyrimidine	9	0.26/0.04	3.0**	ND
Reference Agents				
ICI 176334	2	2.0/0.04	0.33 ± 0.11	1.0
hydroxyflutamide	3	2.6/0.1	2.1 ± 0.61	3.4

[a] Relative binding affinity (1 h/18 h). Values represent the mean of at least three separate determinations of rat ventral prostate androgen receptor binding affinity which is defined as [R1881] at 50% binding inhibition/[test agent] at 50% binding inhibition) × 100. [^{3}H]R1881 is used as the radioligand. [b] Antiandrogen ED_{50}. Values represent graphically determined ED_{50} in (mg/kg per day) × 10 po dose required to inhibit testosterone propionate [(0.8 mg/kg per day) × 10, sc] induced rat ventral prostate weight gain by 50% in castrate, immature male rats. Eight rats per determination. [c] (*) Highest concentration tested. (**) Single determination. ND = not determined.

AR affinity and in vivo antiandrogenic activity for the steroidal heterocycles **1** and **4–9** are shown in Table III. Compounds **1** and **4–9** did not display androgen agonist activity ($p < 0.01$, Dunnett's test) under the assay protocol previously described.[17] Compounds **6** and **7** had receptor affinity commensurate with this class of AR ligands. Thiazole **6** had significantly higher Ar affinity than **1** and equivalent in vivo potency. Oxazole **7** had activity similar to **1** in both assays. As expected, furan **8** failed to interact with AR at the highest concentration tested. AR affinity of **9** illustrates the ability of the receptor to accommodate slightly larger heterocycles fused to the steroid 2,3 position, and variation in the angle of projection of the methanesulfonyl moiety of **9** is illustrated in Figure 3. It is unknown whether these characteristics of **9** are accommodated through repositioning of the steroid skeleton at the receptor or occupancy of available receptor space in the local region.

Conclusions

We have identified a possible determinant in the association of steroidal heterocycles of this class with the androgen receptor. The divergent features of electrostatic potential surfaces and binding affinity observed in a small set of nearly isosteric compounds enabled the logical selection of additional heterocyclic steroids to be synthesized as tests of this hypothesis. The AR affinity of [3,2-*d*]

