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Original article

An improved and practical route for the synthesis of enzalutamide and potential impurities study

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ABSTRACT

An improved and practical synthesis of enzalutamide was accomplished in five steps. Starting from 4-bromo-2-fluoro-benzonic acid, a methyl esterification, Ullmann ligation, methyl esterification, ring closing reaction and final methyl amidation provided the target in 35% total yield with 99.8% purity. Five identified impurities were also synthesized. This efficient and economical procedure avoids the use of highly toxic reagents and multiple recrystallization operations, which is suitable for further industrialization.

1. Introduction

Enzalutamide (**1**, Fig. 1) is a new type of androgen receptor (AR) antagonist [1] that was developed by Medivation Inc for the treatment of castration-resistant prostate cancer [2,3] (CRPC), a serious cancer that afflicts men [4]. The oral capsule of Enzalutamide [5] was approved by the FDA for sale in August 2012. According to the statistics of the American Cancer Society [6], 217,730 new patients were diagnosed with prostate cancer by hospitals and clinics in the United States of America in 2010. Of these, 32,050 patients died as a result of prostate cancer within 2 years. Bicalutamide [7], flutamide [8] and abiraterone [9] were used to treat prostate cancer before the launch of enzalutamide. These drugs controlled CRPC effectively in only a small proportion of patients and caused some obvious side effects [10], such as hypertension, atrial fibrillation and hypokalemia. The cancer became resistant to these treatments in many patients after a period of about 2 years [11–13]. The development of enzalutamide provided a better choice for the treatment of CRPC, achieving sales of up to 1 billion dollars in 2013 and even better returns after that year. Research into new processes to produce the active pharmaceutical ingredient (API) enzalutamide is important and meaningful to continue delivery of this important drug.

Three main routes for the synthesis of enzalutamide have been reported. The first was undertaken by Sawyers et al. [14] in 2006. One obvious deficiency on this route is the very low yield of the last step, which would make producing the API costly at industrial scale. Song et al. [15] made a small improvement to this route using ethyl 2-bromobutyrate in place of 2-cyano-2-propanol, but this route remained unattractive for the production of **1**. Five years later, Thompson and co-workers [16] provided an alternative route to synthesize **1**, which improves on the original synthesis by removing the oxidation and reduction reactions. However, the yields of the last two steps are too low for economical kilo scale production of the API. Scientists from Medivation Inc. [17] also improved the second route and published their results in 2012. This synthesis overcame the poor yields of the final steps in the first and second routes, which justifies the use of high toxic iodomethane at a late stage of the synthesis and makes the third route more reasonable than the procedures of the first and second routes for commercial manufacture, but the crude product of which also need to be recrystallized for 2–3 times by isopropanol to get qualified API. A new route is needed for the efficient synthesis of **1** using moderate and environmentally friendly conditions and reagents. Herein we report a new five-step route to **1** that avoids highly toxic reagents and multiple recrystallization processes.

2. Results and discussion

Our new route [18,19] began with 4-bromo-2-fluoro-benzonic acid (**2a**) (Scheme 1). 5 g of **2a** were subjected to a methyl

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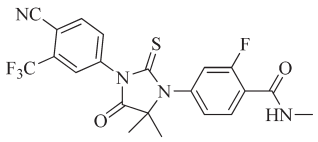
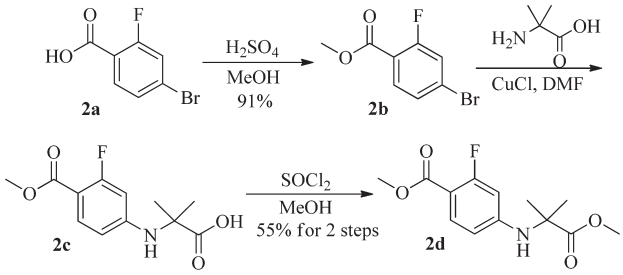
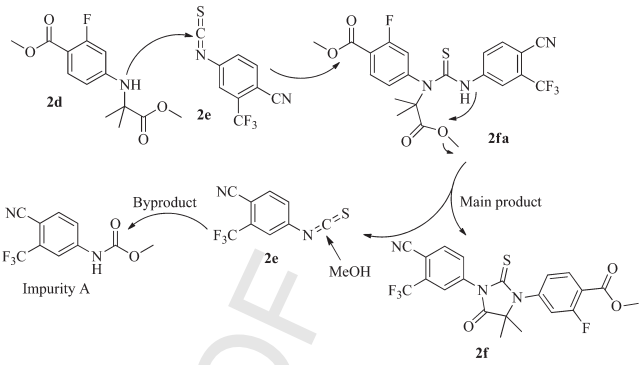


Fig. 1. Structure of enzalutaminde **1**.



