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Der Pharma Chemica, 2013, 5(4):232-239
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

An expeditious synthesis of riociguat, A pulmonary hypertension drug

Veerareddy Arava* and Surendrareddy Gogireddy

R&D Centre, Suven Life Sciences Ltd, Plot No.#18, Phase-III, Jeedimetla, Hyderabad, India

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ABSTRACT

Riociguat: A potent, Oral stimulator of soluble guanylate cyclase for the treatment of pulmonary hypertension, is prepared from commercially available 2-Chloronicotinic acid via (E)-2-(2-chloropyridin-3-yl)-2-(2-(2-fluorobenzyl) hydrazono) acetamide

Keywords: 2-(2-Chloro-pyridin-3-yl)-2-oxo-acetamide, Intramolecular cyclization, 1H-Pyra-Zolo [3,4-b]pyridines and Riociguat.

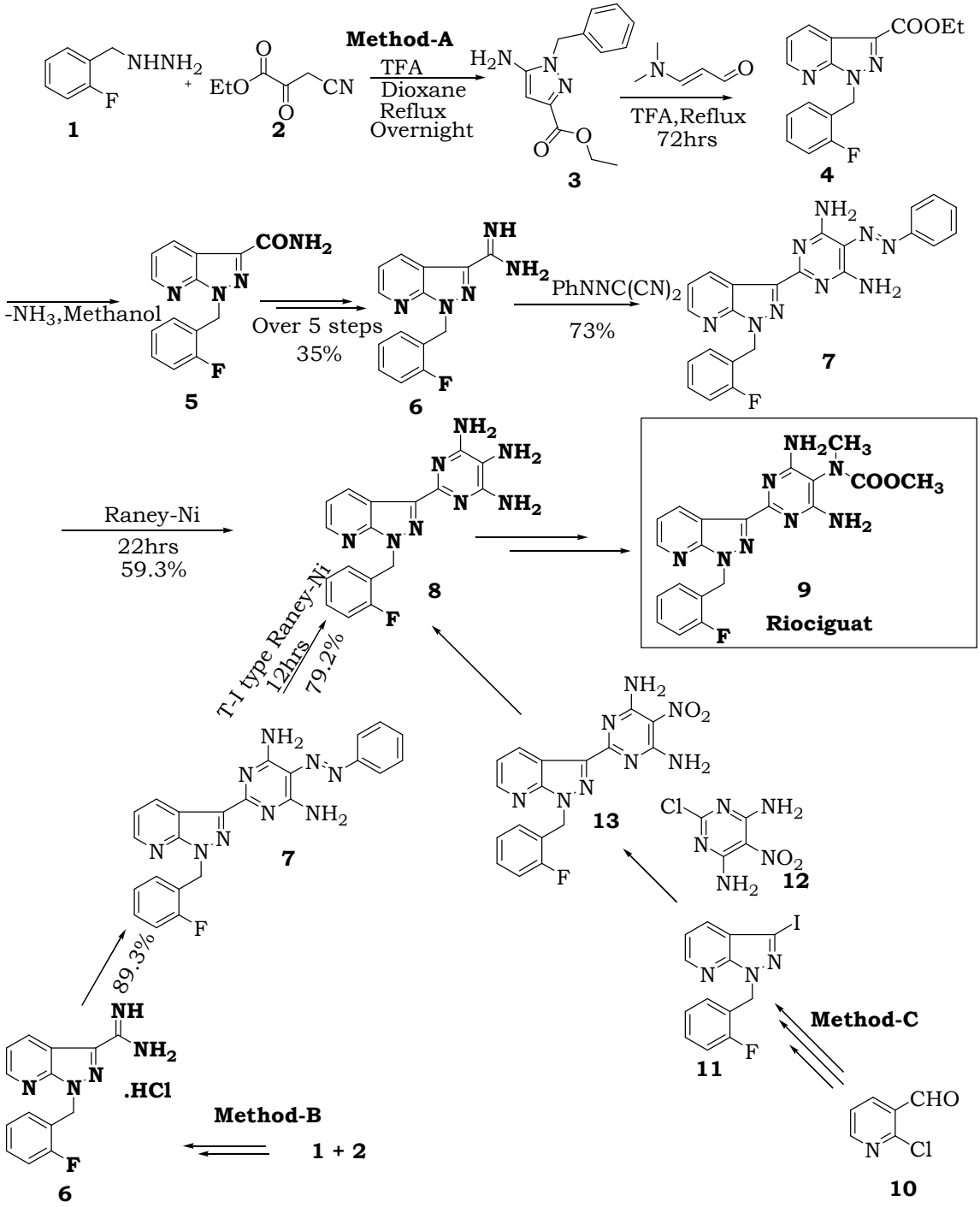
INTRODUCTION

Pulmonary hypertension (**PH**) is a group of condition characterized by increased blood pressure in pulmonary capillaries leading to reduced right heart function and eventual heart failure [1]. It was first identified by Dr. Ernd von Romberg in 1891 [2]. Recent years have seen significant progress in the treatment of Pulmonary Arterial Hypertension (**PAH**) with the development of palliative therapies. However, these developments have improved to some extent for patients with **PAH**, but survival rates and quality of life remain relatively low [3].

