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5-ALKYL 1,2-DIHYDROCHROMENO[3,4-*f*]QUINOLINES: A NOVEL CLASS OF NONSTEROIDAL PROGESTERONE RECEPTOR MODULATORS

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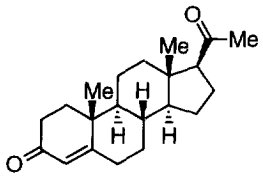
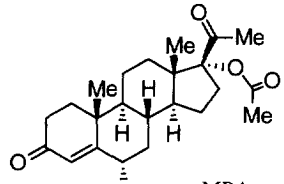
Abstract: A series of nonsteroidal human progesterone receptor (hPR) agonists, 5-alkyl 1,2-dihydrochromeno[3,4-*f*]quinolines, was synthesized and evaluated in cotransfection and competitive receptor binding assays. The 5-alkyl substitution was shown to be responsible for the agonist activity and substitution at C9 dramatically enhanced the potency. A number of analogues in this series showed activities similar to or better than progesterone in the cotransfection and binding assays and analogue **15** exhibited similar in vivo activity as medroxyprogesterone acetate (MPA) in murine uterine wet weight/mammary gland morphology assays.

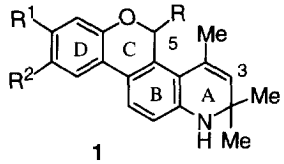
Introduction: We recently reported the development and optimization of a novel class of nonsteroidal hPR agonists, the 5-aryl-1,2-dihydro-5*H*-chromeno[3,4-*f*]quinoline series (**1**, R = aryl)[2] based on our cell-based assays.[3] The structure-activity relationship (SAR) study on the 5-aryl and D-ring substituents generated a number of potent orally available hPR agonists.[4] In this paper we report the results of our new findings that 5-alkyl analogues exhibit potent hPR agonist activities while the 5-H, alkoxy, and thioalkoxy analogues tend to show moderate antagonist activities.



Progesterone



MPA



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Chemistry: Most of the 5-alkyl 1,2-dihydro-5*H*-chromeno[3,4-*f*]quinolines (**1**, R = alkyl) were prepared by a method similar to that described in the synthesis of the 5-aryl analogues (**1**, R = aryl) from the corresponding lactones **2**.[2] The 5-alkyl group was introduced by a nucleophilic addition of an alkyllithium (or Grignard) reagent followed by Et_3SiH reduction in the presence of a Lewis acid such as trifluoroacetic acid (TFA) or BF_3-OEt_2 (Scheme 1).[5] The 5-H compounds (**4**) were synthesized by a stepwise reduction of the corresponding lactones (**2**) with DIBAL-H (to form lactols **3**), followed by treatment with Et_3SiH in the presence of TFA. The 5-alkoxy- and 5-thioalkyl analogues (**5**) were prepared by the treatment of lactols **3** with corresponding alcohols or mercaptans in the presence of a catalytic amount of TsOH.[6] The 5-allyl analogue (**12**) was obtained by treatment of the 5-methoxy compound (**23**) with allyltrimethylsilane in the presence of TMS triflate.[7]

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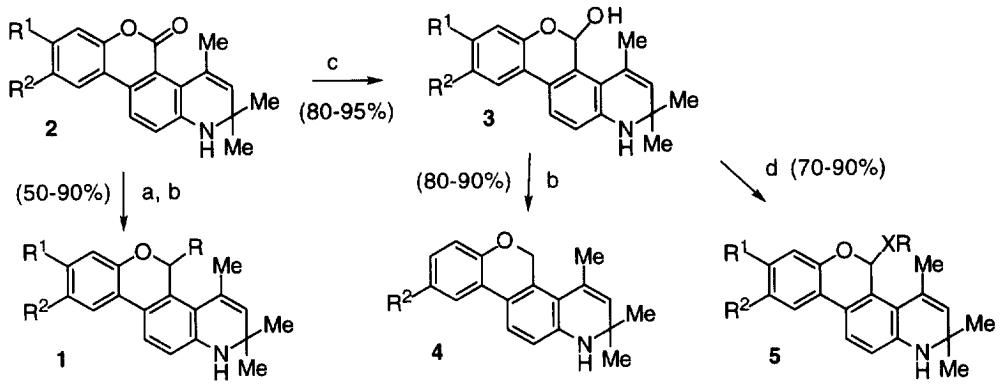
Scheme 1[a]

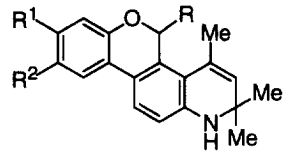


[a]Reagents: (a) RLi, THF, -70 to -50 °C; (b) TFA or BF_3-OEt_2, Et_3SiH, CH_2Cl_2, rt.; (c) DIBAl-H, CH_2Cl_2, -20 to 0 °C; (d) RXH, TsOH, rt. (X = O or S).

