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Synthesis and SAR of novel hydantoin derivatives as selective androgen receptor modulators

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Abstract—A novel series of hydantoin derivatives were identified by in vivo studies as tissue selective androgen receptor modulators. SAR around this series revealed that the function of the ligand could be altered by minor structural modification.

The androgen receptor agonists and antagonists are useful in the treatment of a variety of disorders and diseases.[1] Antagonists of the androgen receptor have shown efficacy in the treatment of prostate cancer, benign prostate hyperplasia, hirsutism in women, alopecia, anorexia nervosa, breast cancer, and acne. Agonists of the androgen receptor could be employed in male contraception, male performance enhancement, as well as in the treatment of cancer and AIDS cachexia. Recent success of novel selective estrogen receptor modulators (SERMs) has provided both preclinical and clinical proof-of-concept that small molecules can be developed with a great degree of tissue selectivity. These novel SERMs specifically target the estrogen receptor which prevents common side effects and maintains the positive protective effects of selective transcriptional receptor activation.[2] A new class of molecules targeting androgen receptors called selective androgen receptor modulators (SARMs) has been developed in response to the success of the SERMs.[3] An ideal SARM has antagonist or weak agonist activity in the prostate (androgenic organ) while presenting strong agonist activity in the muscle and bone (anabolic organ). This profile would allow the molecules to treat muscle-wasting conditions, hypogonadism, or age-related frailty while preventing potential risks for nascent or undetected prostrate cancer. Typical antiandrogens such as bicalutamide and nilutamide have been modified leading to the discovery of novel SARMs such as structure **I**, BMS-564929 and structure **II** (Fig. 1), which behaved as partial agonists in the prostate but full agonists in the levator ani. muscle as indicated by the castrated rat model.[4] These minor structural differences are interesting to explore further because they could greatly alter the nature of receptor–ligand interactions while showing a promising in vivo profile. In the present paper, we describe our design, synthesis, and SAR studies on a novel series of bicyclic structures containing hydantoin moiety as SARMs.

Our design approach was to mimic BMS 564929 by incorporating a novel hydantoin moiety. First, replacement of the angular H with a methyl group resulted in structure **3** (Scheme 1). Second, introduction of another heteroatom such as O or N into the B-ring of the bicyclic structure afforded structure **6** or **8** (Scheme 2). Finally, B-ring of the bicyclic structure was switched from pyrrolidinyl to dihydropyrazolinyl moiety to generate structure **13** (Scheme 3).

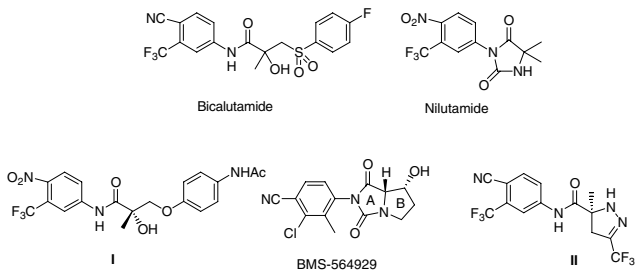

Figure 1.

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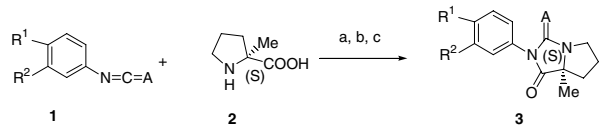
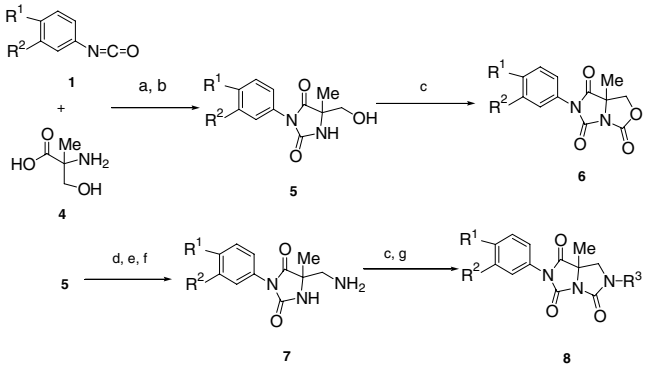
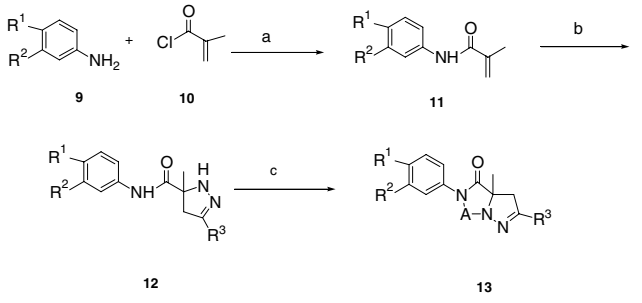


