

A novel process for the synthesis of substantially pure Letrozole

M. Suman,^a B. Vijayabhaskar,^b K. NageswaraRao,^c U. K. Syam Kumar,^{*d} and B. VenkateswaraRao^e

^aResearch & Development, Dr. Reddy's Laboratories Limited, API Plant, IDA, Pydibhimavaram, RanasthalamMandal, Srikakulam District-532 409, India

^bGVK Biosciences PVT LTD, Survey no. 125 (part), 126, IDA, Mallapur, Hyderabad-500076, India

^cChemveda Life Sciences Pvt. Ltd, IDA Uppal, Hyderabad-500039, India

^{*d}Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd., Bachupalli, Qutubullapur, R. R. Dist., 500072, Andhra Pradesh, India

^eDepartment of Engineering Chemistry, Andhra University, Visakhapatnam, 530003, India

Email: kalikinidi@gmail.com

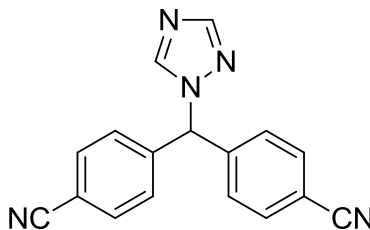
Received 01-24-2019

Accepted 04-26-2019

Published on line 06-09-2019

Abstract

This article demonstrates an improved novel and practical synthesis of oral non-steroidal aromatase inhibitor (AI) Letrozole in a five-stage synthetic process in excellent yields. Key steps of the synthesis involve the condensation of 4-(chloro(4-cyanophenyl)methyl)benzamide with 1H-1,2,4-triazole and further its dehydration to Letrozole by using trifluoroacetic anhydride at low temperature.



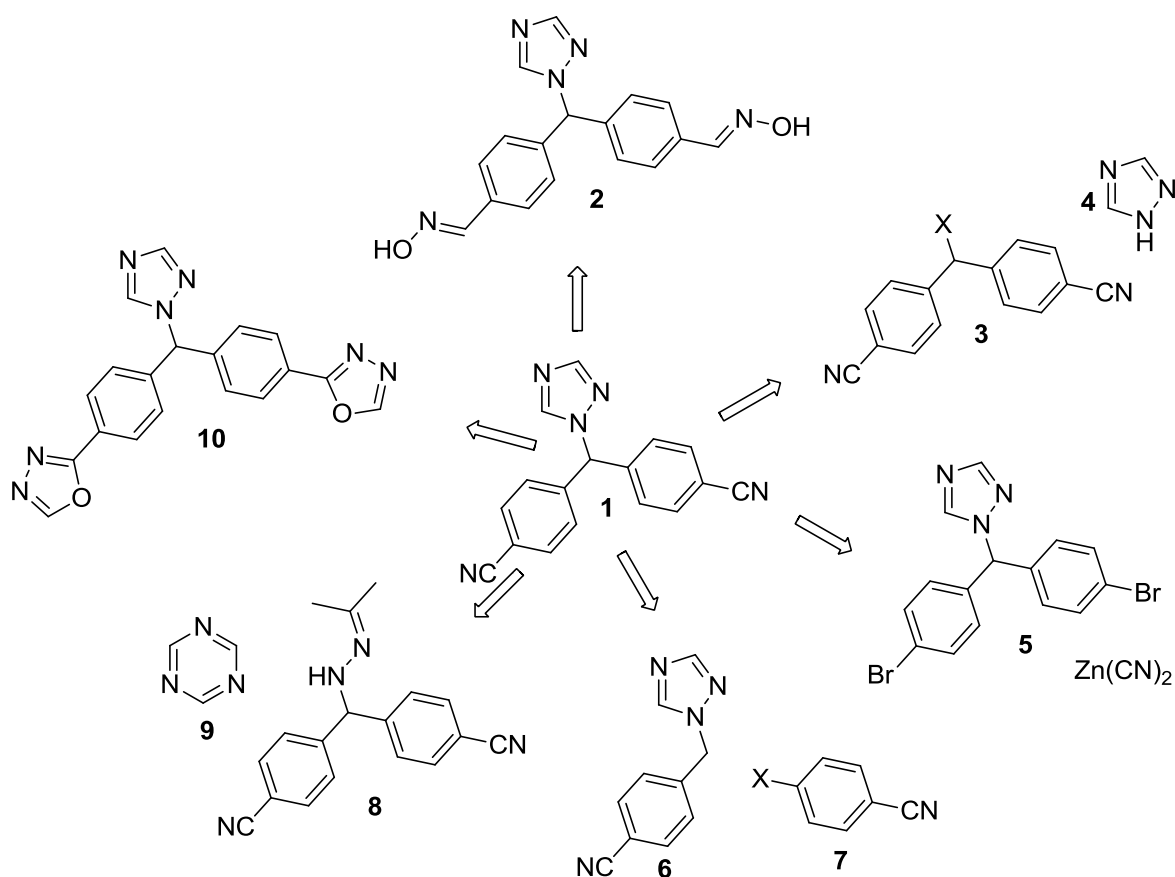
Letrozole (1)

