Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2022, 14(7): 1-10
(http://www.derpharmachemica.com/archive.html)

Indion 190 Resin Catalyzed Environmentally Benign Protocol for Synthesis of an Anticancer Drug Enzalutamide

Sampat Yewale*, YS Malghe

Department of Pharmaceutical Chemistry, Karnataka State Akkamahadevi Women'University Vijayapur, Karnataka, India

***Corresponding author:** Sampat Yewale, Department of Pharmaceutical Chemistry, Karnataka State Akkamahadevi Women'University Vijayapur, Karnataka, India, **E-mail**: ymalghe@yahoo.com*

Received: 13-Sep-2020, Manuscript no: DPC-20-19145, **Editor assigned**: 16-Sep-2020, PreQC No: DPC-20-19145, **Reviewed**: 29-Sep-2020, QC No: DPC-20-19145, **Revised**: 15-Sep-2022, QI No: DPC-20-19145, Manuscript No: DPC-20-19145, **Published**: 13-Oct-2022, **DOI**: 10.4172/0975-413X.14.7.1-10

ABSTRACT

An environmentally benign and economically viable protocol has been developed for the synthesis of the anticancer drug Enzalutamide using Indion 190 resin. Ambient condition, short reaction time, simple work-up procedure, high yield, easily available and reusable heterogeneous Indion 190 catalyst, are some of the striking features of the present method. Enzalutamide is known as 4-{3-[4-cyano-3-(trif1uoromethy1) pheny1]-5,5-dimethy1-4-oxo-2-su1fanylide-neimidazolidin-1-yl}-2-f1uoro-N-methy1benzamide. Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA.

Keywords: Anticancer drug; Enzalutamide; Indion 190 resin; Environmentally benign

INTRODUCTION

A major metabolite, N-desmethyl enzalutamide, exhibited similar *in-vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in-vitro* and decreased tumor volume in a mouse prostate cancer xenograft model (Figure 1). Following to lung cancer death, prostate cancer death is the second major reason of deaths in United States [1]. It was developed by mediyationinc for the treatment of Castration-Resistant Prostate Cancer (CRPC) a serious cancer that affects men [2,3]. The oral capsule of enzalutamide was developed by FDA for sale in August 2012. According to statistics of the American cancer society 217730 new patients were diagnosed with prostate cancer by hospitals and clinics in the United States of America in 2010, of these 32,050 patient died within two years. Bicalutamide, flutemide and Abiraterone were used to treat prostate cancer before the lunch of enzalutamide [4-9].

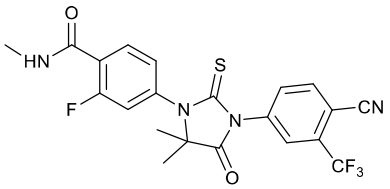

Figure 1: Structure of enzalutamide

These drugs controlled CRPC effectively in only a small proportion of patients and caused some obvious side effects such as hypertension, atrial fibrillation and hypokelekemia. The cancer became resistance to these treatments in many patients after a period of about two years [10-13]. The development of enzalutamide provided a better choice for the treatment of CRPC and achieved sales up to 1 billion dollars in 2013 and even better returns after that year. Research into development of new processes to produce the Active Pharmaceutical Ingredient (API) is continuing to receive enormous attention. Three main routes for the synthesis of enzalutamide have been reported [14]. One obvious drawback of this route is the very low yield of the last step, which would make producing the API costly at industrial scale. Eventually, 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 enzalutamide [15]. Five years later, Thompson and co-workers provided an alternative route to synthesize enzalutamide, which improved the original synthesis by removing the oxidation and reduction reactions. The direct condensation of 2-(4-alkoxycarbonyl-3-fluoro-anilino)-2-methyl-propanoic acid and 4-isothiocyanato-2-(trifluoromethyl)benzonitrile leads to formation of alkyl 4[3-(4-cyano-3-methyl-phenyl)-5,5-dimethyl-4-oxo-2-thioxo-imidazolidine-1-yl]-2-fluoro-benzoate which eventually converted to enzalutamide.

MATERIALS AND METHODS

Further N-methyl-2-fluoro-4-(1,1-dimethyl-cyanomethyl)-aminobenzamide formed by the reaction of N-methyl-2-fluoro-4-aminobenzamide and acetone cyanohydrin treated with 4-isothiocyanato-2-trifluoromethyl benzonitrile to afford enzalutamide. However, the yields of the last two steps are too low for economical kilo scale production of the API. Scientists from Medivation Inc. Also improved the second route and published their results in 2012. This synthesis overcame the poor yield problem of the final step observed in the first and second routes, which justifies the use of highly toxic iodomethane at a later stage of the synthesis and makes the third route more reasonable than the procedures of the first and second routes for commercial manufacture. However the crude product of it also needs to be recrystallized for 2-3 times by isopropanol to get qualified API. Therefore a new route is needed for the efficient synthesis of enzalutamide using moderate and environmentally friendly conditions and reagents. Herein, we report a new three-step route for the synthesis of enzalutamide that avoids highly toxic reagents and multiple recrystallization processes, using Indion 190 resin. We used Indion 190 resin as a heterogeneous catalyst in the context of its unique physical and chemical properties and our earlier reports (Figure 2).

