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Synthesis of novel iodo derived bicalutamide analogs

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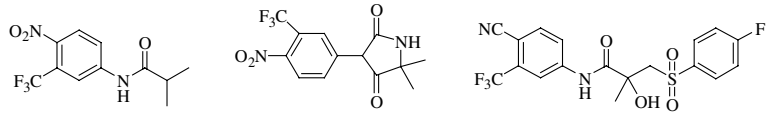
Abstract—A series of optically active nonsteroidal selective androgen receptor modulators with structures analogous to bicalutamide was prepared by replacing the trifluoromethyl group with iodine and the sulfonyl linker by oxygen.

The search for nonsteroidal antiandrogens that will block the pharmacological effects of testosterone, led to the development of compounds like flutamide, nilutamide, and (*R*,*S*)-bicalutamide, which are widely used for the treatment of metastatic prostate cancer (Scheme 1).[1–4] The commonly accepted structure–activity relationship borne out of these ligands suggest the importance of an electron deficient aromatic ring, branched alkyl group α to the amidic carbonyl, the need for a strong hydrogen bonding and a conformational preorganization, which assigns a coplanarity for the amide linkage and hydroxyl group.[5–11] It has been understood that bicalutamide contains a stereogenic center and the stereochemistry at this center is important in maximizing the affinity for the androgen receptor; the (*R*) enantiomer being the active stereoisomer.[12,13] The present paper discusses the synthesis of a new class of optically active bicalutamide analogs namely, (2*S*)-*N*-(4′-cyano-3′-iodophenyl)-3-(4-substituted phenoxy)-2-hydroxy-2-methylpropanamide derivatives **15**, which are nonsteroidal selective androgen receptor modulators (SARM).

A retrosynthetic strategy for the compound **15** leads to the conclusion that it could be synthesized from the synthons 4-amino-2-iodobenzonitrile **5**, (2*R*)-3-bromo-2-hydroxy-2-methylpropanoic acid **11** and 4-substituted phenol **14**. The noncommercial availability of 4-amino-2-iodobenzonitrile prompted us to examine its synthesis. Compound **5** was synthesized initially from 2-amino-4-nitrobenzoic acid as shown in Scheme 2.[6] A solution of 2-amino-4-nitrobenzoic acid **1** in dilute sulfuric acid was diazotized at 0 °C by dropwise addition of an aqueous solution of sodium nitrite. The resulting diazonium salt on treatment with a solution of sodium iodide afforded 2-iodo-4-nitrobenzoic acid **2**. It was converted to the corresponding acid chloride by refluxing with thionyl chloride in anhydrous benzene. Residual thionyl chloride was removed from the reaction mixture by



Flutamide Nilutamide (*R*,*S*)-Bicalutamide

Scheme 1.

Keywords: Bicalutamide; Trifluoromethyl; Sulfonyl; Androgen; Receptor; Nonsteroidal; SARM.
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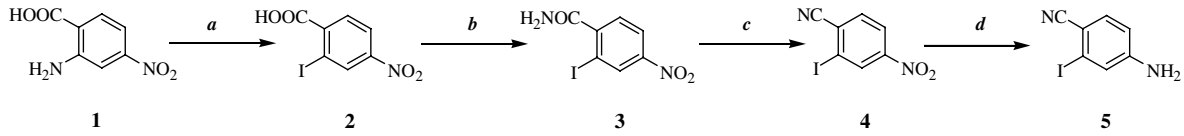


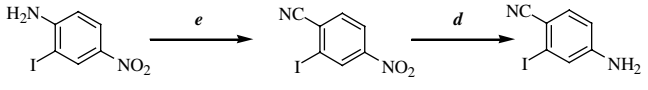
1 2 3 4 5

a: $NaNO_2$, H_2SO_4, NaI *b:* $SOCl_2$, aq. NH_3 *c:* $SOCl_2$ *d:* HCl, $SnCl_2.2H_2O$, EtOH

Scheme 2.

coevaporation with anhydrous benzene. Addition of concentrated aqueous ammonia followed by overnight stirring at room temperature precipitated 2-iodo-4-nitrobenzamide **3**, from which 2-iodo-4-nitrobenzonitrile **4** was prepared by refluxing it with thionyl chloride. Subsequent reduction of the 2-iodo-4-nitrobenzonitrile with tin(II) chloride dihydrate in acidic medium afforded 4-amino-2-iodobenzonitrile **5**. However, due to multi-step reactions with poor yields and drastic reaction conditions, we designed a cost-effective two-step synthetic strategy for the synthesis of 4-amino-2-iodobenzonitrile. Compound **5** was synthesized according to Scheme 3, wherein 2-iodo-4-nitroaniline **6** was dissolved in acetic acid and then treated with 10% H_2SO_4 to obtain a homogeneous solution. The reaction mixture was cooled to 0 °C in an ice-bath, diazotized with cold aqueous solution of $NaNO_2$. Addition of the cold solution of diazonium salt in a dropwise manner to an aqueous solution of copper cyanide and sodium cyanide, afforded 2-iodo-4-nitrobenzonitrile **4**, which was reduced with tin(II) chloride dihydrate in acidic medium to yield 4-amino-2-iodobenzonitrile **5**, which was identified by spectral and elemental analyses.[14]