Keywords: Letrozole, 1H-1, 2, 4-triazole, trifluoroacetic anhydride, 4-(chloro(4-cyanophenyl)methyl)benzamide, 4,4-dibromobenzophenone

Introduction

Letrozole **1** (Trade name: Femara) is an antineoplastic agent invented by Novartis Pharmaceuticals Corporation and is used for the treatment of certain types of breast cancer (such as hormone-receptor-positive breast cancer) in women.¹ Letrozole is also used for the slow or reverse growth of breast cancer in women by decreasing the production of estrogen in breast cancer patients.^{2,3}

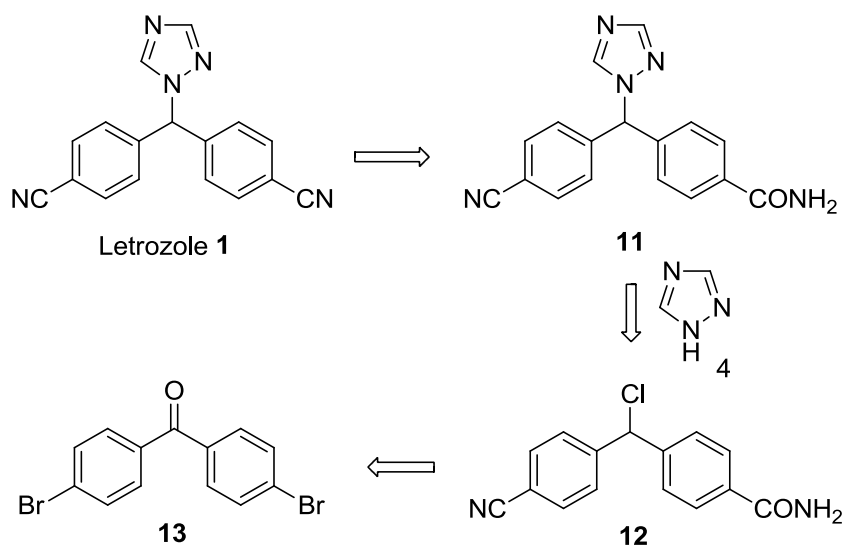
Several reports are available in the literature for the synthesis of Letrozole **1**. Most of these synthetic protocols commenced with 4-((1*H*-1,2,4-triazol-1-yl)methyl)benzonitrile **6** as a key intermediate, which was further converted into letrozole by reaction with 4-halocyanobenzene **7**.⁴⁻⁸ The nucleophilic substitution on 4,4'-methylene-bis-benzonitrile **3** containing good leaving group at methylene bridge with triazole **4** is also reportedly provided letrozole in excellent yields.^{9,10} Other notable synthesis of letrozole include the late stage palladium catalysed cyanation on 1-[bis(4-bromophenyl)methyl]-1*H*-1,2,4-triazole **5** with $Zn(CN)_2$.¹¹ Construction of 1*H*-1,2,4-triazole ring starting from 4,4'-(hydrazonomethylene)dibenzonitrile, removal of amino functionality by diazotization reaction on amino substituted letrozole,¹² late-stage dehydration of bis-oxime **2** to biscyano functionality¹³ (Scheme 1) are the other noticeable protocol adapted for the synthesis of letrozole. Considering the high demand and commercial value of letrozole **1** as a drug substance in oncology treatment, despite all these known synthetic procedures, search for an innovative and cost-effective protocol for the synthesis of Letrozole **1** is always in demand. Here in we report an improved alternate synthesis of Letrozole **1** in excellent yields, and this synthetic route has the freedom to operate from the existing patent landscape.



