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# Total Syntheses of Lonidamine and Adjudin (AF-2364)- Male Hormonal Contraceptives

**Veerareddy. Arava*[1], Surendrareddy. Gogireddy[1] and Dubey. P. K[2]**

[1]*R&D Centre, Suven Life Sciences Ltd, Plot No.#18,Phase-III, Jeedimetla, Hyderabad-500055, India*
[2]*Department of Chemistry, J.N.T. University, Hyderabad-500072, India*

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**ABSTRACT**

*The regiospecific syntheses of Lonidamine and Adjudin are described.*

**Keywords:** Phenylglyoxalates, Benzyl hydrazones, Cu(I)-L-Proline Catalyst, Indazole-3-carboxylic acids.

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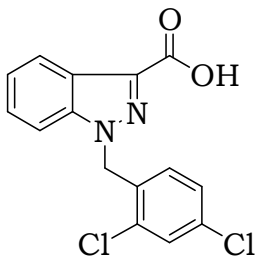
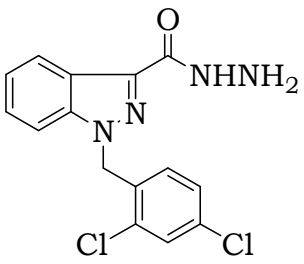
## INTRODUCTION

Lonidamine **1** and Adjudin **2** [1,2] are anti-spermatogenesis compounds. Lonidamine is an experimental drug not only for male hormonal contraception (MHC), but also for treating [3], inhibiting/ or preventing polycystic kidney disease (PKD). This can include administering a therapeutically effective amount of the lonidamine derivatives for inhihibiting CFTR and/ or Hsp90 or biological pathway thereof. Lonidamine derivatives are also useful for prostate proliferative disorders [4].

Among many heterocyclic compounds indazole and its derivatives are important class of compounds with high biological activities such as anti- inflammatory, anti tumor, anti-HIV and antidepressant [5-9].




**Lonidamine 1**




**Adjudin 2**

Last decade (2001-2010) has witnessed an enormous interest on indazole [10] compounds because of their interesting biological activity. Number of papers appeared during this decade on indazole-3-carboxylic acids and $N^1$-substituted indazole compounds. The regiospecific $N^1$-substitution is mostly attempted on indazole-3- carboxylic

acids resulting into a mixture of $N^1$ and $N^2$ derivatives. Simultaneously the regioselective substitution methods were also developed [11-19].

## MATERIALS AND METHODS

All reagents were obtained commercially and were of the highest commercial quality and used without further purification. Solvents were freshly distilled and used. Melting points were determined in open capillaries and are uncorrected. TLC or HPLC routinely checked the purity of all compounds. IR spectra were recorded on a Perkin-Elmer model 2000 instrument in KBr phase. $^1$H-NMR (400 MHz) and $^{13}$C-NMR (100MHz) spectra were recorded in $CDCl_3$ or DMSO using Brucker instrument and Mass spectra were recorded on a Perkin-Elmer mass spectrometer operating at 70 eV.

**Typical procedures for methyl 1-(2,4-dichlorobenzyl)-1H-indazole-3-carboxylate (3):**

**Method A: -**
To a solution of DMSO (15.0ml), methyl 2-(2-Iodochlorophenyl)-2-(2-(2,4-dichlorobenzyl) hydrazono) acetate **4** (5.0g, 0.010 mol), CuI (0.2g, 0.001 mol), L-Proline (0.244g, 0.0021 mol) and $Cs_2CO_3$ (8.6g, 0.026 mol) was added at room temperature. Stirred for 30 minutes at 30-35°C. After completion of reaction, mass quenched into water (75.0ml) and extracted with ethyl acetate (100.0ml) at 20-25°C. The Organic layer was separated and washed with water (10.0ml) and dried over anhydrous $Na_2SO_4$. Organic layer was concentrated to get the crude product, which was purified by silica gel column chromatography [Hexane-Ethyl acetate (8:2)] to give desired compound as a colorless solid to yield 2.7g **(75%)**.