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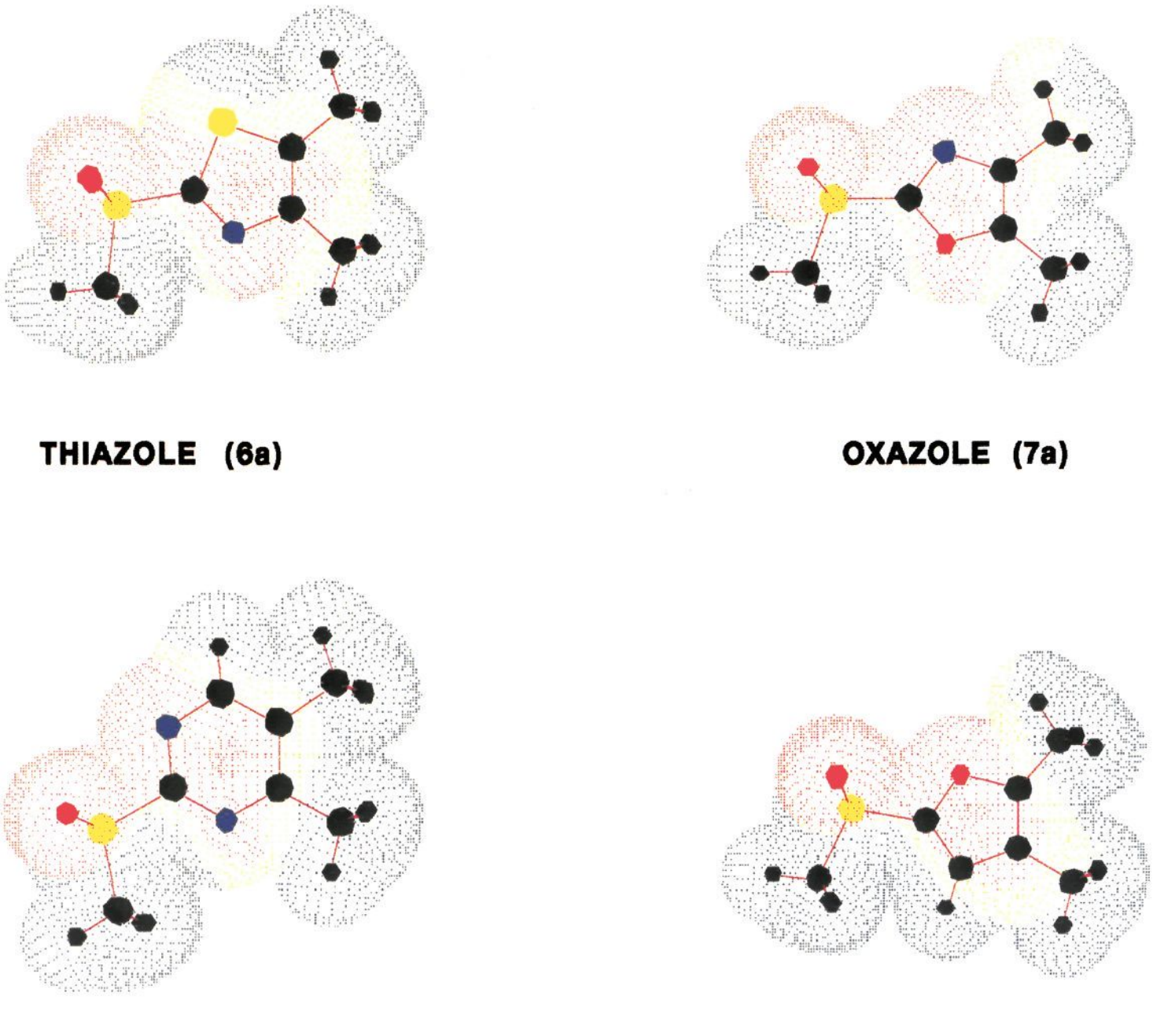

Figure 7. Graphical comparison of electrostatic potential surfaces (MNDO) for substructures **6a**–**9a** coded according to the electrostatic potential (in kcal/mol) experienced at each point on the surface. A potential of >5 kcal/mol is shown as blue (positive), <5 and >−5 is yellow (neutral) and, <−5 kcal/mol is red (negative).

thiazole and [2,3-*d*] oxazole, **6** and **7**, supports the contention of a requirement for an electron-rich heteroatom attached to the C-3 steroid position. In addition, compounds **6** and **7** have shown in vivo antiandrogenic activity in an exogenously stimulated model of prostatic hyperplasia after oral administration.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 20SX FTIR. NMR spectra were acquired in the indicated solvent on a JEOL-FX270, General Electric QE-300, or Bruker-AC200 FTNMR. HETCOR (^1H–^{13}C correlation) and DEPT experiments were utilized to assist in peak assignments. Mass spectra were recorded on a Nermag R10/10 coupled to a Varian 3400 gas chromatograph or on a JEOL JMS-01SC spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated only by symbols of the elements, analytical results are within ±0.4% of the theoretical values. Thin-layer chromatography (TLC) was performed on E. Merck 5 × 20, Kieselgel 60 F-254 plates. Preparative chromatography was performed using a Buchi B680 MPLC system coupled to an ISCO UV-detector and fraction collector. Columns were packed with Kieselgel 60, 230–400 mesh. High-boiling solvents (DMF) were stage-dried over molecular sieves,[29] anhydrous THF was distilled from sodium benzophenone ketyl. Alkyllithium reagents were titrated with diphenylacetic acid.[30]

AMPAC and MOPAC calculations were run on a VAX 11/785 operated under VMS version 5.1. Gaussian 90 calculations were run on a SUN4/490 operated under SunOS 4.0.3.