Results and Discussion: Our initial study focused on the SAR of the 5-alkyl substituents by using the hPR cotransfection assays[8] and the receptor binding assays as guides and the results are summarized in Table 1. Seven analogues without D-ring substitution were prepared and tested. The parent compound **6** behaved as a moderate hPR antagonist in the cotransfection assay with a moderate binding affinity. The introduction of a small alkyl group at C5 (**7, 8, 10–12**) dramatically increased the binding affinity (17- to 88-fold of **6**) and significantly improved the agonist efficacy (**7**) or potency (**8, 10–12**) except 5-hexyl compound (**9**), whose 5-substituent is believed to be too large. In spite of the activity differences among the 5-alkyl analogues, they all showed better agonist activity and binding affinity than their parent 5-H compounds (except the 5-hexyl analogue, **9**). The 5-methyl and 5-butyl analogues exhibited much better (100-fold) agonist potency than their 5-H parent compound in both 9-fluoro and 9-chloro series (comparing **14**, **15** with **13**; **17**, **18** with **16**). The 5-butyl group in the 9-methyl series totally switched a moderate antagonist (**19**) to a potent agonist (**20**).

In comparison with assay results of the analogues having the same 5-alkyl substituent, a dramatic enhancement of the C9 substitution on agonist activity was observed. The 5-methyl 9-fluoro and 9-chloro compounds (**14** and **17**) are hundreds-fold more potent than their parent compound (**7**). The 5-butyl 9-fluoro and 9-chloro compounds exhibited improved efficacy (compare **15**, **18** with **8**). It was noted that a fluoro substitution at C8 decreased both the agonist activity and binding affinity (compare **22** with **8**). Introduction of the electron-donating group methyl or methoxy at C9 enhanced agonist efficacy (compare **20**, **21** with **8**). It is the size of the 9-substituents rather than their electronic properties that play a more important role in boosting the agonist activity. A number of 5-alkoxy and 5-thioalkyl analogues (**5**) were also tested and the results showed that the introduction of oxygen or sulfur in the 5-alkyl chain did not help to make a better agonist (Table 1).

Table 1. Cotransfection and Competitive Binding Data for the Quinoline Analogues.[a]

