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Small Molecule Antagonists of the Nuclear Androgen Receptor for the Treatment of Castration-Resistant Prostate Cancer

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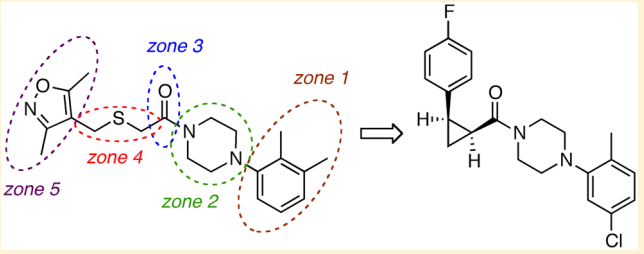
Supporting Information

ABSTRACT: After a high-throughput screening campaign identified thioether **1** as an antagonist of the nuclear androgen receptor, a zone model was developed for structure−activity relationship (SAR) purposes and analogues were synthesized and evaluated in a cell-based luciferase assay. A novel thioether isostere, cyclopropane (1*S*,2*R*)-**27**, showed the desired increased potency and structural properties (stereospecific SAR response, absence of a readily oxidized sulfur atom, low molecular weight, reduced number of flexible bonds and polar surface area, and drug-likeness score) in the prostate-specific antigen luciferase assay in C4-2-PSA-rl cells to qualify as a new lead structure for prostate cancer drug development.



KEYWORDS: *Androgen receptor, CRPC, advanced prostate cancer, luciferase assay, isoxazoles, thioether isostere*

The steroidal hormones testosterone and dihydrotestosterone are the major endogenous androgens that cause nuclear translocation and subsequent activation of androgen receptor (AR).[1] In prostate cancer, AR shows a higher nuclear concentration in the presence of androgens,[2,3] and androgen-deprivation therapy (ADT) is one of the primary treatments.[4] Unfortunately, even with ADT, almost all patients eventually progress to the stage of castration-resistant prostate cancer (CRPC, formerly known as hormone-refractory prostate cancer), a fatal condition that makes prostate cancer the second most deadly cancer type in men in the U.S.[5] Despite a high survival rate with early detection and treatment with surgery or radiation, prostate cancer is responsible for the death of 30,000 patients each year in the U.S.[5,6]

CRPC is postulated to arise through either adaption or selection of cancer cells in a low androgen environment[7] as a result of the initial ADT.[4,8] In the laboratory setting, studies of overexpression[9] and knockdown[10] of AR have shown that this receptor plays a key role in the progression of CRPC.[11,12] Enzalutamide (MDV3100) and bicalutamide are AR antagonists that are currently used as treatments for CRPC and can extend the lifespan of patients for 3−5 months (Figure 1). Enzalutamide, in particular, attenuates nuclear translocation of AR but does not seem to reduce nuclear levels of AR in prostate cancer cells.[13] Since these therapeutics are only partially effective, there is a definite need for new regimens that extend life expectation beyond several months.[14] Unfortunately, there are no known therapies that decisively inhibit nuclear localized AR in CRPC cells.[15−22] Herein, we investigate a novel series of small molecules identified by their ability to reduce the nuclear level of AR and, subsequently, AR activity.

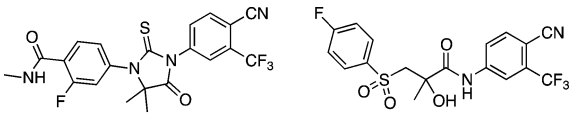


Figure 1. Structures of clinically used AR antagonists enzalutamide and bicalutamide.