Scheme 1. The first three steps of the new route to enzalutamide.



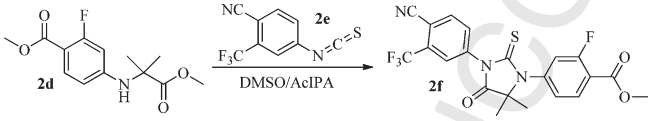
Scheme 2. Possible reaction mechanism of the fourth step on the new route.

esterification reaction catalyzed by sulfuric acid in methanol under reflux in the first step [20] to obtain methyl 4-bromo-2-fluoro-benzoate (**2b**) in 95% yield, which was easily isolated as a white solid by pouring the reaction solution into ice water after 24 h. The second step was an Ullmann reaction [21–23] for the ligation of **2b** with 2-amino-2-methylpropionic acid to give compound **2c**, which was reacted with thionyl chloride in refluxing methanol to obtain 3603 g of intermediate 2-fluoro-4-[(2-methoxy-1,1-dimethyl-2-oxoethyl)amino]-methyl ester (**2d**) in a total yield of 51% for the first three steps.

Intermediate **2d** was reacted with **2e** [24,25] in the fourth step of our new route. The reaction conditions for this step were optimized by the following steps (Table 1). The initial conditions used 1.0 mol of compounds **2d** and **2e** in a solution of dimethyl sulfoxide (DMSO) and isopropyl acetate at 95 °C to give only 30% of the desired product (Table 1, entry 1). Increasing the stoichiometry of compound **2e** resulted in higher yields (Table 1, entries 2–4). The final ratio of reactant **2e** was fixed at two equivalents relative to **2d** to ensure a cost-effective process. Lowering the reaction temperature to 80 °C dropped the yield to 57% (Table 1, entry 5). Ethyl acetate has similar properties to isopropyl acetate but was not suitable to achieve high yields because the lower boiling point of this solvent prevented an adequate reaction temperature (Table 1, entry 6). DMF was investigated as an alternative to DMSO but only a trace amount of the solid was crystalized from the mother solution, that is probably because DMSO is a highly polar solvent which is easier to be removed completely by water washing than that of DMF (Table 1, entry 7). We increased the reaction scale to over 1 kg and lowered the ratio of DMSO from 33% to 16% of the total solvent to obtain a 82% yield of the product after a 24-h reaction (Table 1, entry 8). Extending the reaction time to 36 or 48 h decreased the yields of the product by 5% and 12%, respectively (Table 1, entries 9 and 10).

Although the intermediate **2f** was successfully synthesized in 82% using the optimized conditions, it was unclear why the reaction required two equivalents of **2e**. A likely mechanism to explain this phenomenon is shown in Scheme 2. The lone pair electrons on the nitrogen atom of compound **2d** attack the most positively charged carbon on the isothiocyanate group of compound **2e** in the first step to form an active intermediate **2fa**. An intramolecular ring closing reaction of **2fa**, using the lone pair electrons of the nitrogen atom on the thiourea group to attack the methyl ester group, forms the stable five-member ring of the main product **2f**. A molecule of methanol is released by this process, which is a strong nucleophile and reacts with another molecule of compound **2e** to form methyl *N*-(3-trifluoromethyl-4-cayno-)-phenylcarbonate (impurity A) as a side product. Fortunately, impurity A was easily to be removed by recrystallization with isopropanol to get qualified **2f**. This possible mechanism explains why two molecules of reactant **2e** were consumed to form product **2f** and one molecule of side product impurity A.

Table 1
Optimization of the fourth step of the new route to enzalutamide.



