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Development of Progesterone Receptor Antagonists from 1,2-Dihydrochromeno[3,4-*f*]quinoline Agonist Pharmacophore

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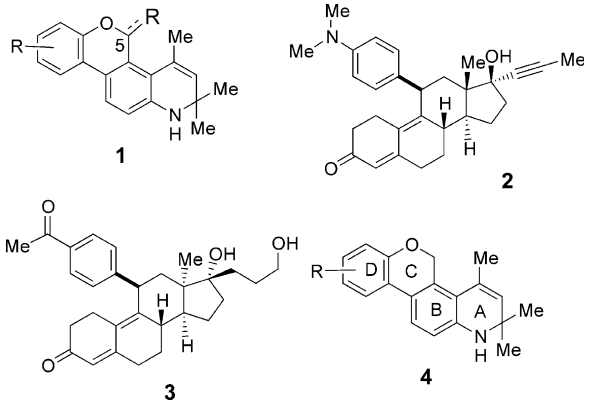
Abstract—A series of 1,2-dihydrochromeno[3,4-*f*]quinoline derivatives was synthesized and tested in biological assays to evaluate the nonsteroidal progesterone receptor modulator pharmacophore (**4**) as antiprogestins. A number of potent analogues were identified by modification of the substituents at the D-ring.

The 5-substituted dihydrochromeno[3,4-*f*]quinolines (**1**) have been demonstrated to be a robust pharmacophore for selective progesterone receptor modulators (SPRMs) with progestational activity.[1] Most of the analogues have high receptor selectivity over other steroid hormone receptors and several demonstrated a desirable tissue-selectivity profile in a rodent model.[2] Development of SPRMs with anti-progestational activity, from either steroidal or non-steroidal molecules, has been pursued to meet the clinical needs in fertility regulation or breast cancer treatment.[3] To maximize SPRM potential of the pharmacophore **1**, we explored the possibility of the development of selective antiprogestins based on the same structural scaffold. It is known that introduction of a substituted aryl group at the 11-β position of a steroidal progestin skeleton generates potent antiprogestins (e.g., Mifepristone, **2**, Onapristone, **3**).[4] This report describes the discovery that removal of the 5-substituents from the quinoline progestins (**1**) affords a novel series of analogues (**4**) with potent anti-progestational activity.

The analogues of general structure **4** were synthesized by sequential DIBAL-H and silane reduction of the corresponding coumarinoquinolines **8** (Scheme 1). The lactones **8** were prepared by either the published routes[1a,b] or an improved version as shown. Suzuki coupling of boronic acids **5**[5] with the arylbromide afforded biaryl compounds **6** in excellent yields. Hydrolysis of methyl ester **6** followed by an intramolecular carboxylate cyclization generated lactone **7**. The dihydroquinoline ring of lactone **8** was formed through tin chloride reduction of the nitro group and a modified Skraup reaction.[6]



Scheme 2 describes a novel route to modify the D-ring substitution after assembly of the tetracyclic core structure developed in order to address the problem that some of the D-ring substituents R can not survive the synthetic sequence of Scheme 1. The quinoline nitrogen needs to be protected to prevent complication in the subsequent steps. The usual tBoc$_2$O reaction conditions failed to derivative the highly hindered nitrogen. Phenyllithium was used to generate the more reactive

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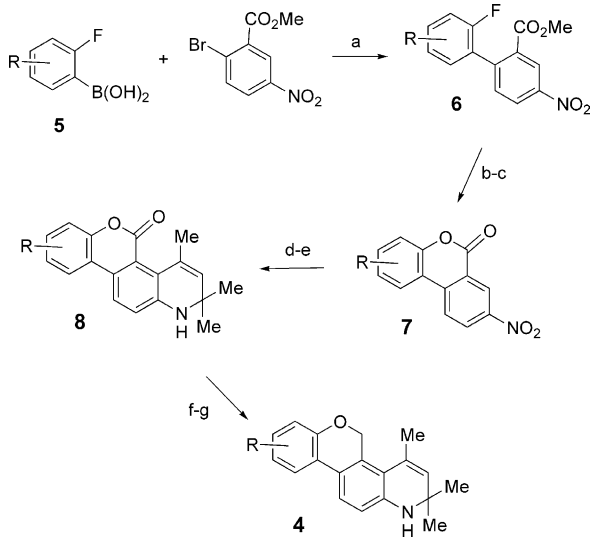
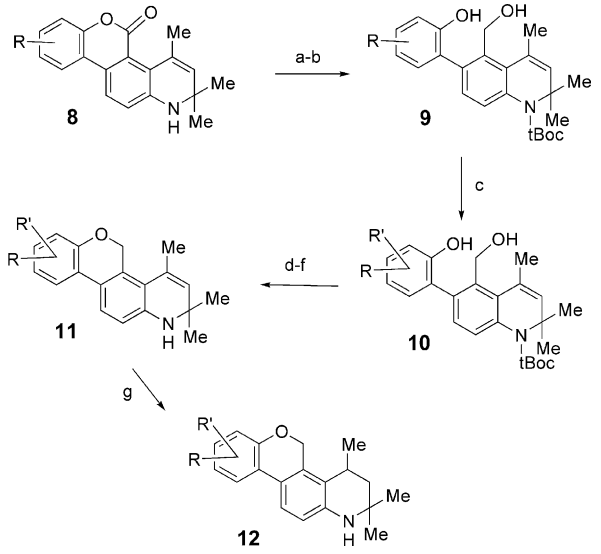


