Rational Design and Synthesis of 4-((1*R*,2*R*)-2-Hydroxycyclohexyl)-2(trifluoromethyl)benzonitrile (PF-998425), a Novel, Nonsteroidal Androgen Receptor Antagonist Devoid of Phototoxicity for Dermatological Indications

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4-((1*R*,2*R*)-2-Hydroxycyclohexyl)-2(trifluoromethyl)benzonitrile [PF-0998425, (−)-**6a**] is a novel, nonsteroidal androgen receptor antagonist for sebum control and treatment of androgenetic alopecia. It is potent, selective, and active in vivo. The compound is rapidly metabolized systemically, thereby reducing the risk of unwanted systemic side effects due to its primary pharmacology. (−)-**6a** was tested negative in the 3T3 NRU assay, validating our rationale that reduction of conjugation might reduce potential phototoxicity.

Introduction

The androgen receptor (AR[a]) is a ligand-activated nuclear hormone receptor. Nonsteroidal AR antagonists, in turn, have been extensively investigated during the past 2 decades.[1,2] The fruits of research and development in the field are exemplified by several marketed drugs as androgen receptor antagonists. Flutamide (**1**, Figure 1) was launched in 1983 by Schering-Plough for the treatment of prostate cancer.[3] Sanofi-Aventis' nilutamide (**2**) and AstraZeneca' bicalutamide (**3**) gained regulatory approval as a prostate cancer therapy in 1987 and 1993, respectively.[4] In addition, dozens of nonsteroidal AR antagonists are in various stages of clinical trials for an array of indications.

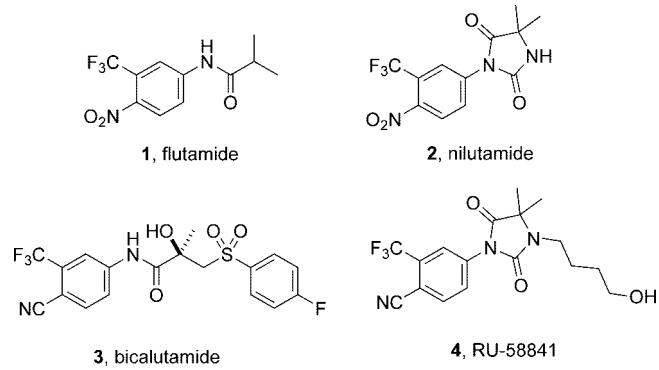

Figure 1. Known nonsteroidal androgen receptor antagonists.

AR is known to be responsible for the activation of genes involved in the pathogenesis of acne and alopecia.[5] Androgens, such as testosterone and dihydrotestosterone (DHT), play a key role in the function of sebaceous glands and hair follicles and are major contributors to the pathogenesis of androgenetic alopecia in genetically susceptible male and female subjects. For instance, prepubertal gonadectomy of male subjects prevents recession of scalp hair. A recent clinical study demonstrated that flutamide (**1**) significantly reduced hair loss in female androgenetic alopecia patients.[6] Compound **4**, a potent AR inhibitor, also showed promise for the treatment of androgenetic alopecia.[7] On the other hand, under the influence of androgens, the sebaceous glands become larger and produce more sebum. Cyproterone acetate[8] and spironolactone,[9] used in women as oral contraceptives, significantly reduced the sebum excretion

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[a] Abbreviations: API, active pharmaceutical ingredients; AR, androgen receptor; b.i.d., twice daily; CYP, cytochrome P450; DDI, drug−drug interaction; DHT, testosterone and dihydrotestosterone; ee, enantiomeric excess; E_H, extraction ratio; HTS, high-throughput screen; NRU, neutral red uptake; q.d., once daily; SAR, structure−activity relationship; TFA, trifluoroacetic acid.