Entry	**2d**:**2e** (molar ratio)[a]	Solvents (v/v)[b]	Temp. (°C)	Time (h)	Yield (%)[c]
1	1:1	DMSO:AcIPA = 1:2	95	24	30
2	1:1.5	DMSO:AcIPA = 1:2	95	24	45
3	1:2	DMSO:AcIPA = 1:2	95	24	65
4	1:3	DMSO:AcIPA = 1:2	95	24	68
5	1:2	DMSO:AcIPA = 1:2	80	24	57
6	1:2	DMSO:AcOEt = 1:2	65	24	45
7	1:2	DMF:AcIPA = 1:2	95	24	Trace
8	1:2	DMSO:AcIPA = 1:5	95	24	82
9	1:2	DMSO:AcIPA = 1:5	95	36	77
10	1:2	DMSO:AcIPA = 1:5	95	48	70

[a] For entries 1–7 the amount of **2d** was 269 g (1.0 mol) and for entries 8–10, the amount of **2d** was increased to 1200 g (4.46 mol).
[b] For entries 1–7, the total solvent volume was 810 mL and for entries 8–10 the total solvents volume was 3600 mL.
[c] Isolated yields.

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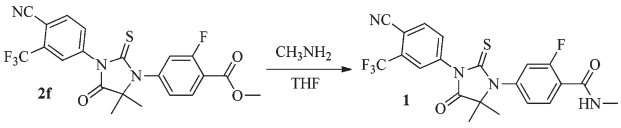
Table 2
Optimization of the last step of the new route to enzalutamide.



Entry[a]	Form of methylamine	Temp. (°C)	Time (h)	Conversion of **2f** (%)[b]	Yield (%)[c]	Purity of crude **1** (%)[d]
1	CH_3NH_2·HCl	r.t.	24	<5	–	–
2	2.0 M in THF	r.t.	48	≈30	–	–
3	2.0 M in MeOH	r.t.	48	≈30	–	–
4	33% in MeOH	r.t.	48	≈60	–	–
5	30% in H_2O	r.t.	48	≈80	–	–
6	40% in H_2O	r.t.	4	>99	55	96.66
7	40% in H_2O	15 ± 3	7	>99	60	97.85
8	40% in H_2O	10 ± 3	10	>99	60	98.99
9	40% in H_2O	5 ± 2	12	>99	70	99.16
10	40% in H_2O	0 ± 2	16	>99	70	99.24
11	40% in H_2O	−5 ± 1	19	>99	72	99.44
12	40% in H_2O	−10 ± 1	24	>99	76	99.65
13	40% in H_2O	−15 ± 1	48	>99	78	99.59
14	40% in H_2O	−8 ± 1	22	>99	75	99.75
15	40% in H_2O	−8 ± 1	22	>99	84	99.80
16	40% in H_2O	−8 ± 1	22	>99	86	99.78

[a] Entries 1–14 were carried out on 100 g scales, and entries 15 and 16 were carried out on a 1.4 kg scale.
[b] Conversion of **2f** was monitored by TLC.
[c] Isolated yield.
[d] HPLC analysis.

The fifth and final step was a methyl amidation reaction of **2f** to give **1**. Initial experiments investigating the solvents tetrahydrofuran (THF), methanol (MeOH), ethanol (EtOH), acetone or dichloromethane (DCM) indicated that this reaction was most successful in THF. Two key points that affect the degree of reaction completion and purity of the final product are the different forms of methylamine and reaction temperature. We began screening tests with different forms of methylamine (Table 2). Methylamine hydrochloride failed to react because of low solubility in THF and weak nucleophilicity (Table 2, entry 1). Solutions of 2.0 mol/L methylamine as a free base in THF and MeOH were attempted to improve solubility (Table 2, entries 2 and 3), but the conversions were around 30%, probably because of the low concentrations of the methylamine solutions. Higher concentrations of 33% methylamine in MeOH and 30% methylamine in water were used to increase conversion, but large amounts of **2f** remained at the end of the reaction, even when the reaction time was extended to 48 h at room temperature (Table 2, entries 4 and 5). The most concentrated methylamine solution commercially available is a 40% aqueous solution. Fortunately, the reactant **2f** was not detected by TLC when treated with the 40% methylamine aqueous solution for 4 h at room temperature and the product was obtained in 55% yield (Table 2, entry 6). HPLC analysis indicated that many unidentified impurities were also formed using these conditions.