The (2*R*)-3-bromo-2-hydroxy-2-methylpropanoic acid was prepared by employing (D)-proline as the starting material as shown in Scheme 4. (D)-Proline **7** was converted to 1-(2-methacryloyl)pyrrolidine-2-carboxylic acid **9** by Schotten Baumann reaction. An acetone solution of 2-methacryloyl chloride **8** and sodium hydroxide solution were simultaneously added to an ice-cold alkaline solution of (D)-proline **7** in acetone. The pH of the reaction mixture was kept alkaline during the addition



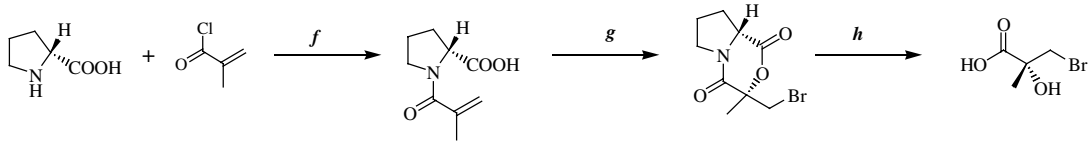
6 4 5

e: $NaNO_2$, H_2SO_4, CuCN, NaCN *d:* HCl, $SnCl_2.2H_2O$, EtOH

Scheme 3.

of the methacryloyl chloride. After the reaction, the reaction mixture was acidified and extracted into ethyl acetate to afford 1-(2-methacryloyl)pyrrolidine-2-carboxylic acid **9**. A solution of *N*-bromosuccinimide in dimethyl formamide was added dropwise to a well stirred solution of 1-(2-methacryloyl)pyrrolidine-2-carboxylic acid in dimethyl formamide at room temperature and the resulting mixture was stirred overnight. The reaction mixture was poured into ice-cold distilled water to obtain a yellow colored precipitate of the bromolactone **10**, which was then hydrolyzed by refluxing with 24% hydrobromic acid. Work-up of the reaction mixture followed by recrystallization afforded colorless crystals of optically active (2*R*)-3-bromo-2-hydroxy-2-methylpropanoic acid **11**, which was identified by spectral and elemental analyses.[14]

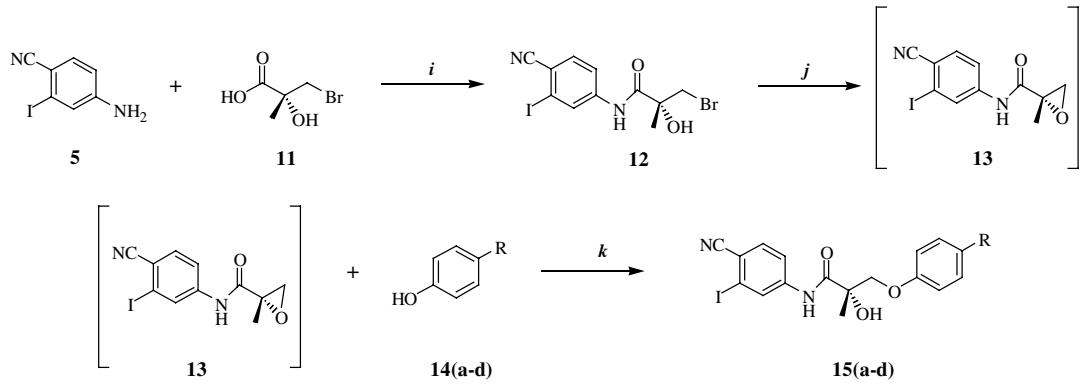
The synthetic procedure employed for the preparation of target compound **15** is depicted in Scheme 5. A solution of (2*R*)-3-bromo-2-hydroxy-2-methylpropanoic acid **11** in tetrahydrofuran was converted to the corresponding acid chloride by thionyl chloride under argon atmosphere at 0 °C. Addition of a solution of 4-amino-2-iodobenzonitrile **5** in tetrahydrofuran followed by overnight stirring at room temperature yielded (2*R*)-*N*-(4′-cyano-3′-iodophenyl)-3-bromo-2-hydroxy-2-methylpropanamide **12**. With two electron withdrawing groups attached, 4-cyano-3-iodobenzonitrile is a relatively poor nucleophile and hence (2*R*)-3-bromo-2-hydroxy-2-methylpropanoic acid was used in a stochiometric excess of 1.5 equiv. A solution of compound **12** in acetone when refluxed with K_2CO_3 generated the epoxide, *N*-(4′-cyano-3′-iodophenyl)-2,3-epoxy-2-methylpropanamide **13**. The epoxide was subsequently opened up by refluxing it with 4-substituted phenol **14** and K_2CO_3 in 2-propanol medium. The conversion of the intermediate **12** to the ether linked target compound **15** through the epoxide formation was carried out in a two-step, one-pot process wherein after the epoxide was formed, the solvent was removed and the resulting residue was immediately carried on to the ring opening step. The (2*S*)-*N*-(4′-cyano-3′-iodophenyl)-3-(4-substituted phenoxy)-2-hydroxy-2-methylpropanamide derivatives obtained were



