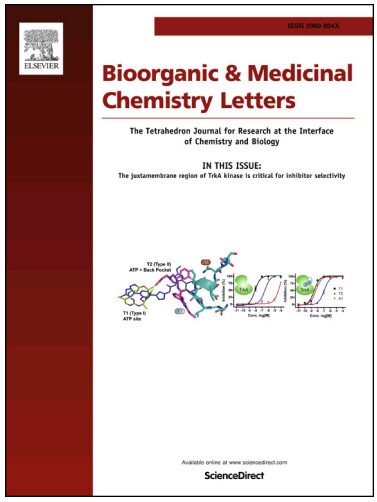
Accepted Manuscript



Synthesis and biological evaluation of novel selective androgen receptor modulators (SARMs). Part II: Optimization of 4-(pyrrolidin-1-yl)benzonitrile derivatives

Moriteru Asano, Takenori Hitaka, Takashi Imada, Masami Yamada, Megumi Morimoto, Hiromi Shinohara, Takahito Hara, Masuo Yamaoka, Takashi Santou, Masaharu Nakayama, Yumi Imai, Noriyuki Habuka, Jason Yano, Keith Wilson, Hisashi Fujita, Atsushi Hasuoka

PII: S0960-894X(17)30276-7
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.03.038
Reference: BMCL 24790

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 14 February 2017
Revised Date: 14 March 2017
Accepted Date: 16 March 2017

Please cite this article as: Asano, M., Hitaka, T., Imada, T., Yamada, M., Morimoto, M., Shinohara, H., Hara, T., Yamaoka, M., Santou, T., Nakayama, M., Imai, Y., Habuka, N., Yano, J., Wilson, K., Fujita, H., Hasuoka, A., Synthesis and biological evaluation of novel selective androgen receptor modulators (SARMs). Part II: Optimization of 4-(pyrrolidin-1-yl)benzonitrile derivatives, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.03.038

Synthesis and biological evaluation of novel selective androgen receptor modulators (SARMs). Part II: Optimization of 4-(pyrrolidin-1-yl)benzonitrile derivatives

Moriteru Asano*[, a], Takenori Hitaka[a], Takashi Imada[a], Masami Yamada[a], Megumi Morimoto[a], Hiromi Shinohara[a], Takahito Hara[a], Masuo Yamaoka[a], Takashi Santou[a], Masaharu Nakayama[a], Yumi Imai[a], Noriyuki Habuka[a], Jason Yano[#,b], Keith Wilson[b], Hisashi Fujita[a], Atsushi Hasuoka*[, a]

[a]*Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd, 26-1 Muraoka-higashi 2-chome, Fujisawa, Kanagawa 251-8555, Japan*
[b]*Structural Biology, Takeda California Inc., 10410 Science Center Drive, San Diego, California 92121, USA*

Keywords: Androgen receptor, Selective androgen receptor modulators (SARMs), 4-(Pyrrolidin-1-yl)benzonitrile, Pharmacokinetics (PK), Liver microsomal metabolic stability.

Corresponding Author

* (M.A.) Tel: +81-466-32-1152. Fax: +81-466-29-4449. E-Mail: mo.masayume@gmail.com
(A.H.) Tel: +81-466-32-2913. E-mail: atsushi.hasuoka@takeda.com

Present Address

[#] (J.Y.) Beryllium Discovery Corp., 3 Preston Ct Bedford, MA 01730, USA

Abbreviations: PK, pharmacokinetics; CL, clearance; *F*, bioavailability; AUC, area under the blood concentration time curve; MS, liver microsomal metabolic stability; sc, subcutaneous; qd, quaque die; CNS, central nervous system; bid, bis in die.

ABSTRACT: We recently reported a class of novel tissue-selective androgen receptor modulators (SARMs), represented by a naphthalene derivative **A**. However, their pharmacokinetic (PK) profiles were poor due to low metabolic stability. To improve the PK profiles, we modified the hydroxypyrrolidine and benzonitrile substituents of 4-(pyrrolidin-1-yl)benzonitrile derivative **B**, which had a comparable potency as that of compound **A**. This optimization led us to further modifications, which improved metabolic stability while maintaining potent androgen agonistic activity. Among the synthesized compounds, (2*S*,3*S*)-2,3-dimethyl-3-hydroxylpyrrolidine derivative **1c** exhibited a suitable PK profile and improved metabolic stability. Compound **1c** demonstrated significant efficacy in levator ani muscle without increasing the weight of the prostate in an in vivo study. In addition, compound **1c** showed agonistic activity in the CNS, which was detected using sexual behavior induction assay.

