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Discovery of a novel series of nonsteroidal androgen receptor modulators: 5- or 6-oxachrysen-2-ones

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Abstract—A novel oxachrysenone series (**2**) of nonsteroidal selective androgen receptor modulators (SARM) was developed based on the 6-aryl-2-quinolinones (**1**). Synthesis and preliminary SAR results based on in vitro assays are discussed. In the cotransfection assay, lead compound **5d** showed AR agonist activity more potent than dihydrotestosterone (DHT), whereas compound **17b** was a potent antagonist similar to bicalutamide.

Testosterone replacement therapy may be beneficial to the quality of life of men in middle age and beyond, akin to the role of estrogen replacement for symptomatic peri- and postmenopausal women.[1] Although the beneficial effects of testosterone on muscle, bone, and physique have been reported, considerable controversy remains for testosterone supplementation in aging men, especially the issue of potential risks (cardiovascular disease, benign prostatic hyperplasia, prostate cancer, hepatotoxicity, etc.).[2] The discovery and development of Selective Androgen Receptor Modulators (SARMs) provide the opportunity to find nonsteroidal, orally active small molecules that are tissue-selective and elicit the desired anabolic activity with reduced side effects.[3,4]

Several different nonsteroidal SARM pharmacophores have been reported,[5] such as aryl-propionamides,[6] bicyclic hydantoins,[7] tetrahydro-quinolines,[8] and indole-containing tetracycles.[9] As part of our efforts[10] to develop novel SARMs with more desirable pharmacological profiles, here we report a novel series of tetracyclic androgen receptor modulators (structure **2**, Figure 1) that was designed based on an early 6-aryl-2-quinolinone SARM lead (**1**) by locking the rotation of the pendent aryl group.[11]

A general route for the synthesis of 6-oxa-chrysen-2-ones is shown in Scheme 1. Treatment of a known aminobromobenzocoumarin **3**[12] with but-3-enoyl chloride provides amide **4**. Intramolecular palladium catalyzed cyclization provides 6-oxa-chrysen-2-ones **5**. Reduction of compound **5** with diisobutylaluminum hydride provides hemiacetal **6**, which can be further reduced with triethylsilane and boron trifluoride etherate to provide analogs of structure **7**. Alternatively, hemiacetal **6** is converted to acetal **8**, by treatment with acid (such as *p*-TSA) in methanol. Racemate mixture of analogues **9** can be prepared by treating acetal **8** with a nucleophile in the presence of boron trifluoride etherate.

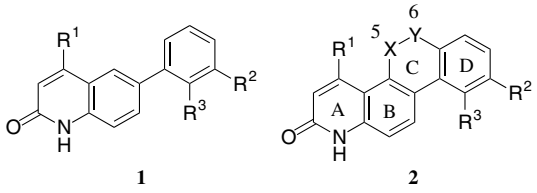

Figure 1.

Regioisomeric 5-oxa-chrysen-2-ones **15** and **17** were synthesized as described in Scheme 2. Selective methylation of known intermediate **10**[13] with methyl iodide and sodium bicarbonate affords compound **11**, which undergoes selective O-alkylation to afford compound **12**. Suzuki coupling of **12** and boronic acids[14] **13** affords intermediates of structure **14**. Cyclization of structure **14** in concd HBr and AcOH affords lactone **15**. Reduction of lactone **15** by diisobutylaluminum hydride affords acetal **16** that was converted to analogues **17** by