Scheme 1. (a) 3 mol % $Pd(PPh_3)_4$, Na_2CO_3, toluene/EtOH/H_2O, reflux, 18 h, 90%; (b) NaOH, THF, rt, 2 h, 95%; (c) NaH, DMF, 80 °C, 2 h, 85%; (d) $SnCl_2$, AcOEt, reflux, 2 h, 95%; (e) acetone, I_2, sealed tube 130 °C, 18 h, 50%; (f) DIBAL-H, toluene, −40 °C, 60–95%; (g) BF_3-OEt_2, Et_3SiH, CH_2Cl_2, rt, 2 h, 70–90%.



Scheme 2. (a) PhLi, THF, −78 °C, tBoc$_2$O, 50–80%; (b) LAH, THF, rt, 2 h, 90%; (c) Et_3N, THF, −40 °C to rt, NBS, 75–95%; (d) DMF, K_2CO_3, MeI, rt, 80–95%; (e) NaH, DMF, 80 °C, 70–80%; (f) TFA, CH_2Cl_2, rt, 2 h, 70–90%; (g) Pd/C, H_2, 80%.

nitrogen anion, which led to the formation of the *t*-butyl carbamate. Reduction of the protected lactone with LAH afforded the biaryl alcohol **9** in good yields. Triethylamine was used to generate the phenoxide to activate the D-ring for chemoselective electrophilic reactions such as the NBS bromination to give structure **10**. Methylation of the phenoxide with MeI in DMF followed by a nucleophilic alkoxide displacement afforded the chromeno[3,4-*f*]quinoline under surprisingly mild conditions. Deprotection of the quinoline nitrogen provided the analogues **11**. The preparation of compound **11p** (R = 7-F, R′ = 9-Br) is illustrative.[7] Analogues **12** were prepared by direct catalytic hydrogenation of the dihydroquinoline **11**. The nitro analogues **12** (R = NO_2) were obtained by controlled nitration of the tetrahydroquinoline precursor **12** (R = H).

Results and Discussion

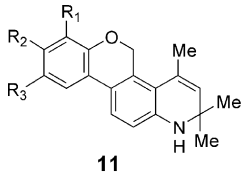
The human progesterone receptor (hPR) competitive binding and co-transfection (in CV-1 cells) assays were employed as primary assays to guide the SAR.[8] The T47D (alkaline phosphatase readout) human breast cancer cell line was used as secondary assay to monitor potential PR modulating activity in breast tissues. The assay results of the new analogues are depicted in Table 1. Mifepristone and Onapristone were used as standard hPR antagonists.