Prior to the onset of our medicinal chemistry efforts, a high-throughput screening (HTS) campaign for antagonists of AR nuclear localization identified compounds **1** and **2** that also reduced levels of prostate-specific antigen (PSA), a key marker for CRPC, in a PSA luciferase reporter assay performed in CRPC cell lines (Figure 2).[23] Both HTS hits demonstrated low micromolar potency with little to no cytotoxicity or activity in AR negative cell lines. Close structural analogues of 3-phenyl-6,7-dihydro-5-pyrrolo[1,2-*a*]imidazole (**2**) were previously found to have antifungal effects, which raised off-target concerns.[24] In contrast, 2-((isoxazol-4-ylmethyl)thio)-1-(4-phenylpiperazin-1-yl)ethanone (**1**) had not yet been bio-

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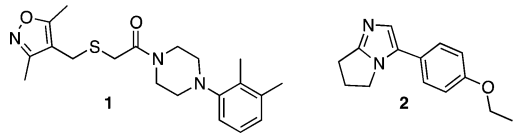


Figure 2. HTS hits that reduced PSA levels in a luciferase assay in CRPC cell lines.[23]

logically annotated, and this structural novelty led us to prioritize this scaffold over **2**. In an effort to determine a structure−activity relationship and identify more potent antagonists of CRPC, we designed and synthesized analogues of **1** in a series of structural modifications of subunits 1−5 (Figure 3).

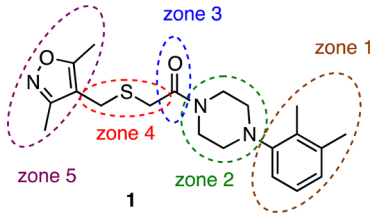
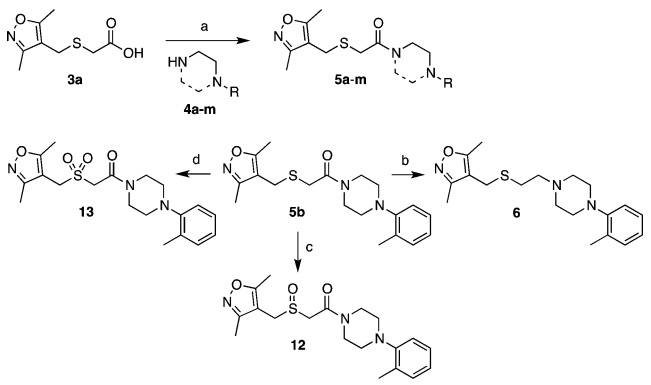


Figure 3. Zones of planned structural modifications of **1**.

Our goal was to probe five key moieties in compound **1**: the benzene substitution pattern (zone 1), modifications at the piperazine (zone 2), carbonyl replacements (zone 3), a sulfur-atom exchange in the 3-atom linker and the use of less flexible linkers (zone 4), and variations of the 3,5-dimethylisoxazole (3,5-DMI) ring (zone 5) (Figure 3).

In the synthesis of zone 1−3 analogues, we used the amide bond as the lynchpin disconnection. Compounds **5a−h** were synthesized directly from commercially available carboxylic acid **3a** and *N*-arylated piperazines **4a−h** under amide coupling conditions with T3P (Scheme 1 and Table 1).[25] We also examined the diamine linker in zone 2 in more detail through the synthesis of analogues **5i−5m**. For these target molecules, the requisite diamines **4i−m** were prepared by a Buchwald−Hartwig cross-coupling of mono-Boc-protected diamines with bromoarenes.[26,27] Reduction of amide **5b** with lithium aluminum hydride led to diamine **6**. For an initial set of zone

Scheme 1. Synthesis of DMI-Containing Analogues 5, 6, 12, and 13[a]



[a]Reagents and conditions: (a) T3P, Et_3N, CH_2Cl_2, rt, overnight, 52−98%; (b) $LiAlH_4$, dry THF, 0 °C, 1 h, 42%; (c) $NaIO_4$, MeOH, H_2O, rt, 15 h, 68%; (d) *m*-CPBA, CH_2Cl_2, rt, 15 h, 44%.