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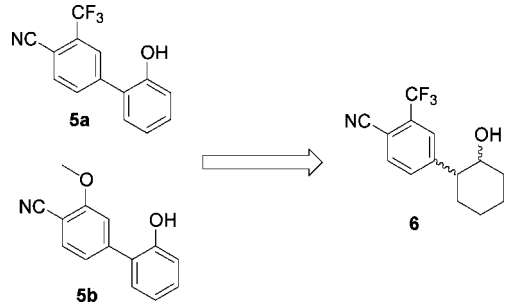


Figure 2. Rational design in reducing the conjugation of the molecule.

rate and decreased the severity of acne. **4** was proven to be efficacious in reducing sebum production in the animal models.[10]

Regrettably the approach to stop or reverse male pattern baldness using systemic antiandrogens (androgen blockade or androgen receptor antagonism) has not been pursued because of the feminizing effect and interference with male sexual functions. In contrast, a topical product is preferred over an oral agent because of a lower risk of side effects stemming from systemic exposure. To that end, our laboratories set out to discover androgen receptor antagonists as treatments for skin related disorders including sebum control and hair growth. We preferred the topical drugs that are active topically and yet devoid of systemic pharmacological activities to avoid deleterious side effects.

Our high-throughput screen (HTS) was carried out with a [^{3}H]DHT competitive ligand binding assay using the human full-length AR as the primary assay.[11] Compounds active (IC_{50} < 100 nM) in the binding assay were further screened using the MDA-MB-453-MMTV-luci cell line as the secondary assay (IC_{50} < 100 nM).[12] From our compound library, we derived a series of diarylphenols as exemplified by **5a** and **5 b**. In vitro, their IC_{50} values were 40 ± 19 and 37 ± 13 nM, respectively. And their IC_{50} values in an AR cellular functional assay were 0.022 and 8.1 nM, respectively. Both compounds also demonstrated greater than 100-fold selectivity against the estrogen and progesterone receptors in vitro. In the in vivo sebum model using male Golden Syrian hamster ear,[13] **5a** and **5b** were active and reduced the production of wax ester, a mechanism biomarker for sebum reduction, by 86% and 87%, respectively, at a 3% dose in a vehicle of 70:30 ethanol/propylene glycol.[14] Unfortunately they were tested positive in the 3T3 neutral red uptake (NRU) phototoxicity test,[15,16] indicating a high risk for causing photoirritation. Consequently, they were deemed unsuitable as topical drugs. Although the correlation between phototoxicity and high conjugation in topical drug molecules has not been systematically investigated, the fundamentals of photochemistry prompted us to rationalize that reduction of the conjugation of a molecule might lower the risk of phototoxicity. Thus, we designed an AR antagonist resembling **6**, where the phenol ring in **5a** was replaced with a cyclohexanol (Figure 2). Molecular modeling[17,18] of **6** in the crystal structure of the ligand-binding domain of the androgen receptor indicated favorable interactions as shown in Figure 3. The structural modifications led to the preparation and evaluation of a novel, potent, selective AR antagonist (−)-**6a** that was also active in vivo and devoid of the phototoxicity consistently seen for biarylphenols such as **5a** and **5b**.

Chemistry and in Vitro Activity

Our initial synthesis of **6** (Scheme 1) commenced with condensation of 4-fluoro-2-(trifluoromethyl)benzonitrile (**7**) with cyclohexanone with the aid of NaH to give the desired C-arylated product **8** as the minor product (26% yield), with the major product as the O-arylated vinyl ether adduct [4-(cyclohex-1-enyloxy)-2-trifluoromethylbenzonitrile, 52% yield; see Supporting Information]. The resulting ketone **8** was reduced to alcohol **6** using $NaBH_4$ to give the cis-isomers **6a** as the minor product (31%) and the trans-isomer **6b** as the major product (64%). While trans-isomer **6b** was inactive in the AR binding assay, the cis-alcohol **6a** was active in the AR binding and the cellular assays. Further separation of the two enantiomers of the cis-alcohol **6a** using chiral HPLC provided (−)-**6a** (PF-998425) and (+)-**6a**, respectively. While (+)-**6a** was essentially inactive in the AR binding assay, (−)-**6a** was active in AR binding and cellular assays with IC_{50} values of 37 and 43 nM, respectively. A chiral carbamate **9** was prepared by treating (−)-**6a** with (*R*)-1-(1-isocyanatoethyl)naphthalene, and the single crystal X-ray crystallography of **9** (Figure 4) determined that the absolute configuration of (−)-**6a** was (1*R*,2*R*).

