

A Novel, Nonsteroidal Inhibitor of Androgen Binding to the Rat Androgen Binding Protein: Diethyl [[3-(2,6-Dimethyl-4-pyridinyl)-4-fluorophenyl]amino]methylene]propanedioate

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In vitro binding studies demonstrate the binding specificity of a series of 4-aryl-2,6-dimethylpyridines for the rat epididymal androgen binding protein (rABP). The compounds bound competitively to rABP but have very weak or no demonstrable affinity for rat ventral prostate androgen receptor and human sex hormone binding globulin. In particular, compound 11, diethyl [[3-(2,6-dimethyl-4-pyridinyl)-4-fluorophenyl]amino]methylene]propanedioate, bound with high affinity to rABP (binding affinity about $1/3$ that of the endogenous ligand 5α -dihydrotestosterone). However, additional in vitro binding studies indicated that 11 did not bind to testicular or epididymal ABP from rabbit, rhesus monkey, and human. Nevertheless, the specificity and relatively high affinity of these nonsteroidal compounds make them unique and potentially ideal agents for the study of the role of ABP in spermatogenesis and sperm maturation in the rat.

An androgen binding protein (ABP) has been characterized in the testis and epididymis from a variety of mammals including man; however, the physiological role of this protein is not well understood.¹ The ABP reportedly functions to transport and concentrate androgens within the seminiferous tubules and epididymis where androgens are known to play a critical role in spermatogenesis and sperm maturation.^{2,3} Increasing ABP levels are closely coupled to the androgen-induced onset and maintenance of fertility in the rat and, therefore, non-androgenic agents which bind specifically to ABP may prove useful as antifertility drugs. However, such a compound should not interact with other high-affinity androgen binding sites, i.e., the intracellular androgen receptor (AR) and plasma sex hormone binding globulin (SHBG).

During the course of studies with steroidal androgen receptor antagonists,⁴ a series of 4-aryl-2,6-dimethylpyridine derivatives was discovered by random screening which bound with high affinity and specificity for rat ABP (rABP). The results of these in vitro studies is the subject of this report.

Chemistry

Dihydropyridine derivative **3**, obtained by the condensation of 2-fluorobenzaldehyde (**1**) with methyl acetate (**2**) and ammonia, was first aromatized and then saponified to afford dicarboxylic acid **5**. Thermal decarboxylation of **5** gave a mixture of fluoro compound **6** and lactone **7** in a ratio of 2:3. Nitration of **6** resulted in the formation of *p*-nitro derivative **8** in 96% yield. The nitro compound was reduced over platinum oxide to amine **9**, which was condensed with diethyl (ethoxymethylene)malonate to produce adduct **11** (Scheme I).

Pharmacological Results and Discussion

In addition to the compounds described above, the known compound diethyl [[3-(2,6-dimethyl-4-pyridinyl)phenyl]amino]methylene]propanedioate (**12**)⁵ and reference androgenic steroids 5α -dihydrotestosterone (DHT) and methyltrieneolone (R1881; 17β -hydroxy-17-methylestra-4,9,11-trien-3-one⁶) were used in these studies. The results of in vitro assays which quantify the binding of reference androgens and substituted phenylpyridines to rABP, rat ventral prostate AR, and human SHBG are summarized in Table I. The endogenous ligand DHT bound with high affinity (K_d s of 5, 1.5, and 0.4 nM, respectively, as determined from computer-generated

Table I. Binding of Phenylpyridines and Reference Androgens to Androgen Binding Protein, Androgen Receptor, and Sex Hormone Binding Globulin

compd	relative binding affinity ^a		
	rABP ^b	rAR ^c	hSHBG ^b
DHT ^b	100	88.3 ± 3.4	100
R1881 ^c	15.2 ± 2.0	100	0.2 ± 0.02
11	32.7 ± 3.3	<0.01	<0.01
8	4.6 ± 1.3	<0.01	<0.01
9	3.0 ± 0.5	<0.01	<0.01
6	2.9 ± 0.9	<0.01	<0.01
12	2.5 ± 0.5	<0.01	<0.01
7	0.03 ± 0.01	<0.01	<0.01

^aRelative binding affinity (RBA) values represent the $X \pm$ SEM for at least three separate assays except in the case of <0.01 values where two consecutive tests in which no significant inhibition of binding was observed. ^bRBA for 5α -dihydrotestosterone (DHT) was set at 100 for rABP and hSHBG assays [IC_{50} s of 23.0 ± 2.4 nM ($n = 12$) and 3.8 ± 0.9 nM ($n = 8$), respectively]. See ref 9 for details. ^cRBA for R1881 (methyltrieneolone) was set at 100 for each assay [IC_{50} of 3.7 ± 0.3 nM ($n = 9$)]. See ref 6 for details.