Treatment of **PH** with Nitric oxide (**NO**)-releasing agents such as nitrates has failed to produce beneficial long-time effects [4]. An alternative therapeutic surgery targets down stream compounds of the NO- signaling pathway inhibiting phosphodiesterase-5. The U.S FDA approved Sildenafil has been the lead substance in this group, showing both acute and long term beneficial effects with **PAH** [5]. However the phosphodiesterase-5 inhibition is not effective in all the patients.

Riociguat **9** offer a new mode of action and it has been shown to stimulate soluble guanylate cyclase directly, increasing the enzymes activity independent of **NO**, while also increasing sensitivity to low levels of **NO**. Direct **NO**-independent of sGC stimulation was demonstrated in 1994[6]. Riociguat: a potent, oral stimulator of soluble guanylate cyclase for the treatment of pulmonary hypertension, [7] is an oral agent being investigated in Phase-III clinical trials as a new approved drug to treat chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). It is the first member of novel class of therapeutics called $_S$GC stimulator.

Cristiana et al [8] reported (Method-A) the synthesis of Riociguat from condensation of 2-Flouorobenzaldehyde and Ethyl cyanopyruvate, where as Liang et al [9] reported (Method-B) from1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide.HCl **6** and Follmann et al [10] reported (Method-C) from 2-chloronicotinaldehyde **10** shown in Scheme 1.



Scheme 1. Reported syntheses of Riociguat

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 the preparation of Riociguat intermediates:
Preparation of 2-(2-Chloro-pyridin-3-yl)-2-oxo-acetamide (17):
To a solution of Conc.H_2SO_4 (15.0 ml), sodium chloride (0.35g, 0.0060 mol) and water (0.15 ml, 0.064 mol), (2-Chloro-pyridin-3-yl)-Oxo-acetonitrile **16** (10.0g, 0.064 mol) was added at 35-40°c over a period of 20 minutes and maintained for 30 minutes at 35-40°C. After completion of the reaction, the reaction mass was cooled and quenched into ice-water and extracted with ethyl acetate (150.0 ml). Separated the organic layer and washed with 10% Na_2CO_3 for removal of 2-chloronicoitinic acid. The organic layer is separated and dried over Na_2SO_4. The organic layer was distilled off under vacuum to get the solid. (Wt 6.09g, yield 55%, mp. 200-205 °C). IR (KBr) (cm^{-1}): 1694.20, 1727.30, 3415.81; ^{1}H-NMR (400 MHz, DMSO): δ 7.57 (dd, 1H, J_1 = 7.45 Hz, J_2 = 4.94 Hz), 8.08 (s, 1H), 8.13 (dd, 1H, J_1 = 7.34 Hz, J_2 = 1.19 Hz), 8.43 (s, 1H), 8.58 (dd, 1H, J_1 = 4.75 Hz, J_2 = 1.44 Hz). ^{13}C NMR (100 MHz, DMSO): δ 123.47, 131.63, 140.64, 147.41, 152.62, 163.88, 190.09. MW for $C_7H_5ClN_2O_2$ calcd. 184.1; observed 185.1, 187.1.

General procedure for the preparation of (E)-2-(2-chloropyridin-3-yl)-2-(2-(2-fluorobenzyl) hydrazono) acetamides (18a-f):
To a solution of IPA (50.0ml), 2-(2-Chloro-pyridin-3-yl)-2-oxo-acetamide **17** (6.0g, 0.032 mol), K_2CO_3 (8.8g, 0.064 mol), 2-Fluorobenzylhydrazine.2HCl **1a** (10.4g, 0.048 mol) was added at RT. Reaction mass was heated to 60-65°c and maintained for 6hrs. Upon completion of reaction solvent was distill off under vacuum to get the crude product. To this crude, water (50.0ml) and ethyl acetate (100.0ml) were added and stirred for 30 minutes. Separated the organic layer and dried over Na_2SO_4. Distill off the solvent to get the crude. Which is purified by column chromatography to get colorless solid **18a**(Wt. 6.4g).