(5α,17β)-17-Acetoxy-2-thiocyanatoandrostan-3-one (11):[31] ^1H NMR ($CDCl_3$) δ 0.82 (s, 3 H), 1.12 (s, 3 H), 2.05 (s, 3 H), 4.35 (q, 1 H), 4.60 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.059 (C19), 12.167 (C18), 82.450 (C17), 111.804 (SCN), 171.026 ($OCOCH_3$), 203.132 (C3); IR (KBr, cm^{-1}) (2969–2830), 2152, 1722, 1713, 1260, 1033; DCI-MS (CH_3^+) *m/z* 390 (MH^+).

(5α,17β)-17-Acetoxy-2′-chloroandrost-2-eno[3,2-*d*]thiazole (12). Anhydrous HCl gas was slowly bubbled into a suspension of **11** (48.0 g, 0.123 mol) in 700 mL of anhydrous Et_2O for 2 h at 5 °C. Filtration of the cold reaction mixture afforded the crude product. Washing the filter cake with anhydrous Et_2O, and drying in vacuo gave 42.1 g (83%) of **12** as a white solid. This material may be used in the subsequent step without further purification. Recrystallization from CH_3CN gave an analytical sample: mp 181–184 °C; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 0.81 (s, 3 H), 4.60 (t, 1 H); IR (KBr, cm^{-1}) 1729, 1256, 1050; DCI-MS (CH_3^+) *m/z* 408 (MH^+). Anal. ($C_{22}H_{30}ClNO_2S$) C, H, N.

(5α,17β)-2′-Chloroandrost-2-eno[3,2-*d*]thiazol-17-ol (13). To a solution of **12** (40.7 g, 0.10 mol) in 400 mL of methanol were added H_2O (40 mL) and K_2CO_3 (13.8 g, 0.01 mol). The resulting mixture was stirred for 24 h at room temperature after which H_2O (800 mL) was added dropwise. The resulting precipitate was collected and washed thoroughly with H_2O and dried to afford **13**, 34.7 g (95%). This material may be used directly in the subsequent step. An analytical sample was prepared by recrys-

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tallization from CH_2Cl_2/hexane: mp 175–178 °C; ^1H NMR ($CDCl_3$) δ 0.65 (s, 3 H), 0.75 (s, 3 H), 3.42 (q, 1 H), 4.40 (br s, 1 H); IR (KBr, cm^{-1}) 3360, 1559, 1429, 1054. Anal. ($C_{20}H_{28}ClNOS$) C, H, N.

(5α,17β)-2′-Chloroandrost-2-eno[3,2-*d*]thiazol-17-one (14). Pyridinium chlorochromate (17 g, 0.079 mol) was added in four portions to a solution of **13** (17 g, 0.0465 mol) in 200 mL of CH_2Cl_2 at room temperature. The reaction was stirred for 4 h and then poured onto a column of Florisil (10 × 10 cm). The column was eluted with EtOAc/hexane (1:1) until 1 L of eluate was collected. Removal of the solvent at reduced pressure afforded **14**, 16.3 g (96%). This material may be used in the subsequent step. An analytical sample was prepared by recrystallization from $CHCl_3$/hexane: mp 218 °C; ^1H NMR ($CDCl_3$) δ 0.84 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 11.573 (C19), 13.623 (C18), 148.11 (C2′), 147.796 (C5′), 130.339 (C4′); IR (KBr, cm^{-1}) 1735, 1429, 1053; DCI-MS (CH_3^+) *m/z* 364 (MH^+). Anal. ($C_{20}H_{26}ClNOS$) C, H, N.

