Nonsteroidal Progesterone Receptor Ligands. 1. 3-Aryl-1-benzoyl-1,4,5,6-tetrahydropyridazines

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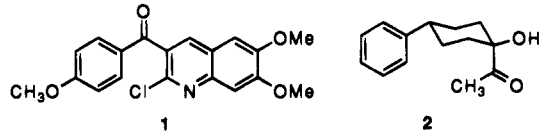
Introduction

Steroid hormone receptors are attractive targets for drug design due to the wide range of effects elicited by ligands binding to these receptors.[1] Synthetic steroidal ligands designed to interact with these receptors often bind to related receptors in addition to their targeted receptors resulting in an increased potential for side effects. This cross-reactivity is not surprising given the close structural similarity of the steroids and the high degree of homology of the ligand binding domain of the receptors in the steroid hormone superfamily.[2]

Nonsteroidal compounds that elicit activity by binding to steroid receptors have the potential for reduced cross-reactivity for nontargeted receptors, are easier to synthesize than steroids, and may be devoid of problematic chiral centers.

There are numerous examples[3] of nonsteroidal estrogens (e.g. diethylstilbesterol), antiestrogens (e.g. tamoxifen), and antiandrogens (e.g. flutamide). However, very little research has been published on nonsteroidal progestins and antiprogestins. Nonsymmetrical diaryl ketones[4] such as compound **1**, steroid D-ring mimics exemplified by 1-acetyl-4-phenylcyclohexanol[5] (**2**), and flutamide analogs[6–8] (e.g. **3**) have been investigated, but were shown to have either poor affinity for the progesterone receptor, weak biological potency, or poor selectivity.[9] More recently, the progesterone receptor binding of some vitamin D analogs[10] (e.g. **4**) and of cyclocymopol monomethyl ether (**5**), a derivative of the natural product cymopol,[11] have been reported.



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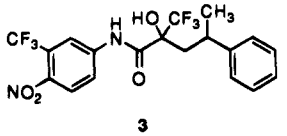

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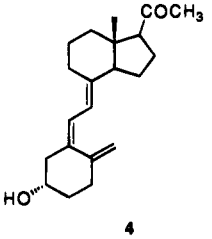

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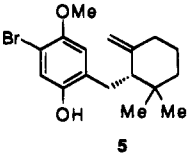

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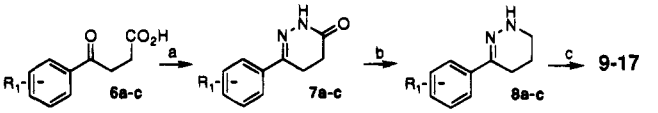
Scheme 1[a]



[a] Reagents: (a) hydrazine, ethanol, 80 °C; (b) $LiAlH_4$, THF, 0 °C; (c) $R_2ArCOCl$, PhMe, 110 °C.

Table 1. Progesterone Receptor Binding Affinity of Tetrahydropyridazines **9**–**11**

cmpd	R_1	R_2	IC_{50} (μM)[b]	*n*	formula[a]	mp (°C)
9a	H	3,4-Cl_2	4	3	$C_{17}H_{14}Cl_2N_2O$	139–140
9b–h			not active			
10a	4-Cl	3,4-Cl_2	3	2	$C_{17}H_{13}Cl_3N_2O$	95–96
10b	4-Cl	4-Br	10	2	$C_{17}H_{14}BrClN_2O$	168–169
10c	4-Cl	4-Cl	4	4	$C_{17}H_{14}Cl_2N_2O$	156–157
10d–h			not active			
11a–h			not active			

[a] Satisfactory analyses (C, H, N) were obtained. [b] Uteri from estrogen-primed New Zealand rabbits were placed in a cold buffer (0.01 M Tris-HCl, pH 8.0, 0.001 M EDTA, 0.25 M sucrose, 4 °C) and were minced, washed, and homogenized. The homogenate (2 g wet tissue/mL buffer) was centrifuged at 200000*g* for 1 h at 4 °C, and the supernatant fraction was used. A competitive binding assay was performed by mixing [^{3}H]R5020 with the receptor preparation and adding various concentrations of unlabeled test compound. This mixture was incubated at 4 °C for 18 h. The [^{3}H]R5020 bound to the receptor was separated from the free fraction using dextran-coated charcoal, and the percentage of [^{3}H]R5020 bound to the receptor was then determined.

There is substantial opportunity for improvement in the design of nonsteroidal progesterone receptor ligands. As part of a program aimed at the discovery of novel nonsteroidal compounds, we have uncovered, through a random screening program, a new class of selective progesterone receptor binding agent. Subsequently, we have improved the progesterone receptor binding affinity of the 3-aryl-1-benzoyl-1,4,5,6-tetrahydropyridazines over 100-fold.