(E)-2-(2-chloropyridin-3-yl)-2-(2-(2-fluorobenzyl) hydrazono) acetamide (18a) (R= 2-Fluorobenzyl): Yield 65%; mp. 82.2-185.1°C; IR (KBr) (cm^{-1}): 1658.74, 3240.41; ^{1}H-NMR (400 MHz, DMSO): δ 4.46 (d, 2H, J = 3.96 Hz), 6.91 (s,1H), 7.09 (s, 1H), 7.14-7.19 (m, 1H), 7.29 (m, 1H), 7.40 (t, 1H, J = 7.50), 7.44 (dd, 1H, J_1 = 7.34 Hz, J_2 = 4.80 Hz), 7.64 (d, 1H, J = 3.62 Hz); ^{19}F NMR (400 MHz, DMSO): δ -119.19 (F);^{13}C NMR (100 MHz, DMSO): δ 47.22, 115.22, 123.58, 124.60, 126.93, 128.30, 129.20, 130.19, 130.61, 141.58, 150.01, 158.98, 161.41, 165.99; MW for $C_{14}H_{12}ClFN_4O$ calcd. 306.7; observed 307.2, 309.2

2-(2-Chloro-pyridin-3-yl)-2-hydrazono-acetamide(18b) (R = H**)**: mp: 167.8-171.8°C; IR (KBr) (cm^{-1}): 1655.28, 3381.51; ^{1}H-NMR (400 MHz, DMSO): δ 6.87 (s, 1H), 7.11 (s, 1H), 7.32-7.47 (m, 3H), 7.61 (d, 1H, J = 7.51 Hz), 8.40 (m, 1H); ^{13}C NMR (100 MHz, DMSO): δ 123.54, 128.01, 132.45, 141.56, 149.83, 150.41, 166.39; MW for $C_7H_7ClN_4O$ calcd. 198.6; observed 199.7, 201.4

2-(2-Chloro-pyridin-3-yl)-2-(methyl-hydrazono)-acetamide (18c) (R = CH_3**):** mp: 159.7-160.8°C; IR (KBr) (cm^{-1}): 1660.13, 3464.48; ^{1}H-NMR (400 MHz, DMSO): δ 2.96 (s, 3H), 6.82 (s, 1H), 7.09 (s,1H), 7.17 (s, 1H), 7.61 (d, 1H, J = 6.15 Hz), 7.68 (s, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 37.65, 12.51, 128.36, 129.24, 141.74, 149.88, 150.23, 166.15 ; MW for $C_8H_9ClN_4O$ calcd. 212.64; observed 213.5, 215.8

2-(2-Chloro-pyridin-3-yl)-2-(phenyl-hydrazono)-acetamide (18d) (R = Phenyl**)**: mp: 117-120°C; IR (KBr) (cm^{-1}): 1656.02, 3481.25; ^{1}H-NMR (400 MHz, DMSO): δ 6.85 (t, 1H, J = 6.16 Hz), 7.13 (s, 1H), 7.20 (t, 1H, J = 7.04 Hz), 7.38 (d, 1H, J = 7.48 Hz), 7.49 (t, 1H, J = 6.25 Hz), 7.51 (s, 1H), 7.64 (d, 1H, J = 6.86 Hz), 8.48 (d, 1H, J = 2.15 Hz) 9.71 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 114.38, 121.32, 123.56, 128.15, 129.17, 132.45, 141.67, 144.31, 150.04, 150.32, 165.94; MW for $C_{13}H_{11}ClN_4O$ calcd. 274.21; observed 275.5, 277.5

2-(Benzyl-hydrazono)-2-(2-chloro-pyridin-3-yl)-acetamide(18e) (R = Benzyl**):** mp: 171.3-175.8°C; IR (KBr) (cm^{-1}): 1663.39, 3256.08; ^{1}H-NMR (400 MHz, DMSO): δ 4.52 (s, 2H), 6.87 (s, 1H), 7.22 (s, 1H), 7.24-7.39 (s, 5H), 7.43 (m, 1H), 7.62 (d, 1H, J = 7.17 Hz), 7.85 (s, 1H), 8.40 (d, 1H, J = 3.76 Hz) ; ^{13}C NMR (100 MHz, DMSO): δ 53.95, 123.58, 127.16, 127.76, 128.42, 129.94, 140.38, 141.62, 149.94, 150.20, 166.14; MW for $C_{14}H_{13}ClN_4O$ calcd. 288.73; observed 289.68, 290.82.