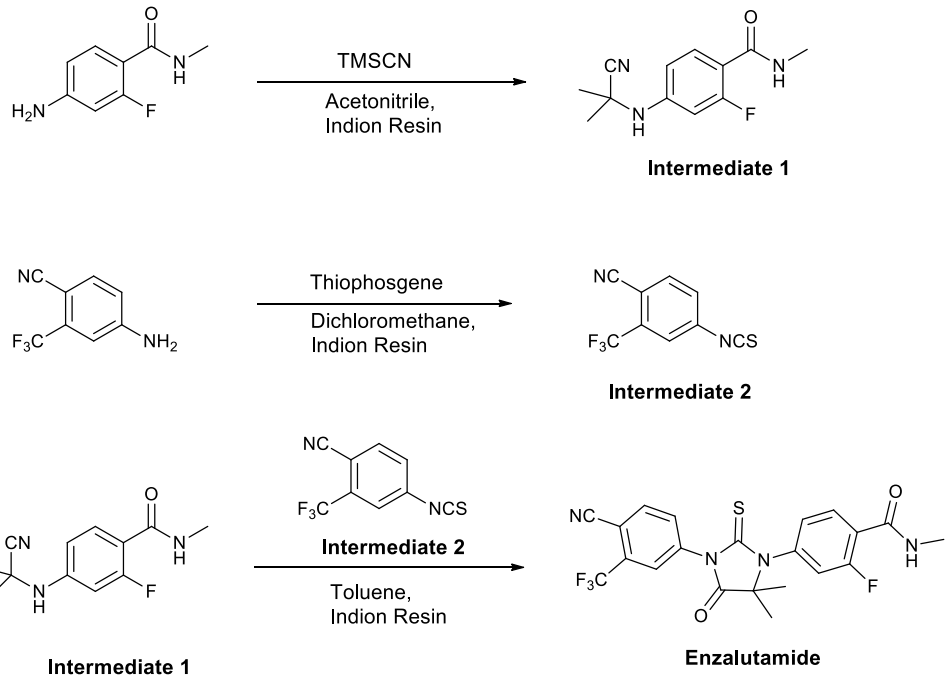

Figure 2: Chemical route for the synthesis of enzalutamide

Chemicals and reagents were purchased from commercial suppliers. All the solvents were purchased from spectrochem and were used as received. All reactions were performed in a round bottom flask and monitored by TLC performed on aluminium plates (0.25 mm, E. Merck) precoated with silica gel (Merck 60 F-254). Developed TLC plates were visualized under a short-wavelength UV lamp. Yields refer to spectroscopically (1H, 13C NMR) homogeneous material obtained after column chromatography performed on silica gel (60 mesh-120 mesh) supplied by S. D. Fine Chemicals Limited, India. 1H and 13C NMR were recorded in CDCl3 on a Bruker 300 MHz spectrometer. Chemical shifts (δ) are quoted in ppm, relative to SiMe4 (δ=0.0) as an internal standard. The number of protons (n) for a given resonance is indicated by nH. Peak multiplicities are designated by the following abbreviations; s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; bs, broad singlet; J, coupling constant in Hz. High Resolution Mass Spectra (HRMS) were obtained by using positive Electrospray Ionization (ESI) by Time of Flight (TOF) method. Absorption spectra were recorded on a UV-Vis-NIR Spectrophotometer. IR spectra were recorded on fourier transform infrared, Perkin Elmer, frontier equipment with KBr pellet. Melting points were recorded on a standard melting point apparatus from Sunder Industrial Product, Mumbai and are uncorrected (Figure 3).

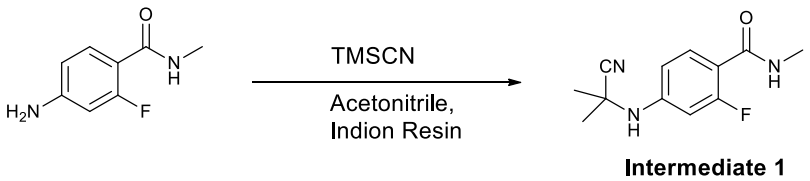

Figure 3: Preparation of N-methyl-2-fluro-4-(1,1 dimethyl-cynomethyl)aminobenzamide

N-methyl-2-fluro-4-aminobenzamide (1.0 mmol), TMSCN (2.5 mmol) and Indion 190 resin (15 mol%) in acetonitrile were taken and refluxed on water bath for 60 min to 90 min. After completion of the reaction, as monitored *via* TLC using $CHCl_3$ and MeOH (9.5 mL:0.5 mL) as eluent, the

reaction mass was filtered and resin was separated. Filtrate was poured into crushed ice and then precipitated solid was separated by filtration and washed with water and recrystallized from cyclohexane to get the desired compound N-methyl-2-fluro-4-(1,1 dimethyl-cynomethyl) aminobenzamide (Figure 4). IR (KBr): 3228, 3347, 2230, 2972 cm^{-1}; 1H-NMR (300 MHz, $CDCl_3$) δ 6.57 (d, 1H), δ 6.63 (dd, 1H), δ 6.64 (d, 1H), δ 4.32 (s, 1H), δ 1.75 (s, 6H), δ 7.95 -8.01 (t, 1H); δ 2.99-3.01 (d, 3H), 13C-NMR (75 MHz, $CDCl_3$) δ 164.17, 163.35, 160.10, 148.66, 148.50, 148.40, 132.79, 120.99, 111.26, 110.97, 101.26, 100.86, 47.90, 27.82, 26.62. UV analysis recorded in methanol 10 ppm absorption maximum observed at 272 nm at intensity 0.84 and 214 nm at intensity 0.55 mass analysis (M+1) 235.8. Anal Calcd. For $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97; Found: C, 84.60; H, 6.42; N, 8.94.

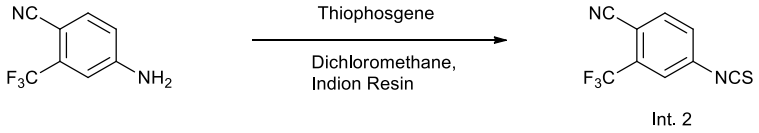

Figure 4: Preparation of 4-Isothiocyanato-2-(trifluoromethyl) benzonitrile

4-Amino-2-(trifluoromethyl)benzonitrile (1.0 mmol), Thiophosgene (2.5 mmol) and Indion 190 resin (15 mol%) in water dichloromethane were taken and refluxed on water bath for 60 min to 70 min. After the completion of the reaction monitored *via* TLC using $CHCl_3$ and MeOH (9.5 mL:0.5 mL) as eluent, the reaction mass was filtered and resin is separated. Aqueous layers were separated from organic layer dichloromethane layer containing product was distilled under vacuum. To this residue n-heptane is added, stirred and filtered to get the desired compound 4-Amino-2-(trifluoromethyl)benzonitrile**.** IR (KBr): 3080, 2037, 1432, 1321, 850, 838, 810, 677 cm^{-1}; 1H NMR (300 MHz, CDCl3) δ 7.58-7.59 (d, 1H), δ 7.82-7.85 (d, 1H), δ 7.46-7.54 (dd, 1H), 13C-NMR (75MHz, CDCl3) δ 141.83, 136.82, 136.15, 135.26, 134.82, 134.37, 133.93, 129.02, 126.98. 124.09, 124.03, 123.97, 123.91, 123.34, 119.70, 116.07, 114.59, 107.76, 107.73. Mass analysis (M+H) 229.1.