(5α)-2′-(Methylthio)androst-2-eno[3,2-*d*]thiazol-17-one (15). Sodium methylthiolate (3.5 g, 50.0 mmol) was added to a solution of **14** (16.3 g, 44.8 mmol) in 150 mL of 1-methyl-2-pyrrolidinone at room temperature. After 2 h of stirring, an additional portion of sodium methanethiolate (3.5 g, 50.0 mmol) was added. The resulting mixture was stirred 2 h and then poured into cold 1 N NaOH with stirring. The precipitate was collected by filtration and partially dried before recrystallizing from 2-propanol to afford **15**, 15.5 g (92%). An analytical sample was prepared by recrystallization from DMF/CH_3CN: mp 189–191 °C; ^1H NMR ($CDCl_3$) δ 0.82 (s, 3 H), 0.90 (s, 3 H), 2.65 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 11.627 (C19), 13.677 (C18), 16.861 (CH_3S), 127.766 (C4′), 149.010 (C5′), 162.473 (C2′); IR (KBr, cm^{-1}) 1732, 1414, 1051; DCI-MS (CH_3^+), *m/z* 376 (MH^+). Anal. ($C_{21}H_{29}NOS_2$) C, H, N.

(5α,17β)-2′-(Methylthio)pregn-2-en-20-yno[3,2-*d*]thiazol-17-ol (16). To a solution of monolithium acetylide[33] (1.2 mol) in THF (900 mL) at −78 °C was added **15** (73.4 g, 0.2 mol) portionwise. After stirring for 1 h at −78 °C, the cooling bath was removed. Once at room temperature the reaction was poured into cold saturated NH_4Cl solution, the organic layer was separated, and the aqueous was extracted with CH_2Cl_2 (2 × 400 mL). The combined organics were dried over $MgSO_4$ and concentrated to afford **16**, 72.88 g (90%) as an off-white solid. An analytical sample was prepared by recrystallization from CH_2Cl_2/hexane: mp 194–195 °C; ^1H NMR ($CDCl_3$) δ 0.82 (s, 3 H), 0.88 (s, 3 H), 2.62 (s, 1 H), 2.68 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 11.600 (C19), 12.652 (C18), 16.834 (CH_3S), 73.789 (C17), 79.644 (C20), 87.576 (C20), 127.857 (C4′), 149.037 (C5′), 162.284 (C2′); IR (KBr, cm^{-1}) 3294, 1382, 1051; DCI-MS (CH_3^+) *m/z* 402 (MH^+). Anal. ($C_{23}H_{31}NOS_2$) C, H, N.

(5α,17β)-2′-(Methylsulfonyl)pregn-2-en-20-yno[3,2-*d*]thiazol-17-ol (6). To a suspension of **16** (8.6 g, 21.0 mmol) in MeOH (180 mL) at −5 °C was added a solution of Oxone (20 g, 65 mmol $KHSO_5$) in H_2O (120 mL) dropwise. After addition, the cooling bath was removed and the reaction was stirred for 16 h at room temperature. The reaction was diluted with H_2O (250 mL), and the resulting precipitate was collected and dried in vacuo to afford **6**, 8.2 g (88%). Recrystallization from EtOAc/hexane gave an analytical sample: mp 239–240 °C; ^1H NMR ($CDCl_3$) δ 0.80 (s, 3 H), 0.85 (s, 3 H), 2.55 (s, 1 H), 3.39 (s, 3 H); ^{13}C NMR δ ($CDCl_3$) 11.654 (C19), 12.598 (C18), 42.735 (CH_3SO_2), 73.897 (C17), 79.617 (C20), 87.441 (C21), 137.003 (C4′), 152.247 (C5′), 161.528 (C2′); IR (KBr, cm^{-1}) 3297, 1411, 1327, 1155, 1067; DCI-MS (CH_3^+) *m/z* 434 (MH^+). Anal. ($C_{23}H_{31}NO_3S_2$) C, H, N.