**Method B:-**
To a solution of DMSO (15.0ml), methyl 2-(2-chlorophenyl)-2-(2-(2,4-dichlorobenzyl) hydrazono) acetate **5** (5.0g, 0.0134 mol), dppf.PdCl2 (1.78g, 0.0020 mol) and $Cs_2CO_3$ (10.5g, 0.0322 mol) was added at room temperature. Stirred for 30 minutes at RT. After completion of reaction, mass quenched into water (75.0ml) and extracted with ethyl acetate (70.0ml) at 20-25°C. The Organic layer was separated and washed with water (10.0ml) and dried over anhydrous $Na_2SO_4$. Organic layer was concentrated to get the crude product (yield 3.9g), which was purified by silica gel column chromatography [Hexane-Ethyl acetate (8:2)] to give desired compound as a colorless solid to yield 3.75g **(83.3%)**, mp142.5-143.5°C; IR (KBr) ($cm^{-1}$): 1711, 1479, 1238, 1168, 754; $^1$H-NMR (400 MHz, DMSO): δ 3.89 (s, 3H), 5.84 (s, 2H), 6.96 (d, 1H, *J* = 8.30 Hz), 7.35(m, 2H), 7.51(t, 1H), 7.68 (d, 1H, *J* = 1.96 Hz), 7.83 (d, 1H, *J* = 8.5 Hz), 8.10 (d, 1H, *J* = 8.16 Hz); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 50.39, 52.20, 109.72, 122.39, 123.57, 123.89, 127.50, 127.65, 129.35, 129.41, 132.10, 133.0, 134.50, 135.71, 140.78, 162.87; ESI-MS (m/z %): 335.2 and 337.1 [M+2].

**Typical procedures for Lonidamine 1 and Adjudin 2 :**

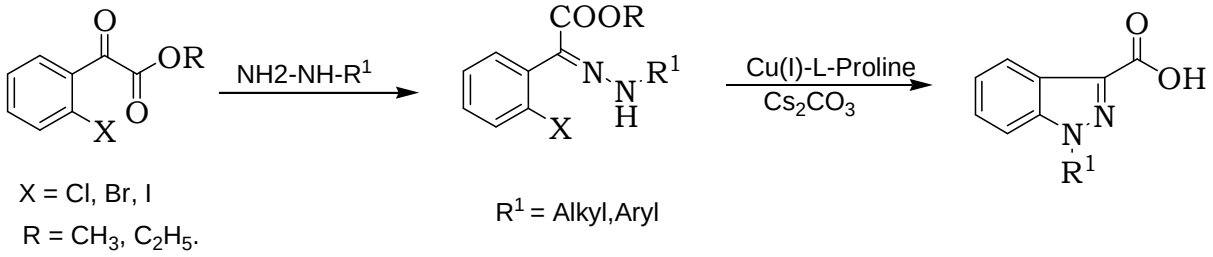
**Preparation of Lonidamine 1:**
To a solution of Sodium hydroxide (1.19g, 0.029 mol) and water (50.0ml), Ethanol (15.0ml), methyl 1-(2,4-dichlorobenzyl)-1H-indazole-3-carboxylate (**3**) (5.0g, 0.0149 mol) was added at RT. Reaction mass heated to 65°C and stirred for 30 minutes. After completion of reaction, solvent was distilled off under vacuum and water (50.0ml) added and stirred for 30 minutes. Reaction mass pH adjusted to 2.0-2.5 with Conc.HCl at 20-25°C. Reaction mass heated to 80°C and stirred for 7hrs and cooled to RT. Filtered the crude Lonodamine, which is purified in acetone to get the pure colorless solid to yield 3.5g, (73%), mp 208.8-210.5°C. IR (KBr) ($cm^{-1}$): 3421, 1699, 1486, 1225; $^1$H-NMR (400 MHz, DMSO): δ 5.83 (s, 2H), 6.93 (d, 1H, *J* = 8.36 Hz), 7.33 (t, 1H), 7.38 (dd, 1H, $J_1$ = 8.34 Hz, $J_2$ = 1.96 Hz), 7.49 (t, 1H), 7.69 (d, 1H, *J* = 1.92 Hz), 7.80 (d, 1H, *J* = 8.52 Hz), 8.10 (d,1H, *J* = 8.16), 13.14 (s, 1H) ; $^{13}$C-NMR (100 MHz, DMSO): δ 50.20, 111.09, 122.09, 123.48,123.60, 127.51, 128.24, 129.53, 131.47, 133.66, 133.72, 133.87, 136.24, 141.37, 163.74; ESI-MS (m/z %): 321.1 and 323.0 (M+2).

**Preparation of Adjudin 2:**
To a solution of Ethanol (12.0ml) and water (2.0ml), methyl 1-(2,4-dichlorobenzyl)-1H-indazole-3-carboxylate (**3**) (2.0g, 0.005 mol) and hydrazine hydrate (16.0ml) were added at RT. Reaction mass heated to 80°C and stirred for 6 hrs. After completion of reaction cooled to 10°C, stirred for 30 minutes. Filtered the desired compound as a white crystalline solid and washed with chilled mixture of ethanol(1.0ml) and water(1.0ml) to yield 1.64g (82%), mp 158-159°C. IR (KBr) ($cm^{-1}$): 3391, 3316, 1661, 1518; $^1$H-NMR (400 MHz, DMSO): δ 4.47 (s, 2H), 5.78 (s, 2H), 6.84 (d,

1H, *J* = 8.38 Hz), 7.28 (t, 1H), 7.34 (dd, 1H, $J_1$ = 8.36 Hz, $J_2$ = 1.97 Hz), 7.45 (t, 1H), 7.68 (s,1H) 7.71 (d,1H, *J* = 8.50 Hz), 8.16 (d, 1H, *J* = 8.14 Hz), 9.56 (s,1H) ; $^{13}$C-NMR (100 MHz, DMSO): δ 49.89, 110.73, 122.28, 122.75, 122.98, 127.57, 128.23, 129.46, 131.03, 133.39, 133.71, 133.88, 137.98, 141.18, 161.69; ESI-MS (m/z %): 335.1 and 337.1 (M+2).