Preparation of 4-(3-(4-Cyano-3-(trifluoromethyl) phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide

N-methyl-2-fluro-4-(1,1 dimethyl-cynomethyl)aminobenzamide (1.0 mmol) , 4-Isothiocyanato-2-(trifluoromethyl) benzonitrile (2.5mmole) and Indioin 190 resin (15 mol%) in toluene were taken and refluxed on water bath for 180 to 240 min. After the completion of the reaction monitored *via* TLC using ethyl acetate and n-Hexane (0.5:9.5 mL) as eluent, the reaction mass filtered and resin is separated. Filtrate was distilled under vacuum. To this residue ethanol and n-heptane is added, stirred and filtered to get the desired compound 4-Amino-2-(trifluoromethyl)benzonitrile (Figure 5)**.**

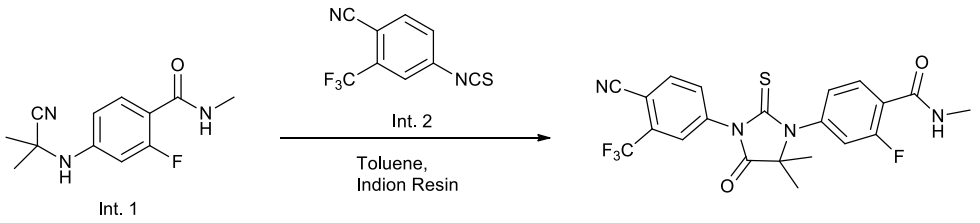

Figure 5: 4-(3-(4-Cyano-3-(trifluoromethyl) phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide

IR (KBr): 3433, 3058, 2234, 1639, 1472, 1313 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$):δ 1.55 (s, 6H), δ 8.3 (s, 1H), δ 8.40 (d, 1H), δ 8.09 (d, 1H), δ 7.44 (d, 1H), δ 7.79 (t, 1H), 7.34 (d, 1H), 8.46 (s, 1H),δ 2.80 (d, 3H), δ 6.5-7.3 (m, 4H); 13C-NMR (75 MHz, $CDCl_3$) δ 180.08, 174.73, 163.43, 160.62, 157.30, 138.37, 138.23, 137.91, 136.23, 133.92, 131.82, 131.39, 130.96, 130.92, 130.87, 130.53, 128.06, 128.01, 127.94, 127.88, 127.65, 126.13, 126.09, 125.23, 125.04, 124.02, 120.39, 118.20, 117.88, 116.76, 115.00, 108.80, 108.77, 108.74, 108.72, 66.59, 26.27, 22.93. UV analysis; absorption observed at 237 nm at intensity 0.59. Mass observed (M+H) 465.567.

Preparation of 4-Amino N-methyl benzamide

2-Fluro-4-amino N-methyl benzamide(1mmole) and 10 % palladium chloride in ethanol were taken in the autoclave with 2 kg pressure for 3 hrs, after completion of the reaction as monitored by TLC, the reaction mass was filtered. The isolated filtrate was distilled to get crude product which eventually purified using column chromatography (Figure 6)**.**

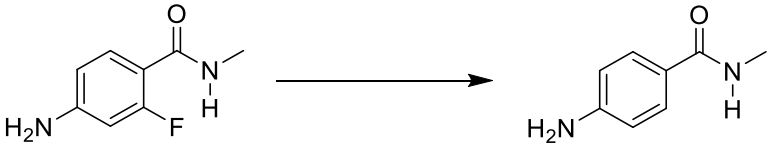

Figure 6: 4-Amino N-methyl benzamide

IR (KBr,v,cm^{-1}): 3338 (N-H stretching),1631 (C=O) amide stretching, 1539,1560 (N-O) Asymmetric stretching. 1 H NMR (300 MHz DMSO-d6),δ=7.52-7.55 (d, 2H, J=6.8 Hz),δ=6.50-6.53 (d, 2H,J=6.8 Hz),δ=7.92 (Bs ,1H,), δ=2.71 (d,3H), δ=5.55 (s, 2H). 13C NMR (75 Mz, DMSO d6): 166.8 (C=O), 151.51 (aromatic), 128.60 (aromatic CH) 121.37, 112.63 aromatic CH), 26.15 (methyl), (M^{+1}): 151.

Preparation of 2-Fluoro-4-hydroxy amino N-methyl benzamide

2-Fluoro-4-amino N-methyl benzamide (1 m mole) was dissolved in the methanol and 20% of Zn was added into it, the reaction mass was stirred for 5 hrs at 50°C. After completion of the reaction as monitored by TLC in (Methanol 0.5 ml and 9.5 ml methylene chloride), the reaction mass was concentrated under reduced pressure to get the residue which was purified by column chromatography using (MDC and methanol**)** (Figure 7)**.**

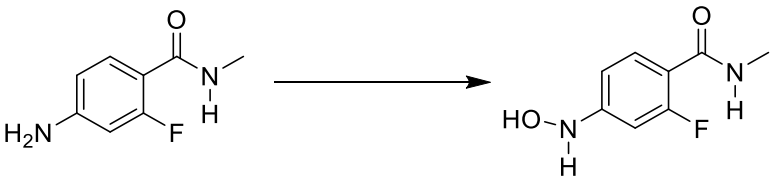

Figure 7: 2-Fluoro-4-hydroxy amino N-methyl benzamide

IR (KBr, v, cm^{-1}): 3002 (C-H aromatic), 2693 (O-H carboxylic), 1619 (C=O acid)1551-1500 (N-O) Asymmetric stretching. 1 H NMR (300 MHz DMSO- d6), δ=8.87 (s, 1H), δ=8.66 (s,1H), δ=7.77-7.74 (t,1H), δ=7.53 (t,1H), δ=6.62-6.52 (m, 2H), δ=2.74 (d, 3H). 13C NMR (75 Mz, DMSO d6): 164 (C=O), 162.5 (aromatic), 159.2 (aromatic),156.1(aromatic),131.2 (CH aromatic)107.9, 98.7(C-H aromatic) 26.4 (methyl), (M^{+1}) : 185.

Preparation of 2-Fluoro-4-nitro-N-methyl benzamide

To the solution of the 2-fluoro-4-nitrobenzoic acid (1 mmole) and (triethylamine 2 mmole) in methylene dichloride, Carboxy Dicarbodimide (CDI) (1.5 mmole) was added in portion wise under nitrogen at room temperature and stirred for 1 hrs. To this reaction mass was added methylamine hydrochloride (2 mmole), the reaction mass was stirred for 4 hrs. After completion of the reaction as monitored by TLC in (ethylacetae 8 ml and n-Hexane 2 ml), water 50 ml was added. The organic layer was washed with HCl 50 ml solution and 50 ml water orderly. Organic layer was concentrated under reduced pressure. Residue was purified by column chromatography using silica gel (ethyl acetate and n-Hexane) to afford the 2-fluoro-N-methyl-4-nitrobenzamide, was established on basis of spectoscopical data (IR,H NMR,13CNMR,and Mass) (Figure 8).