The concentrations of impurities must be minimized to the accepted levels set by the International Conference on Harmonization (ICH) to ensure the safety and quality of a drug substance. The optimal reaction temperature for this reaction was investigated. Temperatures between 15 °C and −15 °C were screened and required extending the reaction time as the temperature was lowered. The purity of crude **1** was 97.85% when the reaction was carried out at 15 °C for 7 h (Table 2, entry 7). The purity improved to 98.99% and 99.16% (Table 2, entries 8 and 9) for reactions at 10 °C and 5 °C, respectively. However, these crude products were needed to be recrystallized two to three times to meet ICH guidelines and more than half of the product was lost to these multiple recrystallization processes. Improving the purity of the crude product and removing the need for multiple recrystallization operations was deemed critical to allow industrialization of our process. Lowering the reaction temperature to 0 °C or −5 °C, the purity was improved to 99.24% and 99.44%, respectively (Table 2, entries 10 and 11). The purity was further improved to 99.65% by decreasing the temperature to −10 °C (Table 2, entry 12). Lowering the temperature further to −15 °C extended the reaction time to 48 h without improving the crude purity of **1** (Table 2, entry 13). The final temperature was fixed at −8 °C and the reaction was completed in 22 h with a crude purity of 99.75% (Table 2, entry 14). Two parallel scale-up reactions at a kilogram scale synthesized **1** with high crude purity and satisfactory yield at −8 °C in 22 h (Table 2, entries 15 and 16). These conditions provide a practical route for further industrialization of our process.

Besides impurity A, four other impurities were identified from the reaction process and synthesized afterwards. Impurity B and C are probably formed by the side reactions of hydrolyzation and

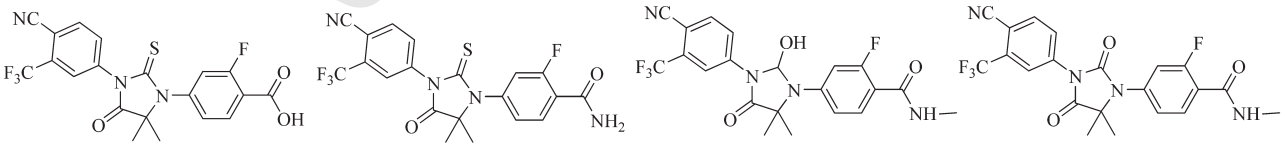


Fig. 2. Four observed impurities in the new route.

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aminolyzation during the process from **2f** to **1**. The impurities D and E were also identified in the process probably because the sulfur atom is easily to be oxidized to oxygen or hydroxide group, which were synthesized and characterized, the structures and relative retention time of which are listed in Fig. 2. The relative retention time of enzalutamide is on 28.00 min. The synthesis procedures and characterization data are provided in the Supporting information.

3. Conclusion

A novel approach to synthesize enzalutamide has been established. This five-step process removes poor yielding steps without the need for highly toxic chemicals and multiple recrystallization processes, five impurities were also identified and synthesized. Compared with the existing process, this approach is the most efficient, economical and convenient route to synthesize enzalutamide on a large scale.

4. Experimental

Nuclear magnetic resonance (NMR) spectra were recorded on a Varian INOVA-400 spectrometer with TMS as an internal standard. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. ESI mass spectra were obtained using on an Agilent 6210 TOF spectrometer. Elemental analyses were performed on a MOD-1106 instrument and are consistent with theoretical values within ±0.3%. Uncorrected melting points were determined on an electrothermal melting point apparatus. Reaction progress and chemical purity were evaluated by HPLC analysis using Waters symmetry C18 (5 μm, 250 mm × 4.6 mm) column with a mobile phase A (MeOH + 0.05% TFA) and B (0.3% TEA), 88:12 v/v; detection at 230 nm; flow rate: 1.0 mL/min; and temperature: 25 °C. TLC analyses were performed on prepared HSGF254 TLC plates. Solvents and reagents were used as received.

*4.1. Synthesis of methyl 4-bromo-2-fluoro-benzonate (**2b**)*

4-Bromo-2-fluoro-benzonic acid (**2a**) (5.0 kg, 22.9 mol) was charged to a 50-L round-bottom glass reaction vessel holding methanol (20.0 L). Concentrated sulfuric acid (500 mL) was added dropwise over 40 min. The reaction mixture was heated under reflux for 12 h, poured into ice water (30 L) and the white solid precipitate filtered. The product was dried by heating (less than 50 °C) in an oven overnight to afford **2b** as white crystals (4851.1 g, 91.2% yield). Mp 60.0–61.0 °C; ^{1}H NMR (400 Hz, DMSO-d_6): δ 3.85 (t, 3H, J = 8.5 Hz), 7.54–7.57 (dd, 1H, J = 8.8, 1.2 Hz), 7.68–7.71 (dd, 1H, J = 10.4, 1.2 Hz), 7.80–7.84 (t, 1H, J = 8.2 Hz).