Scheme 1. Reagents and conditions: (a) dioxane, 100 °C, 4–6 h; (b) HCl, dioxane, 70 °C, 2 steps, 35–62%; (c) compounds **3c**–**3e**, **3d**–**3f**, CuCN, NMP, 200 °C, 10 h, 43–55%.



Scheme 2. Reagents and conditions: (a) dioxane, 100 °C, 4–6 h; (b) HCl, dioxane, 70 °C, 2 steps, 50–65%; (c) triphosgene, Et_3N, 0 °C, rt, 2 h, 70–75%; (d) MsCl, Et_3N, 0 °C, rt, 2 h, 82–85%; (e) KI (cat), NaN_3, DMF, 80 °C, 6 h, 85–90%; (f) Ph_3P, H_2O/THF, 80 °C, 1 h, 85–88%; (g) NaH, MeI, 0 °C, rt, 2 h, 65–70%.



Scheme 3. Reagents and conditions: (a) Et_3N, 0 °C, 0.5–2 h, 71–85%; (b) R^3CH=NNHTs, NaH, 0 °C, 30 min then 70 °C 4–6 h, 45–78%; (c) CDI, triphosgene, $(COCl)_2$, $SOCl_2$ or SO_2Cl_2, Et_3N, 0 °C, rt, 2 h, 55–80%.

The synthetic pathways utilized in the preparation of the bicyclic hydantoins **3**, **6**, **8**, and **13** are outlined in Schemes 1–3. The desired bicyclic compounds **3** were synthesized as described in the literature or with slight modifications to known procedures (Scheme 1).[5] Compound **3e** or **3f** was obtained from **3c** or **3d** by treatment with CuCN.

The synthesis of **6** or **8** was initiated through a manner similar to **3** by condensations of isocyanates **1**[6] with the amino acid **4** followed by acid catalyzed cyclization to afford **5** in reasonable yields (Scheme 2). Compounds **5** could easily fuse into the bicyclic structures **6** by treatment with CDI or triphosgene in the presence of triethyl amine (TEA). Compounds **5** were further transformed into primary amines **7** through mesylation followed by conversion of the mesylates to the corresponding azides and reduction of the azides. Upon treatment with triphosgene and TEA, the bicyclic structures **8** (where R^3 is H) were obtained in good yields. The bicyclic structures **8** (where R^3 is Me) could also be prepared from alkylation of their amide precursors.

The key step in the preparation of **13** consisted of an efficient 1,3-dipolar cycloaddition between the α,β-unsaturated alkenes **11** and the hydrozones (R^3CH=NNHTs)[7] in the presence of NaH to afford **12**.[4c] The alkene precursors **11** were obtained by coupling of methacryl chloride **10** with the corresponding anilines **9**. Compounds **13** were then prepared by intramolecular annulation of **12** with triphosgene, oxalyl chloride, thionyl chloride or sulfuryl chloride in the presence of TEA.