As men age, serum testosterone levels gradually decline due to testicular malfunction and hypothalamic dysregulation.[1] Reduced testosterone levels cause a variety of symptoms, including depression, loss of libido,[2] and decreased bone and lean body mass. This syndrome is called late-onset hypogonadism (LOH),[3] and affects 20% of men aged 60 and older.[4] Currently, several strategies for testosterone replacement therapy (TRT) use testosterone and/or its ester to treat hypogonadism.[5,6] These treatments effectively alleviate symptoms and provide additional health benefits. However, widespread use of testosterone/testosterone ester-based TRT is limited by potential risk of cardiovascular problem, prostate cancer and erythrocytosis.[7] In addition, administration routes are limited to inconvenient intramuscular injection, surgical implantation, or transdermal delivery using gels or patches.

Lack of convenient administration routes has stimulated a growing interest in orally available and nonsteroidal tissue-selective androgen receptor modulators (SARMs).[8-11] The concept of SARMs emerged from the clinical success of selective estrogen receptor modulators (SERMs), such as raloxifene, which acts as an estrogen receptor agonist in bone but an antagonist in the breast and uterus.[12] SARMs are expected to have desired anabolic functions, and lack unwant-

ed androgenic properties such as prostate stimulation. Various nonsteroidal SARMs have been reported[6,13] and some compounds such as GTx-024[14,15] and DT-200[16-18] have reached clinical development (Figure 1).

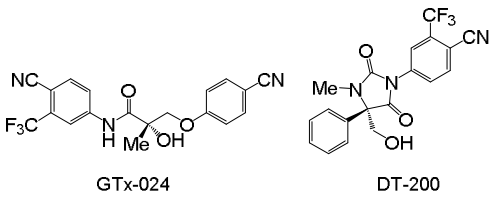


Figure 1. Structures of selected nonsteroidal SARMs

We have previously reported that 1-(4-cyano-1-naphthyl)-2,3-disubstituted pyrrolidine derivatives, represented by compound **A**, showed highly potent AR agonistic activity in vitro, and good tissue selectivity in vivo (Figure 2).[19] However, they were rapidly metabolized in rat and human liver microsomes, and failed to achieve sufficient bioavailability in PK studies in rats (compound **A**: CL = 3081 mL/h/kg, AUC_{po} = 32.2 ng•h/mL, *F* = 9.7%). In addition, replacement of naphthonitrile with 2-chloro-3-methyl benzonitrile, a well-known privileged scaffold for SARMs,[20,21] still provided insufficient metabolic stability, and showed a PK profile similar to that of compound **A** (compound **B**: CL = 5166 mL/h/kg, AUC_{po} = 3.2 ng•h/mL, *F* = 1.6%).

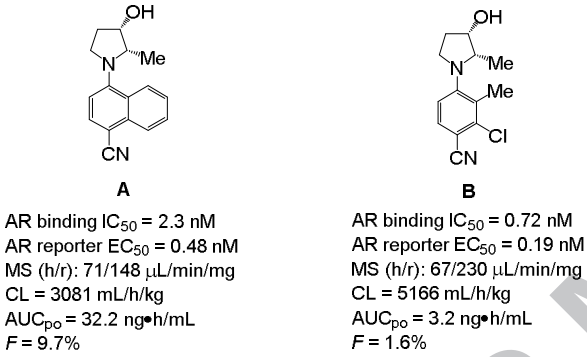


Figure 2. 1-(4-Cyano-1-naphthyl)pyrrolidine derivative **A** and 2-chloro-3-methylbenzonitrile **B**

Therefore, we designed a compound by modifying the pyrrolidine and benzonitrile groups further to improve the PK profile. The X-ray co-crystal structure of compound **B** with the AR ligand binding domain (LBD) revealed two key interactions (Figure 3): water-bridged hydrogen bonds of the cyano group with the side chain of Arg752 and the backbone of Met745, and an interaction of the hydroxyl group with the side chains of Asn705 and Thr877. Since the structural data suggested that potency would be improved if the compounds possessed cyano and hydroxyl groups at the ends of the molecule, we planned to explore substitutions of the hydroxypyrrolidine unit (X) and conduct further optimization of the benzonitrile (Y). In this paper, we describe the design, synthesis, and biological characterization of 4-(pyrrolidin-1-yl)-1-benzonitrile derivatives.