*4.2. Synthesis of 2-fluoro-4-[(2-methoxy-1,1-dimethyl-2-oxoethyl)amino]-methyl ester (**2d**)*

2-Amino-2-methyl-propionic acid (3527.0 g, 34.2 mol, 1.5 equiv.), anhydrous copper monochloride (CuCl, 457.0 g, 4.6 mol, 0.2 equiv.), potassium carbonate (K_2CO_3, 5768.0 g, 41.8 mol), and water (250 mL) were added to a solution of compound **2b** (4851.1 g, 20.9 mol) in DMF (15.0 L) and heated to 105 °C for 12 h. The color of the reaction system turned from deep green to purple then to deep blue over this period. At the end of the reaction the slurry was filtered, water (60.0 L) was added to the deep-blue solution, and the mixture was neutralized with saturated citric acid solution until the pH 3–4 and the solution turned light blue. The solution was extracted with 2-methyltetrahydrofuran (20.0 L × 3) and the combined organic layers concentrated *in vacuo*. The yellow residue (crude compound **2c**) was used for the next reaction step without any further separation or purification process.

Crude **2c** was dissolved in methanol (20.0 L) and thionyl chloride (1.0 L) was added dropwise at 0 °C over 30 min. The solution was heated under reflux for 12 h, concentrated *in vacuo*, and the residue dissolved in ethyl acetate (20.0 L). The ethyl acetate solution was washed with saturated potassium carbonate solution (10.0 L, three times), water (10.0 L, once) and saturated sodium chloride solution (10.0 L, twice). The organic layer was concentrated until about 15 L of ethyl acetate was removed, *n*-heptane (5.0 L) was added and the solution was cooled in an ice bath to precipitate the product. After 1 h, the solids were isolated by filtration and dried in an oven at 60 °C overnight to afford **2d** as white crystals (3088.0 g, 55.1% yield for two steps, 99.2% purity). Mp 109.9–112.0 °C; ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.48 (s, 6H), 3.63 (s, 3H), 3.74 (s, 3H), 6.13–6.17(dd, 1H, J = 14.8, 2.4 Hz), 6.29–6.32 (dd, 1H, J = 8.8, 2.4 Hz), 7.04 (s, 1H), 7.63–7.59 (t, 1H, J = 8.8 Hz); ^{13}C NMR (100 Hz, DMSO-d_6): δ 25.9, 51.8, 52.8, 57.0, 99.7 (d, $J_{F\text{-}C}$ = 20.0 Hz), 104.7 (d, $J_{F\text{-}C}$ = 10.0 Hz), 109.4, 133.3, 152.9 (d, $J_{F\text{-}C}$ = 10.0 Hz), 162.5, 164.2, 164.3 (d, $J_{F\text{-}C}$ = 10.0 Hz), 175.6; MS(ESI): Calcd. for $C_{13}H_{16}FNO_4$ 269.1, found: 270.1 $[M+H]^+$; Anal. Calcd. $C_{13}H_{16}FNO_4$: C 57.99, H 5.99, N 5.20; found: C 57.91, H 6.00, N 5.08.

*4.3. Synthesis of O-methyl-4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]-2-fluoro-benzonate (**2f**)*