Scatchard plots; data not shown) to all three of these sites whereas compound R1881 demonstrated androgen receptor selectivity. The 4-aryl-2,6-dimethylpyridine derivatives bound with a range of affinities for rABP; however, at concentrations as high as 10μ M they did not significantly bind to rat AR or human SHBG. Compound **11** bound to rABP with the highest affinity (approximately $1/3$ that of DHT with an estimated K_i of 12 nM), indicating the importance of both the 4-fluoro and diethyl [(amino)methylene]propanedioate substitutions. A Lineweaver-Burk analysis of the binding of **11** to rABP confirmed the competitive nature of this binding (Figure 1). In contrast to other members of the series, the phenyl ring in compound **7** is not free to rotate, which may explain the weak binding affinity for rABP.

Compounds **11** and **6** were evaluated further for their ability to bind to ABPs from other species. Surprisingly,

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Scheme I

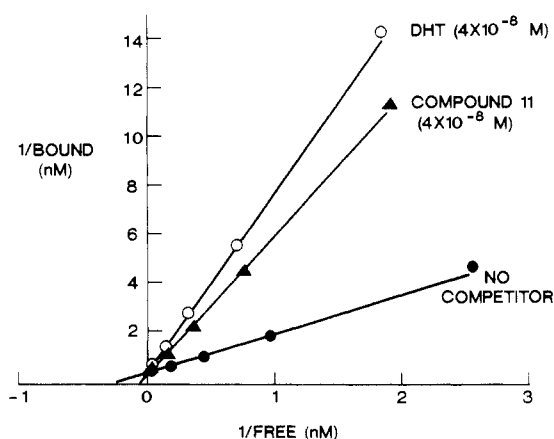
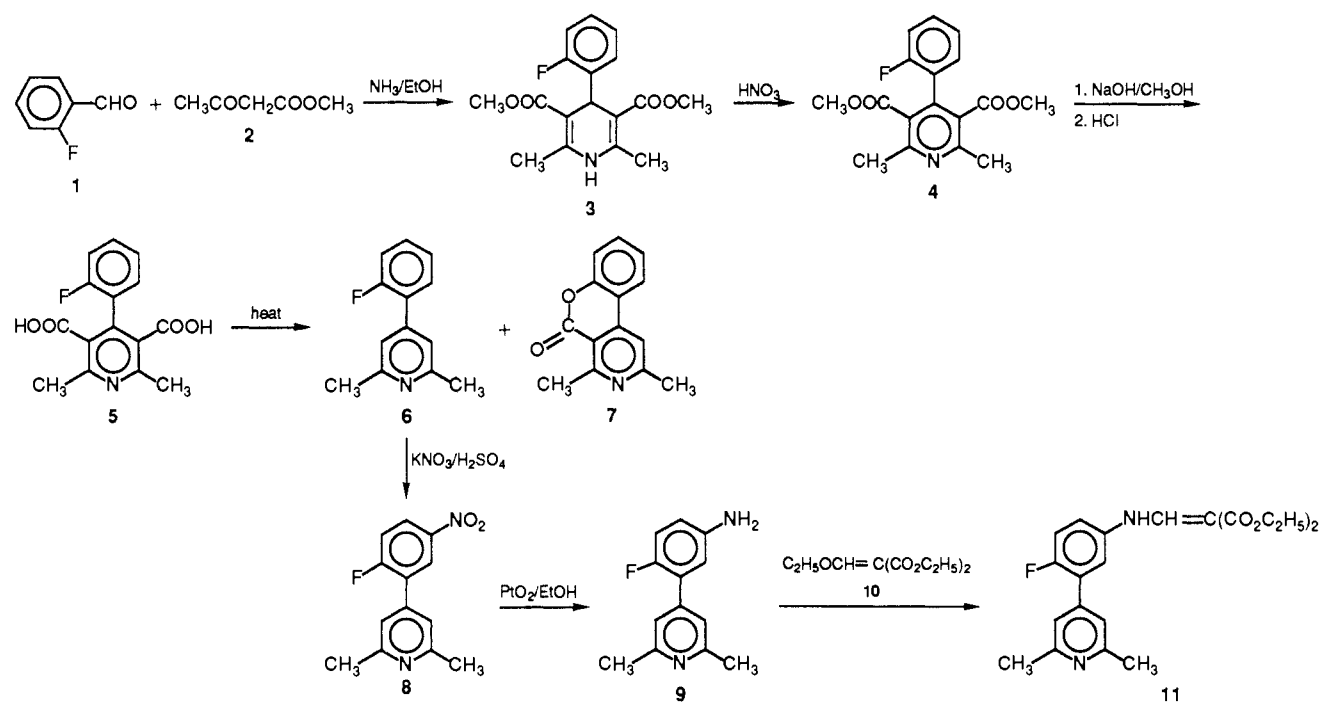