2-(2-Chloro-pyridin-3-yl)-2-[(2,4-dichloro-phenyl)-hydrazono]-acetamide(18f) (R = 2,4-Dichlorophenyl**):** mp: 230.6-232.0°C; IR (KBr) (cm^{-1}): 1672.00, 3385.01; ^{1}H-NMR (400 MHz, DMSO): δ 7.36 (d, 1H, *J* = 1.77 Hz), 7.38 (s, 1H), 7.51 (d, 1H, *J* = 1.81, Hz),
7.32 (dd, 1H, J_1 = 7.33 Hz, J_2 = 4.95 Hz), 7.90 (d, 1H, *J* = 1.01 Hz), 7.92 (s, 1H), 8.02 (d, 1H, *J* = 8.89 Hz), 8.43 (s, 1H), 8.53 (d, H, *J* = 3.22 Hz); ^{13}C NMR (100 MHz, DMSO): δ 118.12, 119.42, 123.64, 125.80, 126.52, 128.46, 128.93, 137.06, 138.73, 141.41, 149.46, 151.07, 165.02; MW for $C_{13}H_9C_{l3}N_4O$ calcd. 343.6; observed 343.7, 345.0

2-(2-Chloro-pyridin-3-yl)-2-[(2,4-dichloro-benzyl)-hydrazono]-acetamide (18g) (R = 2,4-dichlorobenzyl**):** mp: 202.1-203.9°C; IR(KBr) (cm^{-1}): 1654.113, 232.00, 3458.53; ^{1}H-NMR (400 MHz, DMSO): δ 4.47 (d, 2H, *J* = 2.0 Hz), 6.39 (s, 1H), 7.12 (s, 1H), 7.40-7.49 (m, 3H), 7.58 (s,1H), 7.68 (d, 1H, *J* = 7.39 Hz), 7.85 (s, 1H), 8.43 (t, 1H, *J* = 2.12 Hz) ; ^{13}C NMR (100 MHz, DMSO): δ 50.73, 123.62, 127.65, 128.23, 128.83, 131.03, 131.21, 132.58, 133.07, 136.76, 141.56, 150.06, 150.11, 165.89; MW for $C_{14}H_{11}Cl_3N_4O$ calcd. 357.62; observed 359.2, 36.1.2

General procedure for the preparation of 1-(2-fluorobenzyl)-1H-pyrazolo [3,4-b] pyridine-3-carboxamides (5a-f):
To a solution of DMSO (35.0 ml), and (E)-2-(2-chloropyridin-3-yl)-2-(2-(2-fluorobenzyl)hydrazono)acetamide **18a** (7.0g, 0.0228 mol), Cs_2CO_3 (14.8g, 0.045 mol) was added at room temperature. The reaction mass was heated and maintained for 30 minutes at 65-70°C. After completion of the reaction, the reaction mass was quenched into ice water (75.0 ml) and ethyl acetate (150.0 ml) and stirred for 30 minutes. Organic layer was separated and washed with brine solution (25.0 ml), and dried over anhydrous Na_2SO_4. The organic layer was distilled off under vacuum to get the solid **5a** (Wt 4.0g).

1-(2-fluorobenzyl)-1H-pyrazolo [3,4-b] pyridine-3-carboxamide (**5a**) (R= 2-Fluorobenzyl):Yield 65.0%; mp 138.2-140.0°C; IR (KBr) (cm^{-1}): 1688.47, 3487.45; ^{1}H-NMR (400 MHz, DMSO): δ 5.80 (s, 2H), 7.11 (m, 2H), 7.19 (t, 1H, *J* = 9.30 Hz), 7.31-7.40 (m, 2H), 7.56 (s, 1H), 7.82 (s, 1H), 8.54 (d, 1H, *J* = 7.92 Hz), 8.63 (d, 1H, *J*= 4.13 Hz); ^{19}F NMR (400 MHz, DMSO): δ -119.18 (F); ^{13}C NMR (100 MHz, DMSO): δ 44.37, 114.45, 115.68, 119.33, 123.96, 124.94, 130.16, 131.98, 137.70, 150.00, 151.04, 158.86, 161.36, 163.46; MW for $C_{14}H_{11}FN_4O$ calcd. 270.26; observed 271.3.

1H-Pyrazolo[3,4-b]pyridine-3-carboxylic acid amide (5b) (R = H**):** Yield 20.0%; mp: >260°C; IR (KBr) (cm^{-1}): 1663.003, 3461.27; ^{1}H-NMR (400 MHz, DMSO): δ 7.28 (dd, 1H, J_1 = 7.96 Hz, J_2 = 4.4 Hz), 7.45 (s, 1H), 7.54 (s, 1H), 8.49 (d, 1H, *J* = 8.01 Hz), 8.56 (d, 1H, *J* = 3.96 Hz), 14.01 (s, 1H); MW for $C_7H_6N_4O$ calcd. 162.15; observed 163.4.