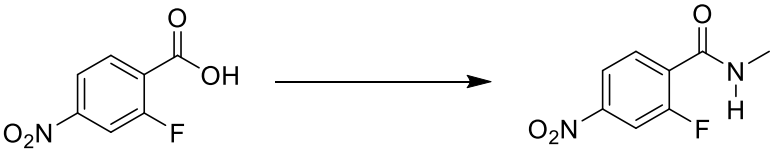

Figure 8: 2-Fluoro-4-nitro-N-methyl benzamide

IR (KBr, v, cm^{-1}): 3397 (N-H), 1655 (C=O amide), 1525 (N-O asymmetric). 1H NMR (300MHz DMSO- d6), δ=8.58(bs, 1H)δ=8.22-8.11 (m, 2H), δ=7.87-7.82 (t,1H), δ=2.81 (d, 3H, J=4.6), 13C NMR (75 Mz, DMSO d6): 162.5 (C=O), 160, 156.7, 149.1, 131.2 (CH aromatic)119.5(C-H aromatic),112.2,26.2 (methyl), (M^{+1}): 198.9

Preparation of 2-Flouro-4-nitro- benzoic acid

2-fluoro-4-nitro N-methylbenzamide (1 mmole) was dissolved in methanol, added 2 (mmole) sodium hydroxide and heated to 75°C-80°C for 5 hrs, after completion of the reaction as monitored by TLC in (Methylene dichloride 9.5 ml and methanol 0.5 ml), reaction mass was diluted with HCl and product was extracted in ethyl acetate, ethylacetate layer was distilled to get the crude product. Pure product was purified by column chromatography using (0.2 ml methanol and 9.8 ml methylene dichloride) to gives pure product. Product was characterized by 1H NMR, 13-NMR, IR and Mass (Figure 9).

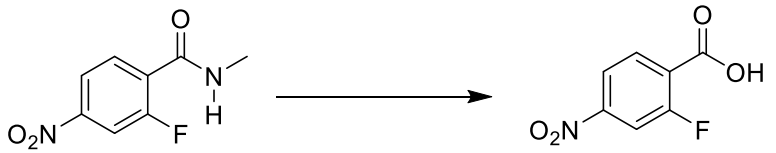

Figure 9: 2-Flouro-4-nitro- benzoic acid

IR (KBr, v, cm^{-1}): 3063 (C-H), 2669 (N-O asymmetric), 1701 (C=O acid), 1542-1445(N-O). 1 H NMR (300 MHz DMSO- d6), δ=13.9(bs, 1H), δ=8.22-8.08 (m, 3H), 13C NMR (75 Mz, DMSO d6): 163.7 (C=O), 162, 1(C-H aromatic), 158.7, 150.4, 133 (CH), 119.3 (CH) 112.9(CH), (M^{+1}): 184.1.

Preparation of 2-Flouro-4-nitro-toluene

To a stirred solution of the 2-fluoro-4-nitro N-methylbenzamide (1 mmole) in dioxane were added chromium (III) oxide 100 mg and copper (II) oxide 100 mg reaction was stirred in autoclave at 2 kg pressure of the H_2 at 100°C for 4 hrs product formation was confirmed by TLC and then reaction was cooled and filtered filtrate was concentrated under vacuum to get the crude product and desired product was isolated by column chromatography using silics gel (ethyl acetate 4 ml-n-Hexane 6 ml). Desired product was characterized by HNMR, mass and C-13NMR (Figure 10).

Figure 10: 2-Flouro-4-nitro-toluene

IR (KBr, v, cm^{-1}): 3433 (N-H),3088 (C-H),1556,1520,1493 (N-O asymmetric). 1 H NMR (300MHz DMSO- d6), δ=8.05-7.99 (m, 2H) δ=7.63-7.58 (t, 1H), δ=2.37 (s, 3H), 13C NMR (75 Mz, DMSO d6): 1615,158.2, 133.2, 132.2(CH), 119.3(C-H), 110.6(CH).14.3(methyl). (M^{+1}): 155.9.

Preparation of 4-{3-[4-cyano-3-(trif1uoromethy1)phenyl]-5,5- dimethyl-2,4-dioxo- neimidazolidin-1-yl}-2-f1uoro-N-methy1benzamide

In clean RBF a solution of the Enzalutamide (1 mmole) and 5% aqueous solution of potassium hydroxide in acetonitrile was added Dihydroperoxy Dimethyl Dioxolane (DHPDMO) (0.3 mmole) resulting reaction mass was stirred at room temperature for 3 hrs-4 hrs after completion of the reaction as monitored by TLC in (Ethyla aceate 8 ml and 2 ml n-Hexane) reaction mass was diluted with water 10 ml product was extracted in dichloromethane (3 ml × 5 ml). The combined organic layer was washed with water (2 ml × 5 ml) dried over sodium sulphate. Under reduced pressure gives almost pure product. Structure of the known product were established on the basis of the physical and spectroscopic method (IR 1HNMR, 13 CNMR and Mass) which were consistent with those reported (Figure 11).

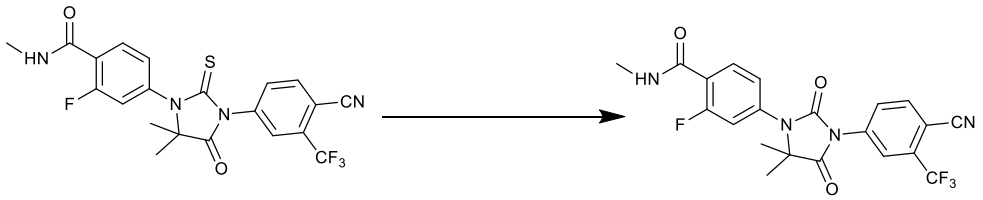

Figure 11: 4-{3-[4-cyano-3-(trif1uoromethy1)phenyl]-5,5- dimethyl-2,4-dioxo- neimidazolidin-1-yl}-2-f1uoro-N-methy1benzamide

IR (KBr, v, cm^{-1}): 3444.48 (N-H), 2232.39 (CN), 1724-1666 (C=O), 1499 (C=C), 1383 (C-F).1 H NMR (300 MHz DMSO- d6), δ=8.26-8.20(t, 1H), δ=8.16 (d, 1H, J=1.53), δ=8.04-8.0 (dd, 1H, J=8.5, J=1.92), δ=7.95 (d, 1H, J=8.5), δ=7.29-7.20 (dd, 1H, J=8.0, J=1.9), δ=7.20 (d, 1H, J=1.95), δ=6.73 (m, 1H), δ=3.05 (d, 3H, J=4.5), δ=1.64 13C NMR (75 Mz, DMSO d6): 173.5 (C=O), 162.6 (C=O), 161.9 (C=O), 158.6, 152, 137.6, 135.3(CH), 128.7(C-H) 123.6 (C-H),115.3, 108.6, 64, 26 (methyl).24.1 (2 methyl). (M^{+1}): 449.