Figure 1. Lineweaver-Burk analysis demonstrating competitive inhibition of [³H]dihydrotestosterone (DHT) binding to rat ABP by DHT and compound 11. The binding of 2.5 nM [³H]DHT to rat epididymal cytosol was determined at 4 °C for 2 h in the absence (no competitor) and presence of a constant concentration of unlabeled competitor (indicated in parentheses). Each data point represents the mean of two determinations.

both the high and lower affinity competitors for rABP demonstrate only weak or no binding to ABPs from rabbit, rhesus monkey, or human sources (at least 1000 less than DHT in two separate assays), which bound with high affinity ($K_i < 10$ nM) to all three ABPs. Recent studies have suggested that human ABP and human SHBG are structurally more homologous than are rat and human ABP.⁷ The results of our study support this contention in that at least some structural diversity in the binding site region between rat ABP and rabbit and primate ABPs would explain the specificity of 11 for rat ABP.

It has been postulated that a nonandrogenic agent which binds specifically to ABP and effectively displaces endogenous androgen from the ABP within the testis and epididymis may prove useful as a male antifertility drug.^{8,9}

Two different series of ABP selective compounds have been reported previously.^{10,11} Modification of 13 to 2-methyl-17-methoxydihydrotestosterone or 17-methoxydihydrotestosterone produced steroidal compounds with ABP binding selectivity (ABP/AR) of 6:1. The compounds were patented in 1981 by Upjohn Co.¹² as potential male contraceptives, but no detailed animal studies have followed. Subsequently, a series of nonsteroidal dicyclohexane derivatives were reported as ABP specific ligands. However, their affinity for ABP is at least 10-fold lower than 11. One member of the series reportedly lowered epididymal sperm motility, but no detailed studies have followed.¹³ Compound 11 did not bind with high affinity to human ABP and therefore does not represent a new drug to study the role of ABP in human reproduction; however, it does represent a novel, high-affinity, rat ABP specific ligand and should be useful as a tool to help understand the role of this binding site in spermatogenesis and sperm maturation in the rat. Furthermore, this series of compounds may serve as a prototype for the discovery of specific inhibitors of androgen binding to the human androgen binding protein and to explore the differences in the binding site specificity among various androgen binding proteins.

Experimental Section

Melting points were obtained in open capillaries in an oil bath and are uncorrected. ¹H NMR spectra were recorded on Varian HA-100 spectrometer with tetramethylsilane as an internal standard. Infrared spectra were recorded as KBr pellets with

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Perkin-Elmer 467 spectrometer. All the compounds exhibited NMR and IR spectral data consistent with the proposed structures. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and the results were within 0.4% of the theoretical values.