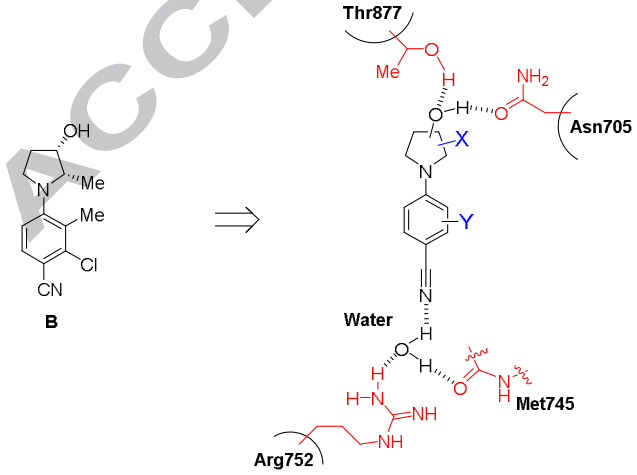
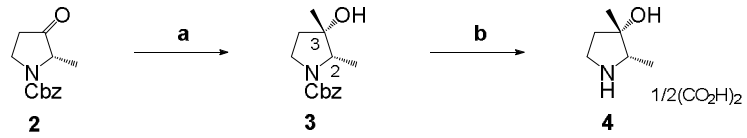


Figure 3. Strategies for identification of novel SARMs from compound **B**.

(2*S*,3*S*)-2,3-Dimethyl-3-hydroxypyrrolidine **4** was prepared using our previously reported method (Scheme 1).[22] A methyl group was introduced at the C3-position of **2** using methyl magnesium bromide. In this reaction, the Grignard substitution was achieved in a highly stereo-selective manner and with an 85% yield, driven by the optically active 2*S*-methyl group, but without cleavage of the Cbz group, using $CeCl_3$ as an additive.[23] The Cbz group of **3** was removed by hydrogenation, and successive treatment with oxalic acid afforded a hemioxalate salt **4** at 88% yield.

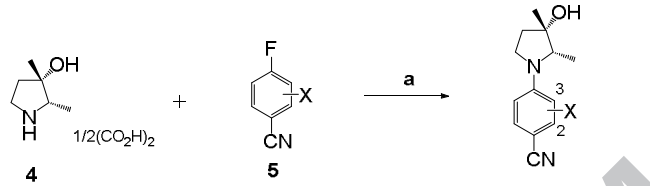
Scheme 1. Preparation of (2*S*,3*S*)-2,3-dimethyl-3-hydroxylpyrrolidine **4**[a]



[a] Reagents and conditions: (a) MeMgBr, $CeCl_3$, THF, -78–0 °C, 1 h 85%; (b) H_2 (1 atm), Pd/C, MeOH, rt, 1.5 h, then $(CO_2H)_2$, 88%.

The coupling reactions of pyrrolidines **4** with 4-fluorobenzonitriles **5** were performed using lithium carbonate in dimethylsulfoxide at 70–80 °C to afford **1a–c** in 57–75% yield (Scheme 2). [24]

Scheme 2. Synthesis of compound **1a–c** and **B**[a]

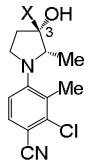


[a] Reagents and conditions: (a) Li_2CO_3, DMSO, 70–80 °C, 57–75%.

AR binding affinities were evaluated by competitive displacement of radiolabeled [^{3}H]mibolerone from AR. The data are reported as IC_{50} values. Functional activities using an AR responsive luciferase reporter were determined in Cos-7 cells and are given as EC_{50} values.