Preliminary in vitro evaluation of the activity, metabolic stability, and safety characteristics of (−)-**6a** proved favorable; consequently, a more efficient synthesis was mandated to prepare enough active pharmaceutical ingredients (API) to support subsequent in vivo studies. To that end, we carried out a halogen/metal exchange of 4-iodo-2-(trifluoromethyl)benzonitrile using *n*-BuLi followed by treatment with cyclohexanone to afford tertiary alcohol **10** (Scheme 2). Exposure of **10** to neat trifluoroacetic acid (TFA) gave rise to olefin **11**, which was then subjected to an asymmetric epoxidation using Jacobsen's (*S,S*)-Mn(III)-salen complex as the catalyst to give epoxide **12** in 94% ee.[19] Epoxide **12** was subsequently hydrogenated to deliver (−)-**6a** in 57% yield for the two steps with 94% ee. The aforementioned synthesis allowed preparation of a large quantity of API to complete a panel of in vivo investigations (vide infra).

Structure−Activity Relationship (SAR) and Selectivity

We chose **4** as our reference compound because it was efficacious in vivo for hair growth and sebum reduction.[7] Again, the AR binding assay was carried out with the [^{3}H]DHT competitive ligand binding assay using the human full-length AR and the AR cellular assay was carried out with the MDA-MB-453-MMTV-luci cell line. Because of the high homology at the ligand-binding region between androgen receptor and progesterone receptor (80−90%), the progesterone receptor binding assay was conducted according to the manufacture's manual using the commercial kit.[20] As shown in Table 1, biaryls **5a** and **5b** were active in the AR binding and cellular assays and were especially potent in the AR cellular assay. Our initial hit aminopyridylnitrile **13** was also tested active in the AR binding and cellular assays.[10] Unfortunately, **5a**, **5b**, and **13** were not further pursued for their dermatological indications because they were all tested positive in the 3T3 neutral red uptake (NRU) phototoxicity test, indicating a high risk for causing photoirritation. As far as our rationally designed arylcyclohexanols were concerned, the trans-isomer **6b** was inactive in our AR binding assay although the racemic cis-isomer **6a** had IC_{50} values of 26 and 90 nM in the AR binding and cellular assays, respectively. After separation of the racemate **6a**, (+)-**6a** (1*S*,2*S*) was tested inactive in our AR binding assay although the enantiomer (−)-**6a** (1*R*,2*R*) had IC_{50} values of 37 and 43 nM for the AR binding and cellular assays, respectively.

With potent AR antagonists in hand, we proceeded to investigate their selectivity against other nuclear hormone receptors. Compound (−)-**6a** had low binding affinity to the progesterone receptor (IC_{50} > 10 μM), demonstrating a greater