Preparation of 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethyl-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-2-f1uoro-benzoic acid

To the stirred solution Enzalutamide API, (1 mmole) in ethanol, added NaOH (1.5 mmole) resulting solution was stirred in autoclave at 80°C for 4 hrs after completion of the reaction as monitored by TLC in (ethyl acetate 8 ml and n-Hexane 2 ml). Resulting mixture was evaporated under reduced pressure product was extracted in dichloromethane (3 ml × 5 ml) by dilution of organic layer afford crude product, pure product was isolated by column chromatography in (ethyl acetae 4 ml and n-Hexane 6 ml) gives Pure product were established on the basis of their physical and spectroscopic data (IR, 1HNMR, 13 CNMR and Mass) (Figure 12).

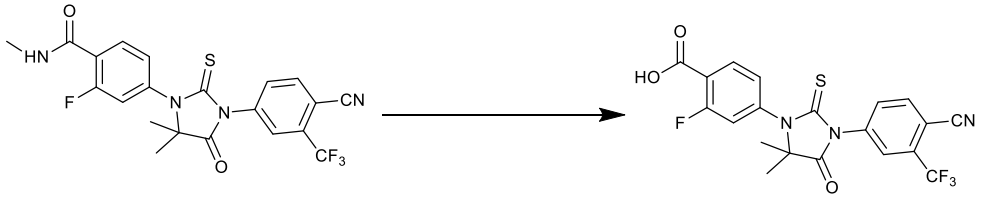

Figure 12: 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5-dimethyl-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-2-f1uoro-benzoic acid

IR (KBr, v, cm^{-1}): 3070-2983 (O-H), 2233(CN), 1785 (C=O), 1724-1684 (C=O), 1316 (C-F). 1 H NMR (300 MHz DMSO-d6), δ=13.43(bs, 1H), δ=8.38 (d, 1H, J=8.4) δ=8.25 (s, 1H), δ=8.12-8.09 (dd, 1H, J=8.4, J=1.45), δ=8.00 (t, 1H), δ=7.54-7.50 (m, 1H), δ=7.45-7.42 (m, 1H), δ=1.57 (s,6H), 13C NMR (75 Mz, DMSO d6): 173.9 (C=O), 164.3 (C=O),162.7 (C=S), 159.3, 139.8, 137.9, 136.4 (CH), 132.6 (CH), 131.(C-H), 130.7 (C-H), 124.6 (CH), 123.3 (CH), 118.4, 107.4, 66.6, 63.88, 23.31 (2 methyl). (M^{+1}): 450.

Preparation of 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5-dimethy1-4-oxo-2-sulfanylide-neimidazolidin-1-yl}-2-f1uoro-benzamide

Enzalutamide API (1 mmole) 1 mmole of potassium bromide were dissolved in 10 ml water and 10 dichloromethane. Reaction mixture was subjected to sealed tube and stirred at room temperature for 8 hrs. Reaction progress was monitored by TLC in (ethyl aceate 4 ml and 6 ml n-Hexane) and

reaction mass was quenched with saturated sodium bicarbonate solution. The product was extracted in dichloromethane (3 ml × 5 ml). Combines organic layer was distilled under reduced pressure to get the crude residue and pure product was isolated by column chromatography using silica gel (ethyl acetate 3 ml and n-Hexane 7 ml) solvent system. Product was characterized by spectroscopic methods (IR, 1HNMR, 13C NMR and Mass) (Figure 13).

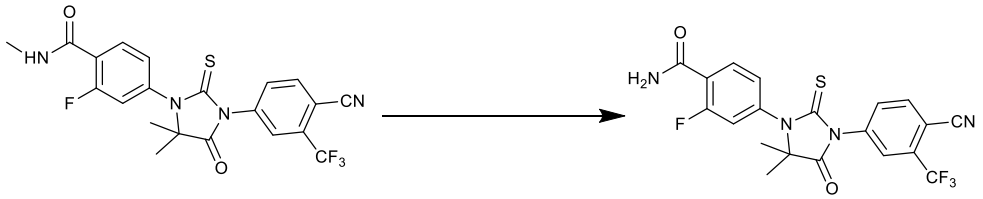

Figure 13: 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethy1-4-oxo-2-sulfanylide- neimidazolidin-1-yl}-2-f1uoro- benzamide

IR (KBr, v, cm^{-1}): 3474(N-H), 2236(CN), 1758-1678 (C=O), 1444-1427 (C=C), 1312.89 (C-F). 1 H NMR (300 MHz DMSO- d6), δ=8.41(d, 1H, J=8.2), δ=8.29 (d, 1H, J=1.7) δ=8.10-8.07 (dd, 1H, J=8.2, J=1.7), δ=7.93-7.84 (s, 2H), δ=7.82 (d, 1H, J=8.1) δ=7.44-7.40 (m, 1H), δ=7.34-7.31 (dd, 1H, J=8.22, J=1.7), δ=1.54 (s, 6H), 13C NMR (75 Mz, DMSO d6): 180 (C=O), 174.6 (C=S), 164.6 (C=O), 157.4, 138.5, 137.9, 136.4, 136.3 (CH), 133.9 (CH), 131.8(C-H), 125.1 (C-H), 118.1 (CH), 115, 108, (CH), 66, 22.95 (2 methyl). (M^{+1}): 450.9.

Preparation of 4-{3-[4-cyano-3-(trif1uoromethy1)phenyl]-5,5- dimethy1-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-N-methylbenzamide

Enzalutamide API (1 mmole) was dissolved in ethanol, 10% palladium chloride catalyst were added into it and taken in the autoclave with 2 kg pressure for 3 hrs, after completion of the reaction as monitored by TLC in (ethyl acetate 6 ml and n-Hexane 4 ml).The reaction mass was filtered and filtrate was distilled out under reduced pressure to get the crude product. The pure product was isolated by column chromatography recorded 1H NMR, 13-CMR, IR and Mass (Figure 14).