Scheme 1. Various synthetic routes for the synthesis of Letrozole **1**.

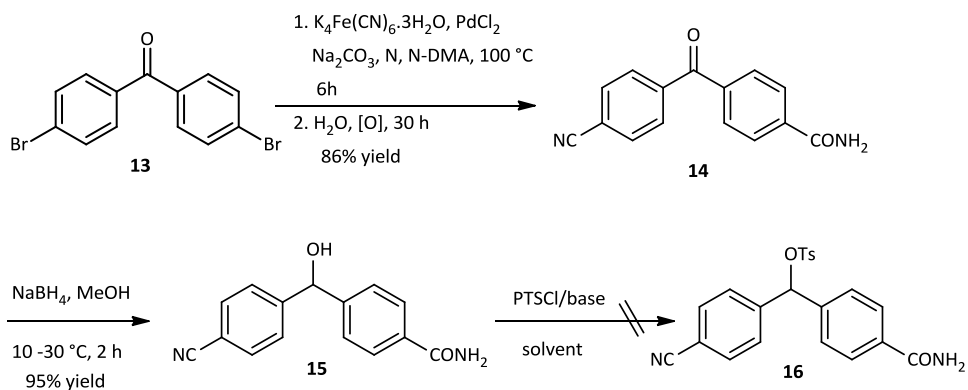
Results and Discussion

The retrosynthetic design for the preparation of letrozole **1** is depicted in Scheme 2. Letrozole can be prepared from 4-((4-cyanophenyl)(1*H*-1,2,4-triazol-1-yl)methyl)benzamide **11** by the amide dehydration in 1,4-dioxane with a suitable dehydrating agent.^{14,15} The C-N bond formation between N-1 of 1,2,4-triazole **4** with 4-(chloro(4-cyanophenyl)methyl)benzamide **12** under nucleophilic substitution reaction conditions can yield compound **11**. The 4-(chloro(4-cyanophenyl)methyl)benzamide **12** in turn can be synthesized from bis(4-bromophenyl)methanone **13** involving a series of reactions such as cyanation¹⁶, *in situ* conversion to amide¹⁷ **14**, reduction of keto functionality of **14**¹⁸⁻²⁰ with sodium borohydride, and finally chlorination **12** using thionyl chloride.



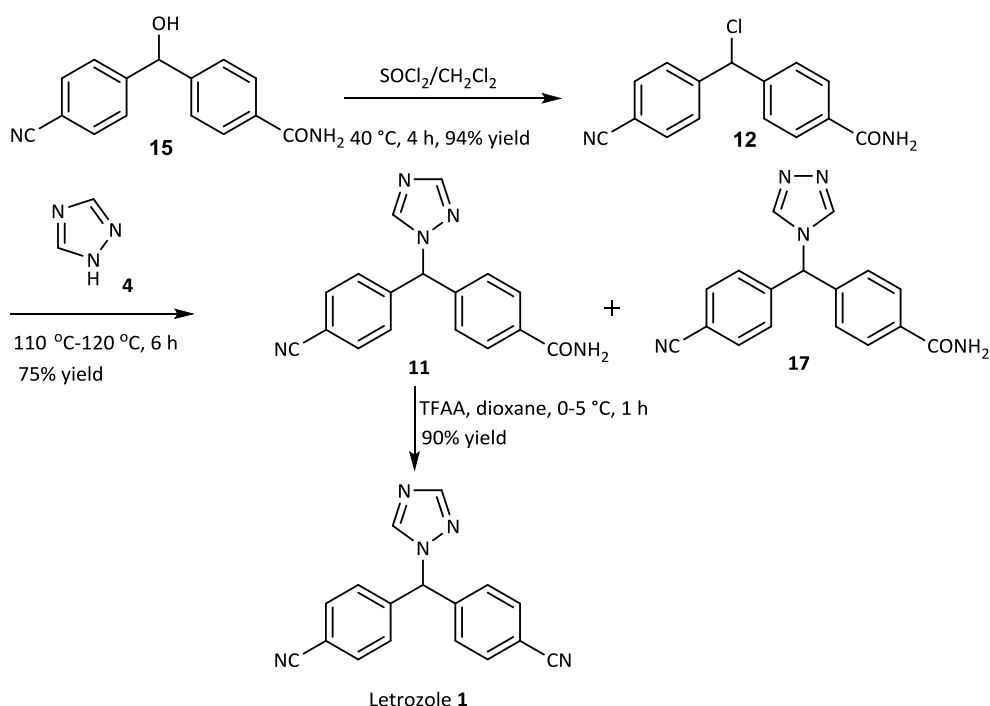
Scheme 2. Retrosynthetic analysis of Letrozole **1**.

