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4-(Alkylthio)- and 4-(arylthio)-benzonitrile derivatives as androgen receptor antagonists for the topical suppression of sebum production

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ABSTRACT

The first examples of thioether-substituted benzonitriles as potential soft-drug androgen receptor antagonists are reported. A number of 4-(alkylthio)- and of 4-(arylthio)-benzonitrile analogs were evaluated in human androgen receptor binding and cellular functional assays. Analogs with potent in vitro binding and cellular activities were evaluated for topical in vivo efficacy in the Golden Syrian hamster ear model. Analogs from both the 4-(alkylthio)- and of 4-(arylthio)-benzonitrile series showed moderate reduction of wax esters in vivo.

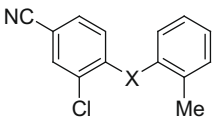
The androgen receptor (AR) is responsible for the activation of genes involved in the pathogenesis of acne and alopecia.[1] The onset of acne vulgaris infections in the pilosebaceous unit is associated with excess sebum production. The production of sebum is regulated by the androgens testosterone and 5α-dihydrotestosterone (5α-DHT). Androgen receptor antagonists, such as cyproterone acetate[2,3] and RU-58841[4] have been shown to suppress sebum production when applied topically.

Mining of data from our AR agonist program identified a number of compounds that bound to the androgen receptor but did not possess agonist activity. A reevaluation showed that some of these were full antagonists (for example diphenyl ethers such as **1**), and we have used them as starting points for our program to identify AR antagonists for the topical suppression of sebum production.[5]

Part of our design strategy to access compounds devoid of systemic antiandrogen effects and suitable for topical delivery centered on introducing metabolic lability into our target compounds. In the current work we investigated replacement of the ether linkage with a thioether as a potential soft-drug approach.[6]

We found that the oxygen linker of diphenyl ether **1** could be replaced with sulfur (**2**) with retention of AR binding (ARB)[7] and

Table 1
Human androgen binding and cellular activities for oxygen, sulfur, and sulfoxide-linked analogs[a]



Compound	X	ARB (nM)	ARCELL (nM)
1	O	64	46
2	S	43	78
3	S=O	>10000	–

[a] Values (IC_{50}) are given as an average of ⩾2 experiments; –, not tested; **ARB**, human androgen receptor binding assay; **ARCELL**, human androgen receptor cellular functional assay.

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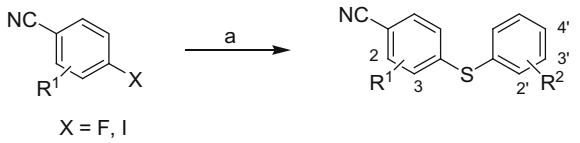


Scheme 1. Reagents and conditions: (a) ArSH, Cs_2CO_3 (10–90%).

full antagonist activity in a cellular assay (ARCELL)[8] (Table 1). The readily prepared sulfoxide of this (**3**) was inactive in the AR binding assay suggesting that thioether linked compounds could have potential as soft-drugs.[9]

The diphenyl thioethers were synthesized by displacement of fluorine or iodine from the appropriate 4-halobenzonitrile with arylthiols under basic conditions (Scheme 1).[10]

We chose not to synthesize further chlorobenzonitriles since some of them exhibited photoinstability, which is not desirable in a topically applied agent. The 2-trifluoro-methyl-benzonitrile was selected as an alternative, based on known AR binders.[11] Starting materials for 2- or 3-methoxy derivatives were also readily available and gave targets with an alternative metabolic soft-spot, although the chemistry proved not to be as general (the displacement reactions were lower yielding and had more synthetic failures for the electron-rich methoxy templates than the trifluoromethyl template).

We initially explored a series of tolyl ethers based on hit **1** because they presented an additional metabolizable group. Perhaps surprisingly, diphenyl ethers with a 2-methoxy-benzonitrile (**4a–c**) were found to have better AR binding activity than either their 3-methoxy- (**5a–c**) or 2-trifluoromethyl-(**6a–c**) analogs. For a particular benzonitrile, potency of R^2 was found to follow *ortho* > *meta* >> *para* (Table 2).