To improve the PK profile of **B**, we first focused on modification of the pyrrolidine. The co-crystal structure of **B** with AR LBD suggests that the C3-hydroxyl group on the pyrrolidine ring is essential for potency. However, the hydroxyl group and pyrrolidine ring are considered to be metabolized by oxidation and conjugation.[25] We hypothesized that introduction of a methyl group at the C3-position on the pyrrolidine ring would prevent both oxidative and conjugative metabolism due to the steric hindrance, while not influencing the potency on the basis of the co-crystal structural information of **B** with AR LBD. Based on this hypothesis, (2*S*,3*S*)-2-methyl-3-hydroxylpyrrolidine derivative **B** was converted into (2*S*,3*S*)-2,3-dimethyl-3-hydroxylpyrrolidine derivative **1a** (Table 1). As expected, compound **1a** demonstrated better metabolic stability in human and rat assays than that of compound **B**, while maintaining potent AR binding affinity and agonistic activity. In addition to improved metabolic stability, compound **1a** exhibited a dramatically improved PK profile (**1a**: CL = 1886 mL/h/kg, AUC_{po} = 236.7 ng•h/mL, *F* = 44.5%) relative to that of compound **B** (**B**: CL = 5166 mL/h/kg, AUC_{po} = 3.2 ng•h/mL, *F* = 1.6%).

Table 1. Biological data of (2*S*,3*S*)-2,3-dimethyl-3-hydroxylpyrrolidine **1a** and (2*S*,3*S*)-2-methyl-3-hydroxylpyrrolidine **B**



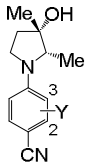
1a (X = Me)
B (X = H)

Compd.	AR binding IC_{50} (95%CI) (nM)[a]	AR reporter EC_{50} (95%CI) (nM)[a]	Metabolic stability (μL/min/mg)[b] human	rat	CL (mL/h/kg)[c]	AUC_{po} (ng•h/mL)[c]	*F* (%)[d]
1a	0.49 (0.31–0.78)	0.20 (0.13–0.31)	24	96	1886	236.7	44.5
B	0.72 (0.51–1.02)	0.19 (0.12–0.31)	67	230	5166	3.2	1.6

[a] IC_{50} (EC_{50}) values are presented as means of duplicate experiments, with 95% confidence intervals (95%CI) in parentheses. [b] Metabolic stability was determined based on disappearance of parent compound after incubation with human or rat liver microsomes for 20 min. [c] Rat dosing at 0.1 mg/kg, i.v., and 1 mg/kg, p.o. (n = 3). [d] *F* means bioavailability

With its modified hydroxypyrrolidine unit, compound **1a** demonstrated an improved PK profile while maintaining excellent potency. However, its metabolic stability in rats was still insufficient to select **1a** as a suitable in vivo candidate. To further improve PK profiles, we optimized the substituents on the benzonitrile of compound **1a** using the calculated Log *P* (cLog *P*) value as an indicator of metabolic stability.[26] We designed and synthesized 2-chlorobenzonitrile derivative **1b** (cLog *P* 2.60) and 3-fluoro-2-methylbenzonitrile derivative **1c** (cLog *P* 2.66), which has low lipophilicity compared to compound **1a** (cLog *P* 3.10). As expected, both compounds demonstrated improved metabolic stability over compound **1a** in rat liver microsomes, and maintained potent AR agonistic activities. Furthermore, these compounds showed good bioavailabilities (*F*; **1b**: 53.4% and **1c**: 46.3%, respectively) and improved plasma exposures (AUC_{po} >380 ng•h/mL) relative to those of compound **1a** (AUC_{po} = 236.7 ng•h/mL) in rat PK tests in accordance with the increased metabolic stabilities. From these results, we selected compound **1b** and **1c** for in vivo efficacy tests.