7 8 9 10 11

f: NaOH, acetone *g:* NBS, DMF *h:* HBr

Scheme 4.



i: $SOCl_2$, THF *j:* K_2CO_3, acetone *k:* K_2CO_3, 2-propanol

R: **a** = F, **b** = Cl, **c** = Br, **d** = I

Scheme 5.

characterized by spectral and elemental analyses (data shown for **15a**).[14]

In general, this work provides a facile route to the synthesis of a new class of optically active bicalutamide analogs with trifluoromethyl and sulfonyl groups being replaced by iodine and oxygen, respectively. Preliminary biological results have shown that these compounds exhibited good activity and binding affinity to the androgen receptor.[15] However studies are ongoing for the development of these target compounds as drug candidates for therapeutic and diagnostic uses in prostate cancer. Investigations are also carried out to replace the iodine with a radioactive isotope (I^{125}), through a trimethyltin intermediate, for imaging studies so as to convincingly establish the mechanism of action of the tissue selective androgen receptor modulator, which we discovered in 1998.[16]

Acknowledgements

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14. Spectral data **5**: white solid (yield: 40%), mp 137 °C; NMR (^{1}H, 300 MHz, $CDCl_3$): 6.62 (m, 1H, ArH, J = 1.9 Hz, 8.3 Hz), 7.15 (m, 1H, ArH, J = 0.5 Hz, 8.3 Hz) 7.35 (m, 1H, ArH, J = 0.5 Hz, 1.9 Hz); MS: 245 CHN: $C_7H_5IN_2$ calcd: C, 34.45; H, 2.07; N, 11.48; found: C, 34.39; H, 1.96; N, 11.41. Compound **11**: White solid (yield: 85%), mp 108 °C; $[\alpha]_D^{25}$ +10.5 (*c* 2.6, MeOH); NMR (^{1}H, 300 MHz, DMSO): 1.35 (s, 3H, CH_3), 3.5 (s, 1H, CH), 3.6 (s, 1H, CH), 4.0 (br, 1H, OH); MS: 205 ($M+Na^+$) CHN: $C_4H_7BrO_3C$, 26.25; H, 3.86; found: C, 26.28; H, 3.75. Compound **12**: white solid (yield: 35%), mp 152 °C; $[\alpha]_D^{25}$ +47.3 (*c* 1.0, MeOH); NMR (^{1}H, 300 MHz, $CDCl_3$): 1.7 (s, 3H, CH_3), 3.1 (br, 1H, OH), 3.6 (s, 1H, CH), 4.1 (s, 1H, CH), 7.6 (m, 1H, ArH, J = 1.8 Hz, 7.2 Hz), 7.7 (m, 1H, ArH, J = 0.5 Hz, 7.2 Hz), 8.3 (m, 1H, ArH, J = 0.5 Hz, 1.8 Hz), 8.9 (br, 1H, NH); MS: 407.8 $C_{11}H_{10}BrIN_2O_2$ calcd: C, 32.30; H, 2.46; N, 6.85; found: C, 32.28; H, 2.35; N, 6.82. Compound **15a**: (R = F) white solid (yield: 65%), mp 101 °C; $[\alpha]_D^{25}$ −72.1 (*c* 1.0, MeOH); NMR (^{1}H, 300 MHz, $CDCl_3$): 1.5 (s, 3H, CH_3), 3.3 (br, 1H, OH), 3.9 (s, 1H, CH), 4.4 (s, 1H, CH), 6.9 (m, 2H, ArH, J = 3.0 Hz, 9.2 Hz,), 7.0 (m, 2H, ArH, J = 3.0 Hz, 9.2 Hz), 7.6 (m, 1H, ArH, J = 1.8 Hz, 7.2 Hz), 7.7 (m, 1H, ArH, J = 0.4 Hz, 7.2 Hz), 8.3 (m, 1H, ArH, J = 0.4 Hz, 1.8 Hz), 8.9 (br, 1H, NH); MS: 438.9 (M−H) $C_{17}H_{14}FIN_2O_3$ calcd: C, 46.38; H, 3.21; N, 6.36; found: C, 46.27; H, 3.15; N, 6.24.
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