In our SAR study of the SPRM pharmacophore (i.e., **1**) we discovered that 5-substitution was essential for hPR agonist activity.[1] The synthetic intermediates **8** (5-oxo analogues) were found to be moderate hPR antagonists.[1a] The anti-progestational activity of the tetracyclic lactones **8** were expected as a conformationally constrained analogue of the bi-aryl series (6-aryl-1,2-dihydroquinolines), discovered in our early anti-progestin effort.[9] This intriguing discovery led us to optimize the lactone lead for hPR antagonist activity. We subsequently found that reduction of the lactone to an ether linkage improved biological activity. A number of novel analogues of the chromenoquinoline series were prepared and evaluated in the in vitro assays (Table 1). Several general SAR information can be summarized as follows: (1) 7-substituents larger than fluorine decreased activity (compare **11a** with **11e**, **f**, **m**, **n**, **r**, and **s**); (2) small 9-substituents, especially electron-withdrawing groups, enhanced the antagonist activity (compare **11a** with **11b**, **c**, **d**, **g**, **j**, and **q**); (3) 7-fluorine is tolerated (compare **11a**, **b**, **c**, **d** with **11e**, **m**, **o**, **p**); (4) saturation of 3,4-olefin resulted in decreased activity especially binding affinities (compare **11j** with **12a**, **11m** with **12b**). In contrast to the steroidal anti-progestins which demonstrated similar potency and efficacy in both cotransfection and T47D assays, the new nonsteroidal antiprogestins tend to have partial activity in the T47D assay with reduced potency compared to the CV-1 assay. These results are consistent with the hPR agonist series derived from the same structure scaffold and may lead to tissue-selective antagonists.

The cross-reactivity of selected new nonsteroidal hPR antagonists with other steroid receptors was assessed using human androgen (hAR), glucocorticoid (hGR), estrogen (hER), and mineralocorticoid receptor (hMR) cotransfection assays (Table 2). No agonist activity was observed for any of the test compounds, but antagonist activities were detected, most notably on hAR and hGR. However, several new compounds still offered an improved cross-reactivity profile in comparison with Mifepristone. The separation of hPR antagonist activity over hAR and hGR was generally greater for the more active analogues.

In summary, the new nonsteroidal series exhibited potent hPR antagonist activity with improved cross-reactivity profile. The new analogue **11q** demonstrated anti-progestational activity in an ovulation inhibition mature rat assay via oral administration (data not shown). The SAR study, in addition to our early results in the area, provide new opportunities to develop both receptor- and tissue-selective hPR antagonists.

Table 1. hPR agonist and antagonist activity in cotransfected CV-1 cells and binding affinitites to hPR[a]



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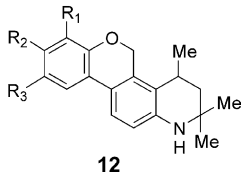

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No.	Compd			hPR cotransfection assay in CV-1 cells[b]		T47D assay in human breast cancer cell				hPR binding K_i (nM)
	R_1	R_2	R_3	Antagonist efficacy (%)	EC_{50} (nM)	Antagonist efficacy (%)	IC_{50} (nM)	Agonist efficacy (%)	EC_{50} (nM)	
	Mifepristone (RU486)			93±1	0.3±0.1	92±1	3.3±0.3	—[c]	—	1.1±0.3
	Onapristone (ZK299)			95±1	2.2±0.4	83±8	3.3±2.2	—	—	18±3
11a	H	H	H	85±3	111±55	67	138	66	>1000	84
11b	H	H	F	67±4	30.3±5.5	24±9	335	34	351	19.3±2.4
11c	H	H	Cl	56±3	35.7±8.6	—	—	41	171	12.9±1.2
11d	H	H	Br	72±2	45±14	47	485	23	552	15.0±2.6
11e	F	H	H	90±2	118±37	73	368	38	>1000	248
11f	Cl	H	H	85	576	84	782	—	—	273
11g	H	H	Me	72±11	76±23	64	100	34	>1000	45
11h	H	H	OMe	76	170	74	187	41	>1000	86
11i	H	H	Ph	92	2030	84	811	—	—	>1000
11j	H	H	NO_2	71±2	28.6±3.9	55±1	152±8	32	257	6.8±0.2
11k	H	CF_3	H	—	—	—	—	—	—	>1000
11l	H	OMe	H	85±3	193±53	83±1	514±33	24	>1000	357
11m	F	H	F	83±3	25.4±4.6	52±6	86±74	42±3	244±143	13.5±4.8
11n	Br	H	Br	86±9	1871±432	nt[d]	nt	nt	nt	>1000
11o	F	H	Cl	74±6	13.5±3.5	nt	nt	Nt	nt	5.6±0.7
11p	F	H	Br	76	57	52	461	—	—	12.4±1.3
11q	F	H	CN	74±7	16.7±2.9	52	149	25	86	4.5±0.3
11r	Me	H	Cl	95	178	86	374	nt	nt	205
11s	OMe	H	Br	45	43	nt	nt	nt	nt	476
11t	F	CHO	Br	59	576	nt	nt	nt	nt	290
12a	H	H	NO_2	91±3	52±12	82	104	—	—	144±56
12b	F	H	F	89±2	40±10	75	217	—	—	45±7
12c	NO_2	H	F	99	781	89	483	—	—	370
12d	Me	H	F	89	637	89	499	—	—	391

[a]Efficacy for agonist assays is defined in % versus progesterone = 100. Efficacy for antagonist assays is % inhibition of transcriptional activity observed at an EC_{50} concentration of progesterone.
[b]Values are in nM, mean±SEM, $N>2$. If no SEM is noted, value is from $N<3$.
[c]'—' = not active (<20% efficacy and/or >10 μM potency).
[d]'nt', not tested.