Figure 14: 4-{3-[4-cyano-3-(trif1uoromethy1)phenyl]-5,5- dimethy1-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-N-methylbenzamide

IR (KBr, v, cm^{-1}): 3426(N-H), 2233(CN), 1768-1628 (C=O), 1444-1424 (C=C), 1312 (C-F). 1 H NMR (300 MHz DMSO-d6), δ=8.42-8.39 (d, 1H, J=1.43), δ=8.32-8.31 (d, 1H, J=1.4) δ=8.11-8.08 (dd, 1H, J=8.2, J=1.7), δ=8.00-7.97 (d, 2H J=8.4), δ=7.50-7.47 (d, 2H, J=8.4) δ=4.36 (d, 1H), δ=2.50 (d, 3H), δ=1.52 (s, 6H), 13C NMR (75 Mz, DMSO d6): 179.9 (C=O), 174.68 (C=S), 165.9 (C=O), 138, 137.7, 136.2, 135.2 (CH), 134 (CH), 131.3 (C-H), 129.7 (2xC-H), 26.3 (methyl), 23.0 (2x methyl). (M^{+1}): 447.

Preparation of 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)thiourea

4 cyanobenzene-3 trifluoromethyl isothiocyanate (1.55 mmole) was added to solution of the 4cyano-3-trifluoromethyl benzamine (1.3 mmole) in ethyl acetate and reaction mass was stirred at room temperature for 9 hrs, resulting reaction mass was distilled out under reduced pressure to get the crude product. The crude product was purified by column chromatography to get the desired product. Characterized by (IR, 1HNMR, 13 CNMR and Mass) (Figure 15).

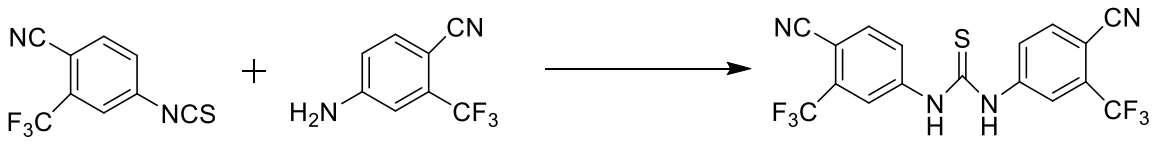

Figure 15: 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)thiourea

IR (KBr, v, cm^{-1}): 3389, 3201(N-H), 2236.81 (CN), 1743(C=O), 1175, 1146, 1139 (CF), 1598, 1543, 1506(C=C). 1 H NMR (300 MHz DMSO- d6), δ=8.09-8.06 (d, 2H, J=8.5), δ=9.93 (s, 2H) δ=8.20 (s, 2H), δ=7.85-7.83 (d, 2H J=8.5).13C NMR (75 Mz, DMSO d6): 143.9, 151.7, 136.2 (CH), 131.8 (CH), 121.4 (CH), 115.7 (CH).124.2, 100.6. (M^{+1}): 397.

Preparation of 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)urea

4 cyanobenzene-3 trifluoromethyl isocyanate (1.55 mmole) was added to solution of the 4cyano-3-trifluoromethyl benzaamine (1.3 mmole) in ethyl acetate and reaction mass was stirred at room temperature for 9 hrs, resulting reaction mass was distilled out under reduced pressure to afford crude product. The crude product was purified by column chromatography to get the desired product. (IR, 1HNMR, 13CNMR and Mass) (Figure 16).

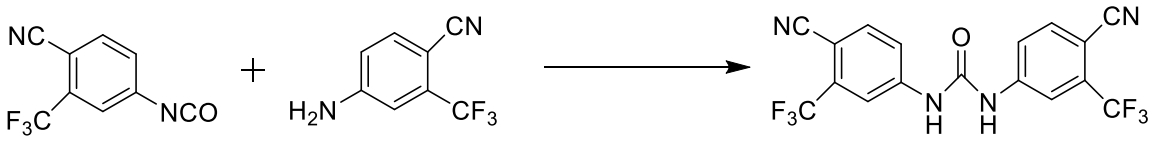

Figure 16: 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)urea

IR (KBr,v,cm^{-1}): 3344-3260(N-H),3105-3078 (CH) ,2232(CN),2232 (CF),1542, 1502, 1442(C=C). 1 H NMR (300 MHz DMSO- d6), δ=10.9(s,2H), δ=8.27-8.26(d, 2H,J=1.8)δ=8.15-8.12 (d, 2H,J=8.5),δ=8.02-7.99 (dd, 2H J=8.5,J=1.8).13C NMR (75 Mz, DMSO d6): 179.6,143.9,136.4, (CH),125.6 (CH),120.6 (CH)131.7,121.6,120.3,102.6. (M^{+1}): 413.

RESULTS AND DISCUSSION

Molecular docking

Synthetic route for the Enzalutamide is depicted in scheme 1 which involves the three steps. Step 1 involves the protection of primary amino group in 4-amino-2-fluoro-N-methylbenzamide using Trimethylsilyl Cyanide (TMSCN) which yields intermediate 1 in 90% yield. In the second step intermediate 2 is obtained in 95% yield when 4-amino-2-(trifluoromethyl)benzonitrile reacted with thiophosgene in dichloromethane using Indion 190 as a catalyst. Finally, the last step involves the condensation followed by cyclization of intermediate 1 with intermediate 2 in toluene using indion 190 resin as a catalyst. The key requirement of all the three steps is acidic conditions. Keeping this acidic condition in mind we screened various acids along with indion 190 resin. Among the various organic acids been screened, tartaric, succinic, oxalic and cinnamic acid resulted in good yields of enzalutamide (65%-75%). Further excellent yields were observed when trichloroacetic acid, chloroacetic acid, malonic acid and formic acid were used (80%-90%). Interestingly, Indion 190 resin showed highest yield (95%) amongst all the catalyst screened. Moreover, easy availability and reusability of Indion 190 resin catalyst makes it best candidate for this reaction (Table 1).

Table 1: Screening of catalysts

Sr.no	Catalyst	Time (h)	Yield %
1	Malonic acid	1	80
2	Cinnamic acid	1	75
3	Oxalic acid	1	72
4	Succinic acid	1	70
5	Formic acid	1	85
6	Trichloroacetic acid	1	90
7	Tartaric acid	1	65
8	Chloroacetic acid	1	92
9	Indion 190 resin	1	95

Reaction conditions: Intermediate 1 (1.0 mmol), Intermediate 2 (1.0 mmol), catalyst (15 mol%), Toluene (3.0 mL). Bisolated yields. Inspired with the results obtained in catalyst screening we further decided to screen the catalyst amount. When 5 mol% of the Indion 190 resin is used we got Enzalutamide in 85% yield. We now increased the catalyst amount to 10 mol% which showed slight improvement in the product yield (87%). But when we reacted both the intermediates (Int. 1 and 2) using 15 and 20 mol% of Indion 190 resin in toluene that interestingly resulted in 95% yield of enzalutamide (Table 2).

Table 2: Optimization of amount of Indion 190 resin for the synthesis of enzalutamide.

