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NONSTEROIDAL PROGESTERONE RECEPTOR ANTAGONISTS BASED ON A CONFORMATIONALLY-RESTRICTED SUBSERIES OF 6-ARYL-1,2-DIHYDRO-2,2,4-TRIMETHYLQUINOLINES

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Abstract. A series of nonsteroidal human progesterone receptor (hPR) antagonists based on conformationally-restricted analogues of a 6-aryl-1,2-dihydro-2,2,4-trimethylquinoline pharmacophore were synthesized and evaluated for their ability to bind to the human progesterone receptor and inhibit progesterone-stimulated reporter gene expression in mammalian cells.

Introduction. Over the past several years, we[5] and others[6] have focused on the discovery of structurally novel modulators of the human progesterone receptor (hPR) to address unmet clinical needs in women's health.[7] Efforts to avoid the low selectivity of steroidal agents, such as mifepristone (**1**),[8] have led us to explore other templates from natural products (**2**)[5b–d] and screening libraries (**3**). The latter nonsteroidal antagonist lead for hPR was discovered through cell-based screening of our internal libraries, and SAR studies have established N-1 and the 6-aryl group of **3** as a pharmacophore for this important receptor.[9] The present series of analogues investigates the effects of restricting rotation about the biaryl bond, with conformational rigidity conferred by a one-atom bridge linking either *ortho*-position of the outer aryl ring to the dihydroquinoline. Carbon, nitrogen, and oxygen bridges were examined.

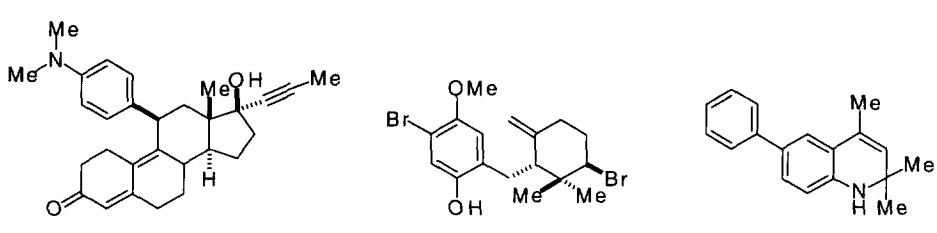

Figure 1. Mifepristone (**1**), Cyclocymopol monomethyl ether (**2**), 6-Phenyl-1,2-dihydro-2,2,4-trimethylquinoline (**3**).

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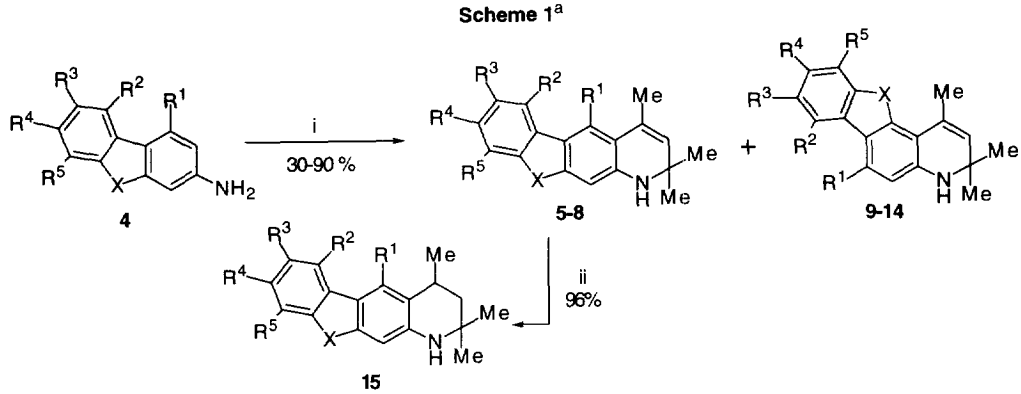
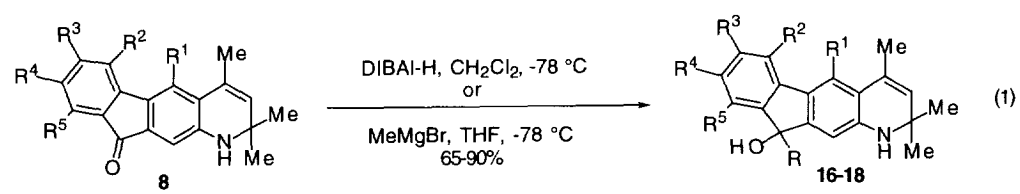
Chemistry. All analogues synthesized involved use of the Skraup cyclization[10,11] (acetone, 5 mol% iodine) reaction of tricyclic aromatic amines (2-aminofluorenes, 3-aminofluorenones, 2-aminodibenzofuran, or 2-aminocarbazole) as the ultimate or penultimate step (Scheme 1). Most substrates used in this cyclization approach were readily derived from commercially available starting materials, though Skraup cyclization precursors for several key analogues (**5m**, **8m**, **9m**, **16m**, **17m**, **18m**) required synthesis by modified literature routes.[12] Cyclization substrates with strongly electron-withdrawing substituents generally required sealed tube conditions and elevated temperatures, affording lower yields. Typically, regioselectivities in the Skraup reaction favored linear (**5–8**) over angular (**9–14**) products in an 85/15 ratio.