A variety of *ortho*-aryl substitution was then explored (Table 3). In the 2-trifluorobenzonitrile template the unsubstituted aryl analog **7a** had similar potency in the AR binding assay as the *ortho*-tolyl analog **6a**. Replacement of the *ortho*-methyl with fluorine (**8b**) or methoxy (**7c**) was tolerated in terms of AR binding and both these compounds had functional activity less than 100 nM. *Ortho*-disubstituted analogs, such as **7d** and **7e**, did not offer improvement in binding activity, in the case of **7d**, or were less active, in the case of **7e**. By comparison in the 2-methoxybenzonitrile template the *ortho*-methyl (**4a**) *ortho*-methoxy (**8a**), dimethyl (**8b**), and mesityl (**8c**) analogs all possessed good AR binding and functional activity.

Although our previous AR agonist program had found that ethers of benzonitriles with small alkyl groups had no AR activity, we were interested in investigating the alkyl thioether case. Since many of the desired alkyl thiols were not commercially available, we prepared 4-thiobenzonitrile templates by Newman–Kwart rearrangement[12] and alkylated them with commercially available alkyl halides (Scheme 2).[13]

Intriguingly, even small alkyl thioethers such as isopropyl and propyl were active in the binding assay and shown to be full antagonists. By contrast, the direct ether analogs of **10a** and **10c** had ARB IC_{50}'s >1000 nM.

In contrast to the diphenyl thioethers, alkyl thioethers from the 2-trifluoromethyl-benzonitrile series (**10a–f**) had similar AR binding activity to those from the 2-methoxy-benzonitrile series (**9a–10f**) (Table 4).

Selected compounds with good in vitro profiles were tested in vivo in Golden Syrian hamsters for their ability to reduce wax and cholesterol esters. Wax and cholesterol esters constitute 28% of total human sebum[14] and it has been shown that there is a direct correlation between reduction in wax esters and reduction in total sebum production in a clinical trial with oral cyproterone acetate.[15] The hamster ear model is a widely used animal model to test drug effects on sebaceous glands (Table 5).[16]

All compounds tested in the hamster ear model showed some activity but all were only moderately active compared to the positive control, RU-58841, which gave a 95% reduction in wax esters.

Table 2
SAR of tolyl analogs[a]

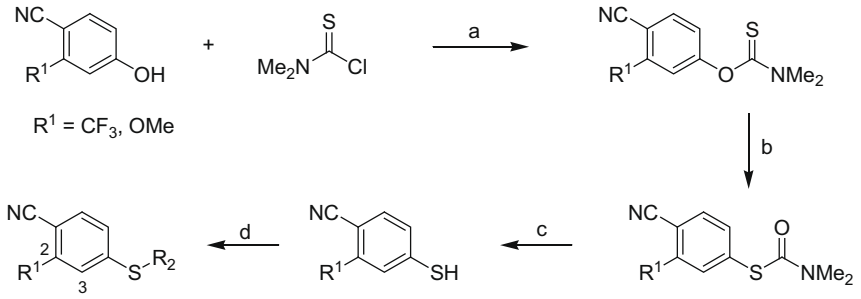
Compound	R^1	R^2	ARB (nM)	ARCELL (nM)
4a	2-OMe	2′-Me	24	81
4b	2-OMe	3′-Me	57	197
4c	2-OMe	4′-Me	200	209
5a	3-OMe	2′-Me	115	48
5b	3-OMe	3′-Me	353	–
5c	3-OMe	4′-Me	5210	–
6a	2-CF_3	2′-Me	535	–
6b	2-CF_3	3′-Me	1680	–
6c	2-CF_3	4′-Me	5330	–

[a] Values (IC_{50}) are given as an average of ⩾2 experiments; –, not tested; ARB, human androgen receptor binding assay; ARCELL, human androgen receptor cellular functional assay.

Table 3
SAR of other diphenyl thioethers[a]

Compound	R^1	R^2	ARB (nM)	ARCELL (nM)
7a	2-CF_3	H	225	123
7b	2-CF_3	2′-F	184	54
7c	2-CF_3	2′-OMe	56	37
7d	2-CF_3	2′,6′-diMe	411	–
7e	2-CF_3	2′,4′,6′-triMe	1340	–
8a	2-OMe	2′-OMe	20	35
8b	2-OMe	2′,6′-diMe	43	30
8c	2-OMe	2′,4′,6′-triMe	39	69

[a] Values (IC_{50}) are given as an average of ⩾2 experiments; –, not tested; ARB, human androgen receptor binding assay; ARCELL, human androgen receptor cellular functional assay.



Scheme 2. Reagents and conditions:, (a) DABCO, DMF, 65 °C (89–93%); (b) 200–240 °C, neat (92–100%); (c) NaOH, MeOH, thf (63–78%); (d) R_2Br, Cs_2CO_3, DMF, r.t (10–90%).