(5α,17β)-17-Acetoxy-2′,3′-dihydro-2′-oxoandrost-2-eno[2,3-*d*]oxazole (17). A stirred solution of 17β-acetoxy-2α-bromo-5α-androstan-3-one[32] (**10**) (25 g, 0.06 mol) in 250 mL of 90% EtOH was treated with KOCN (7.5 g, 0.09 mol) and refluxed for 3 h. The resulting reaction mixture from three runs were combined, concentrated in vacuo, suspended in 500 mL of $CHCl_3$, and filtered. The filtrate was dried over $MgSO_4$, filtered, and concentrated in vacuo to give a viscous oil. Crystallization from Et_2O afforded 41 g (41%) of **17** as an off-white solid. An analytical sample was purified by MPLC on a 25 × 450 cm column packed with SiO_2 eluted with EtOAc/hexanes (1:1) giving **17** as a white crystalline solid: mp 302–304 °C; ^1H NMR (Me_2SO-d_6) δ 0.76 (s, 3 H), 0.77 (s, 3 H), 2.0 (s, 3 H), 4.5 (t, 1 H); IR (KBr, cm^{-1}) 3140, 2920, 1760, 1730; DCI-MS (CH_3^+) *m/z* 374 (MH^+). Anal. ($C_{22}H_{31}NO_4$) C, H, N.

(5α,17β)-17-Acetoxy-2′-(methylthio)androst-2-eno[2,3-*d*]oxazole (18). Part A: A solution of **17** (100 g, 0.2667 mol) in 1 L of $POCl_3$ containing 1.0 g of P_2O_5 was heated at reflux for 6 h. The resulting solution was cooled, concentrated in vacuo, dissolved in 1 L of $CHCl_3$, washed with H_2O (2 × 500 mL) and saturated NaCl (1 × 500 mL), and dried over K_2CO_3. The volatiles were removed in vacuo, and the resulting viscous brown oil was used in procedure B without further manipulation. Part B: To a suspension containing 13.9 g (0.56 mol) of 97% NaH in 1 L of dry DMF at 0 °C under atmosphere of N_2 was added 2.71 g (0.56 mol) of CH_3SH. Stirring was continued for 2 h after which a solution of the product from part A in 800 mL of dry DMF was added dropwise while maintaining the internal temperature below 8 °C. The cooling bath was not replenished, and the reaction was stirred at room temperature for 3 d. The resulting solution was poured into 6 L of ice–water mixture and filtered affording a tan solid. The filtrate was extracted with ether (4 portions, 2 × 500 mL each). The above solid was also dissolved in the ethereal extracts, and the combined organics were washed 3× with saturated NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a brown oil. Crystallization from Et_2O gave 39 g (36%) of **18** as light brown crystals. An analytical sample was obtained after MPLC chromatography on SiO_2 eluting with EtOAc/hexanes (1:9) affording **18** as a white solid: mp 186–188 °C; ^1H NMR (Me_2SO-d_6) δ 0.76 (s, 3 H), 0.77 (s, 3 H), 2.0 (s, 3 H), 2.58 (s, 3 H), 4.5 (t, 1 H); IR (KBr, cm^{-1}) 2960, 2920, 1720, 1490; DCI-MS (CH_3^+) *m/z* 404 (MH^+). Anal. ($C_{23}H_{33}NO_3S$) C, H, N.

(5α,17β)-2′-(Methylthio)androst-2-eno[2,3-*d*]oxazol-17-ol (19). A suspension containing **18** (39 g, 0.097 mol) and 20 g of K_2CO_3 in 1.3 L of CH_3OH was stirred at room temperature for 24 h. The resulting solution was concentrated in vacuo, redissolved in $CHCl_3$, washed with H_2O and saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo to give 35 g (100%) of **19**. The resulting solid was utilized in the next reaction without further purification. An analytical sample was obtained after MPLC chromatography on SiO_2 eluting with *i*PrOAc/cyclohexane (1:1) and crystallization from the same solvent mixture to give **19** as a white crystalline solid: mp 181–182 °C; ^1H NMR (Me_2SO-d_6) δ 0.62 (s, 3 H), 0.72 (s, 3 H), 2.58 (s, 3 H), 4.42 (d, 1 H); IR (KBr, cm^{-1}) 3410, 2960, 2920, 1490; DCI-MS (CH_3^+) *m/z* 362 (MH^+). Anal. ($C_{21}H_{31}NO_2S$) C, H, N.