Table 1. Structures of Amine Building Blocks 4 and Analogues 5, 7−11, and 16 (Schemes 1 and 2)

Analog	Amine 4	R	X
5a	4a	Ph	-
5b	4b	(2-Me)Ph	-
5c	4c	(3-Me)Ph	-
5d	4d	(4-Me)Ph	-
5e	4e	(2-NC)Ph	-
5f	4f	(2-F)Ph	-
5g	4g	1-Naphthyl	-
5h	4h	(2-MeO)Ph	-
5i	4i	(2-Me)Ph	-
5j	4j	(2-Me)Ph	-
5k	4k	(2-Me)Ph	-
5l	4l	Ph	-
5m	4m	(3-Me)Ph	-
7	4b	(2-Me)Ph	CH_2SCH_2
8	4b	(2-Me)Ph	$(CH_2)_3$
9	4b	(2-Me)Ph	SCH_2
10	4b	(2-Me)Ph	C≡C
11	4b	(2-Me)Ph	(*E*)-HC=CH
16	4b	(2-Me)Ph	(*E*)-*c*-C_3H_4

4 analogues, thioether **5b** was also oxidized to sulfoxide **12** and sulfone **13** in good yields with sodium periodate and *m*-chloroperbenzoate, respectively (Scheme 1).

Additional zone 4 and zone 5 analogues with a phenyl group in place of the isoxazole ring were obtained from carboxylic acids **3b−3g** (Scheme 2 and Table 1). Coupling to piperazine **4b** provided amides **7−11** and **16** in high yields. Alkynyl amide **10** was further hydrogenated to *cis*-alkene **14** using a Lindlar

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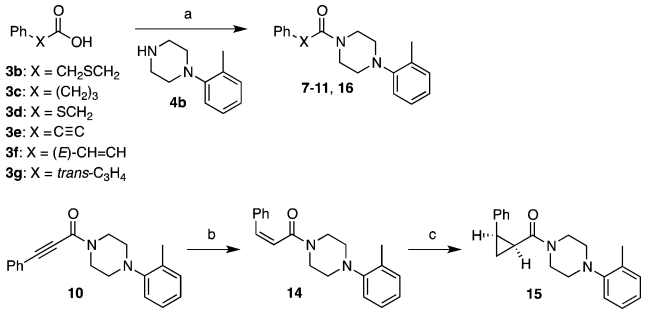
Scheme 2. Synthesis of Piperazines 7−11 and 14−16[a]

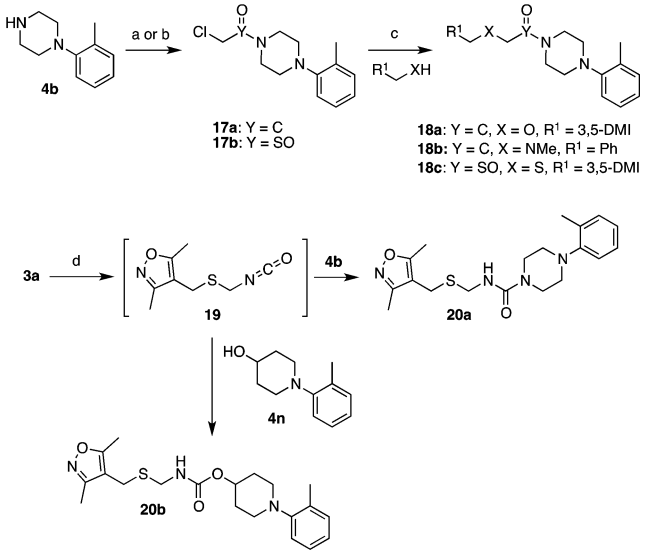


[a]Reagents and conditions: (a) T3P, Et_3N, CH_2Cl_2, rt, overnight, 62−96%; (b) Lindlar's catalyst, quinoline, H_2, EtOAc, quant.; (c) $CrCl_2$, CH_2ICl, THF, reflux, overnight, 57%.

catalyst. The *cis*-cyclopropane **15** was prepared by a Simmons−Smith cyclopropanation of *cis*-alkene **14**,[28] whereas the *trans*-cyclopropane **16** was obtained by coupling of commercially available *trans*-2-phenylcyclopropanecarboxylic acid **3g** with piperazine **4b**.