Table 2. Biological data of 4-[(2*S*,3*S*)-2,3-dimethyl-3-hyroxylpyrrolidin-1-yl] benzonitrile derivatives **1a–c**



1a (Y = 2-Cl,3-Me)
1b (Y = 2-Cl)
1c (Y = 2-F,3-Me)

Compd.	AR binding IC_{50} (95%CI) (nM)[a]	AR reporter EC_{50} (95%CI) (nM)[a]	Metabolic stability (μL/min/mg)[b] rat	CL (mL/h/kg)[c]	AUC_{po} (ng•h/mL)[c]	*F* (%)[d]
1a	0.49 (0.31–0.78)	0.20 (0.13–0.31)	96	1886	236.7	44.5
1b	0.52 (0.34–0.78)	0.32 (0.16–0.62)	39	581	930.6	53.4
1c	1.0 (0.7–1.3)	0.29 (0.16–0.50)	44	1236	387.9	46.3

[a] IC_{50} (EC_{50}) values are presented as means of duplicate experiments, with 95% confidence intervals (95%CI) in parentheses. [b] Metabolic stability was determined based on the disappearance of parent compound after incubation with human or rat liver microsomes for 20 min. [c] Rat dosing at 0.1 mg/kg, i.v., and 1 mg/kg, p.o. (n = 3). [d] *F* means bioavailability

Tissue selectivity of the selected compounds was investigated using the Hershberger assay.[27] Twice daily doses (5.0 mg/kg/day, po, bid) of compounds **1b** and **1c** were administered with testosterone propionate (TP) (0.5 mg/kg, sc, qd) to 4-week-old castrated rats for 4 days (Table 3). The control group was administered TP only (0.5 mg/kg, sc, qd), and the increases in weight of prostates and levator ani muscles were expressed relative to 100%. Compound **1c** exhibited tissue selectivity and strong anabolic activity in levator ani muscle (>300%), whereas compound **1b** enhanced the weight of not only levator ani muscle (>300%) but also of the prostate (>140%). Thus, we selected compound **1c** as a tissue-selective analogue for further in vivo evaluations.

Table 3. Tissue selectivity in immature rats (n = 5)[a]

Compd.	Increase in tissue weight (%) Prostate	Levator ani muscle
1b	147*	>300*
1c	102	>300*
Control[b]	100	100

[a] Test compounds were administered orally twice daily with a dose of 5 mg/kg/day with TP (0.5 mg/kg, sc, qd). [b] TP only (0.5 mg/kg, sc, qd) was administered as a control. * $P<0.05$ versus control group by Dunnet's test.

To evaluate anabolic potency and tissue selectivity for comparison with TP (1.2 mg/kg/day, sc, qd), compound **1c** (0.15, 0.5. 1.5, 5, 15 mg/kg/day) was administrated orally twice daily with TP (0.4 mg/kg/day, sc, qd) to 8-week old castrated rats for 7 days at each dose (Figure 4). Compound **1c** exerted significant dose dependent effects (to more than 5 mg/kg/day) on levator ani muscle that were superior to the effects of TP (1.2 mg/kg/day, sc, qd) alone. On the other hand, **1c** did not influence the weight of the prostate, at doses up to 15 mg/kg/day, while TP (1.2 mg/kg/day, sc, qd) increased prostate weight significantly. Accordingly, compound **1c** is a promising tissue selective androgen receptor modulator.