Amount of catalyst mol %	Yield %
20	95
15	95
10	87
5	85

Reaction conditions: Intermediate 1 (1.0 mmol), Intermediate 2 (1.0 mmol), catalyst (5-20 mol%), Toluene (3.0 mL) Isolated yields. Further we focused on synthesis of significant impurities associated with enzalutamide (Figures 17-27).

Synthesis of 4-Amino N-methyl benzamide

2-Fluro-4-amino N-methylbenzamide on reaction with 10% palladium chloride in ethanol in the autoclave with 2 kg pressure for 3 hrs offered 4-Amino N-methyl benzamide.

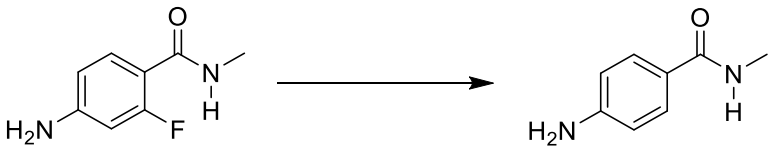

Figure 17: 4-Amino N-methyl benzamide

Synthesis of 2-Fluoro-4-hydroxy amino N-methyl benzamide

The 2-Fluoro-4-amino N-methyl benzamide on reaction with Zn in methanol at 50°C offered 2-Fluoro-4-hydroxy amino N-methyl benzamide.

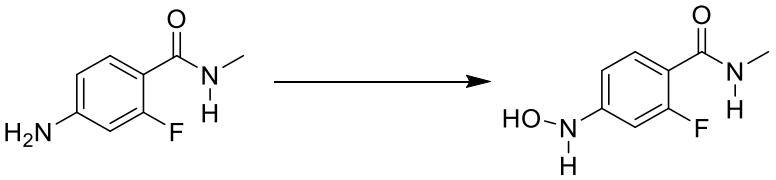

Figure 18: 2-Fluoro-4-hydroxy amino N-methyl benzamide

Synthesis of 2-Fluoro-4-nitro-N-methyl benzamide

The 2-fluoro-4-nitrobenzoic acid was reacted with methylamine hydrocholoride in presence of triethyl amine and Carboxy Dicarbodimide (CDI) in methylene dichloride and offered 2-Fluoro-4-nitro-N-methyl benzamide.

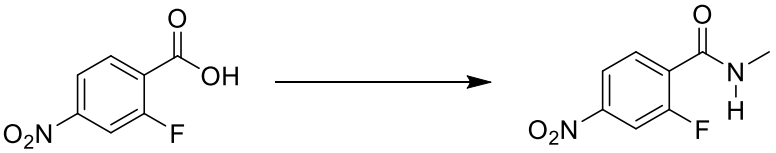

Figure 19: 2-Fluoro-4-nitro-N-methyl benzamide

Synthesis of 2-flouro-4-nitro-benzoic acid

2-Fluoro-4-nitro N-methyl benzamide on reaction with sodium hydroxide at 75°C-80°C yielded 2-Flouro-4-nitro-benzoic acid after 5 hrs.

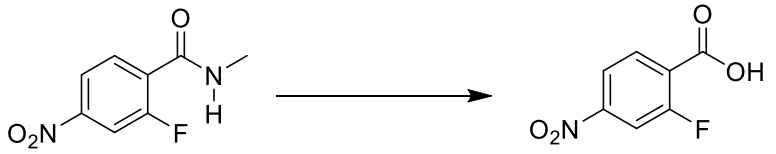

Figure 20: 2-Flouro-4-nitro- benzoic acid

Synthesis of 2-flouro-4-nitro-toluene

2-Flouro-4-nitro-toluene was obtained from 2-fluoro-4-nitro N-methyl benzamide using chromium (III) oxide and copper (II) oxide in autoclave at 2 kg pressure of the H_2 at 100°C for 4 hrs.

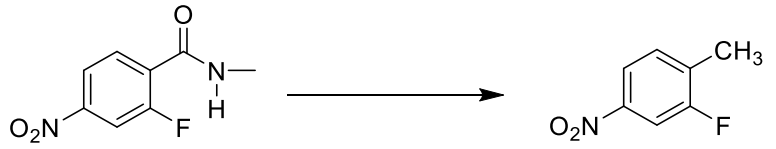

Figure 21: 2-Flouro-4-nitro-toluene

Synthesis of 4-{3-[4-cyano-3-(trif1uoromethy1) phenyl]-5,5-dimethyl-2,4-dioxo- neimidazolidin-1-yl}-2-fluoro-N-methy1benzamide

4-{3-[4-Cyano-3-(trifluoromethy1) phenyl]-5,5- dimethy1-2,4-dioxo- neimidazolidin-1-yl}-2-f1uoro-N-methy1benzamide was synthesized from enzalutamide using potassium hydroxide and DHPDMO.

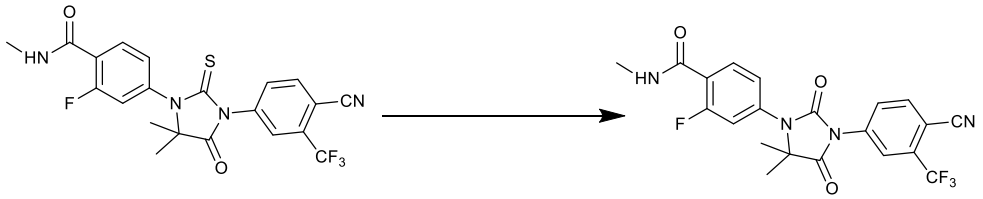

Figure 22: 4-{3-[4-cyano-3-(trif1uoromethy1) phenyl]-5,5-dimethyl-2,4-dioxo- neimidazolidin-1-yl}-2-fluoro-N-methy1benzamide

Synthesis of 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethyl-4-oxo-2-sulfanylide- neimidazolidin-1-yl}-2-f1uoro-benzoic acid

Enzalutamide on reaction with NaOH in autoclave at 80°C for 4 hrs offered 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethyl-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-2-f1uoro-benzoic acid.