(5α,17β)-2′-(Methylthio)androst-2-eno[2,3-*d*]oxazol-17-one (20). A stirred solution of pyridinium chlorochromate (34.9 g, 0.162 mol, PCC) in 400 mL CH_2Cl_2 was cooled to 0 °C. To this was added a solution of **19** (39 g, 0.11 mol) in 100 mL of CH_2Cl_2 in one portion. The reaction mixture was warmed to room temperature, stirred for 2.5 h, and treated with an additional 2 g of PCC. After 3 h the resulting mixture was filtered through Florisil eluting with Et_2O affording 20 g of a light green solid after concentration in vacuo. Further washing with EtOAc afforded 9 g of a green oil after concentration. The solid and oil were combined and purified by MPLC chromatography on SiO_2 eluting with EtOAc/hexanes (1:1) affording 19.8 g (57%) of **20** as a white solid: mp 178–179 °C; ^1H NMR (Me_2SO-d_6) δ 0.72 (s, 3 H), 0.80 (s, 3 H), 2.58 (s, 3 H); IR (KBr, cm^{-1}) 2920, 1740, 1660, 1490; DCI-MS (CH_3^+) *m/z* 360 (MH^+). Anal. ($C_{21}H_{29}NO_2S$) C, H, N.

(5α,17β)-2′-(Methylthio)pregn-2-en-20-yno[2,3-*d*]oxazol-17-ol (21). A 3-L, five-neck roundbottom flask equipped with a magnetic stirrer, two addition funnels, gas dispersion inlet, condenser, and argon bubbler was flame-dried while purging with argon. The cooled flask was charged with anhydrous THF (400 mL) and cooled to −78 °C. Acetylene, purified by passing through concentrated H_2SO_4 and then soda lime,[33] was dispersed into the THF until saturation occurred. *n*-Butyllithium (91 mL, 0.21 mol) in hexane was added dropwise over 45 min while maintaining the temperature below −70 °C. After stirring at −78 °C for 30 min, **20** (18.8 g, 0.052 mol) in 150 mL THF was added dropwise, while maintaining the temperature below −75 °C. The cooling bath was maintained for 3.5 h after which time the reaction mixture was warmed to room temperature, stirred an additional 1 h, and

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quenched with 800 mL of saturated NH_4Cl. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 200 mL). The organics were combined, washed with saturated NaCl, and dried over anhydrous $MgSO_4$. Filtration and concentration in vacuo afforded 21 g of an orange solid. Recrystallization from Et_2O/CH_2Cl_2 gave 15 g (74%) of **21** as a light tan solid: mp 206–208 °C; ^1H NMR (Me_2SO-d_6) δ 0.72 (s, 6 H), 2.50 (s, 1 H), 2.58 (s, 3 H); IR (KBr, cm^{-1}) 3340, 2100, 1670; DCI-MS (CH_3^+) m/z 386 (MH^+). Anal. ($C_{23}H_{31}NO_2S \cdot {}^1/_4H_2O$) C, H, N.