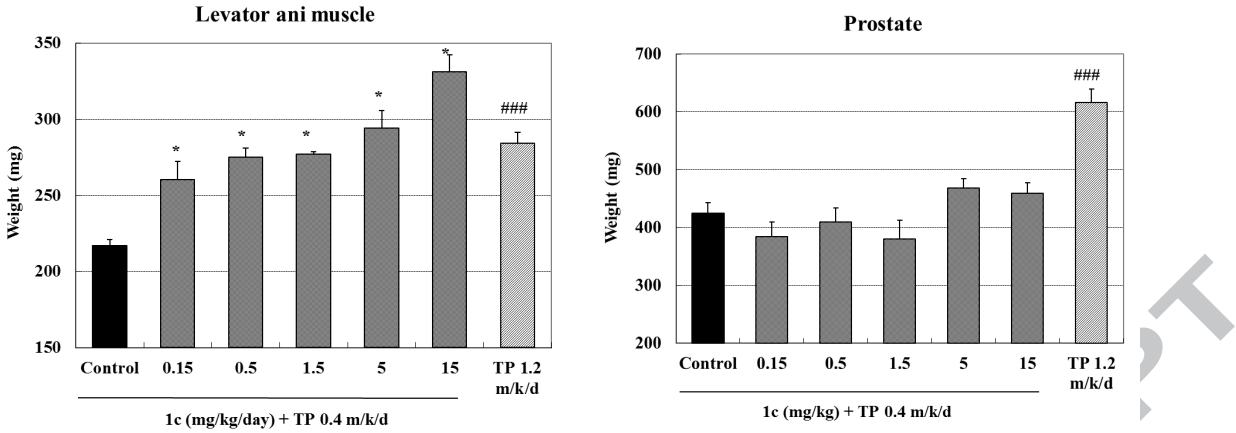


Figure 4. Mean weight of levator ani muscle and prostate in castrated mature rats dosed with compound **1c** and TP. **P*<0.025 versus control group (Williams test), ###*P*<0.001 versus control group (unpaired Student's t test).

Next, we performed a sexual behavior induction assay to confirm agonistic activity of **1c** on the CNS (Table 4). Selected fertile male rats were castrated to eliminate sexual behavior. Sexual behavior induction was then quantitated on the basis of pseudopregnancy rate in female rats. After treatment with **1c** (7.5 mg/kg/day, po, bid) for 3 weeks, sexual behavior increased to 87.5% compared to that in the non-treated control group (10%). This result suggested that **1c** could act as an androgen agonist in the CNS.

Table 4. Sexual behavior induction assay[a]

Compd.	Dose (mg/kg/day for 18–21 days)	Sexual behavior (positive/total, %)
1c	7.5	87.5*
Control		10

[a] n = 8 (**1c**), 10 (**Control**). **P*<0.01, versus control (Fisher's Exact test).

To confirm the binding mode of compound **1c**, we solved the X-ray co-crystal structure of this compound bound to the AR LBD (Figure 5). The co-crystal structure of compound **1c** with the AR LBD, residues 671–919, was obtained at 2.70 Å resolution. The binding mode of compound **1c** was almost identical to that of compound **B**. Based on this result, the 3-methyl group on the pyrrolidine ring of **1c** was confirmed to be tolerated without influencing the surrounding amino acid residues such as Thr877 or Asn705.

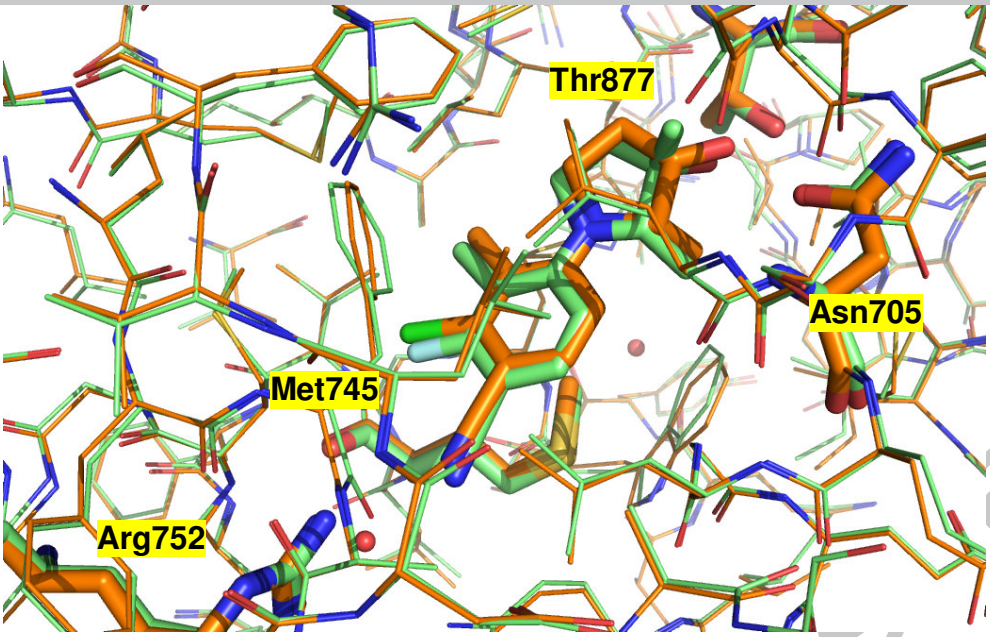


Figure 5. Superimposed X-ray co-crystal structures of **1c** (green) and **B** (orange) bound to androgen receptor LBD (PDB code 5T8J, 2.70 Å resolution (**1c**), PDB code 5T8E, 2.71 Å resolution (**B**)).