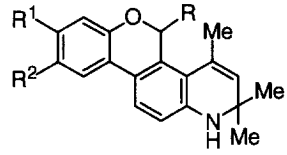


#	R	R^1	R^2	hPR Agonist[b] Eff(%)	hPR Agonist[b] EC_{50} (nM)[c]	hPR Antagonist[b] Eff(%)	hPR Antagonist[b] IC_{50} (nM)[c]	hPR-A Binding[e] K_i (nM)
	Progesterone			100	2.9 ± 0.9	-[d]	-	3.5 ± 0.2
	MPA			80 ± 7	0.15 ± 0.05	-	-	0.34 ± 0.04
	ZK98,299			-	-	99 ± 0	1.6 ± 0.35	18 ± 3
6	H	H	H	34 ± 12	3081 ± 98	85 ± 5	71 ± 26	84 ± 10
7	Me	H	H	114 ± 9	2066 ± 348	47 ± 2*	43 ± 25*	3.3 ± 0.8
8	$(CH_2)_3Me$	H	H	38 ± 7	11 ± 8	40 ± 3	997 ± 851	0.95 ± 0.15
9	$(CH_2)_5Me$	H	H	-	-	77 ± 13	375 ± 61	23 ± 3
10	$(CH_2)_2CHMe_2$	H	H	64 ± 11	13 ± 5	66 ± 19	307 ± 47	1.7 ± 0.2
11	$(CH_2)_4Cl$	H	H	53 ± 7	33 ± 21	32	6700	3.2 ± 0.4
12	$CH_2CH{=}CH_2$	H	H	62 ± 4	9.0 ± 1.0	61 ± 23*	561 ± 146*	4.8 ± 0.2
13	H	H	F	111 ± 58	2112 ± 638	65 ± 4	26 ± 5	6.1 ± 0.9
14	Me	H	F	88 ± 32	14 ± 9	-	-	1.1 ± 0.2
15	$(CH_2)_3Me$	H	F	77 ± 7	15 ± 2	-	-	2.9 ± 0.3
16	H	H	Cl	105 ± 38*	2194 ± 160*	56 ± 3	45 ± 11	3.6 ± 0.4
17	Me	H	Cl	138 ± 12	3.2 ± 0.9	-	-	0.44 ± 0.03
18	$(CH_2)_3Me$	H	Cl	70 ± 17	6.8 ± 0.8	-	-	0.87 ± 0.13
19	H	H	Me	-	-	72 ± 11	75 ± 22	50.2 ± 4.5
20	$(CH_2)_3Me$	H	Me	58 ± 2	16 ± 6	-	-	1.2 ± 0.8
21	$(CH_2)_3Me$	H	Ome	66 ± 10	9.3 ± 4.0	-	-	3.5 ± 0.3
22	$(CH_2)_3Me$	F	H	22	5285	83 ± 10	538 ± 338	26.5 ± 0.2
23	OMe	H	H	-	-	90 ± 3	75 ± 17	400 ± 90
24	$O(CH_2)_2Me$	H	H	40	890	88 ± 11	69 ± 7	64 ± 9
25	OMe	H	F	-	-	75 ± 10	46 ± 21	38.4 ± 2.6
26	$O(CH_2)_2Me$	H	F	46 ± 3	26 ± 28	-	-	6.0 ± 0.8
27	OMe	H	Cl	-	-	73 ± 9	57 ± 21	16.4 ± 3.2
28	$O(CH_2)_2Me$	H	Cl	104 ± 10	14 ± 9	-	-	1.5 ± 0.5
29	OMe	F	H	-	-	89 ± 3	49 ± 14	80.5 ± 0.5
30	$S(CH_2)_2Me$	H	H	-	-	86 ± 9	187 ± 43	24.3 ± 4.3
31	$S(CH_2)_2Me$	H	F	38 ± 9	12 ± 8	63 ± 32*	345 ± 163*	6.6 ± 0.7

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments with triplicate determinations and values without standard deviation represent a single experiment and values with * represent the mean value of two experiments with standard deviation. [b] Agonist efficacies were compared to that of progesterone (100%) and antagonist efficacies were determined as a function (%) of maximal inhibition of progesterone (EC_{50}). [c] All EC_{50} and IC_{50} values were determined from full dose-response curves ranging from 10^{-12} to 10^{-5} M in CV-1 cell. [d] Stands for the efficacy < 20% or potency >10000 nM. [e] The radioligand used in the competitive binding assay was progesterone.

The cross-reactivity profile of selected new nonsteroidal hPR agonists were examined in human androgen receptor (hAR) and human glucocorticoid receptor (hGR) competitive binding assays and the results are summarized in Tables 2. These nonsteroidal compounds showed excellent hPR selectivity over the other two steroid receptors.

Table 2. Competitive Binding Data of Quinoline Analogues with hPR-A, hAR, hGR.[a]



#	R	R^1	R^2	hPR-A K_i (nM)	hAR K_i (nM)	hGR K_i (nM)
	Progesterone			3.5 ± 0.2	8.5 ± 3.1	30.5 ± 1.9
	MPA			0.34 ± 0.04	2.9 ± 0.2	13.2 ± 1.8
8	$(CH_2)_3Me$	H	H	0.95 ± 0.15	2046 ± 1034	813 ± 82
10	$(CH_2)_2CHMe_2$	H	H	1.7 ± 0.2	1485 ± 265	158 ± 71
14	Me	H	F	1.1 ± 0.2	456 ± 36	749 ± 430
15	$(CH_2)_3Me$	H	F	2.9 ± 0.3	1330 ± 496	533 ± 304
17	Me	H	Cl	0.44 ± 0.03	621 ± 409	367 ± 236
18	$(CH_2)_3Me$	H	Cl	0.87 ± 0.13	886 ± 268	394 ± 334
20	$(CH_2)_3Me$	H	Me	1.2 ± 0.8	903 ± 366	51 ± 12
21	$(CH_2)_3Me$	H	OMe	3.5 ± 0.3	785 ± 234	130 ± 69
28	$O(CH_2)_2Me$	H	Cl	1.5 ± 0.5	697 ± 303	260 ± 173
12	$CH_2CH=CH_2$	H	H	4.8 ± 0.2	> 1000	889

[a] Values with standard errors (SEM) represent the mean value of at least three separate experiments on receptor expressed in SF_{21} cells in a baculovirus expression system and the radioligands used in the assays were progesterone for hPR-A, DHT for hAR, and dexamethasone for hGR.

