Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(8):65-70
(http://www.derpharmachemica.com/archive.html)

Synthesis, Characterization and Antibacterial Activity of Substituted Quinoxaline-pyrrolidine Derivatives Catalyzed by Polymer Supported Reagents

Narasimha Reddy Y[1*], Kondaiah S[2], Nagaraja Reddy G[1], Sreenivasulu Reddy T[1]

[1]*Department of Chemistry, Sri Krishna Devaraya University, Anantapur-515002, Andhra Pradesh, India*
[2]*Department of Chemistry, Vignan Institute of Technology and Science, Nalgonda, Telangana, India*

ABSTRACT

An improved and economically viable process is described to prepare N-(1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-yl) derivatives. Initially tert-butyl 1-(3-chloroquinoxalin-2-yl) pyrrolidin-3-yl carbamate (2) was prepared by treating of 2, 3-dichloroquinoxaline (1) with tert-butyl pyrrolidin-3-ylcarbamate and sodium carbonate in t-butanol. Tert-butyl 1-(3-chloroquinoxalin-2-yl) pyrrolidin-3-yl carbamate (2) is reacted with Bis-(diphenylphosphino)-ferrocene dichloropalladium (II), complex $PdCl_2$ (dppf). DCM (6% mol) and substituted phenyl boronic acid is refluxed overnight in presence toluene to form tert-butyl 1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-ylcarbamate and its related substituted compounds (3a-c). Deprotection of (3a-c) by TFA at 0-5°C in dichloroethane in presence of microporous tosic acid (MP-TSOH) to give 1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-amine and its related compounds (4a-c). Amidation of deprotected product (4a-c) by dissolved in dichloroethane with Polymer Supported Triethylamine (PL-TEA) and respective acid chloride to obtained 1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-amine derivatives (5a-d). Antibacterial activities of these compounds were studied.

Keywords: N-(1-(3-(2-fluorophenyl)quinoxalin-2-yl)pyrrolidin-3-yl) derivatives, Polymer, Triethylamine, Antibacterial activity

INTRODUCTION

Quinoxaline and its derivatives are significant nitrogen containing heterocyclic compounds of various biologically attractive properties with several pharmaceutical applications. Substituted quinoxalines are an important class of benzoheterocycles, which constitute the building blocks of wide range of pharmacologically active compounds having antibacterial antifungal, anticancer, antitubercular, antileishmanial, antimalarial and antidepressant activities [1,2]. Quinoxaline derivatives are of significant interest as they are noteworthy intermediates for the manufacturing of pharmaceuticals and advanced materials. Quinoxalines are very important to pharmaceutical industry and have been to acquire a broad spectrum of biological activity [3,4] such as anticancer, antibacterial, and activity as kinase inhibitors. Considering the significant applications in the fields of medicinal, industrial and synthetic organic chemistry, there has been tremendous interest in developing efficient methods for the synthesis of quinoxalines. They are recognizable for their application in rigid subunits in macrocyclic [5,6] receptors, electroluminescent materials, organic semiconductors and DNA cleaving agents.

The growing demand for synthesis of novel organic compounds with therapeutic potential remains the major driving force for the pharmaceutical industry to adopt novel technologies for organic synthesis [7-9]. The use of polymer-supported reagents and scavengers is an effective technique [10-12] for integrated organic synthesis and purification.

The pyrrolidine-quinoxalines were reported as having serotonin agonists and neuronal serotonin-reuptake inhibitor activity; pyrazine amides are shows the superior enzyme inhibitory and antiviral potencies. Nitro pyrazines have been shown to possess hypoxic cell radio sensitizer activity. The study of quinoxaline derivatives has been develop into a great extent of interest in recent years due to their antibacterial, antiviral, anticancer, antifungal, antihelminthes and insecticidal activities.

Quinoxaline derivatives are used in the invention [13,14] for the manufacture of a medicament to pharmaceutical compositions comprising the quinoxaline derivatives of the invention and methods of treating a disorder, disease or condition is responsive to positive modulation of Alpha-Amino-S-hydroxy-delta-methylisoxazole Propionic Acid (AMPA) receptor mediated synaptic responses. Hence it is significant to synthesis, characterization of a novel quinoxaline pyrrollidine derivative using polymer-supported reagents/scavengers and studies of their anti-bacterial and anti-microbial activity [15-17].

Polymer-supported reagents and scavengers can be used to selectively eliminate excess reagents and by-products through simple filtration, rather than liquid-liquid extraction and chromatographic separation. In addition, polymer-supported reagents offer advantages that include the reaction of active intermediates by 'catch and release', selectivity, and control of toxic reagents and byproducts.

One-pot synthesis of quinoxaline derivatives using polymer supported sulphonic acid under mild conditions [18] is used to overcome the drastic reaction conditions, low yields, tedious work-up, use of toxic metal salts as catalyst, long reaction times and relatively expensive reagents.