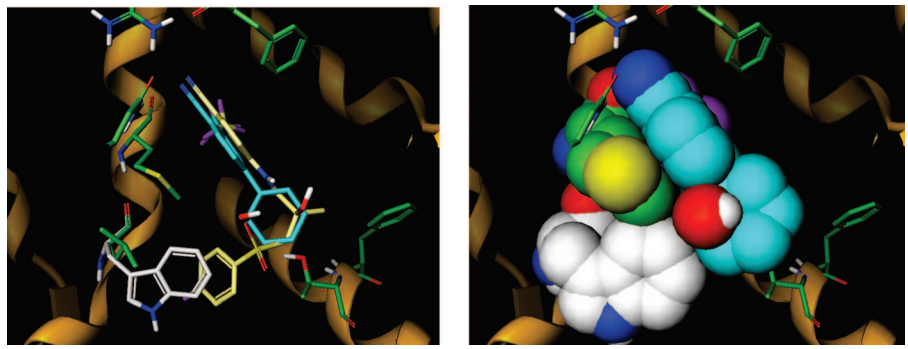
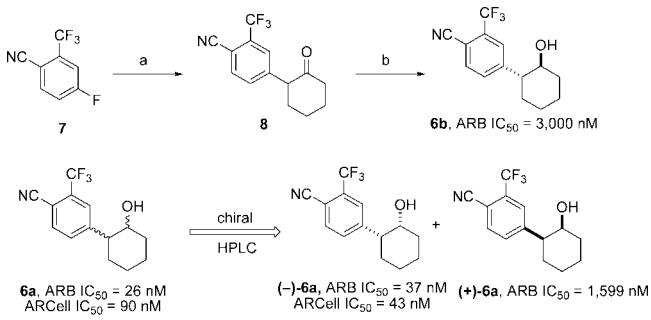


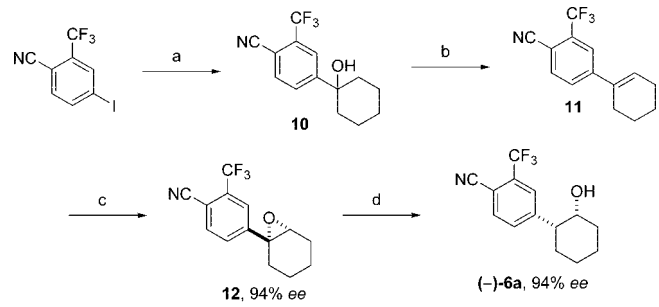
Figure 3. (Left) Model of **6** (cyan) in the crystal structure of AR W741L ligand-binding domain (orange backbone). Bicalutamide (**3**) is shown in yellow for reference. Key side chain residues are displayed in green. Trp741 from WT AR crystal structure is shown in white for reference. (−)-**6a** forms favorable interactions with Arg752, Gln711, and Leu. (Right) Trp741 and Met 745 are shown in CPK rendering to indicate contacts with (−)-**6a** which destabilizes the WT AR LBD conformation and stabilizes W741L mutant AR LBD conformation.

Scheme 1. Orginal Synthesis[a]



[a] Reagents and conditions: (a) cyclohexanone, NaH, DME, reflux, 1 h, 31%; (b) $NaBH_4$, MeOH, 24 h, 95% (64% for **6b**, 31% for **6a**).

Scheme 2. Improved Synthesis[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, then cyclohexanone, THF, −78 °C → room temp, overnight; (b) TFA, 60 °C, 4.5 h, 58%, two steps; (c) (*S*,*S*)-Jacobsen's Mn(III)-salen chiral catalyst {[[(*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]manganese(III)] chloride}, NaOCl, 4-phenylpyridine *N*-oxide, CH_2Cl_2, 0 °C, overnight; (d) H_2 (50 psi), Pd/C, MeOH, Et_3N, 7 h, 57%, two steps.

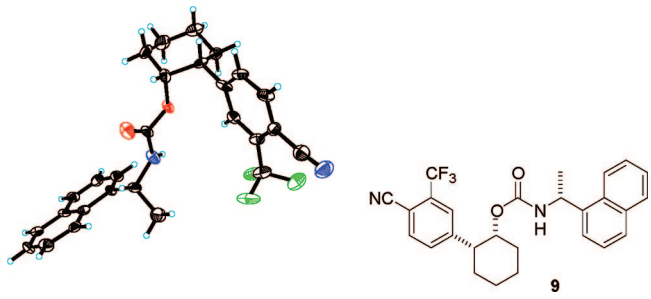


Figure 4. ORTEP plot of carbamate derivative **9**.

than 100-fold selectivity. Subsequently, (−)-**6a** had low binding affinities when screened against a panel of common receptors and enzymes.