Our early discovery of structure **II** (Fig. 1) showed that it was active in both in vitro binding assay and in vivo assay via oral administration. Here, we started to investigate the SAR of its structural derivatives (**3**, **6**, **8**, and **13**).[4c] A modified Hershberger assay[8] was utilized as our primary guide for screening purposes to eliminate the complexity of in vitro and ADME data analysis. All compounds were tested in five-day immature (approximately 50 g) castrated male Sprague–Dawley rat (Charles River) agonist and antagonist assays. In these studies, the weights of the ventral prostate and seminal vesicle were used as the indicators of androgenic activity, while the weight of levator ani muscle was used as the indicator of anabolic activity. Thus, rationalization of these results should combine a test compound's ADME properties and intrinsic efficacy. Initial studies on structure **3** revealed that these hydantoin derivatives acted like a pure antiandrogen. None of the compounds listed in Table 1 showed any substantial agonist activity on the ventral prostate or the levator ani muscle (data not shown). The substitution pattern R^1 and R^2 on the aniline portion of the molecule dictated the antiandrogenic activity. Potent ventral prostate weight inhibition activities were found in compound **3e** and its sulfur analog **3f** where R^1 = CN and R^2 = CF_3 on the phenyl rings, which correlated to the SAR of known toluidide antiandrogens such as hydroxyflutamide, nilutamide, and bicalutamide. Electron-donating or neutral group at either the R^1 or R^2 position of the phenyl group diminished the antiandrogenic activity, as shown with compounds **3a**–**3d**. Table 2 illustrates the in vivo antiandrogenic activities for compounds **6** and **8** containing urea or oxazolidinone functionality in the B-ring of the bicyclic hydantoin structures. Similar to compounds **3** in Table 1, compounds **6** and **8** demonstrated the AR antagonist activities in the testosterone treated castrated immature rats, while they did not present clear agonistic potency. As the data indicated, both the substitutions at R^1 or R^2 positions of the phenyl rings and the substitution at R^3 position contributed to the overall activities of this series of compounds. Strong prostate weight inhibition was observed with oxazolidinone **6b** (75% inhibition) and urea **8b** (79% inhibition), **8e** (87% inhibition). Replacement of R^1 from CN to Cl group significantly reduced the potency (**6a** and **8a**). Masking of R^3 with a methyl group seemed to improve the potency, as illus-

Table 1. SAR at substitutions R^1, R^2 and A of structure **3**[a]

Compound	R^1	R^2	A	Prostate inhibition (%)	Seminal vesicle inhibition (%)
Bicalutamide[b]				70	80
3a	Cl	Cl	O	11	16
3b	Cl	Cl	S	17	27
3c	Cl	CF_3	O	32	na[c]
3d	Cl	CF_3	S	19	na
3e	CN	CF_3	O	69	na
3f	CN	CF_3	S	78	95

[a] All compounds were administered via po (vehicle: 20% cyclodextrin) once daily in the presence of 0.1 mg/d (approximately 1.3 mg/kg) testosterone propionate (subcutaneous dosing; vehicle: sesame oil) at a dose rate of 2 mg/day for 5 days. The data were normalized to control group administered with vehicle (n = 3/group).
[b] Average value (n = 10).
[c] na, not active (<10% inhibition at a dose rated of 2 mg/day).

Table 2. SAR at substitutions R^1, R^2, and R^3 of structures **6** and **8**[a]

Compound	R^1	R^2	R^3	Prostate inhibition (%)	Seminal vesicle inhibition (%)
Bicalutamide				70	80
6a	Cl	CF_3	—	55	51
6b	CN	CF_3	—	75	80
6c	NO_2	CF_3	—	43	28
8a	Cl	CF_3	H	33	19
8b	CN	CF_3	H	79	86
8c	NO_2	CF_3	H	32	15
8d	Cl	CF_3	Me	77	85
8e	CN	CF_3	Me	87	85

[a] All footnotes in Table 1 apply in this table.

trated in **8d**. Overall, compounds **6** and **8** containing urea or oxazolidinone moiety at the B-ring of the bicyclic hydantoin structure were well tolerated for antiandrogenic activity compared with their carbon analogs of compounds **3**.