(5α,17β)-2′-(Methylsulfonyl)pregn-2-en-20-yno[2,3-*d*]oxazol-17-ol (7). A solution containing 141 g of Oxone[34] in 400 mL of H_2O was added to a solution of **21** (14.6 g, 0.038 mol) in 400 mL of acetic acid, maintaining the internal temperature below 15 °C. After stirring for 1 h at −15 °C, the cooling bath was removed and the reaction warmed to room temperature overnight. The resulting mixture was diluted with 2 L of H_2O affording a light yellow precipitate. The precipitate was collected by filtration, washed with H_2O, and redissolved in EtOAc. The EtOAc solution was washed with saturated NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo affording 12.5 g of a yellow oil which was again dissolved in EtOAc and filtered through a pad of Florisil, rinsing with EtOAc. The filtrate was concentrated to 200 mL and cooled affording 9.5 g (60%) of **7** as a white crystalline solid: mp 183–185 °C; ^1H NMR (Me_2SO-d_6) δ 0.81 (s, 3 H), 0.87 (s, 3 H), 2.6 (s, 1 H), 3.3 (s, 3 H); IR (KBr, cm^{-1}) 3480, 3280, 2100, 1640, 1320, 1150; DCI-MS (CH_3^+) m/z 418 (MH^+). Anal. ($C_{23}H_{31}NO_4S \cdot {}^1/_4H_2O$) C, H, N.

(5α,17β)-2′-(Methylthio)pregn-2-en-20-yno[3,2-*d*]pyrimidin-17-ol (23). To a stirred solution containing **22**[17] (68 g, 0.152 mol) and Et_3N (25.5 mL, 0.18 mol) in 200 mL of EtOH was added 2-methyl-2-thiopsuedourea hemisulfate (25.4 g, 0.18 mol). The resulting mixture was refluxed under an N_2 atmosphere for 24 h after which the reaction mixture was concentrated in vacuo. The concentrated mixture was dissolved in CH_2Cl_2, washed 3× with 10% $NaHCO_3$ and 1× with saturated NaCl, and the organic layer was dried over $MgSO_4$. Filtration and concentration in vacuo afforded an oil which was passed through a pad of Florisil eluting with Et_2O. Removal of the volatiles in vacuo afforded a solid. Recrystallization from Et_2O gave 46.5 g (77%) of **23** as an off-white powder: mp 282 °C dec; ^1H NMR ($CDCl_3$) δ 0.76 (s, 3 H), 0.89 (s, 3 H), 2.57 (s, 3 H), 2.62 (s, 1 H), 8.22 (s, 1 H); IR (KBr, cm^{-1}) 3540, 3250, 2920, 2120. Anal. ($C_{24}H_{32}N_2OS$) C, H, N.

(5α,17β)-2′-(Methylsulfonyl)pregn-2-en-20-yno[3,2-*d*]pyrimidin-17-ol (9). To a mechanically stirred slurry of **23** (3.96 g, 0.01 mol) in 80 mL of CH_3OH at −10 °C was added 40 mL of a 0.76 M aqueous solution of Oxone (49.5% $KHSO_5$) over a 15-min period. After completion of addition, the reaction mixture was warmed to room temperature and stirred overnight. The volatiles were removed in vacuo, and the concentrated reaction was poured into 500 mL of H_2O. The resulting precipitate was collected by filtration and washed with H_2O. The filter cake was dissolved in $CHCl_3$, washed with saturated NaCl, dried over $MgSO_4$, and concentrated in vacuo to give an off-white solid. Recrystallization from CH_2Cl_2 gave 3.1 g (78%) of **9** as a white solid: mp 284 °C; ^1H NMR ($CDCl_3$) δ 0.81 (s, 3 H), 0.90 (s, 3 H), 2.62 (s, 1 H), 3.33 (s, 3 H), 8.54 (s, 1 H); IR (KBr, cm^{-1}) 3540, 3250, 2920, 2120, 1320; DCI-MS (CH_3^+) m/z 429 (MH^+). Anal. ($C_{24}H_{32}N_2O_3S$) C, H, N.

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Supplementary Material Available: Complete crystallography results for compounds **4**, **6**, and **9** including tables of atomic coordinates, thermal parameters, and bond distances and angles (45 pages). Ordering information is given on any current masthead page.

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