Table 2. Antagonist cross-reactivities of selected new compounds with hAR, hGR, hER, and hMR[a,b]

Compd	hAR Eff. (%)	hAR IC_{50} (nM)	hGR Eff. (%)	hGR IC_{50} (nM)	hER Eff. (%)	hER IC_{50} (nM)	hMR Eff. (%)	hMR IC_{50} (nM)
Mifepristone	79±2	8.3±2.6	95±1	0.8±0.1	59	2244	76	1155
Onapristone	93±4	269±57	100±0	27±4	—	—	49	470
11b	81	1248	—	—	—	—	30	3162
11c	75	788	—	—	—	—	—	—
11d	76	395	79	1929	—	—	—	—
11j	86	60	99	689	—	—	79	1889
11m	87	644	57	3026	—	—	—	—
11o	79	428	95	753	—	—	—	—
11p	64	90	88	2170	—	—	—	—
11q	80	60	89	194	—	—	—	—
12a	89	63	57	1872	—	—	58	2871
12b	89	147	—	—	—	—	—	—

[a]Efficacy is % inhibition of transcriptional activity observed at an EC_{50} concentration of DHT for AR, dexamethasone for GR, estradiol for ER and aldosterone for MR.
[b]See Table 1 for legend.

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7. To a solution of **8** (R = 7-F) (4 g) in THF (100 mL) at −78 °C was slowly added phenyllithium (1.2 equiv) in THF. The resulting dark red solution was stirred at −78 °C for 10 min and a solution of tBoc$_2$O (1.6 equiv) in THF was added via cannula. The reaction mixture was warmed up to 0 °C and quenched with water. Standard work up followed by chromatography afforded 5.1 g (96%) of product, which was reduced in THF at rt by $LiAlH_4$ powder and gave **9** (R = 3′-F) as a white solid (92%). ^{1}H NMR ($CDCl_3$) 7.26 (d, J = 8.5 Hz, 1H), 7.12 (m, 1H), 7.01 (d, J = 8.5 Hz, 1H), 6.97–6.90 (m, 2H), 5.87 (bs, 1H), 5.72 (s, 1H), 4.72 (d, J = 13 Hz, 1H), 4.52 (d, J = 13 Hz, 1H), 2.37 (d, J = 1.2 Hz, 3H), 1.55 (s, 3H), 1.51 (s, 9H) and 1.40 (s, 3H). To **9** (R = 3′-F) (1.9 g) in dichloromethane (100 mL) at rt was added Et_3N (3 mL) and NBS (1.1 equiv) and the reaction completed in 10 min to give **10** (R = 3′-F, R′ = 5′-Br) as a yellow oil (90%). ^{1}H NMR ($CDCl_3$) 7.30–7.23 (m, 2H), 7.10 (t, J = 1.8 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 5.72 (d, J = 1.1 Hz, 1H), 4.74 (d, J = 12 Hz, 1H), 4.46 (d, J = 12 Hz, 1H), 2.35 (d, J = 1.1 Hz, 3H), 1.53 (s, 3H), 1.51 (s, 9H) and 1.35 (s, 3H). The mixture of **10** (R = 3′-F, R′ = 5′-Br) (2 g), K_2CO_3 (1.2 equiv) and MeI (1.5 equiv) in DMF (50 mL) was stirred at rt for 2 h to give the methylated product after purification (78%), which was treated with NaH (1 equiv) in DMF at 80 °C for 10 min to provide the cyclized product in 72% yield. Removal of *N*-tBoc protection by standard procedure afforded **11p** (R = 7-F, R′ = 9-Br) as colorless oil, ^{1}H NMR (acetone-d_6) 7.58 (t, J = 1.7 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.17 (dd, J = 9.8 and 2.3 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 5.68 (br s, 1H), 5.51 (s, 1H), 5.40 (s, 2H), 2.12 (s, 3H) and 1.26 (s, 6H).

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