Scheme 1[a]



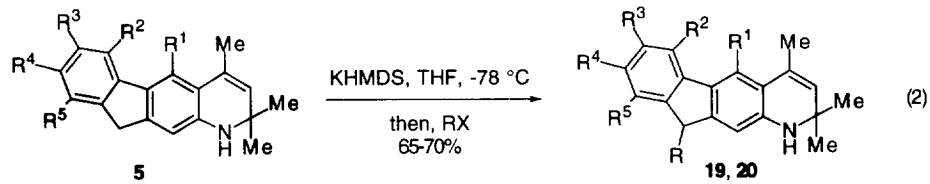
[a](i) acetone, I_2, 56-120 °C; (ii) H_2, 10% Pd on C, EtOAc / EtOH, rt.

Reduction of 10-oxo derivatives was accomplished using DIBAl-H, in CH_2Cl_2 (eq 1). Similarly, **18m** was prepared from **8m** by addition of MeMgBr in THF.



(1)

Alkylated methylene compounds **19e** and **20e** were obtained by low-temperature deprotonation of **5e** with KHMDS (2.5 equiv), followed by trapping with either MeI or BnBr (eq 2). Alkylation of amines (**12a** and **13a**) and acylation of alcohols (**17m**) proceeded under standard conditions.



5 19, 20

Biological Results and Discussion. In general, linear analogues (**5-8**, **15–20**) had much higher affinities for hPR-A in receptor binding assays and more potent inhibition of progesterone stimulated reporter activity in cotransfection assays[13] with hPR-B than the corresponding angular tetracyclic analogues (**9-14**) (Table 1). In the course of investigations into the SAR of freely rotating 6-aryl analogues, it was observed that electron-withdrawing substituents on the 6-aryl ring contributed to a significant enhancement in potency in the bioassays. This trend is conserved in the present series of conformationally-restricted analogues, and is most markedly exhibited in those analogues with an unsubstituted methylene spacer as the bridging group (**5a–m/9a–m**). In particular, fluoro and nitro substituents, most notably when substituted at R^4, provided the greatest enhancement of receptor binding, with several analogues exhibiting single-digit nanomolar affinity for hPR-A (**5d**, **5g**, **5h**, **5j**, **5k**). Furthermore, it may be significant that these favored electronegative substituents have powerful electronic effects while simultaneously maintaining or enhancing the overall lipophilic properties of the molecule, and activity drops off with both decreasing electronegativity and decreasing lipophilicity (**5a**, **5c**, **5e**, **5f**).