The representative 5-alkyl analogue **15** was evaluated for its progestational activity on the inhibitory effect on estrogen-induced uterine wet weight and stimulation of mammary alveolar bud formation in rats using a modified literature method.[9] Figure 1 shows the comparison results between **15** and MPA in the uterus at three doses (0.3, 1.0, and 3.0 mg/rat) and Figure 2 summarized the results in the mammary gland . Compound **15** exhibited similar activity to MPA in mammary gland and in uterus.

Summary: A novel series of nonsteroidal hPR modulators was developed from the 1,2-dihydro-5*H*-chromeno [3,4-*f*]quinoline pharmacophore. The 5-alkyl substituents were responsible for the hPR agonist activity and the high PR binding affinity and a substitution at C9 dramatically increased the agonist potency. A number of the new progestins showed similar or better activities than progesterone in the cotransfection and the binding assays. Compound **15** demonstrated similar oral in vivo activities to MPA in the mammary gland morphology/uterine wet weight assay. Most of the 5-alkoxy and 5-thioalkoxy analogues behaved as hPR antagonists in the cotransfection assay. In addition, this series of compounds had much better receptor selectivity than progesterone and MPA.

Figure 1. Inhibition of estrone-induced uterine wet weight in the ovariectomized rat by quinoline derivatives or MPA (3.0 mg/rat, n = 4). All values represent the mean percent change ± SEM of uterine wet weight from animals treated with estrone (E) alone (* = $p < 0.05$ *vs.* E ANOVA).

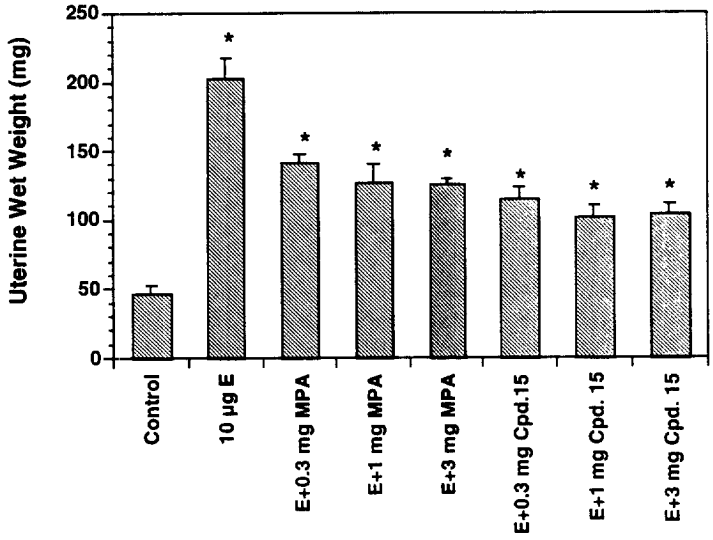
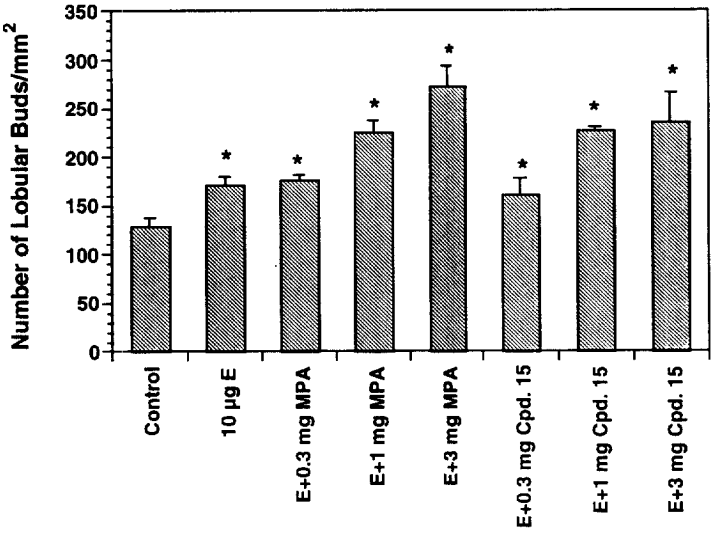


Figure 2. Stimulation of lobular aveolar bud formation in the ovariectomized rat by quinoline derivatives or MPA (3.0 mg/rat, n = 4). All values represent the mean percent change ± SEM of lobular aveolar buds from animals treated with E alone (* = $p < 0.05$ *vs.* E ANOVA).