1-Methyl-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide (5c) (R = CH_3**)**: Yield 35.0%; IR (KBr) (cm^{-1}): 1675.04, 3419.80; ^{1}H-NMR (400 MHz, DMSO): δ 4.11 (s, 3H), 7.32 (dd, 1H, J_1 = 7.74 Hz, J_2 = 4.41 Hz), 7.49 (s,1H), 7.83 (s, 1H), 8.50 (d, 1H, *J* = 7.90 Hz), 8.61 (d, 1H, *J* = 3.47 Hz); ^{13}C NMR (100 MHz, DMSO): δ 34.39, 114.37, 118.98, 131.73, 136.69, 149.67, 151.04, 163.52; MW for $C_8H_8N_4O$ calcd. 176.18; observed 177.6

1-Phenyl-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide (5d) (R = Phenyl**):** Yield 58.0%; mp: 162.1-164.1°C; IR (KBr) (cm^{-1}): 1688.21, 3467.31; ^{1}H-NMR (400 MHz, DMSO): δ 7.37 (t, 1H, *J* = 7.30 Hz), 7.44 (dd, 1H, J_1 = 7.99 Hz, J_2 = 4.48 Hz), 7.57 (d, 1H, *J* = 7.74 Hz), 7.60 (s, 1H), 7.51 (s, 1H), 8.14 (s, 1H), 8.34 (d, 1H, *J* = 7.98, Hz), 8.63 (d, 1H, *J* = 8.0 Hz), 8.70 (d, 1H, *J* = 4.32 Hz); ^{13}C NMR (100 MHz, DMSO): δ 115.99, 119.97, 121.66, 127.11, 129.52, 132.34, 138.51, 138.98, 150.28, 150.88, 163.34; MW for $C_{13}H_{10}N_4O$ calcd. 238.24; observed 239.6.

1-Benzyl-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide (5e) (R = Benzyl**):** Yield 52.0%; mp: 136-139.8°C; IR (KBr) (cm^{-1}): 1654.61, 3414.01; ^{1}H-NMR (400 MHz, DMSO): δ 5.74 (s, 2H), 7.24-7.35 (m, 4H), 7.36 (dd, 1H, J_1 = 7.68 Hz, J_2 = 4.49 Hz), 7.54 (s, 1H), 7.86 (s, 1H), 8.54 (d, 1H, *J* = 7.94 Hz), 8.63 (d, 1H, *J* = 3.79 Hz); ^{13}C NMR (100 MHz, DMSO): δ 50.71, 114.51, 119.30, 127.75, 128.02, 128.96, 131.97, 137.15, 137.44, 149.99, 150.98, 163.50; MW for $C_{14}H_{12}N_4O$calcd. 252.27; observed 253.3

1-(2,4-Dichloro-phenyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide (5f) (R = 2,4-Dichlorophenyl**):** Yield 73.0%; mp: 227.3-229.1 °C; IR (KBr) (cm^{-1}): 1698.53, 3463.41; ^{1}H-NMR (400 MHz, DMSO): δ 7.43 (dd, 1H, J_1 = 7.93 Hz, J_2 = 4.52 Hz), 7.66 (s, 1H), 7.68 (dd, 1H, J_1 = 8.30 Hz, J_2 = 1.12 Hz), 7.80 (d, 1H, *J* = 8.52 Hz), 7.98 (d, 1H, *J* = 1.64 Hz), 8.05 (s, 1H), 8.60 (d, 1H, *J* = 3.65 Hz), 8.63 (d, 1H, *J* = 8.05 Hz); ^{13}C NMR (100 MHz,

DMSO): δ 114.62, 119.91, 128.75, 130.21, 132.20, 132.36, 133.04, 134.34, 135.62, 139.61, 150.62, 152.07, 163.21; MW for $C_{13}H_8Cl_2N_4O$ calcd. 307.5; observed 308.5.