Compound **2d** (1200.0 g, 4.46 mol) and 4-cayno-3-trifluoromethyl-phenylisothiocyanate (**2e**, 2000.0 g, 8.77 mol) were added to a mixture of dimethyl sulfoxide (DMSO, 600 mL) and isopropyl acetate (AcIPA, 3.0 L) in a 10-L round-bottom flask with four necks and the resulting solution was mixed well. The reaction was heated to 95 °C for 24 h, then transferred into a separation vessel. Isopropyl acetate (6.0 L) and water (3.0 L) were added to the deep-brown reaction solution and the mixture stirred for 1 min. Isopropanol (IPA, 600 mL) was added to break the emulsification layer, and DMSO was washed out with the aqueous phase. These operations were repeated three times to remove almost all of the DMSO and the organic phase was concentrated *in vacuo*. Fresh isopropanol (7.0 L) was added to the residue and mixed well. The mixture was heated to 70 °C to fully dissolve the residue and then cooled to 10 °C to precipitate the product. The yellow solids were isolated by filtration and recrystallized from isopropanol (9.0 L) once to afford **2f** as a white solid (1700.0 g, 82.0% yield, 99.7% purity). Mp 152.0–154.0 °C; ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.57 (s, 6H), 3.93 (s, 3H), 7.44 (dd, 1H, J = 1.6, 6.8 Hz), 7.54 (dd, 1H, J = 1.6, 6.8 Hz), 8.10–8.14 (m, 2H), 8.33 (s, 1H), 8.43 (d, 1H, J = 8.0 Hz); ^{13}C NMR (100 Hz, DMSO-d_6): δ 22.8, 52.6, 66.7, 108.7, 114.9, 119.1, 123.5, 126.2, 127.8 (d, $J_{F\text{-}C}$ = 10.0 Hz), 131.1 (q, $J_{F\text{-}C}$ = 30.0 Hz), 132.7, 133.9, 136.2, 137.8, 140.9, 159.6, 162.1, 163.3, 174.6, 179.9; MS(ESI): Calcd. for $C_{21}H_{15}F_4N_3O_3S$ 465.1, found: 466.1 $[M+H]^+$; Anal calcd.: C 54.19, H 3.25, N 9.03; found: C 53.98, H 3.24, N, 8.99.

*4.4. Synthesis of N-methyl-4-[3-(4-cyano-3-trifluoromethylphenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl]-2-fluoro-benzamide (enzalutamide, **1**)*

Compound **2f** (1500.0 g, 3.23 mol) was charged to a 10-L round-bottom flask with four necks containing tetrahydrofuran (3.0 L) and mixed well to dissolve all the solids. The solution was cooled to −11 °C and a 40% methylamine aqueous solution (3.0 L) pre-cooled to −10 °C was added dropwise over 40 min. The reaction temperature was increased by 2–3 °C during the addition. The reaction was kept at −8 ± 1 °C for 22 h then quenched by adding ethanol (3.0 L). The whole solution was concentrated *in vacuo* to

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remove the tetrahydrofuran, ethanol and more than half of the water. The product precipitated from the solution was transferred to a filter with an isopropanol rinse. The isolated solids were heated in an oven at 65 °C for 6 h to afford **1** as white crystals (1252.0 g, 83.6% yield, 99.8% purity). Mp 198.2–199.1 °C; ^{1}H NMR (400 Hz, DMSO-d_6): δ 1.56 (s, 6H), 2.82 (d, 3H, J = 4.0 Hz), 7.35 (dd, 1H, J = 8.0, 1.2 Hz), 7.43 (d, 1H, J = 10.8 Hz), 7.81 (t, 1H, J = 8.4 Hz), 8.09 (dd, 1H, J = 8.4, 1.2 Hz), 8.29 (s, 1H), 8.38 (s, 1H), 8.39 (d,, 1H J = 8.0 Hz); ^{13}C NMR (100 Hz, DMSO-d_6): δ 23.0, 26.3, 66.4, 108.8, 115.0, 118.0, 122.8 (q, J_{CF3-C} = 30.0 Hz), 125.1, 126.1, 128.0, 130.8, 131.2, 133.9, 136.2, 138.0, 138.4, 157.8 (d, J_{F-C} = 10.0 Hz), 163.4, 174.7, 180.1. MS(ESI): Calcd. for $C_{21}H_{16}F_4N_4O_2S$ 464.1, found: 465.1 $[M+H]^+$, 487.1 $[M+Na]^+$. Anal calcd. C 54.31, H 3.47, N 12.06, found: C 54.34, H 3.73, N 11.99.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.09.007.