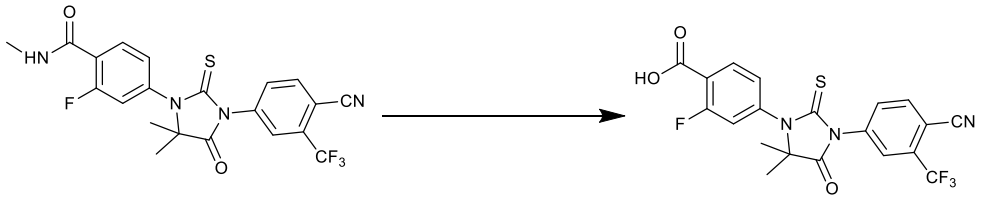

Figure 23: 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethyl-4-oxo-2-sulfanylide- neimidazolidin-1-yl}-2-f1uoro-benzoic acid

Synthesis of 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethy1-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-2-f1uoro- benzamide

4-{3-[4-cyano-3-(trif1uoromethy1)phenyl]-5,5- dimethyl-4-oxo-2-su1fanylide-neimidazolidin-1-yl}-2-f1uoro- benzamide was synthesized from Enzalutamide using potassium bromide in sealed tube**.**

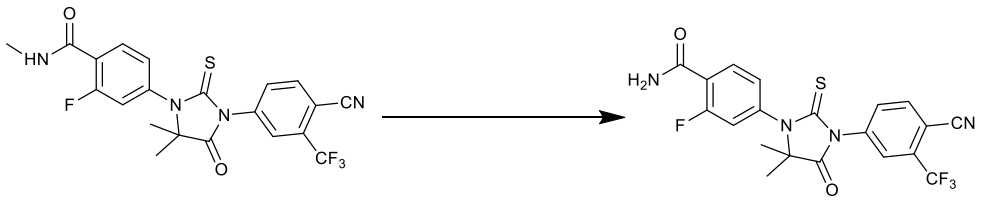

Figure 24: 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethy1-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-2-f1uoro- benzamide

Synthesis of 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethy1-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-N-methy1benzamide

Desfluoroimpurity, 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethy1-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-N-methy1benzamide was synthesized from enzalutamide using 10% palladium chloride in the autoclave with 2 kg pressure for 3 hrs.

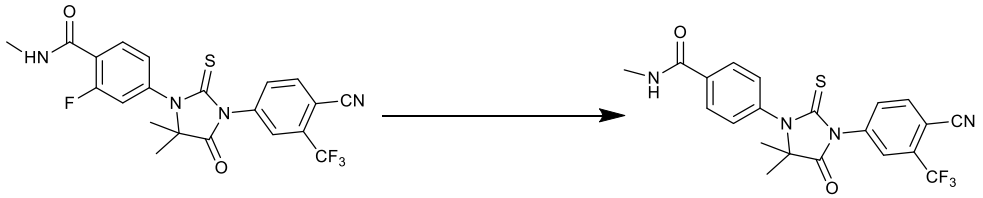

Figure 25: 4-{3-[4-cyano-3-(trif1uoromethy1)pheny1]-5,5- dimethy1-4-oxo-2-su1fanylide- neimidazolidin-1-yl}-N-methy1benzamide

Synthesis of 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)thiourea

1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)thiourea was synthesized from 4 cyanobenzene-3 trifluoromethyl isothiocyanate and 4 cyano-3-trifluoromethyl benzamine.

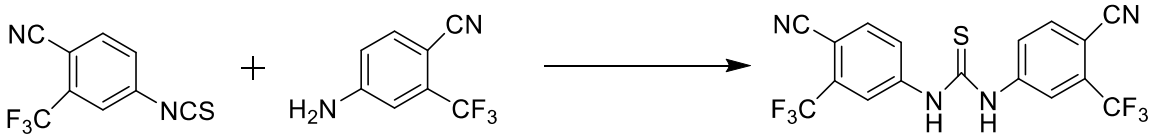

Figure 26: 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)thiourea

Synthesis of 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)urea

4-Cyanobenzene-3-trifluoromethyl isocyanate on reaction with 4-cyano-3-trifluoromethyl benzaamine in Ethyl acetate offered 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)urea.

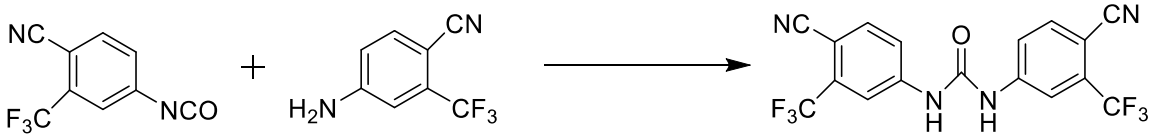

Figure 27: 1,3-bis(4-cyano-3-(trifluoromethyl)phenyl)urea

CONCLUSION

In conclusion, Indion 190 resin was found to be a mild and efficient catalyst for the formation of benzoxazoles, benzothiazoles, and benzimidazoles. The use of this inexpensive, easily available, and reusable catalyst makes this protocol practical, environment-friendly, and economically attractive. A novel and practical approach for the synthesis of the enzalutamide has been established. We have studied the catalytic activity of various easily available aliphatic acids and found Indion resin as an efficient, inexpensive catalyst for the synthesis of enzalutamide. The use of Indion Resin catalyst gives high yield and selectivity, makes this protocol an attractive and user friendly alternative for the synthesis of enzalutamide.

ACKNOWLEDGEMENT

The authors are thankful to University of Mumbai for cooperation in getting the spectral data. Publication cost of this paper was supported by the Korean chemical society.

REFERENCES

1. Scher HI, Fizazi K Saad F, et al., New Engl J Med. **2012**, 367: p. 1187-1197.
2. Tran C, Ouk S, Clegg NJ, et al., Science. **2009**, 324: p. 787-790.
3. Jung ME, Ouk S, Yoo D, et al., J Med Chem. **2010**, 53: p. 2779-2796.
4. Chen CD, Welsbie DS, Tran C, et al., Nat Med. **2004**, 10: p. 33-39.
5. Antonio DP, Sagrera PC. Int Appl, **2011**.
6. Jemal A, Siegel R, Ward E, et al., J Clin. **2006**, 56: p. 106-130.
7. Tyrrel CJ, Kaisary AV, Iversen P, et al., Eur Urol. **1998**, 33: p. 447-456.
8. Small EJ, Vogelzang NJ. J Clin Oncol. **1997**, 15: p.382-388.
9. Ha YS, Goodin S, Dipaola RS, et al., Drugs Today. **2013**, 49: p. 7-13.
10. Li Q, Int. J. Urol. Nephrol, **2013**, 33: p. 76-80.
11. Feldman BJ, Feldman D. Nat Rev Cancer. **2001**, 1: p. 34-45.
12. Gelmann EP. J Clin Oncol. **2002**, 20: p. 3001-3015.
13. Balk SP. Urology. **2002**, 60: p. 132-138.
14. Padalkar V, Phatangare K, Takale S, et al., Saudi Chem Soc. **2015**, 19: p. 42.
15. Chaskar, A, Yewale, S, Langi, B, et al., Korean Chem Soc. **2009**, 53(4): p. 422.