During the synthesis of Letrozole **1**, initial attempts were focused on the preparation of 4-((4-cyanophenyl)(hydroxy)methyl)benzamide **15**. Compound **15** was prepared from 4-(4-cyanobenzoyl)benzamide **14** by reduction of keto functionality **14** with sodium borohydride in an alcoholic solvent (Scheme 3). The 4-(4-(cyanobenzoyl)benzamide **14** in turn prepared from 4,4-dibromo benzophenone **13** by cyanation with potassium ferrocyanidetrihydrate in presence of palladium(II)chloride followed by the selective hydrolysis of the cyano group to amide functionality at 100 °C under aerial oxidation in 86% of yield. Tosylation²¹ of 4-((4-cyanophenyl)(hydroxy)methyl)benzamide **15** was attempted under various conditions using *p*-toluenesulfonyl chloride in presence of base such as sodium hydroxide, sodium carbonate, triethylamine, sodium bicarbonate, potassium carbonate, potassium bicarbonate, in various solvents like CH₂Cl₂, THF, toluene, DMF, acetonitrile, water; however these reactions were not successful and the required product was not observed under these reaction conditions probably due to the increased steric repulsion of phenyl groups on the incoming tosyl group. In all these attempts, 4-(4-cyanobenzoyl) benzamide **14** was isolated as one of the major product under these conditions, and formation of this product can be attributed to the aerial oxidation of benzylic hydroxyl group at elevated temperature in presence of air/oxygen as well as the less reactivity of 4-((4-cyanophenyl)(hydroxy)methyl)benzamide **15** towards the tosylation reaction. Thus, we have decided to peruse halogenations followed by 1*H*-1,2,4-triazole **4** introduction as the alternate strategy for the synthesis of letrozole **1**.



Scheme 3. Attempt for the synthesis of tosylate **16**.

Attributing to the increased strain may be a probable root cause for the failure of tosylation on compound **15**, we focused our attention for converting hydroxyl group in **15** to the chloro derivative **12** (Scheme 4). Thus the alcohol **15** was treated with thionyl chloride in dichloromethane and the required compound **12** was isolated in excellent yields. After the successful synthesis of **12**, we focused our attention on the synthesis of the target molecule Letrozole **1** by reacting it with 1H-1,2,4-triazole **4**. Several attempts have been carried out for the introduction of 1H-1,2,4-triazole **4** by the nucleophilic substitution on halo compound **12** in presence of a base in polar protic as well as aprotic solvents. All these reactions resulted in poor conversion to the required product. Reaction performed at higher temperatures in presence of polar protic solvents resulted in the formation of 4-(4-cyanobenzoyl) benzamide **14** probably formed *via* aerial oxidation. However, when the reaction was conducted under neat conditions at elevated temperature ($110\text{ }^\circ\text{C}$ - $120\text{ }^\circ\text{C}$) over a period of 6 h, the required product **11** was isolated in around 75% yield, along with the corresponding regioisomer **17** as shown in Scheme 4.



Scheme 4. Completion of the synthesis of Letrozole **1**.

In the above process, formation of an appreciable amount of undesired regioisomer 4,4'-(4*H*-1,2,4-triazol-4-ylmethylene)bisbenzimidazole **17** is observed. This product **11** was separated from its regioisomer **17** by silica gel column chromatography (SiO₂, 100-200 mesh, 4% Methanol/CH₂Cl₂). The amide **11** to nitrile **1** conversion was then carried out by using trifluoroacetic anhydride in 1,4-dioxane, and Letrozole **1** was isolated in excellent yields (Scheme 4). The crude letrozole was further recrystallized from a mixture of methanol and water (1:5) to afford Letrozole **1** in overall 90% of isolated yield.