References

[1] H.I. Scher, K. Fizazi, F. Saad, et al., Increased survival with enzalutamide in prostate cancer after chemotherapy, New Engl. J. Med. 367 (2012) 1187–1197.
[2] C. Tran, S. Ouk, N.J. Clegg, et al., Emerging therapeutic approaches in the management of metastatic castration-resistant prostate cancer, Science 324 (2009) 787–790.
[3] M.E. Jung, S. Ouk, D. Yoo, et al., Structure–activity relationship for thiohydantoin androgen receptor antagonists for castration-resistant prostate cancer (CRPC), J. Med. Chem. 53 (2010) 2779–2796.
[4] C.D. Chen, D.S. Welsbie, C. Tran, et al., Molecular determinants of resistance to antiandrogen-therapy, Nat. Med. 10 (2004) 33–39.
[5] D.P. Antonio, P.C. Sagrera, Capsule of active pharmaceutical ingredients and polyunsaturated fatty acid for the treatment of prostate cancer, PCT Int. Appl. WO 2012013331, July 2011.
[6] A. Jemal, R. Siegel, E. Ward, et al., The malignant pleural effusion as a model to investigate intratumoral heterogeneity in lung cancer, CA Cancer J. Clin. 56 (2006) 106–130.
[7] C.J. Tyrrel, A.V. Kaisary, P. Iversen, et al., Treating prostate cancer in elderly men: how does aging affect the outcome, Eur. Urol. 33 (1998) 447–456.
[8] E.J. Small, N.J. Vogelzang, Second-line hormonal therapy for advanced prostate cancer: a shifting paradigm, J. Clin. Oncol. 15 (1997) 382–388.
[9] Y.S. Ha, S. Goodin, R.S. Dipaola, I.Y. Kim, Enzalutamide for the treatment of castration-resistant prostate cancer, Drugs Today 49 (2013) 7–13.
[10] Q. Li, Research and development on the abiraterone, Int. J. Urol. Nephrol. 33 (2013) 76–80.
[11] B.J. Feldman, D. Feldman, The development of androgen, Nat. Rev. Cancer 1 (2001) 34–45.
[12] E.P. Gelmann, Molecular biology of the androgen receptor, J. Clin. Oncol. 20 (2002) 3001–3015.
[13] S.P. Balk, Androgen receptor as a target in androgen-independent prostate cancer, Urology 60 (2002) 132–138.
[14] C.L. Sawyers, M. Jung, C.D. Chen, et al., Diarylhydantoin compounds, PCT Int. Appl. WO 200611417, March 2006.
[15] L.J. Song, Y. Wang, X.F. Lu, Z.Y. Li, Synthesis of androgen receptor antagonists MDV3100, Fine. Chem. Intermediates 42 (2012) 34–36.
[16] J.R. Parasmal, A. Remy, T. Andrew, L. Carol, G. Scott, Processes for the synthesis of diarylthiohydantoin and diarylhydantoin compounds, PCT Int. Appl. WO 2011026135, February 2011.
[17] B.O. Buckman, J.B. Nicholas, K. Emayan, S.D. Seiwert, S.D. Yuan, N-Heteroaryl carbamates as lysophosphatidic acid receptor antagonists and their preparation, PCT Int. Appl. WO 2014113485, July 2014.
[18] J.Q. Li, Y.Y. Zheng, L.X. Xing, X.B. Wu, N.Y. Shi, Preparation method of enzalutamide, CN 104803918, January 2014.
[19] J.Q. Li, L.X. Xing, Y.Y. Zheng, X.B. Wu, N.Y. Shi, Preparation method of enzalutamide intermediate F, CN 104803919, January 2014.
[20] Y. Youichi, Y. Takeshi, M. Sumumu, I. Akiko, PAI-1 inhibitor, US Patent 2009312315, December 2009.
[21] F. Monnier, M. Taillefer, Catalytic C–C, C–N, and C–O Ullmann-type coupling reactions, Angew. Chem. Int. Ed. 48 (2009) 6954–6971.
[22] I.P. Beletskaya, A.V. Cheprakov, Copper in cross-coupling reactions, Coord. Chem. Rev. 248 (2004) 2337–2364.
[23] D.W. Ma, Q. Cai, Copper/amino acid catalyzed cross-couplings of aryl and vinyl halides with nucleophiles, Acc. Chem. Res. 41 (2008) 1450–1460.
[24] F. Nique, S. Hebbe, C. Peixoto, et al., Discovery of diarylhydantoins as new selective androgen receptor modulators, J. Med. Chem. 55 (2012) 8225–8235.
[25] R. Wong, S.J. Dolman, Isothiocyanates from tosyl chloride mediated decomposition of in situ generated dithiocarbamic acid salts, J. Org. Chem. 72 (2007) 3969–3971.