Keywords: Androgen receptor; SARM; AR agonist; AR antagonist; Oxachrysen-2-ones.
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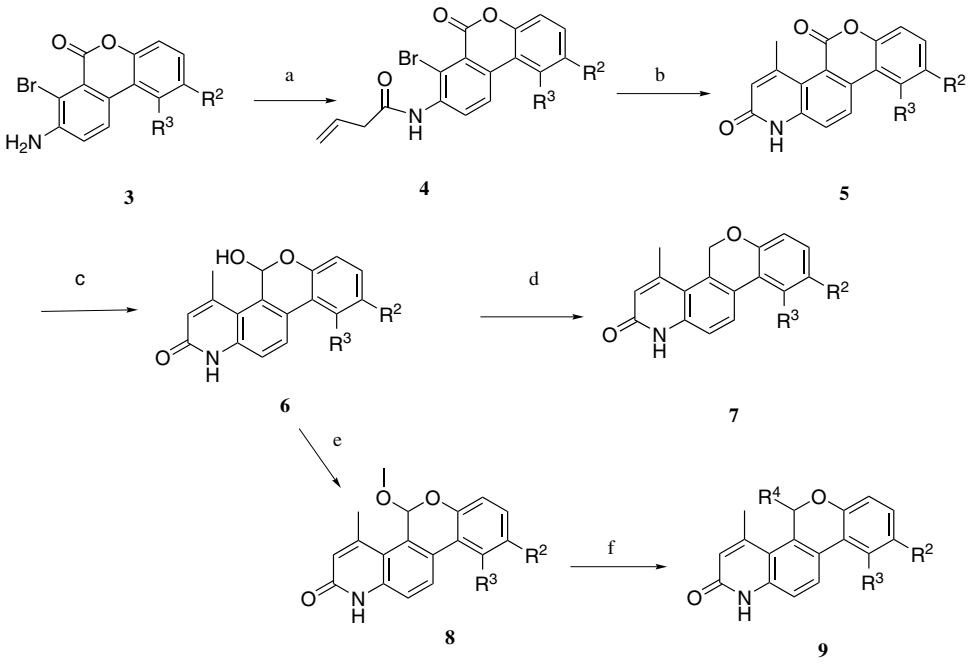
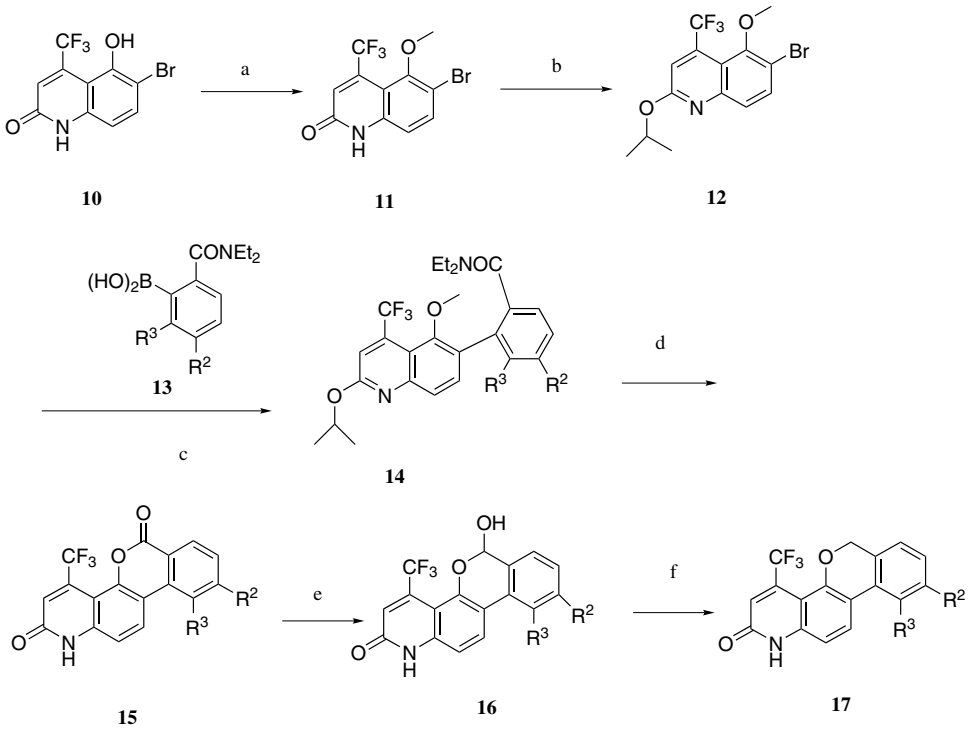


Scheme 1. Reagents and conditions: (a) $CH_2{=}CHCH_2COCl$, DMAP, DMF, reflux, 50–70%; (b) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, Et_3N, DMF, 90 °C, 30–60%; (c) DIBAL-H, CH_2Cl_2, 0 °C, 40–85%; (d) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 to 0 °C, 40–80%; (e) *p*-TSA, MeOH, rt, >95%; (f) trimethylsilanes, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 to 0 °C, 50–90%.

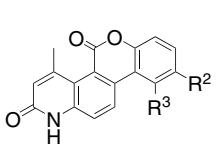


Scheme 2. Reagents and conditions: (a) CH_3I, $NaHCO_3$, DMF, rt, 85%; (b) 2-iodopropane, CsF, DMF, rt, 89%; (c) $Pd(PPh_3)_4$, 2 M Na_2CO_3, 1,4-dioxane, 110 °C, 40–60%; (d) 48% HBr/HOAc, reflux, 50–70%; (e) DIBAL-H, CH_2Cl_2, 0 °C, 70–85%; (f) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 to 0 °C, 30–65%.

treatment of acetal **16** with triethylsilane in the presence of boron trifluoride etherate.