Dimethyl 4-(2-Fluorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate (3). To a stirred solution of 119.0 g (1 mol) of 2-fluorobenzaldehyde (1), 225 mL (2.1 mol) of methyl acetoacetate, and 600 mL of methanol was added 200 mL of concentrated ammonium hydroxide solution whereupon an exothermic reaction ensued. The reaction mixture was stirred at ambient temperature for 30 min, next refluxed for 2 h, and then allowed to stand at room temperature overnight. The light yellow solid that crystallized was collected, washed with ether, and dried to yield 201 g (63%) of 3: mp 206–208 °C (lit.¹⁴ mp 207–208 °C). Anal. (C₁₇H₁₈FNO₄) C, H, N.

Dimethyl 4-(2-Fluorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (4). To 600 mL of 4 N nitric acid heated to 70 °C was added with stirring 302.9 g (0.95 mol) of 3 over a period of 20 min and then heated on a steam bath for 1 h. After it had cooled to room temperature, the reddish solution was chilled in an ice bath and made basic with ammonium hydroxide solution. The resulting yellow precipitate was filtered, washed with water, dried, and recrystallized from hexane to give 273.7 g (91%) of 4 as a pale yellow solid: mp 94–96 °C. Anal. (C₁₇H₁₆FNO₄) C, H, N.

4-(2-Fluorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylic Acid (5). A mixture containing 69 g (0.22 mol) of 4, 300 mL of methanol, and 100 mL of 35% aqueous sodium hydroxide solution was refluxed with stirring for 5 h and then allowed to stand at room temperature overnight. The methanol was removed under reduced pressure and to the residual liquid was added 200 mL of water and the mixture was filtered. The filtrate was acidified with hydrochloric acid whereupon there precipitated a cream colored solid, which was collected, washed with water, and dried to yield 52.6 g (88%) of 5: mp >285 °C. Anal. (C₁₅H₁₂FNO₄) C, H, N.

Thermal Decarboxylation of 5. To stirred and boiling 1.2 L of Dowtherm was added 200 g (0.69 mol) of 5 over a 40-min period, and the resulting mixture was further boiled for 50 min. After it had cooled to room temperature, the reaction mixture was diluted with 500 mL of hexane and left at room temperature overnight. The tan solid that crystallized was filtered, washed with ether, and dried to give 80.2 g (52%) of lactone 7: mp 198–200 °C; IR (KBr) 1718 cm⁻¹; ¹H NMR (CF₃COOD) δ 8.5–7.48 (5 H, aromatic), 3.39 (s, 3 H, CH₃), 3.04 (s, 3 H, CH₃). Anal. (C₁₄H₁₁NO₂) C, H, N. The filtrate from above was extracted with 600 mL of 6 N aqueous hydrochloric acid. The aqueous phase was first extracted with 300 mL of hexane and then made basic with aqueous ammonia. The light brown oil that separated was extracted with 400 mL of chloroform. Removal of chloroform gave a brown oil, which was dissolved in 300 mL of hexane and left at room temperature overnight. More of lactone 7 (8.2 g) was collected and the filtrate was treated with charcoal and then concentrated to give 58.4 g (42%) of 6 as light brown oil. The analytical sample was crystallized as a white hydrochloride salt from 2-propanol: mp 200–203 °C; ¹H NMR (CF₃COOD) δ 11.33 (1 H, exchanged), 7.9 (s, 2 H, pyridine 3-H, 5-H) 7.25–7.78 (4 H, aromatic), 2.95 (s, 6 H, 2 × CH₃). Anal. (C₁₃H₁₂FN·HCl) C, H, N.

4-(2-Fluoro-5-nitrophenyl)-2,6-dimethylpyridine (8). To 55 mL of concentrated sulfuric acid cooled in a salt-ice bath to -15 °C was added 10.1 g (0.1 mol) of potassium nitrate, and the mixture was stirred for 10 min and then 18.5 g (0.9 mol) of 6 was added over a 30-min period. The internal temperature rose to 0 °C and a very viscous mixture was obtained. In order to facilitate stirring, another 50 mL of concentrated sulfuric acid was added over a 15-min period, and the resulting mixture was further stirred in ice bath for 1 h and then allowed to come to room temperature over a 5-h period. After this, the reaction mixture was poured on ice and neutralized by adding aqueous ammonium hydroxide. The resulting light yellow, fluffy precipitate was filtered, washed

with water, dried, and recrystallized from 1:1 ether-hexane to afford 21.2 g (96%) of 8 as off-white plates: mp 169–171 °C; ¹H NMR (CDCl₃) δ 8.48–8.19 (2 H, aromatic), 7.48–7.25 (1 H, aromatic), 7.18 (s, 2 H, pyridine, 3-H, 5-H), 2.65 (s, 6 H, 2XCH₃). Anal. (C₁₃H₁₁FN₂O₂) C, H, N.