Conclusions

In summary, we have developed a novel and efficient synthetic route for the preparation of Letrozole **1** in excellent yields, which is free from regioisomeric impurities. The developed process utilizes environmentally benign reagents as well as milder reaction conditions.

Experimental Section

General. ¹H and ¹³C NMR spectra were recorded in 500 MHz & 125 MHz. All chemical shifts were reported in parts per million (δ) and were internally referenced to residual proton solvents, unless otherwise noted. All spectral data were reported as follows: chemical shift multiplicity [singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), and multiplet (*m*)], coupling constants [Hz]. Trifluoroacetic anhydride used in the reaction was distilled from P₂O₅ and all other chemicals used were purchased from commercial suppliers and used without further purification. All flash column purifications were performed by using silica gel (100-200) mesh.

4-(4-cyanobenzoyl)benzamide (14). To a solution of compound **13** (25 g, 73.53mmol) in *N,N*-dimethylacetamide (125mL) was added to potassium ferrocyanide.3H₂O (31 g, 73.53 mmol) followed by PdCl₂ (0.65 g, 3.6 mmol), and Na₂CO₃ (15.58 g, 147 mmol) at room temperature. The reaction mixture was heated to 100 °C and stirred for 6 h. Later water (2 mL) was added to the reaction mixture and air was purged into the solution at 100°C for 5 h and stirring was continued at the same temperature for 30 h. Then TLC (Thin Layer Chromatography) (10% MeOH/CH₂Cl₂) showed complete conversion to compound **14**. The reaction mixture was cooled to room temperature and filtered through celite bed and washed with *N,N*-DMA (25 mL). To the obtained filtrate added CH₂Cl₂ (25 mL) and water (250 mL). Stirred the reaction mixture at ambient temperature for 1h. The precipitated product was filtered and dried under vacuo at 60 °C for 8 h afforded 15.7 g (86%) of compound **14** as a pale yellow solid. R_f =0.4 (SiO₂, 5% MeOH/CH₂Cl₂). mp 205-207, IR (Neat):ν_{max}:3483.7, 3062.4, 2231.2,2036.3, 1943.8, 1693.1, 1650.7, 1615.0, 1500.3, 1280.5, 1187.9, 1124.3, 1016.3, 990.2, 931.4, 864.9, 755.9, 691.3, 673.0, 638.3, 592.0, 539.9, 480.1 cm⁻¹. ¹H NMR (500MHz, DMSO-d₆): δ 8.20 (brs, 1H), 8.05 (m, 4H), 7.90 (d, *J* 6 Hz, 2H), 7.83 (d, *J* 6 Hz, 2H), 7.62 (brs, 1H) ppm. ¹³C NMR (125 MHz, DMSO-D₆): δ 194.9, 167.4, 141.0, 138.7, 138.5, 133.1, 130.6, 130.2, 128.2, 118.6, 115.3 ppm. HRMS (ESI): [M+H]⁺.calcd.for C₁₅H₁₁N₂O₂251.0821, found 251.0822.

4-((4-cyanophenyl)(hydroxy)methyl)benzamide (15). A stirred solution of compound **14** (10 g, 39.9 mmol) in MeOH (100 mL) was treated with NaBH₄ (3.77 g, 99.75 mmol) in equal portions over a period of 15 minutes at 0 °C-5 °C and the resulting solution was warmed to room temperature and stirred for 2 h. After which time, TLC (10% MeOH/CH₂Cl₂) showed consumption of compound **14**. Now, the reaction was quenched with saturated aqueous NH₄Cl (20 mL) at 0°C and the volatile solvents were evaporated under pressure and diluted