We used the cotransfection assay[9,15] data to guide SAR studies and to characterize analogs, and binding assay[9] data as references. The IL-6 promoter assay in bone cells[16] was used as secondary assay to indicate potential anabolic bone activity for agonists and potential bone-sparing antagonists. The human androgen receptor (hAR) competitive binding affinities of the analogs, their

Table 1. hAR agonist and antagonist activity in the cotransfection assay in CV-1 cells, binding affinities to hAR, and repression activity in IL-6 assay[a]



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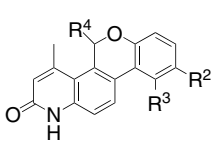

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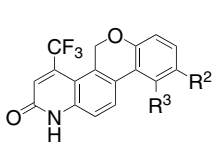

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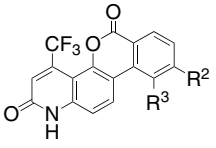

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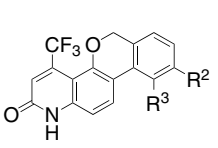

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Compound	R^2	R^3	R^4	hAR[b] EC_{50} in nM (Eff.)	hAR[c] IC_{50} in nM (Eff.)	hAR binding K_i (nM)	Saos-2 IL-6 repression[d] IC_{50} in nM (Eff.)
5a	F	H		240 ± 99 (22 ± 5%)	27 ± 2 (57 ± 11%)	1000	101 ± 0 (50 ± 1%)
5b	OCH_3	H		—	48 ± 14 (62 ± 17%)	610	0.8 ± 0.0 (55 ± 10%)
5c	H	OCH_3		11 ± 8 (72 ± 19%)	—	28 ± 1.0	21 ± 28 (97 ± 18%)
5d	H	$O_2CC(CH_3)_3$		1.1 ± 0.1 (132 ± 8%)	—	8.7	1.9 ± 0.2 (104 ± 4%)
5e	OH	OCH_3		21 ± 6 (117 ± 11%)	—	4.0 ± 1.5	0.2 ± 0.0 (110 ± 3%)
5f	$O_2CC(CH_3)_3$	OCH_3		43 ± 14 (97 ± 13%)	—	10 ± 4	0.2 ± 0.1 (112 ± 4%)
5g	OCH_2CH_3	OCH_3		18 ± 0.7 (33 ± 13%)	—	62	10 ± 9.4 (84 ± 2%)
5h	$OCH(CH_3)_2$	OCH_3		23 ± 8 (21 ± 6%)	20 ± 3 (29 ± 9%)	21	2.8 ± 1.2 (76 ± 1%)
9a	H	OCH_3	H	50 ± 14 (70 ± 13%)	—	59	12 ± 9 (70 ± 5%)
9b	H	CH_2OH	H	12 ± 2.0 (156 ± 22%)	—	26	0.3 (99%)
9c	OH	OCH_3	H	306 ± 102 (118 ± 0.2%)	19 ± 0 (47 ± 24%)	5	1.2 ± 0.5 (96 ± 18%)
9d	H	OCH_3	OH	208 ± 78 (93 ± 8%)	—	1300	50 ± 0 (72 ± 17%)
9e	H	OCH_3	OCH_3	184 ± 23 (27 ± 1%)	19 ± 0 (49 ± 3%)	2346	112 ± 0 (54 ± 5%)
9f	H	OCH_3	CH_3	—	62 ± 30 (63 ± 10)	250	No data
9g	H	OCH_3	Allyl	—	144 ± 77 (63 ± 6%)	1593	No data
18a	H	OCH_3		20 ± 3 (67 ± 10%)	—	11 ± 5	14 ± 3 (97 ± 3%)
18b	H	OH		16 ± 12 (138 ± 6%)	—	1.3	1.1 ± 0.2 (97 ± 6%)
15a	H	OCH_3		90 ± 0 (33 ± 9%)	—	50	89 ± 17 (76 ± 3%)
15b	H	OH		97 ± 52 (65 ± 55%)	—	3	22 ± 3 (93 ± 6%)
17a	H	H		60 ± 2 (34 ± 8%)	—	8 ± 4	40 (91%)
17b	H	OCH_3		—	78 ± 57 (68 ± 9%)	27	477 ± 0 (42 ± 12%)
DHT				5.1 ± 0.1 (100%)	—	0.20 ± 0.02	0.05 (100%)
Bicalutamide				—	162 ± 99 (85 ± 9%)	151 ± 36	232 ± 84 (28 ± 8%)

[a] Values with standard errors represent the mean value of at least 2 separate experiments with triplicate determinations. A dash indicates an efficacy of <20% and/or a potency of >10,000 nM.
[b] Agonist efficacies were determined relative to DHT (100%).
[c] Antagonist efficacies (%) were determined as a function of maximal inhibition of DHT at the EC_{50} concentration.
[d] Due to the repression format of the assay, IC_{50} may not be accurate for activity comparison if efficacy is below 60%.

hAR functional activity in CV-1 cells, and IL-6 repression assay results are summarized in Table 1. DHT and bicalutamide were used as references.