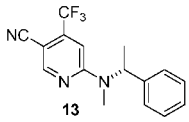
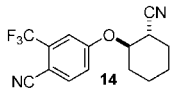
Pharmacokinetics, in Vivo Activity, and Safety

Ideally, topical drugs exert their desired effects locally but are rapidly inactivated via metabolism once they reach the systemic circulation, thereby reducing unwanted systemic effects. The pharmacokinetic characteristics of (−)-**6a** were favorable for a topical agent. Compound (−)-**6a** was rapidly metabolized in rat liver microsomes ($t_{1/2}$ = 4 min, CL_{int} = 350 (μL/min)/mg protein). The hepatic extraction ratio (E_H) predicted from these in vitro data approached liver blood flow in rat, with a predicted E_H value of 0.90.[21] In vivo clearance data in dogs were consistent with the high clearance predicted in vitro in rat (see Figure 5). Following intravenous administration of (−)-**6a**, mean systemic plasma clearance was 40 (mL/min)/kg. This value was similar to hepatic blood flow in this species, indicating that (−)-**6a** is a high clearance compound in dogs. The mean apparent of volume of distribution at steady state was 6.5 L/kg, and the mean terminal phase half-life was 2.6 h.[22]

We proceeded to investigate the drug's safety profile. As we predicted, (−)-**6a** tested negative in the 3T3 neutral red uptake (NRU) phototoxicity test, a desired attribute for a dermatology drug. The risk for QT elongation was low because there was no detectable activity in the dofetilide binding assay. Since there is a direct correlation between wax ester reduction and a reduction in total sebum production,[23,24] the drug was found to be active in vivo in male Golden Syrian hamster ear model for sebum reduction (Figure 6).[13] At 3% concentration in 70:30 ethanol/propylene glycol, (−)-**6a** reduced sebum by 85%. Its estimated ED_{50} was 0.4% in the male Golden Syrian hamster ear model for sebum reduction when tested in a vehicle of ethanol/propylene glycol (70/30, v/v). In comparison, at 3% concentration, reference **4** reduced sebum by 92% and aminopyridine 83%, respectively. On the other hand, it seems that the relative in vivo efficacy for sebum reduction may correspond to the potency in cellular assay. For instance, one of our lead compounds, **14** with an IC_{50} of 12 nM in the AR cellular assay and an ED_{50} value of 0.1%,[25] was more efficacious than (−)-**6a**, which had IC_{50} of 43 nM in the AR cellular assay and an ED_{50} value of 0.4%. Despite the less efficacious than **14**, (−)-**6a** provides an alternative candidate with a unique overall profile, especially considering that severe reduction of sebum could cause dry skin. Finally, (−)-**6a** was evaluated and found to be active in the C3H/HeN mouse hair growth model (see Supporting Information).[26]

In summary, we designed and synthesized a novel, nonsteroidal AR antagonist (−)-**6a** for the sebum control and treatment

Table 1. SAR and Selectivity of the Benzonitrile Series

Entry	Compound	AR Binding IC_{50} (nM)	AR Cellular IC_{50} (nM)	PR Binding IC_{50} (nM)
1	**4**	16 ± 11	40 ± 5	1000 (n = 1)
2	**5a**	39.9 ± 19	0.02 ± 0.1	4450 (n = 1)
3	**5b**	37.0 ± 13	20.1 ± 19	3250 ± 3000
4	 **13**	20 ± 5	45 ± 20	1660 ± 990
5	**6b**	> 3,000	-	-
6	**6a** (racemate)	26 ± 7	90 ± 15	> 10,000
7	**(+)-6a**(1*S*,2*S*)	1,599 ± 900	-	-
8	(−)-**6a**(1*R*,2*R*)	37 ± 10	43 ± 12	> 10,000
9	 **14**	60 ± 19	12 ± 4	> 10,000

of androgenetic alopecia. The drug is potent, selective, and active in vivo in a male Golden Syrian hamster ear model for sebum reduction and a C3H/HeN mouse model for hair growth. The antagonist is rapidly metabolized systemically, thereby reducing the risk of unwanted systemic side effects due to its primary pharmacology. More importantly, (−)-**6a** was tested negative in the 3T3 NRU assay, validating our speculation with regard to the reduction of conjugation that might alleviate potential phototoxicity. In addition, the risk of drug−drug interaction (DDI) is low for (−)-**6a**-mediated CYP inhibition.