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5. For example, to a yellow solution (0.2–0.5 M) of **2** ($R^1 = R^2 = H$)[2a] (50 mg, 0.17 mmol) in THF at – 78 °C was added *n*-BuLi (1.6 M in hexane, 2.5 equiv) and the resulting dark red mixture was slowly warmed up untill the red color faded (around – 30 °C) and was quenched immediately with water. The reaction mixture was extracted with EtOAc, washed with brine, and concentrated to afford the hemiacetal intermediate as a yellowish oil. A solution of the intermediate in CH_2Cl_2 (0.1 M) was treated with Et_3SiH (5 equiv) and TFA (0.2 equiv) at rt. for 3 h till the reaction went to completion by TLC. The reaction then was quenched with aqueous Na_2CO_3 and extracted with EtOAc, washed with brine and concentrated. Purification by flash chromatography afforded 40 mg (71%) of **8** as a colorless oil; ^1H NMR (400 MHz, $CDCl_3$) 7.62 (d, J = 7.8, 1 H), 7.44 (d, J = 8.3, 1 H), 7.14 (t, J = 7.8, 1 H), 6.98 (t, J = 7.8, 1 H), 6.92 (d, J = 7.8, 1 H), 6.59 (d, J = 8.3, 1 H), 5.88 (dd, J = 9.8 and 3.1, 1 H), 5.49 (s, 1 H), 3.88 (br s, 1 H), 2.25 (s, 3 H), 1.90–1.79 (m, 1 H), 1.55–1.25 (m, 5 H), 1.28 (s, 3 H), 1.20 (s, 3 H) and 0.84 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.0, 147.1, 134.5, 133.7, 129.1, 128.0, 125.2, 123.9, 122.5, 122.3, 119.3, 118.1, 118.0, 115.1, 75.2, 50.9, 34.7, 29.7, 28.8, 28.7, 24.3, 23.0, 14.3.
6. Spectral data for new compound **3** ($R^1 = R^2 = H$) and **23**. **3**: ^1H NMR (400 MHz, $CDCl_3$) 7.71 (d, J = 7.5, 1 H), 7.53 (d, J = 8.4, 1 H), 7.19 (t, J = 7.5, 1 H), 7.08 (t, J = 7.5, 1 H), 7.07 (d, J = 8.4, 1 H), 6.85 (d, J = 5.8, 1 H), 6.70 (d, J = 7.5, 1 H), 5.52 (s, 1 H), 3.92 (br s, NH), 2.94 (d, J = 5.8, 1 H), 2.37 (s, 3 H), 1.32 (s, 3 H) and 1.20 (s, 3 H). **23**: ^1H NMR (400 MHz, $CDCl_3$) 7.69 (d, J = 7.7, 1 H), 7.48 (d, J = 8.3, 1 H), 7.15 (t, J = 7.7, 1 H), 7.05 (m, 2 H), 6.65 (d, J = 8.3, 1 H), 6.35 (s, 1 H), 5.50 (s, 1 H), 3.90 (br s, NH), 3.49 (s, 3 H), 2.28 (s, 3 H), 1.33 (s, 3 H) and 1.28 (s, 3 H).
7. Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383. Spectral data for new compound **12**: ^1H NMR (400 MHz, acetone-d_6) 7.67 (d, J = 7.4 , 1 H), 7.49 (d, J = 8.3 , 1 H), 7.11 (t, J = 7.4, 1 H), 6.98 (t, J = 7.4, 1 H), 6.87 (d, J = 7.4, 1 H), 6.70 (d, J = 8.3, 1 H), 5.94 (dd, J = 8.6 and 3.5, 1 H), 5.90 (m, 1 H), 5.52 (s, 1 H), 5.03 (d, J = 1.8, 1 H), 5.00 (dd, J = 8.6 and 1.8, 1 H), 2.55 (m, 1 H), 2.24 (m, 4 H), 1.27 (s, 3 H) and 1.19 (s, 3 H).
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