3-(2,6-Dimethyl-4-pyridinyl)-4-fluorobenzeneamine (9). A mixture containing 45 g (0.18 mol) of 8, 200 mL of ethanol, and 800 mg of platinum oxide was catalytically hydrogenated until the hydrogen uptake ceased (4 h). The catalyst was filtered and the filtrate was concentrated on a rotary evaporator. The light brown residual solid was recrystallized from ether-2-propanol to afford 34.5 g (89%) of tan crystals of 9: mp 141–144 °C. Anal. (C₁₃H₁₃FN₂) C, H, N.

Diethyl [[[[3-(2,6-Dimethyl-4-pyridinyl)-4-fluorophenyl]-amino]methylene]propanedioate (11). A mixture containing 122 g (0.56 mol) of 9 and 130 g (0.6 mol) of diethyl (ethoxymethylene)malonate in 120 mL of toluene was heated with stirring in an oil bath at 130–135 °C for 3.5 h while ethanol was allowed to escape from the reaction mixture with use of an air condenser. The reaction mixture was cooled and dissolved in 1 L of boiling hexane and filtered. The filtrate was allowed to stand at room temperature overnight. The light tan, crystalline solid that separated was collected, washed with cold hexane, and dried to give 159.6 g (74%) of 11: mp 99–100 °C; ¹H NMR (CDCl₃) δ 11.1 (brd, 1 H, J = 13 Hz, NH), 8.44 (d, 1 H, J = 13 Hz, =CH), 7.5–7.0 (5 H, aromatic), 4.35 (q, 2 H, OCH₂), 4.28 (q, 2 H, OCH₂), 2.62 (s, 6 H, 2 × CH₃), 1.4 (t, 3 H, 1.4 (t, 3 H, CH₂CH₃), 1.3b (t, 3 H, CH₂CH₃). Anal. (C₂₁H₂₃FN₂O₄) C, H, N.

Rat Epididymal Androgen Binding Protein Competition Assay. This assay was a modification of a previously published method.⁹ Adult Sprague-Dawley rats (~250 g body weight, Taconic Farms, Germantown, NY) were killed by cervical dislocation, and epididymides were removed, weighed, and placed in ice-cold TEG buffer (10 mM Tris, pH = 7.4 at room temperature, 2 mM EDTA, 10% glycerol). The tissue was homogenized on ice at 250 mg of tissue/mL of buffer and centrifuged at 135000g for 1 h, and the supernatant was diluted to 150 mg/mL. Dry charcoal (Norit A, Mallinckrodt) was added to the cytosol (2 mg of charcoal/mL of cytosol) and incubated overnight (~18 h) at 4 °C. Following the incubation period, the charcoal was pelleted by centrifugation at 15000g for 20 min followed by centrifugation at 130000g for 1 h. Aliquots of the supernatant were frozen within a dry ice-acetone bath and stored at -70 °C. Frozen epididymal cytosol was thawed and diluted to the equivalent of 40–50 mg of tissue/mL with TEG buffer. Duplicate aliquots were incubated for 2 h at 4 °C with [1,2-³H(N)]-5α-dihydrotestosterone (New England Nuclear; 2.5 nM final concentration) either alone or in the presence of increasing concentrations (10⁻⁹–10⁻⁴ M) of 5α-dihydrotestosterone (Sigma Chemical Co.) or test compounds. Following the incubation period, a suspension of dextran-coated charcoal (0.5% charcoal, 0.05% dextran T-70) was added to the ligand-cytosol mixture and incubated for 2 min. The charcoal was pelleted by centrifugation at 1500g for 10 min and the supernatant (protein-bound [³H]DHT) was counted. Relative binding affinities (RBA), used to quantify rABP binding competition, were calculated as the ratio of the molar concentration of unlabeled DHT to competitor required to inhibit [³H]DHT binding by 50% (after correction for nonspecific binding, i.e., [³H]DHT bound in the presence of 1 μM unlabeled DHT). The RBA for DHT was set at 100 for all assays.