While many analogues in this simple methylene bridging subseries had strong affinity for hPR-A in receptor binding assays, they lacked the ability to achieve full antagonist efficacy in functional assays. Some exhibited partial agonist properties at the higher concentrations. This inability to fully block a progesterone-stimulated transcriptional event in the cellular assays was partially overcome by the installation of a heteroatom either replacing the methylene linker (**6a** and **7a**), or as a substituent at the bridging carbon (**8** and **16**, **17**). However, simply the presence of a heteroatom at this position was not sufficient to maintain the level of potency previously acheived in the methylene-bridged analogues. It was observed that a hydrogen-bond donor group (**7a** and **16e–m**) could restore potency to the 60–160 nM range in the functional assays. Alkyl substitution at this bridging position was not tolerated with (**18m**) or without (**19e** and **20e**) a hydroxyl group.

Table 1. hPR-B Antagonist Activity in Cotransfected CV-1 Cells and Binding Affinities for hPR-A.

Ligand	R^1	R^2	R^3	R^4	R^5	X	Cotransfection Assay IC_{50} (nM)	Cotransfection Assay Efficacy (%)	Binding K_i (nM)
1	mifepristone						0.3 ± 0.04	99 ± 0	1.1 ± 0.3
3	6-phenyl-1,2-dihydro-2,2,4-trimethylquinoline						783 ± 162	72 ± 4	133 ± 71
5a	H	H	H	H	H	CH_2	220 ± 46	78 ± 4	14 ± 1.2
5b	H	H	H	H	CH_2OH	CH_2	10,000	24	12.4 ± 3
5c	H	H	H	$COCH_3$	H	CH_2	164 ± 39	75 ± 4	176 ± 29
5d	H	H	H	NO_2	H	CH_2	90	30	3.6 ± 0.4
5e	H	H	H	Br	H	CH_2	434 ± 116	66 ± 3	24 ± 4
5f	H	H	H	Cl	H	CH_2	248	58	29 ± 5
5g	H	H	H	F	H	CH_2	10	36	3.5 ± 0.4
5h	H	H	H	H	F	CH_2	1772 ± 1021	65 ± 7	2.3 ± 0.3
5i	H	F	H	H	H	CH_2	146 ± 65	58 ± 7	11.2 ± 3
5j	H	F	H	H	F	CH_2	146	25	3.1 ± 0.4
5k	H	H	F	NO_2	H	CH_2	100 ± 0	40 ± 3	1.9 ± 0.2
5m	F	H	H	F	H	CH_2	650 ± 300[14]	96 ± 3	1.5
6a	H	H	H	H	H	O	1847 ± 149	84 ± 1	184 ± 24
7a	H	H	H	H	H	NH	59 ± 13	80 ± 4	113
8a	H	H	H	H	H	C=O	353	91	3553 ± 420
8i	H	F	H	H	H	C=O	158 ± 67	78 ± 7	29.1 ± 4.8
8m	F	H	H	F	H	C=O	365	59	>10,000
9a	H	H	H	H	H	CH_2	549 ± 105	85 ± 2	13 ± 4
9d	H	H	H	NO_2	H	CH_2	1674	81	57 ± 7
9e	H	H	H	Br	H	CH_2	2330 ± 318	43 ± 12	200 ± 22
9h	H	H	H	H	F	CH_2	496 ± 150	71 ± 5	15.5 ± 3
9k	H	H	F	NO_2	H	CH_2	3331 ± 67	68 ± 3	97 ± 8
9m	F	H	H	F	H	CH_2	5685	19 ± 4	20.9
10a	H	H	H	H	H	O	1144 ± 549	88 ± 2	77 ± 10
11a	H	H	H	H	H	NH	662	87	>1,000
12a	H	H	H	H	H	NEt	284	94	169
13a	H	H	H	H	H	NBu	416	90	77
14m	F	H	H	F	H	C(H)OH	10,000	16 ± 22	2580 ± 305
15a	H	H	H	H	H	CH_2	424 ± 74	74 ± 3	87 ± 11
16a	H	H	H	H	H	C(H)OH	609	93	483 ± 32
16e	H	H	H	Br	H	C(H)OH	3443 ± 547	73 ± 5	1858 ± 208
16g	H	H	H	F	H	C(H)OH	122 ± 10	72 ± 9	101 ± 21
16i	H	F	H	H	H	C(H)OH	99 ± 27	85 ± 4	449 ± 61
16m	F	H	H	F	H	C(H)OH	80 ± 17	74 ± 3	25.5 ± 4.1
16n	Cl	H	H	H	H	C(H)OH	163 ± 44	73 ± 1	53.1 ± 8
16p	H	H	F	H	F	C(H)OH	74 ± 23	80 ± 2	202 ± 31
17m	F	H	H	F	H	$C(H)OCOCF_3$	46 ± 22	72 ± 5	62.5 ± 7.1
18m	F	H	H	F	H	$C(CH_3)OH$	10,000	20	>10,000
19e	H	H	H	Br	H	$C(H)CH_3$	10,000	0	>10,000
20e	H	H	H	Br	H	$C(H)CH_2Ph$	10,000	8 ± 0	>10,000