Interestingly, replacement of pyrrolidine with dihydropyrazoline ring led to the discovery of a novel series of hydantoin structures as selective androgen receptor modulators, as shown in Table 3. Unlike compounds **3**, **6**, and **8**, compound **13d** bearing a CF_3 group at R^3 position demonstrated the AR agonist activities in castrated immature rats. In the agonist model, **13d** prevented castration caused tissue weight loss and behaved as partial agonist in the prostate (11% stimulation of the prostate weight at 3 mg/d) but full agonist in the levator ani muscle (75% stimulation of the levator ani muscle weight at 2 mg/d). The activity observed on **13d** was further confirmed by a four-point dose-dependent study to generate ED_{50} 2.9 mg/d. On the other hand, it worked as a weak AR antagonist in the prostate (26% inhibition of the prostate weight at 2 mg/d) in the antagonist model. Compound **13e**, *R*-enantiomer of **13d**,[9] presented similar dose-dependent response (ED_{50} > 3 mg/d) to the rat prostate and levator ani muscle in the agonist model, while the efficacy was substantially decreased, suggesting **13d** acted as eutomer in the racemate. Any modification of R^3 group, including removal (**13a**), replacement with hydrophilic (**13b** and **13g**) or bulky group (**13c**), resulted in total loss of agonistic activity. Several replacements of the carbonyl linker at the A position of the bicyclic structure were well tolerated for in vivo efficacies. As illustrated in **13k** and **13l**, these compounds containing sulfonyl or sulfinyl linker still maintained both agonistic activity in the levator ani muscle and antagonistic activity in the ventral prostate.

In summary, we have shown that modification of hydantoin-based antiandrogens led to the discovery of a novel series of bicyclic hydantoin derivatives as selective androgen receptor modulators. The lead compound **13d**, upon further optimization, has the opportunity to be a novel therapeutic agent with potential application in treatment of androgen-related disorders.

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Table 3. SAR at substitutions R^1, R^2, and R^3 of structures **13**[a]

Compound	R^1	R^2	R^3	A	Prostate stimulation (%)	Levator ani muscle stimulation (%)	Prostate inhibition (%)
TP[b]					100	100	
Bicalutamide							70
13a	CN	CF_3	H	CO	na	na	26
13b	CN	CF_3	CO_2Et	CO	na	na	16
13c	CN	CF_3	4-NHAc-Ph	CO	na	13	25
13d (*S*)	CN	CF_3	CF_3	CO	11[c]	75[d]	26
13e (*R*)	CN	CF_3	CF_3	CO	14[c]	42[c]	21
13f	NO_2	CF_3	CF_3	CO	51	73	39
13g	NO_2	CF_3	CO_2Et	CO	na	na	35
13i	CN	CF_3	CO_2Et	COCO	na	na	15
13j (*S*)	CN	CF_3	CF_3	COCO	12	21	27
13k (*S*)	CN	CF_3	CF_3	SO_2	41	66	28
13l (*S*)	CN	CF_3	CF_3	SO	58	117	41

[a] All footnotes in Table 1 apply in this table.
[b] Testosterone propionate was administered subcutaneously by injection at the nape of the neck at 5 mg/kg, in a volume of 0.1 mL in sesame oil.
[c] 11% prostate weight stimulation at a dose rate of 3 mg/d.
[d] Compound **13d** was further tested in a four-point dose-dependent study at doses from 0.1, 0.3, 1 to 3 mg/d to generate ED_{50} 2.9 mg/d. Compound **13e** in the similar test showed ED_{50} > 3.0 mg/d.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bmcl.2006.08.084.

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7. TMSdiazomethane and ethyl diazoacetate were used to prepare compounds **13a**, **13b**, **13g** and **13i**.
8. Hershberger, L. G.; Shipley, E. G.; Meyer, R. K. *Proc. Soc. Exp. Biol. Med.* **1953**, *83*, 175; (a) Antagonist assay: Test compound activity was determined as the percent inhibition of testosterone-enhanced tissue weights, with a vehicle-treated control group set to 100% and a testosterone alone-treated control group set to 0 percent; (b) Agonist assay: Test compound activity was determined as the percent stimulation of tissue weight, with the vehicle-treated control group set to zero percent and the testosterone alone-treated control group set to 100%.
9. Compounds **13d** and **13e** were prepared from the enantiomeric pure precursors **12**, which were separated by ChiralPak AD column, also see Ref. 4c.