Rabbit, Monkey, and Human ABP Competition Assays. Essentially the same procedure as described above was used with the following exceptions: Rabbit epididymides were obtained frozen from Pel Freeze, Rogers, AR and homogenized at 40–140 mg of tissue/mL of buffer. Monkey testes and epididymides obtained from our rhesus monkey colony were homogenized at 300 and 150 mg of tissues/mL, respectively. Human testes and epididymides obtained through an arrangement with the Northeast Regional Transplant Center, Albany Medical College, were frozen in liquid N₂ for storage and subsequently homogenized at 200–300 mg of tissue/mL of buffer. Assay of testicular ABP was accomplished with 10 nM [³H]DHT.

Human Sex Hormone Binding Globulin Competition Assay. Blood from healthy, young, female volunteers was allowed to clot for at least 1 h at 4 °C and was centrifuged at 1500g for 20 min. The serum was pooled and diluted 1:4 with ice-cold TG

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buffer (10 mM Tris, pH = 7.4 at room temperature, 10% glycerol). Solid ammonium sulfate was added slowly to a final concentration of 40% and the precipitate was pelleted by centrifugation at 4000g for 10 min. The pellet was gently resuspended in TG buffer to a final dilution of 1:10. Dry charcoal was added (2 mg/mL) and the mixture was incubated overnight at 4 °C. The charcoal was removed by centrifugation at 15000g for 20 min followed by another centrifugation at 135000g for 1 h. Samples were frozen and stored at -70 °C. The hSHBG preparation was thawed at room temperature and diluted an additional 1:4 with TG buffer. Duplicate aliquots were incubated for 2 h at 4 °C with [1,2-³H(N)]-5 α -dihydrotestosterone (1 nM final concentration) in either the absence or the presence of increasing concentrations (10⁻⁹-10⁻⁴ M) of DHT or test compounds. Following the incubation period, a suspension of dextran-coated charcoal (0.5% charcoal, 0.05% dextran T-70) was added to the ligand-cytosol mixture and incubated for 2 min. The charcoal was pelleted by centrifugation at 1500g for 10 min and the supernatant (protein-bound [³H]DHT) was counted. Relative binding affinities were calculated as described for rABP. Compounds that did not inhibit [³H]DHT binding by 50% at a competitor concentration of 10 μ M were considered to be inactive (RBA \leq 0.01).

Rat Prostate Androgen Receptor Competition Assay. This procedure was run as previously described.¹⁴ Cytosol, prepared

with the prostates from castrated adult male Sprague-Dawley rats, was incubated with 17 α -methyl-[³H]R1881 (New England Nuclear; methyltrienolone, 5 nM final concentration) in either the absence or the presence of increasing concentrations (10⁻⁹-10⁻⁵ M) of R1881 (New England Nuclear) or test compounds for 18 h at 4 °C. After the incubation period, a suspension of dextran-coated charcoal (1% charcoal, 0.05% dextran T-70) was added to the ligand-cytosol mixture and incubated for 5 min. The charcoal-bound ³H-R1881 was removed by centrifugation and the supernatant was counted. Relative binding affinities were calculated as the ratio of the concentration required to inhibit [³H]R1881 specific binding by 50% (with R1881 arbitrarily set at 100). Compounds that did not inhibit [³H]R1881 binding by 50% at a competitor concentration of 10 μ M were considered to be inactive (RBA < 0.01). A Lineweaver-Burk analysis of the binding of 11 to rat ABP was run as previously described.¹⁵

Registry No. 1, 446-52-6; 2, 105-45-3; 3, 86408-08-4; 4, 104431-82-5; 5, 104431-76-7; 6, 104431-77-8; 6-HCl, 104431-83-6; 7, 104431-78-9; 8, 104431-72-3; 9, 104431-73-4; 10, 87-13-8; 11, 104431-74-5.