Chemistry

3-Aryl-1,4,5,6-tetrahydropyridazin-6-ones (**7a–c**) are easily accessible from the corresponding 4-aryl-4-ketobutyric acids (**6a–c**) by addition of hydrazine.[12] Reduction of these compounds with excess lithium aluminum hydride affords the partially reduced 1,4,5,6-tetrahydropyridazines (**8a–c**).[13] Benzoyl chlorides with substituents designed to explore a number of steric and electronic parameters were condensed with the cyclic hydrazones, giving the title compounds (see Scheme 1).[14]

Discussion

Initially, 24 1-(arylcarbonyl)-3-aryl-1,4,5,6-tetrahydropyridazines (**9a–h**, **10a–h**, and **11a–h**) were prepared by acylation of 3-phenyl- (**8a**), 3-(4-chlorophenyl)- (**8b**), or 3-(4-methoxyphenyl)-1,4,5,6-tetrahydropyridazine (**8c**), with eight benzoyl chlorides (**a** = 3,4-Cl_2, **b** = 4-Br, **c** = 4-Cl, **d** = 3-Cl, **e** = H, **f** = Me, **g** = OMe, **h** = *t*-Bu) having diverse functionality. As part of a random screening program, these compounds were evaluated for the ability to compete with radiolabeled R5020[15] for the cytosolic progesterone receptor obtained from rabbit uterus. The rabbit receptor has been shown to have a high degree of homology with the human progesterone receptor[16] and is easily obtained in large quantity. While most of the analogs did not bind to the progesterone receptor (IC_{50} >10 μM), four showed a weak

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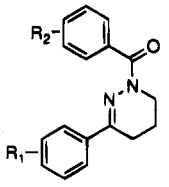
Table 2. Progesterone Receptor Binding Affinity of Tetrahydropyridazines **12–17**

compd	R_1	R_2	IC_{50} (μM)	n	range	formula[a]	mp (°C)
12	4-F	4-NO_2	1.02	3	1.0–1.3	$C_{17}H_{14}FN_3O_3$	179–180
13	4-Br	3,5-Cl_2	0.47	1		$C_{17}H_{13}BrCl_2N_2O$	144–145
14	4-Cl	4-NO_2	0.27	3	0.21–0.28	$C_{17}H_{14}ClN_3O_3$	172–174
15	4-F	3,4-Cl_2	0.25	3	0.21–0.29	$C_{17}H_{13}Cl_2FN_2O$	112–113
16	3,4-Cl_2	3,4-Cl_2	0.10	4	0.088–0.16	$C_{17}H_{12}Cl_4N_2O$	118–119
17	3,4-Cl_2	4-NO_2	0.10	4	0.073–0.15	$C_{17}H_{13}Cl_2N_3O_3$	181–183
progesterone		0.005					

[a] Satisfactory analyses (C, H, N) were obtained for all new compounds.

binding affinity with IC_{50} values ranging from 3 to 10 μM (Table 1) compared to progesterone which has a binding affinity of 0.005 μM.



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An examination of the relationship between structure and binding affinity of this series revealed a pattern. Affinity was only observed in compounds where one or both aromatic rings were electron-deficient.

Using the same chemical and biological methodology, six additional compounds were prepared (**12–17**) bearing electron-withdrawing halogen and nitro groups on both aromatic rings, and IC_{50} values were obtained in the progesterone receptor binding assay (Table 2). All six of these compounds showed improved binding affinity with IC_{50} values of between 0.1 and 1.02 μM. The 3,4-dichlorophenyl analogs bearing a 3,4-dichlorobenzoyl (**16**) or 4-nitrobenzoyl group (**17**) had the greatest affinity. Compounds **12–17** were also screened as potential ligands for androgen, estrogen, and glucocorticoid receptors and showed no binding affinity for these receptors at concentrations of up to 10 μM.

Perhaps because these novel compounds demonstrated only modest binding affinities to the progesterone receptor, they elicited no progestational or antiprogestational biological activity in the Clauberg test[17] (*in vivo* proliferation or inhibition of progestin induced proliferation of estrogen primed rabbit endometrium) at doses up to100 mg/kg. Encouraged by the predictability and success of the structure–activity relationship study and by the lack of binding affinity to other steroid receptors, we are currently investigating the further development of this and related chemical series to identify progesterone receptor ligands with potent and selective activity *in vivo*.[18]

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Supporting Information Available: Experimental details and analytical data (3 pages). Ordering information is given on any current masthead page.

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