with water (100 mL). The pH of the solution was adjusted to 6.5-7.0 by the addition of aqueous 1N HCl and stirred at room temperature for 1 h. The solution was filtrated to obtain solid, which was washed with water (50 mL) and dried under vacuum to get 9.57 g (95%) of compound **15** as a pale yellow solid. $R_f = 0.5$ (SiO₂, 10%MeOH/CH₂Cl₂). mp 173-175. IR (Neat) ν_{\max} : 3396.9, 3307.3, 3185.8, 2932.2, 2859.9, 2364.3, 2236.0, 1678.7, 1612.2, 1564.9, 1509.9, 1412.6, 1331.6, 1310.3, 1266.0, 1194.6, 1110.8, 1052.9, 865.8, 781.9, 620.9, 562.1 cm⁻¹. ¹H NMR (500MHz, DMSO-d₆): δ 7.92 (brs, 1H), 7.80 (m, 4H), 7.60 (d, *J* 6.4Hz, 2H), 7.46 (d, *J* 6.4 Hz, 2H), 7.30 (brs, 1H), 6.26 (d, *J* 3.2 Hz, 1H), 5.86 (d, *J* 2.8 Hz, 1H) ppm. ¹³C NMR (125 MHz, DMSO-d₆): δ 168.2, 151.2, 148.2, 133.7, 132.7, 128.0, 127.6, 126.5, 119.4, 110.1, 73.7 ppm. HRMS (ESI): [M+H]⁺ calcd. for C₁₅H₁₃N₂O₂ 253.0977, found 253.0965.

4-(chloro(4-cyanophenyl)methyl)benzamide (12). A solution of compound **15** (9.0 g, 35.67 mmol) in CH₂Cl₂ (90 mL) was added thionyl chloride (21.22g, 178.38mmol) at 0 °C and the solution was warmed to 40 °C and stirred for 4 h. TLC (2% MeOH/CH₂Cl₂) showed consumption of compound **15**. The reaction mixture was concentrated under reduced pressure at 50°C and diluted with CH₂Cl₂ (30 mL). Reaction mixture was neutralized with saturated 10% aqueous NaHCO₃ (30 mL) at 0 °C. The layers were separated and aqueous layer was extracted with CH₂CH₂ (2 x 20 mL) twice. The combined organic extracts were washed with water (30 mL) and aqueous NaCl solution (30 mL) and dried over anhydrous Na₂SO₄. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel flash column chromatography (SiO₂, 100-200 mesh, 2% MeOH/CH₂Cl₂) to afford 9.06 g (94%) of compound **12** as a white solid. $R_f = 0.6$ (SiO₂, ethyl acetate); mp 152-156 °C. IR (Neat): ν_{\max} : 3399.8, 3342.0, 3604.3, 2944.7, 2749.0, 2223.5, 1810.8, 1728.2, 1651.7, 1499.3, 1251.5, 1103.0, 1013.4, 816.7, 755.9, 633.5 cm⁻¹. ¹H NMR (500MHz, DMSO-d₆): δ 8.0 (brs, 1H), 7.88 (m, 4H), 7.69 (d, *J* 6.8 Hz, 2H), 7.48 (d, *J* 6.8 Hz, 2H), 6.70 (brs, 1H). ¹³C NMR (125 MHz, DMSO-d₆): δ 167.4, 145.8, 143.0, 134.3, 132.7, 128.4, 128.0, 127.3, 118.4, 111.0, 61.8. HRMS (ESI): [M+H]⁺ calcd. for C₁₅H₁₂N₂OCl 271.0638, found 271.0629.

4-((4-cyanophenyl)(1H-1,2,4-triazol-1-yl)methyl)benzamide (11) and isomer 4,4'-(4H-1,2,4-triazol-4-ylmethylene)bisbenzoxitrile (17). A mixture of compound **12** (5.0 g, 18.46 mmol) and 1H-1,2,4-triazole **4** (3.18 g, 46.17 mmol) was heated under neat conditions at 110 °C-120 °C for 6h. After which time, TLC (10% MeOH/CH₂Cl₂) showed complete consumption of compound **12**. The reaction mixture was cooled to room temperature and diluted with water (20 mL) and extracted with CH₂Cl₂ (2 x 30 mL) twice. The combined organic extracts were washed with water (30 mL), aqueous NaCl solution (30 mL) and dried over anhydrous Na₂SO₄. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO₂, 100-200 mesh, 1% MeOH/CH₂Cl₂) to afford 4.20 g (75%) of compound **11** as a white solid. $R_f = 0.4$ (SiO₂, 10% MeOH/CH₂Cl₂). mp: 130-134 °C. IR (Neat): ν_{\max} : 3429.7, 2923.0, 1629.0, 1552.4, 1382.7, 1219.2, 1019.1, 772.3, 678, 6 cm⁻¹. ¹H NMR (500MHz, DMSO-d₆): δ 8.71 (brs, 1H), 8.11 (s, 1H), 8.0 (brs, 1H), 7.88 (dd, *J* 6.4, 2.4 Hz, 4H), 7.41 (m, 3H), 7.32 (3, 3H), 7.34 (s, 1H), 7.31 (d, 2H). ¹³C NMR (125 MHz, DMSO-D₆) δ : 167.3, 152.2, 144.9, 143.9, 140.9, 134.2, 132.7, 129.0, 128.0, 127.9, 118.4, 110.9, 64.3; HRMS (ESI): [M+H]⁺ calcd. for C₁₇H₁₄N₅O 304.1198, found 304.1213