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Anticandidal Properties of N³-(4-Methoxyfumaroyl)-L-2,3-diaminopropanoic Acid Oligopeptides

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Tri-, tetra-, and pentapeptides containing N³-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP), an inactivator of glucosamine 6-phosphate synthase of fungal origin (a key enzyme in the biosynthesis of macromolecular components of the fungal cell wall) have been synthesized and investigated as anticandidal agents. Structure-activity relationships of a series of peptides revealed that tripeptides were generally more active than the other peptides examined. In this study, the lysyl peptide, Lys-Nva-FMDP has been found to be the most active compound in the series.

Our previous report demonstrated that dipeptides composed of aliphatic amino acids and N³-(4-methoxyfumaroyl)-L-2,3-diaminopropanoic acid (FMDP), especially in the C-terminal position, exhibited remarkable antimicrobial activity against a range of fungal organisms, including the pathogenic fungus *Candida albicans*.¹ The anticandidal properties of these peptides are connected with the presence of the FMDP residue, which, after release from dipeptide by intracellular peptidases, irreversibly inactivates glucosamine 6-phosphate synthase from *C. albicans*.² This enzyme catalyzes the formation of D-glucosamine 6-phosphate from L-glutamine and D-fructose 6-phosphate. D-Glucosamine 6-phosphate is a key molecule in the biosynthetic formation of amino-sugar-containing macromolecules of the microbial cell wall.³ Therefore, glucosamine 6-phosphate synthase inhibitors offer a potentially useful approach to the rational design of anticandidal agents. It has been shown that dipeptides with FMDP as the "warhead" utilize a peptide transport system for entry into the cell according to the "portage transport", a concept described by Gilvarg.⁴ Moreover, we have re-

Table I. Analytical and Physical Data of Protected Peptides

no.	compd	% yield	mp, °C	[α] _D ²⁵ ₇₇₅ ^a	anal.
1	Boc-Ala-FMDP-Ala	73	142-145	-29.5	C ₁₉ H ₃₀ N ₄ O ₉
2	Boc-Met-FMDP-Met	51	148-150	-26.2	C ₂₃ H ₃₈ N ₄ O ₉ S ₂
3	Boc-Met-Ala-FMDP	82	74-76	-23.2	C ₂₁ H ₃₄ N ₄ O ₉ S ₂
4	Boc-Met-Met-FMDP	88	162-163	-27.0	C ₂₃ H ₃₈ N ₄ O ₉ S ₂
5	Boc-Met-Nva-FMDP	88	152-154	-24.2	C ₂₃ H ₃₈ N ₄ O ₉ S ₂
6	Boc-FMDP-Met-Ala	75	102-104	-16.8	C ₂₁ H ₃₄ N ₄ O ₉ S
7	Boc-FMDP-Met-FMDP	72	105-107	-15.2	C ₂₆ H ₃₉ N ₅ O ₁₂ S
8	Boc-Sar-Nva-FMDP	82	145-150	-28.2	C ₂₁ H ₃₄ N ₄ O ₉
9	Boc-Nva-Nva-FMDP	92	82-84	-34.4	C ₂₃ H ₃₈ N ₄ O ₉
10	Boc-Nva-FMDP-Nva	62	172-174	-27.2	C ₂₃ H ₃₈ N ₄ O ₉
11	Boc-Lys-Boc-Nva-FMDP	84	oil	^b	C ₂₉ H ₄₉ N ₅ O ₁₁
12	Boc-Met ₃ -FMDP	86	114-116	-28.5	C ₂₈ H ₄₇ N ₅ O ₁₁ S ₃
13	Boc-Met-FMDP ₂	58	182-184	-19.8	C ₃₁ H ₄₈ N ₆ O ₁₃ S ₂
14	Boc-FMDP-Met ₂ -FMDP	61	144-146	-19.6	C ₃₁ H ₄₈ N ₆ O ₁₃ S ₂
15	Boc-Met ₄ -FMDP	88	152-155	-29.8	C ₃₃ H ₅₆ N ₆ O ₁₁ S ₄

^a In degrees (c = 1, MeOH). ^b Not determined.

ported that FMDP tripeptides, in contrast to dipeptides with FMDP residues, are carried into *C. albicans* cells via two permeases. The first is specific for di- and tripeptides and the second permease transports peptides containing three through six amino acid residues.⁵ This finding prompted us to synthesize a set of FMDP-containing tripeptides in order to establish a structure-activity rela-

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