Further modifications in zones 3−4 were accomplished by acylation of piperazine **4b** with either 2-chloroacetyl chloride or chloromethanesulfonyl chloride to form the corresponding amide **17a** or sulfonamide **17b** in good yields (Scheme 3). S_N2

Scheme 3. Alkylation of 17a and 17b To Give Analogues 18a−18c and Conversion of Isocyanate 19 To Give Thioethers 20a/b[a]

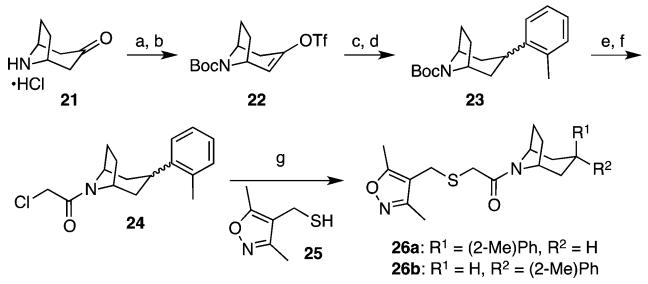


[a]Reagents and conditions: (a) 2-chloroacetyl chloride, Et_3N, CH_2Cl_2, rt, overnight, 99%; (b) chloromethanesulfonyl chloride, Et_3N, CH_2Cl_2, rt, overnight, 85%; (c) NaH, THF, rt, 1−2 d, 4−99%; (d) DPPA, Et_3N, toluene, reflux, overnight, 17−65%.

reaction of **17a** and **17b** led to ether **18a**, amine **18b**, and thioether **18c**. Starting with carboxylic acid **3a**, urea **20a** and carbamate **20b** were obtained in moderate yields via a Curtius rearrangement and addition of the intermediate isocyanate **19** to amine **4b** and alcohol **4n**, respectively (Scheme 3).[29]

A bridged bicyclic ring was introduced to add a strong conformational constraint in zone 2 (Scheme 4). Boc-protection of nortropinone hydrochloride **21** followed by enolization with NaHMDS and trapping of the enolate with *N*-

Scheme 4. Synthesis of Bridged Analogues 26a and 26b[a]



[a]Reagents and conditions: (a) Boc_2O, DMAP, CH_2Cl_2, rt, overnight, 78%; (b) NaHMDS, $PhNTf_2$, THF, −78 °C to rt, 4 h, 78%; (c) $Pd(PPh_3)_4$, LiCl, Na_2CO_3, $(2\text{-Me})PhB(OH)_2$, DME, H_2O, 60 °C, 3 h, 78%; (d) H_2, Pd/C, EtOH, rt, 14 h, 90%; (e) TFA, CH_2Cl_2, rt, 16 h, quant.; (f) 2-chloroacetyl chloride, Et_3N, THF, rt, 22 h, 79%; (g) **25**, NaH, THF, rt, 1 d, 30%.

phenyltriflimide provided vinyl triflate **22** in good yield. A Suzuki coupling was used to install the *o*-tolyl group, and the styrene double bond was reduced with Pd/C to afford **23** as a mixture of diastereomers. Without separation, this mixture was deprotected and acylated with α-chloroacetyl chloride. Finally, the chloride was displaced using thiol **25** and sodium hydride to afford the thioether. Diastereomers **26a** and **26b** were separated by chromatography on SiO_2 to afford both analogues in modest yields.

The biological activity of analogs **5−16**, **18**, **20**, and **26** was determined and compared to HTS hit **1** (EC_{50} 7.3 μM) and enzalutamide (EC_{50} 1.1 μM) using the Dual-Glo luciferase system (Promega, WI, USA) in the presence of 1 nM synthetic androgen R1881 in C4-2-PSA-rl cells, which were generated by stable cotransfection of C4-2 cells with a PSA promoter driven luciferase reporter vector (pPSA6.1) and a Renilla luciferase reporter vector as a control. Relative luciferase activity was calculated as the quotient of androgen-induced PSA-firefly/Renilla luciferase activity. Since PSA promoter activity correlates to AR transcriptional activity, inhibition of AR will result in decreased PSA-luciferase activity. EC_{50} values were calculated using graphpad prism, and data represent the mean and SD of 2−6 independent experiments (Table 2). To verify that these compounds did not have undesirable electrophilic properties, their stability was tested in the presence of thiols. Neither thiophenol in $CDCl_3$ nor 2-mercaptoethanol in PBS resulted in any trapping products by ^1H NMR and LCMS analysis.