Regioisomer 4,4'-(4H-1,2,4-triazol-4-ylmethylene)bisbenzoxitrile (17). White solid (0.3 g), mp 138-142 °C, IR (Neat): ν_{\max} : 3356.2, 3189.4, 2229.8, 1669.4, 1613.5, 1569.1, 1507.4, 1416.7, 1390.7, 1167.9, 1066.6, 862.2, 748.4, 668.3, 622.0, 556.4 cm⁻¹; ¹H NMR (500MHz, DMSO-D₆): δ 8.62 (s, 2H), 8.02 (brs, 1H), 7.91 (m, 4H), 7.41 (m, 3H), 7.29 (d, *J* 6.4 Hz, 2H), 7.19 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 167.2, 143.7, 142.9, 140.7, 134.5, 133.0, 128.8, 128.2, 127.8, 118.4, 111.3, 61.1. HRMS (ESI): [M+H]⁺ calcd. for C₁₇H₁₄N₅O 304.1198, found 304.1204.

Letrozole (1). A solution of compound **11** (3.0 g, 9.8 mmol) in 1,4-dioxane (3.0 mL) was treated with trifluoroacetic anhydride (4.15 g, 19.7mmol) at 0 °C and the solution was warmed to room temperature and stirred for 1h. After which time, TLC (10% MeOH/CH₂Cl₂) showed complete consumption of compound **11**. The

reaction was quenched with water (20 mL) and the aqueous layer was extracted with CH₂Cl₂ (2 x 30 mL) twice. The combined organic extracts were washed with a saturated aqueous NaHCO₃ solution (30 mL) and aqueous NaCl solution (30 mL) and dried over anhydrous Na₂SO₄. The filtrate was concentrated under reduced pressure to give the crude material which was crystallized in methanol (6 mL) and water (30 mL) to afford 2.55 g (90%) of Letrozole **1** as a white solid. mp= 185-186 °C. IR (Neat) ν_{\max} : 3407.4, 3122.8, 2230.7, 1607.7, 1503.5, 1433.1, 1412.9, 1378.2, 1275.0, 1199.7, 1138.0, 1009.7 cm⁻¹. ¹H NMR (500MHz,CDCl₃) δ ppm: 8.09 (s, 1H), 8.06 (s, 1H), 7.70 (m, 4H), 7.28 (m, 4H), 6.81 (s, 1H). ¹³C NMR (125 MHz,CDCl₃): δ 153.0, 143.7, 141.8, 132.9, 128.9, 117.8, 113.3, 66.36. HRMS (ESI): [M+H]⁺ calcd. for C₁₇H₁₂N₅ 286.1093, found 286.1099.

Acknowledgements

The authors would like to thank Andhra University, Visakhapatnam for permitting the research work and for constant encouragement.

Supplementary Material

Proton and carbon-13 NMR spectra of compounds and their synthetic intermediates are presented as supporting information in Supplementary Material. Readers will be able to access this supporting information using the link "Supplementary Material" in the journal issue contents page.