1-(2,4-Dichloro-benzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide (5g)
(R = 2,4-dichlorobenzyl**):** Yield 50.0%; mp: 176-196 °C; IR (KBr) (cm^{-1}): 1681.31, 3458.66; ^{1}H-NMR (400 MHz, DMSO): δ 5.81 (s, 2H), 6.92 (d, 1H, *J* = 8.40 Hz), 7.33 (dd, 1H, J_1 = 8.34 Hz, J_2 = 1.75 Hz), 7.38 (dd, 1H, J_1 = 8.00 Hz, J_2 = 4.47 Hz), 7.56 (s, 1H), 7.67 (d, 1H, *J* = 1.77 Hz) 7.82 (s, 1H), 8.56 (d, 1H, *J* = 7.99 Hz), 8.62 (d, 1H, *J* = 3.33 Hz) ; ^{13}C NMR (100 MHz, DMSO): δ 47.79, 114.47, 119.47, 128.04, 129.28, 130.97, 132.10, 133.21, 133.54, 133.58, 138.00, 150.11, 151.19,163.36; MW for $C_{14}H_{10}Cl_2N4O$ calcd. 321.6; observed 321.5, 323.0

Preparation of 1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile (19):
To a solution of toluene (50.0 ml), 1-(2-fluorobenzyl)-1H-pyrazolo [3,4-b] pyridine-3-carboxamide (**5a**) (2.0g, 0.0074 mol), $SOCl_2$ was added at room temperature. Reaction mass heated and maintained for overnight at 110°C. Reaction mass cooled to room temperature and quenched into ice water. Separated the organic layer and dried over Na_2SO_4. Distilled off the solvent to get the crude product, which is purified by column chromatography.(Wt 1.4g, yield 75%, mp. 80.4-82.0°C). IR (KBr) (cm^{-1}): 2238.57; ^{1}H-NMR (400 MHz, DMSO): δ 5.85 (s, 2H), 7.12-7.21 (m, 2H), 7.28-7.38 (m, 2H), 7.48 (dd, 1H, J_1= 8.08 Hz, J_2= 4.44 Hz), 8.45 (d, 1H, *J* = 8.08 Hz), 8.76 (d, 1H, *J* = 4.08 Hz); ^{13}C NMR (100 MHz, DMSO): δ 45.42, 113.36, 115.78, 116.58, 116.60, 120.58, 122.79, 125.01, 129.75, 130.80, 149.49, 151.50, 159.17, 161.62; MW for $C_{14}H_9FN_4$ calcd. 252.0; observed 253.2.

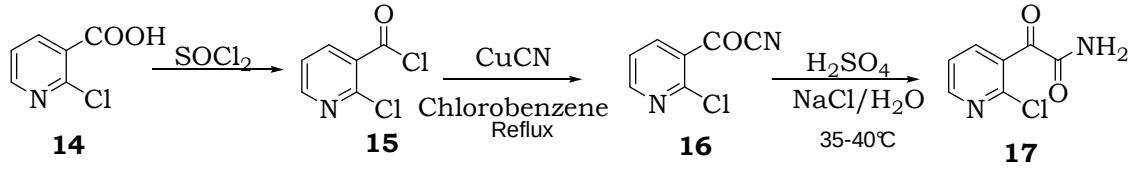
Preparation of 1-(2-Fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxamidine .HCl (6):
To a solution of methanol (150.0ml) and 1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile **19** (3.645g, 0.0144 mol), $NaOCH_3$ was added at room temperature. Maintained for 6hrs at 25-30°C. After completion of reaction, the resulting solution having Imidate **20.** To this solution, glacial acetic acid (3.376g, 0.034 mol) and ammonium chloride (1.85g, 0.034 mol) were added at RT. Reaction mass heated and maintained for 12 hrs at reflux temperature. After completion of reaction, quenched into ice water (25.0ml) and extracted with ethyl acetate (50.0ml). Separated the organic layer and washed with brine solution (25.0ml). The organic layer was distilled off under vacuum to get the compound **6** as free base (Wt 2.63g) and was converted to **6**.HCl.

(DSC. 204.22°C). IR (KBr) (cm^{-1}): 1663.20; ^{1}H-NMR (400 MHz, DMSO): δ 5.89 (s, 2H), 7.13-7.29 (m, 3H), 7.36-7.38 (m, 1H), 7.51-7.54 (m, 1H), 8.53 (d, 1H, *J* = 8.04 Hz), 8.77 (s, 1H), 9.38 (s, 2H), 9.48 (s, 2H); ^{13}C NMR (100 MHz, DMSO): δ 45.13, 113.27, 115.82, 119.89, 123.01, 125.06, 130.65, 131.32, 132.14, 150.65, 151.10, 158.48, 158.98.

RESULTS AND DISCUSSION

We recently developed [11-12] a methodology for regioselective synthesis of indazole-3-carboxylicacids and its derivatives from 2-halobenzoic acids via 2-haloketo amides. Based in this methodology, we attempted to synthesize key intermediates of Riociguat from commercially available 2-chloronicotinic acid **14** via 2-(2-Chloro-pyridin-3-yl)-2-oxo-acetamide **17**.