Simple modifications of the substituents on the benzene ring in zone 1 revealed that methyl groups in the 3- and 4-positions (**5c**, **5d**) led to loss of activity, while the 2-methyl analogue **5b** (EC_{50} 14.5 μM) retained about half of the activity of the 2,3-dimethylated **1** (Table 2). Removal of the 2-methyl group in **5a** deleted activity. In agreement with this trend in zone 1, the bulky 1-naphthyl substituent (**5g**) recovered activity (EC_{50} 11.1 μM). Analogues with electron-withdrawing substituents at the benzene 2-position (2-NC, **5e**, and 2-F, **5f**) also maintained or slightly increased activity (EC_{50} 12−13 μM); however, the electron-donating 2-methoxy substituted **5h** was not tolerated and resulted in a complete loss of activity, possibly due to an increase in the pK_a of the aniline and/or an unfavorable increase in the π-electron density of the aromatic ring.[30] To potentially reduce the expected rapid metabolism of benzylic methyl groups by cytochrome P450 enzymes,[31] we selected the minimally required substitution in zone 1, e.g., the 2-methyl

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Table 2. In Vitro Activity of Analogues in the PSA Luciferase Assay in C4-2-PSA-rl Cells

entry	compd	EC_{50} (μM)	entry	compd	EC_{50} (μM)
1	**1**	7.3 ± 2.5[c]	19	**10**	20.3 ± 11.6[a]
2	**5a**	>25[a]	20	**11**	>25[a]
3	**5b**	14.5 ± 3.2[b]	21	**12**	>25[b]
4	**5c**	>25[a]	22	**13**	16.1 ± 3.3[b]
5	**5d**	>25[a]	23	**14**	12.7 ± 0.8[a]
6	**5e**	12.0 ± 1.6[b]	24	**15**	2.9 ± 1.0[b]
7	**5f**	12.6 ± 7.7[b]	25	**16**	>25[b]
8	**5g**	11.1 ± 5.3[b]	26	**18a**	>25[b]
9	**5h**	>25[a]	27	**18b**	>25[b]
10	**5i**	18.4 ± 9.2[b]	28	**18c**	7.2 ± 2.7[c]
11	**5j**	11.1 ± 3.3[a]	29	**20a**	>25[a]
12	**5k**	3.1 ± 1.1[a]	30	**20b**	>25[c]
13	**5l**	14.7 ± 4.4[a]	31	**26a**	7.7 ± 1.6[b]
14	**5m**	16.6 ± 4.8[b]	32	**26b**	7.9 ± 2.8[a]
15	**6**	10.8 ± 5.7[b]	33	enzalutamide	1.1 ± 0.5[e]
16	**7**	13.7 ± 0.8[b]	34	**27**	2.7 ± 1.1[d]
17	**8**	14.4 ± 3.7[b]	35	(1*S*,2*R*)-**27**	1.7 + 0.2[a]
18	**9**	>25[a]	36	(1*R*,2*S*)-**27**	15.2 ± 3.3[a]

[a]Assay repeats. n = 2. [b]n = 3. [c]n = 4. [d]n = 5. [e]n = 6. For assay description and complete structural information, please see the Supporting Information and Table S1.

group, for further structure−activity relationship (SAR) investigations.

The piperazine core (zone 2) was queried through substitutions with flexible as well as constrained acyclic and cyclic diamines. The flexible *N*,*N*′-dimethylethylenediamine linker in **5i** (EC_{50} 18.4 μM) and the 7-membered diazepane **5j** (EC_{50} 11.1 μM) both dropped off in activity. The dimethylated piperazines **5l** and **5m** (EC_{50} 15−17 μM) were also less active than the initial hit. In contrast, the conformationally more highly constraint 2,6-dimethylpiperazine **5k** was more active with an EC_{50} of 3.1 μM. Installment of an ethylene bridge and a carbon-linked (2-Me)Ph group decreased activity again since both diastereomers of the bicyclo[3.2.1] ring systems **26a** and **26b** showed an EC_{50} of 8 μM.