Conclusion. Tying the terminal aryl ring of **3** more closely into coplanarity with the remainder of the π-system results in a higher affinity interaction with hPR. For example, compound **5a** has an order of magnitude tighter binding affinity (14 nM) compared with the corresponding freely rotating biphenyl version, **3** (133 nM). Interestingly, this higher affinity interaction does not fully translate into improved efficacy in functional cellular assays. Efficacy can be enhanced, albeit accompanied with minor diminishment in potency, by installation of a hydroxyl group on the bridging methylene. Halogens at R_1 and R_4 also improve activity in the cellular assays. The present compounds and related sub-series of the 6-aryl-1,2-dihydro,2,2,4-trimethylquinoline class of PR antagonists are under continued investigation and may yield novel agents useful for female reproductive oncology and treatment of gynecological diseases.

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References and Notes.

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11. A typical experimental procedure for the Skraup reaction is illustrated for compounds **5e/6e** as follows: To a flame-dried 200-mL round-bottom flask containing 2-amino-7-bromofluorene (obtained from Aldrich Chemical Co., Milwaukee, WI) (**4**, where X = CH_2, R^4 = Br, and R^1, R^2, R^3, and R^5 = H) (2.00 g, 7.69 mmol) in acetone (75 mL, approx. 0.1 M), was added iodine (50 mg, 0.39 mmol, 5.0 mol%), and the mixture was heated to reflux. The reaction progress was followed by TLC (hexanes/EtOAc, 3/1), visualized by short wave UV, where the products appear as bright blue spots. After 40 h, the mixture was cooled to room temperature, and Celite™ (1 g) was added. The mixture was then concentrated under reduced pressure to give a free flowing powder. The mixture thus obtained was purified by flash column chromatography (50 g silica gel, hexanes/EtOAc, 20/1-4/1 gradient elution) to afford pure isomers **5e** (1.28 g, 49%) as a rose-colored solid, and **6e** (226 mg, 8.6%) as a tan solid. Data for compound **5e**: R_f = 0.57 (silica gel, hexanes/EtOAc, 3/1). ^{1}H NMR (400 MHz, C_6D_6) 7.38 (m, 2H, 7,9-H), 7. 30 (m, 2H, 5,6-H), 6.17 (s, 1H, 11-H), 5.15 (s, 1H, 3-H), 3.34 (s, 2H, CH_2), 3.27 (br s, 1H, N*H*), 1.93 (d, 3H, *J* = 1.0, 4-CH_3), 1.08 [s, 6H, C(CH_3)$_2$]. Data for compound **6e**: R_f = 0.53 (silica gel, hexanes/EtOAc, 3/1). ^{1}H NMR (400 MHz, C_6D_6) 7.38 (d, 1H, *J* = 8.3, 8-H), 7.31 (s, 1H, 6-H), 7.29 (d, 1H, *J* = 8.0, 9-H), 7.19 (d, 1H, *J* = 8.0, 10-H), 6.25 (d, 1H, *J* = 8.1, 11-H), 5.16 (s, 1H, 3-H), 3.52 (s, 2H, CH_2), 3.32 (br s, 1H, N*H*), 1.91 (d, 3H, *J* = 1.4, 4-CH_3), 1.05 [s, 6H, C(CH_3)$_2$].
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14. Data shown for **5m** is an EC_{50}, as this compound exhibited essentially full hPR-B agonist activity.