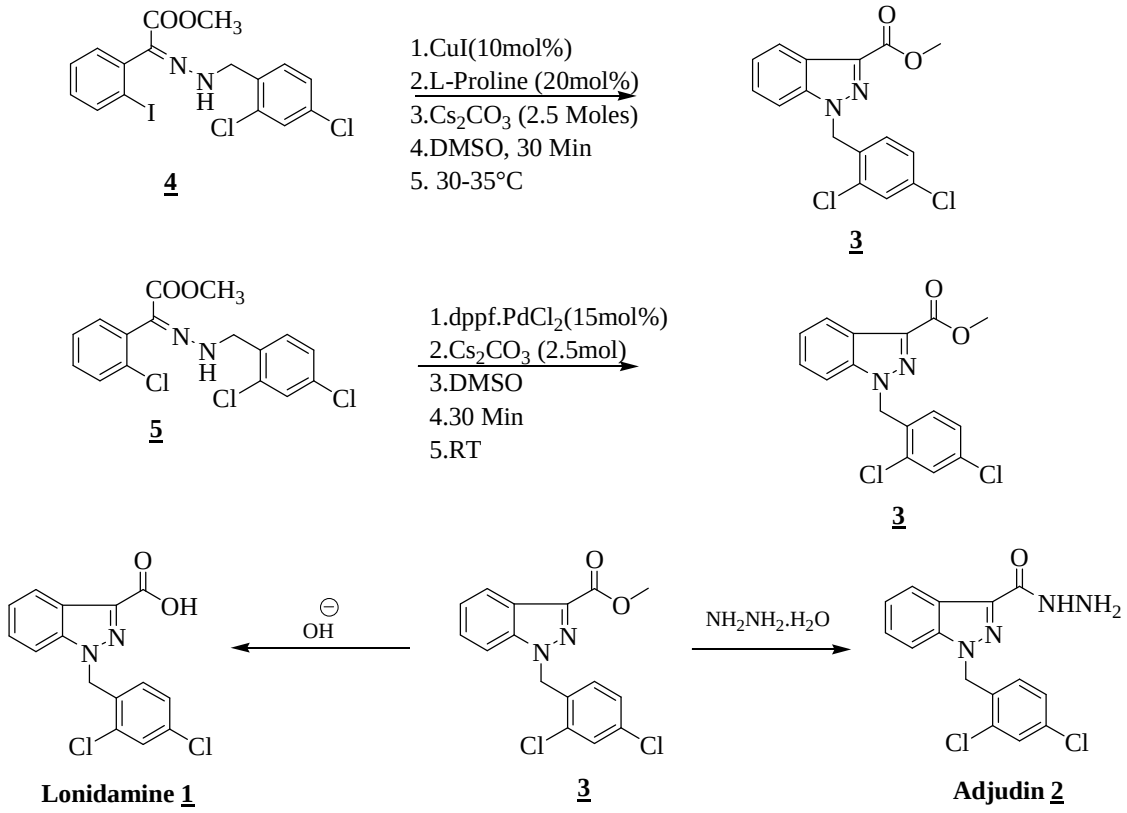
## RESULTS AND DISCUSSION

We recently [20] developed a regiospecific method of preparing indazole-3-carboxylic acids via phenylglyoxalates as shown in scheme-I.




**Scheme-I: N$^1$-Substituted Indazole-3-caroxylic acid derivatives.**

After establishing the method, we attempted the syntheses of Lonidamine **1** and Adjudin **2**. The synthesis of these compounds is achieved as shown in scheme-II.




**Scheme-II: Synthesis of Lonidamine 1 and Adjudin 2**

The Cyclization to indazole was achieved easily when X = I, **4** with Copper catalyst. Where as when X = Cl, **5** the cyclization did not proceed. The cyclization was effected in this case with PdCl2.dppf-$Cs_2CO_3$ catalyst. The ester **3** is hydrolyzed to give Lonidamine **1** and is when reacted with hydrazine hydrate gave Adjudin **2**.

## CONCLUSION

In conclusion we achieved the regiospecific syntheses of Lonidamine **1** and Adjudin **2**.

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