Supporting Information Available: Experimental conditions for all intermediates and final products; ^{1}H, ^{19}F, ^{13}C NMR spectra and HPLC chromatograms of all intermediates and products; lipid analysis for hamster ear samples; C3H/HeN mouse hair growth model and histological analysis of hair follicular changes in C3H mice; single X-ray crystallographic coordinates of **9**; experimental conditions for androgen receptor binding assays; androgen receptor cellular assays; C3H/HeN mouse hair growth model; male Syrian hamster ear model for sebum reduction; metabolic stability in rat liver microsomes; pharmacokinetics in dogs; molecular modeling; lipid extraction and HPLC-ELSD methodology; mobile phase gradient utilized for separation of sebum components in HPLC-ELSD method; C3H/HeN mouse hair growth model; histological analysis of hair follicular changes in C3H mice. This material is available free of charge via the Internet at http://pubs.acs.org.

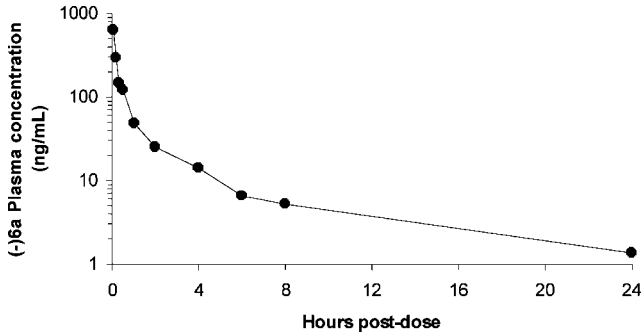


Figure 5. Plasma concentration−time profile of (−)-**6a** in dogs following intravenous administration of a 0.8 mg/kg dose.

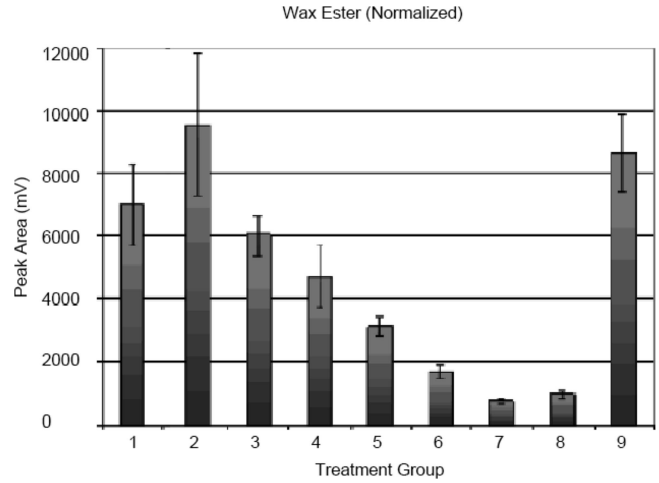


Figure 6. Dose response relationship of (−)-**6a** and sebum wax ester content in the male Golden Syrian hamster ear model: 1, vehicle control (70:30 ethanol/propylene glycol); 2, 0.03% (−)-**6a** (b.i.d.); 3, 0.1% (−)-**6a** (b.i.d.); 4, 0.3% (−)-**6a** (b.i.d.); 5, 1% (−)-**6a** (b.i.d.); 6, 3% (−)-**6a** (b.i.d.); 7, 1% **4** (b.i.d.); 8, 1% **4** (q.d.); 9, untreated.

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