SAR studies of the series were initiated from the lactone compounds of structure **5**. Early compounds **5a** and **b** showed interesting partial antagonistic activities regardless of their distinct property of substitution groups at the 9-position and weak AR binding as seen in many antagonists. These results are consistent with the parent analogs of structure **1**. When the methoxy group at 9-position (**5b**) was moved to 10-position (**5c**), the functional activity in the hAR cotransfection assay totally shifted from a partial antagonist to agonist. In the IL-6 assay, the substitution position change increased efficacy of compound **5c** to 97% of DHT from 55% for compound **5b**. Compound **5d** with an ester functionality at 10-position represented an example of a potent hAR full agonist with good binding affinity. The bis-substitution at 9- and 10-positions was briefly studied and compound **5e** with 9-hydroxyl-10-methoxy gave the best full agonist activity (1.1 nM EC_{50} and 132% efficacy). Compound **5f** with a bulky ester group at 9-position also showed excellent agonist activity similar to that of **5e**, which may be the result of partial hydrolysis of the ester in the assays since compounds **5g** and **h**, which have similar bulky 9-substituents, had only partial activity.

To assess necessity of the lactone moiety, the carbonyl group of two compounds at 5-position was fully reduced to give cyclic ether compounds **9a** and **c**. Removal of the carbonyl group reduced the hAR EC_{50} of **5c** (11 nM) by 5-fold (**9a**, EC_{50} = 50 nM) and of **5e** (21 nM) by 30-fold (**9c**, EC_{50} = 306 nM), although the binding affinity of **9c** and **5e** is similar. Interestingly, replacement of the 10-methoxy group of **9a** with 10-methylalcohol (**9b**) generated a potent full agonist. The lactone analog of **9b** is not prepared due to synthetic challenges so that generality of the substitution enhancement is difficult to say. Another intriguing profile is the mixed agonist/antagonist compound **9c**, which had both moderate agonist activity (EC_{50} = 306 nM with 118% efficacy) and potent partial antagonist activity (IC_{50} = 19 nM with 49% efficacy) in the cotransfection assay. Additionally, it had excellent hAR binding affinity and DHT-like activity in the bone cell assay.

Partially reducing the lactone to hemiacetal significantly decreases the agonist potency (comparing **9d** and **5c**). Introduction of a small group at 5-position generated several partial antagonists, **9e**–**g**. These analogs were tested as racemate mixtures. The 4-trifluoromethyl analogs[17] **18a** and **b** were prepared to enhance activity or pharmacokinetic property based on results of other 2-quinolinone series[10] in our laboratory. Analog **18a** showed improved agonist activity over its 4-methyl analog, **9a**. Compound **18b** is a much better agonist than compound **18a** in all three assays tested (Table 1), which indicates that 10-hydroxyl is an optimal substituent relative to 10-methoxy in the series.

The reversed lactone analog **15a** showed much less hAR agonist activity in comparison to parent compound **5c** despite potential enhancement by the 4-trifluoromethyl group. The 10-hydroxyl analog **15b** also demonstrated significant improvement to the 10-methoxy compound **15a** in all three assays tested. Finally, the 5-oxa analog **17a** had interesting partial agonist activity, although it has no substitution at the 10-position. Compound **17b** had decent antagonist activity in comparison with bicalutamide in the assays, which is quite distinct from the 6-oxa analog **18a**.

Cross-reactivity of the new compounds with other steroid hormone receptors was assessed using human PR (hPR) and glucocorticoid receptor (hGR) cotransfection assays. The results (not shown) indicate that the compounds are highly selective towards hAR. Only compound **5d** showed appreciable hPR antagonist activity (IC_{50} = 269 nM and 67% efficacy).

In summary, the oxachrysenone hAR modulator pharmacophore was successfully established, which provides additional SAR opportunities to develop more selective SARMs to meet the unmet patient needs. Several full agonist compounds (**5d**, **5e**, **9b**, and **18b**) were generated with potential anabolic bone activity and a couple of partial antagonists (**9c** and **17b**) were also generated with potential advantage over bicalutamide. The pharmacokinetic property and the in vivo tissue selectivity profiles of the compounds remain to be characterized.

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