To improve the PK profile of the previously reported naphthalene derivative **A**, we modified its 4-(pyrrolidin-1-yl)benzonitrile derivative **B** having comparable potency to that of compound **A**. To improve PK profiles, we investigated introduction of a methyl group at the C3-position of the pyrrolidine ring and identified 4-[(2*S*,3*S*)-2,3-dimethyl-3-dhyroxylpyrrolidin-1-yl]benzonitrile derivative **1a**. Further optimization of the substituents on the benzonitrile led us to discover compound **1c,** which shows a suitable agonistic activity and a promising PK profile together with sufficient metabolic stability. In in vivo studies, compound **1c** was confirmed to exhibit potent anabolic effects on levator ani muscle in a dose-dependent manner without increasing the weight of the prostate. In addition, compound **1c** induced sexual behavior in rats. Accordingly, we concluded that compound **1c** was a useful in vivo probe molecule to study the fundamental biology and therapeutic potential of a SARM. Further pharmacological and toxicological studies of these benzonitrile derivatives will be reported in due course.

Acknowledgments

We are grateful to Satoshi Yamamoto, Katsuji Aikawa, Douglas R. Cary and Ryo Mizojiri for helpful discussions on chemistry and manuscript preparation. We express our gratitude to Yoichi Nagano and Mitsuyoshi Nishitani for measurement of the small-molecule X-ray single-crystal structure and their assistance in crystallographic data deposition to the Cambridge Crystallographic Data Centre. We thank Ken Bragstad and Jasmine Nguyen for protein chemistry efforts, and Gyorgy Snell for X-ray data collection of protein complexes. We also thank the Berkeley Center for Structural Biology, which is supported in part by the National Institutes of Health, National Institute of General Medical Sciences, and the Howard Hughes Medical Institute. The Advanced Light Source is supported by the Director, Office of Science, Office of Basic Energy Sciences, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231

Supplementary material

Supplementary data (chemical synthesis procedures, compound data, in vitro and in vivo assay methods, PK analysis methods, and single and co-crystal structural data) associated with this article can be found, in the online version.