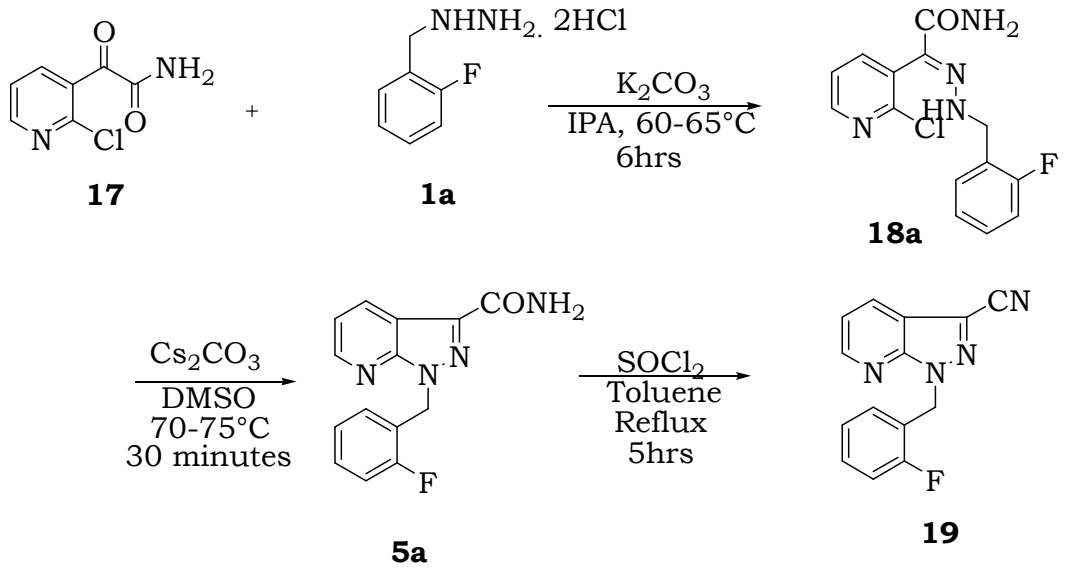
2-Chloronicotinic acid **14** is converted into 2-Chloro-nicotinoyl chloride **15** and then to (2-Chloro-pyridin-3-yl)-oxo-acetonitrile **16** in overall quantitative yield. The (2-Chloro-pyridin-3-yl)-oxo-acetonitrile **16** is converted to 2-(2-Chloro-pyridin-3-yl)-2-oxo-acetamide **17** in 55% yield as shown in scheme 2.



Scheme 2: Synthesis of 2-(2-Chloro-pyridin-3-yl)-2-oxo-acetamide

The 2-(2-Chloro-pyridin-3-yl)-2-oxo-acetamide **17** is reacted with 2-Fluorobenzy- lhydrazine.2HCl **1a** to give (E)-2-(2-chloropyridin-3-yl)-2-(2-(2-fluorobenzyl) hydrazono acetamide **18a** and is cyclised to 1-(2-Fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amide **5a**, which is one of the key intermediate of the drug. This

cyclisation is best conducted (see Table. 1) in the presence of Cesium carbonate in DMSO with 65% yield. Later it was converted to 1-(2-Fluoro-benzyl)-1H-pyrazolo [3,4-b]pyridine-3-carbonitrile **19** with75% yield as shown scheme 3.

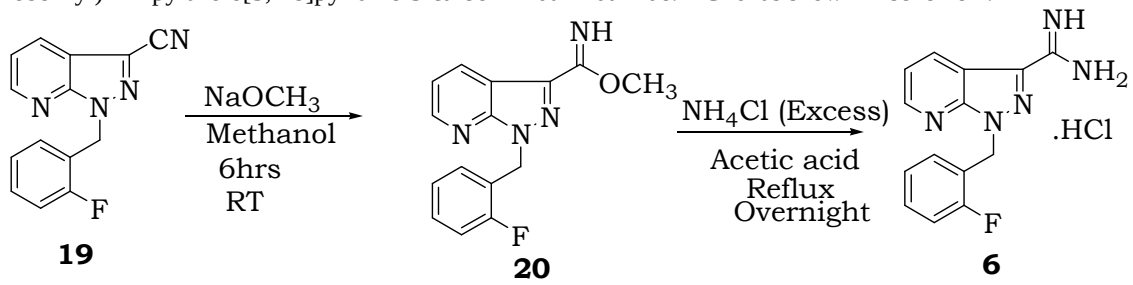


Scheme 3: Synthesis of 1-(2-Fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile

Table 1. Conversion of 18 to 5

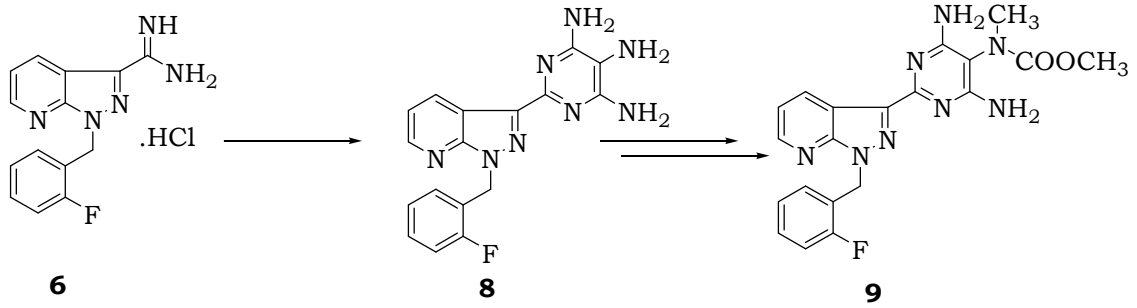
S.NO	Catalyst/base/solvent	Temp. (°C)	(%) Yield
1	CuI/L-Proline/Cs_2CO_3/DMSO	50-80	20
2	K_2CO_3/DMSO	80-100	35
3	Cs_2CO_3Error! Not a valid link.	70-75	65
4	$CaCO_3$Error! Not a valid link.	70-100	----
5	Na_2CO_3Error! Not a valid link.	70-100	---

1-(2-Fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridine-3-carbonitrile **19** is converted to imidate **20** and then to 1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidami damide. HCl **6** as shown in scheme 4.



Scheme 4: Synthesis of 1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboximidamide.HCl

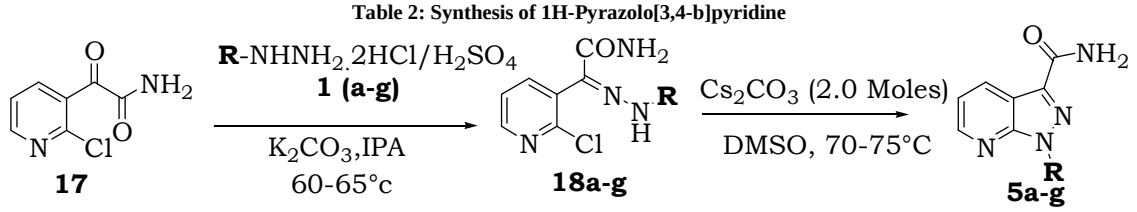
Compound **6** structure is confirmed and compared the spectral data with the reported one [10] and can be converted easily to Riociguat **9** as per the reported procedure shown as in scheme 5.

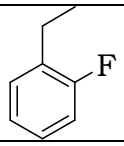
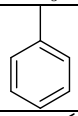
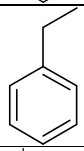
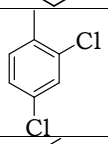
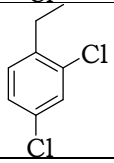


Scheme 5: Synthesis of Riociguat

Generally poly substituted derivatives of 1H-Pyrazolo [3,4-b] pyridine have been synthesized as potentially biologically active materials such as anti tumor, orexin receptor antagonists, TTX-S channels blockers, cardiovascular agents, infertility management and used in the treatment of CB1-mediated diseases [13-20]. Based on this concept and to check the generality of conversion of 2-(2-Chloro-pyridin-3-yl)-2-oxo-acetamide **17** to 1-(2-Fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylic acid amides **5** by reacting with different substituted hydrazines **1(a-g)** (see Table-2) has been studied. Amides are hydrolyzed to acids, which are key intermediates in some for various biologically active compounds.

Table 2: Synthesis of 1H-Pyrazolo[3,4-b]pyridine



S.NO	R	Reaction Conditions	MP(°C)	Yield (%)
5a		**70-75°C**	138.2-140	65%
5b	H	**70-75°C**	>260	20
5c	CH_3	**70-75°C**	-	35
5d		**70-75°C**	162-164	58
5e		**70-75°C**	136-139.8	52
5f		**70-75°C**	227.3-229	73
5g		**70-75°C**	176-196	50

CONCLUSION

In conclusion we have developed a new high yielding method from commercially available 2-chloronicotinic acid for the synthesis of Riociguat. The key intermediates are characterized and compared with the known ones. [7]

Acknowledgments
The authors are grateful to Suven Life Sciences management for allowing them to publish these results.

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