Reduction of amide **5b** to amine **6** resulted in a 1.3-fold increase in activity to an EC_{50} of 10.8 μM. Sulfonamide **18c** (EC_{50} 7.2 μM) was as active as the initial hit **1**, but urea **20a** and carbamate **20b** were inactive.

The replacement of the thioether linkage in zone 2 with an ether group abolished activity in **18a**. Substituting the thioether with the *N*-methylated amine in **18b** also abolished activity. In contrast, in an analogous system with a phenyl group in place of the isoxazole, both thioether **7** as well as the all-carbon chain containing **8** showed decreased yet consistent activity (EC_{50} ≈ 14 μM).

In order to verify that the biological effect in the thioether series was not a result of *S*-oxidation in the cellular assay, common products of thioether oxidation, i.e., sulfoxide **12** and sulfone **13**, were tested. While sulfone **13** retained some activity (EC_{50} 16.1 μM), sulfoxide **12** was inactive. Shortening the three-atom chain to afford the two-atom thioether-linked **9** also abolished activity. The rigidified alkyne **10** and the corresponding (*E*)-alkene **11** and its cyclopropane isostere **16** were also found to be essentially inactive. In contrast, we were pleasantly surprised to find that the (*Z*)-alkene **14** showed an EC_{50} of 12.7 μM and that the corresponding *cis*-fused cyclopropane isostere[32] **15** was even more potent than analogue **1**, showing an EC_{50} of 2.9 μM (Table 2). More significantly, chiral resolution of the bis-halogenated cyclopropane **27** (EC_{50} 2.7 μM, entry 34) provided a more potent enantiomer (1*S*,2*R*)-**27** (EC_{50} 1.7 μM, entry 35) and the ca. 10-fold less potent (1*R*,2*S*)-**27** (EC_{50} 15.2 μM, entry 36), and supporting specific contact of this scaffold at a still to be defined AR binding site (Figure 4).

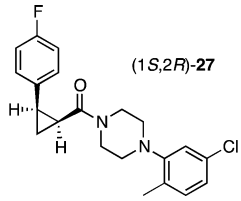

Figure 4. More potent enantiomer of cyclopropane **27**.

In summary, 35 analogues were synthesized, and the resulting SAR evaluated 5 zones of modification in the starting hit, compound **1**. We discovered several attributes that proved essential for activity. Zone 1 modifications showed that the *ortho*-substituent on the phenyl ring was important for activity. In zone 2, the sterically encumbered 2,6-dimethylpiperazine proved superior to flexible, unsubstituted, and bridged analogues. In zone 3, a carbonyl group was not required, and a sulfonamide and even the reduced amine were well tolerated. In zone 4, thioether oxidation reduced activity, and only the *cis*-cyclopropane significantly improved the EC_{50}. Limited substitutions were performed in zone 5, but in general, analogues with a phenyl group were equipotent with their 3,5-dimethylisoxazole congeners (see, for example, **7** vs **5b**). The *cis*-cyclopropane (1*S*,2*R*)-**27** was found to be substantially equipotent to the commercial AR antagonist, enzalutamide. Compound (1*S*,2*R*)-**27** is of particular interest in comparison to **1** due to the isosteric replacement of the thioether linker with the metabolically more stable cyclopropane, a reduction of the topological polar surface area (TPSA) from 49.6 to 23.6 Å^2, a reduction of the number of rotatable bonds from 3 to 2, and an improvement in the drug-likeness score from 6.3 to 8.0.[33] Further modifications of lead structure **27** based on these SAR results as well as *in vivo* tumor xenograft data will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00186.

Methods for all assays, cell cultures, treatment conditions, and compound synthesis (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

AR, androgen receptor; 3,5-DMI, 3,5-dimethylisoxazole; CRPC, castration-resistant prostate cancer; HTS, high-throughput screen; MW, molecular weight; PSA, prostate-specific antigen; SAR, structure−activity relationship; SD, standard deviation

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