References and notes

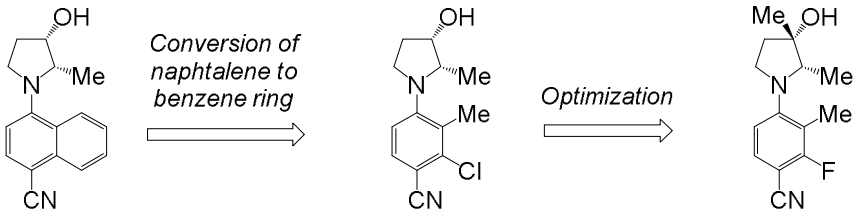
1. Ahern T, Wu FCW. *Age Ageing* 2015;44:188–195.
2. Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB. *J. Clin. Endocrinol. Metab.* 2006;91:2509–2513.
3. Isidori AM, Greco EA, Aversa A. *BJU Int.* 2005;96:212–216.
4. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. *J. Clin. Endocrinol. Metab.* 2001;86:724–731.
5. Udedibia E, Kaminetsky J. *Expert Opin. Investig. Drugs* 2014;23:1605–1618.
6. Choi SM, Lee, B-M. *Expert Opin. Drug Saf.* 2015;14:1773–1785.
7. Grech A, Breck J, Heidelbaugh J. *Ther Adv Drug Saf.* 2014; 5:190-200.
8. Narayanan R, Mohler ML, Bohl CE, Miller DD, Dalton JT. *Nucl. Recept. Signal.* 2008;6:e010.
9. Haendler B, Cleve A. *Mol. Cell. Endocrinol.* 2012;352:79–91.
10. Mohler ML, Bohl CE, Jones A, Coss CC, Narayanan R, He Y, Hwang DJ, Dalton JT, Miller DD. *J. Med. Chem.* 2009;52:3597–3617.
11. Zhang X, Sui Z. *Expert Opin. Drug Discov.* 2013;8:191–218.
12. Cosman F, Lindsay R. *Endocr Rev.* 1999;20:418–434.
13. Zhang X, Lanter JC, Sui Z. *Expert Opin. Ther. Pat.* 2009;19:1239–1258.
14. Jones A, Chen J, Hwang DJ, Miller DD, Dalton JT. *Endocrinology* 2009;150:385–395.
15. Srinath R, Dobs A. *Futur. Oncol.* 2014;10:187–194.
16. Nique F, Hebbe S, Triballeau N, Peixoto C, Lefrançois J-M, Jary H, Alvey L, Manioc M, Housseman C, Klaassen H, Beeck KV, Guédin D, Namour F, Minet D, Ellem VdA, Feyen J, Fletcher S, Blanqué R, Robin-Jagerschmidt C, Deprez P. *J. Med. Chem.* 2012;55:8236–8247.
17. Cozzoli A, Capogrosso RF, Sblendorio VT, Dinardo MM, Jagerschmidt C, Namour F, Camerino GM, Luca AD. *Pharmacol. Res.* 2013;72:9–24.
18. Nique F, Hebbe S, Peixoto C, Annoot D, Lefrançois J-M, Duval E, Michoux L, Triballeau N, Lemoullec J-M, Mollat P, Thauvin M, Prangé T, Minet D, Clément-Lacroix P, Robin-Jagerschmidt C, Fleury D, Guédin D, Deprez P. *J. Med. Chem.* 2012;55:8225–8235.
19. Aikawa K, Miyawaki T, Hitaka T, Imai YN, Hara T, Miyazaki J, Yamaoka M, Kusaka M, Kanzaki N, Tasaka A, Shiraishi M, Yamamoto S. *Bioorg. Med. Chem.* 2015;23:2568–2578.
20. Saeed A, Vaught GM, Gavardinas K, Matthews D, Green JE, Losada PG, Bullock HA, Calvert NA, Patel NJ, Sweetana SA, Krishnan V, Henck JW, Luz JG, Wang Y, Jadhav P. *J. Med. Chem.* 2016;59:750–755.
21. Nirschl AA, Zou Y, Krystek SR, Sutton JC, Simpkins LM, Lupisella JA, Kuhns JE, Seethala R, Golla R, Sleph, PG, Beehler BC, Grover GJ, Egan D, Fura A, Vyas VP, Li Y-X, Sack JS, Kish KF, An Y, Bryson JA, Gougoutas JZ, DiMarco J, Zahler R, Ostrowski J, Hamann LG. *J. Med. Chem*. 2009;52:2794–2798.
22. Yamamoto S, Kobayashi H, Kaku T, Hara T, Ymaoka M, Kanzaki N, Hasuoka A, Baba A, Ito M. *Bioorg. Med. Chem.* 2013;21:70–83.
23. Imamoto T, Takiyama N, Nakamura K. *Tetrahedron Lett.* 1985;26:4763–4766.

24. The stereochemical configuration of compound **1c** was confirmed by X-ray crystallographic analyasis, see supplementary material.

25. Bolleddula J, DeMent K, Driscoll JP, Worboys P, Brassil PJ, Bourdet DL. *Drug Metab. Rev.* 2014;46:379–419.

26. cLog *P* was calculated by daylight.

27. Hershberger LG, Shipley EG, Meyer RK. *Proc. Soc Exp. Biol. Med.* 1953;83:175–180.



A

AR binding IC_{50} = 2.3 nM
AR reporter EC_{50} = 0.48 nM
MS (h/r): 71/148 μL/min/mg
F = 9.7%

SARM profiles in vivo

B

AR binding IC_{50} = 0.72 nM
AR reporter EC_{50} = 0.19 nM
MS (h/r): 67/230 μL/min/mg
F = 1.6%

1c

AR binding IC_{50} = 1.0 nM
AR reporter EC_{50} = 0.29 nM
MS (h/r): 12/44 μL/min/mg
F = 46.3%

SARM profiles in vivo