References

1. Torrisi, R.; Bagnardi, V.; Pruneri, G.; Ghisini, R.; Bottiglieri, L.; Magni, E.; Veronesi, P.; D'Alessandro, C.; Luini, A.; Dellapasqua, S.; Viale, G.; Goldhirsch, A.; Colleoni, M. *Br. J. Cancer* **2007**, *97*, 802-808. <http://DOI:10.1038/sj.bjc.6603947>
2. Pfister, C. U.; Martoni, A.; Zamagni, C.; Lelli, G.; Braud F. D.; Souppart, C.; Duval, M.; Hornberger, U. *Biopharm. Drug. Dispos.* **2001**, *22*, 191-197. <http://DOI.Org/10.1002/bdb.273>
3. Krainick-Strobel, U. E.; Lichtenegger, W.; Wallwiener, D.; Tulusan, A. H.; Jänicke, F.; Bastert, G.; Kiesel, L.; Wackwitz, B.; Paepke, S. *BMC Cancer* **2008**, *8*:62. <http://DOI:10.1186/1471-2407-8-62>
4. Bowman, R. M.; Steele, R. E.; Browne, L. *Alpha-heterocyclic substituted tolunitriles*. US Patent 4 978 672, 1990.
5. Wadhwa, L. K.; Saxena, R. *Process for producing 4-(1H-1,2,4-triazol-1-ylmethyl)benzotrile*. US Patent 2005/0209294 A1, 2005.
6. MacDonald, P. L.; Bigatti, E.; Rossetto, P.; Harel, Z. *Process for the preparation of letrozole*. US Patent 7 705 159 B2, 2010.
7. Hussain, H.; Saijansinh, S. K.; Gautam, P.; Kumar, S. M.; Shantilal, K. J.; Kumar, A. V., *Process for the preparation of letrozole*. WO Patent 2007/054964 A2, 2007.

8. Laxminarayan, S. P.; Narayanrao, K. R.; Ramachandradra, R. D.; Sandip, V. C. *Synthesis of 4-[1-(4-cyanophenyl)-(1,2,4-triazol-1-yl)methyl] benzonitrile and 4-[1-(1H-1,2,4-triazol-1-yl)methylene benzonitrile intermediate*. WO Patent 2007/107733 A1, 2007.
9. Hasson, M.; Isenberg, H.; Manoff, E.; Bentolila, M.; Friedman, O.; Zelikovitch, L.; *Letrozole purification process*. US Patent 2007/0112203 A1, 2007.
10. Friedman, O.; Freger, B.; Etlin, O.; Ditzkovitch, J.; Danon, E.; Seryi, Y.; Davidi, G.; Arad, O.; Kaspi, J.; *Letrozole production process*. US Patent 2007/0112202 A1, 2007.
11. Ohshima, T.; Ipposhi, J.; Nakahara, Y.; Shibuya, R.; Mashima, K. *Adv. Synth. Catal.* **2012**, 354, 2447-2452.
<http://doi.org/10.1002/adsc.201200536>
12. Patel, H. V.; Jani, R. J.; Thennati, R. *Regiospecific process for the preparation of 4-[1-(4-cyanophenyl)-1-(1,2,4-triazol-1-yl)methyl]benzonitrile*. US Patent 2006/0128775A1, 2006.
13. Kumar, A. S.; Chandra, M. G.; Pradipta, K.; *Novel intermediates for preparation of Letrozole*. WO Patent 2007/074474 A1, 2007.
14. Foss, F. W.; Mathews, T. P.; Kharel, Y.; Kennedy, P. C.; Snyder, A. H.; Davis, M. D.; Lynch, K. R.; Macdonald, T. L.; *Bioorg. Med. Chem.* **2009**, 17, 6123-6136.
<http://DOI:10.1016/j.bmc.2009.04.015>
15. Li, Z.; Fang, L.; Wang, J.; Dong, L.; Guo, Y.; Xie, Y.; *Org. Process Res. Dev.* **2015**, 19, 444-448.
<http://DOI:10.1021/op500395b>
16. Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, 689, 4576-4583.
<http://DOI:10.1016/j.jorganchem.2004.08.020>
17. Liu, Y.-M.; He, L.; Wang, M.-M.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Chem. Sus. Chem.* **2012**, 5, 1392-1396.
<http://DOI:10.1002/cssc.201200203>
18. Rao, K. N.; Kumar, K.; Ghosh, S. *Eur. J. Org. Chem.* **2018**, 398-412.
<http://DOI.Org/10.1002/ejoc.201701562>
19. Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, 71, 122-125.
<http://DOI:10.1021/ja01169a033>
20. Rao, K. N.; Kanakaraju, M.; Kunwar, A. C.; Ghosh, S. *Org. Lett.* **2016**, 18, 4092-4095.
<http://DOI:10.1021/acs.orglett.6b01981>
21. Palle, V. R. A.; Kalaria, A. J.; Shelke, S. A.; *Process for preparing Letrozole*. US Patent 2007/0100149 A1, 2007.