We report a noval, economical and viable synthetic method for the preparation of 1-(3-(2-fluorophenyl) quinoxalin-2-yl)pyrrolidin-3-amine derivatives (5a-d) and including increasing quantity of yield. In this method concerning the mild reaction conditions to synthesize pyrrollidine-quinoxaline derivatives starting from stable reactants 2,3-dichloroquinoxaline and tert-butyl pyrrolidin-3-ylcarbamate by using polymer supported reagents and scavengers with four reaction stages.

MATERIALS AND METHODS

Materials

Compounds used as starting materials and reagents were obtained from Aldrich Chemicals, Fluka, Flurochem, Spectrochem, and S.D. Fine chemicals; these were utilized without further purification. Thin-layer Chromatography (TLC) Kieselgel 60 F254 (Merck) coated aluminum plates and Column Chromatography (CC) were performed with silica gel 200-400 mesh. Since all the compounds prepared contain aromatic ring, they were visualized and detected on TLC plates with UV light. NMR spectra were recorded on a Bruker (300 or 400 MHz) for ^{1}HNMR and 75 MHz for ^{13}CNMR, and TMS as an internal reference standard Chemical shifts were calibrated in δ, ppm and coupling constants (J) in hertz (Hz). IR spectrophotometer used Schimadzu FT-IR. Melting points were determined in open capillary tubes on electrothermal 1A 9100 digital melting point apparatus and were uncorrected.

LCMS analyses were performed with an Auto sampler as a CTC PAL HTC 2777 configured for single and multi-value operation. Pump used waters 1525 LCMS/MS spectrometry utilizing open lynx software_ program. For ESI LCMS, LC was performed on a Waters Atlantis dC18 2.1 × 50 mm, 5 µm column with a phenomenex security guard using reverse-phase gradient elution from 5%-100% of B in A for 3 min followed by 100-5% of B in A for 3 min and 5% of B in A for 2.5 min at a flow rate of l.0 ml/min, where mobile phase A was 0.1% Formic acid in distilled water and mobile phase B was 0.1% Formic acid in Acetonitrile (ACN). Mass spectrometer conditions were: waters LCT premier, configured 4-way MUX analysis, typically the cone voltage is in the range 10-25V. Capillary temperature was sufficient to generate molecular ion in both polarities, capillary voltage range from 2400 V (ES-*ve*) to 3000 V (ES+ve), Retention time was given in minutes.

Methods

Synthesis of tert-butyl 1-(3-chloroquinoxalin-2-yl) pyrrolidin-3-ylcarbamate (2)

The 2, 3-dichloro quinoxaline (28 g, 140 mmol), tert-butyl pyrrolidin-3-ylcarbamate (24.8 g, 133 mmol) and sodium carbonate (14.9 g, 140 mmol) were taken in 1000 ml round bottom flask, and dissolved in *t*-butanol (650 ml). This reaction was refluxed overnight. Reaction was monitored by TLC and LCMS. The reaction mixture was cooled to RT. The *t*-butanol solvent was evaporated under reduced pressure. To the residue dichloromethane 350 ml and water 700 mml (until Na_2CO_3 dissolves) were added. The aqueous layer was extracted with dichloromethane (2 × 350 ml). The combined organic layer was washed with brine solution (350 ml), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified over silica (200-400 mesh) column chromatography (5% EtOAc: Hexane R_f=0.39) to give the product.

Tert-butyl 1-(3-chloroquinoxalin-2-yl) pyrrolidin-3-ylcarbamate (3)

(42 g, 85%). Yield: 85%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.47 (s, 9 H, $CCH_3)_3$), 1.98-2.01 (m, 1 H, CH_2), 2.26 (m, 1 H, CH_2, chiral), 3.72 (dd, 1 H,), 3.95 (t, 2 H, N-CH_2), 4.08 (m, 1 H, CH_2), 4.30 (b s 1 H, CH-N), 4.73 (b s 1 H, NH), 7.39 (dt, 1 H, Ar-H), 7.58 (dt, 1 H, Ar-H), 7.72 (d, *J*=7.5, 1 H, Ar-H), 7.81 (dd, 1 H, Ar-H). HPLC-MS: U.V (λ_{max}=215 nm) 100%, TIC 97%, Calcd. Av. Mass 348, found m/z 293.2, 349.2, 351.2 ($M+H^+$).

Procedure for synthesis of 3a-c compounds

Synthesis of Tert-butyl 1-(3-(2-methoxyphenyl) quinoxalin-2-yl) pyrrolidin-3-ylcarbamate (3a)

To a solution of tert-butyl 1-(3-chloroquinoxalin-2-yl) pyrrolidin-3-ylcarbamate **(2)** (4.5 g, 12.93 mmol) weighed into a round bottom flask and was charged $PdCl_2$ (dppf). DCM (6% mol, 0.633 g). A toluene: ethanol mixture in 2:1 ratio (40 ml+20 ml) was degassed with nitrogen gas, and then added into the flask. 1 M sodium bicarbonate solution (24 ml, 19.30 mmol) was degassed and added to the reaction mixture. It was stirred at RT for 15 min under nitrogen. The 2-methoxy boronic acid (2.35 g, 5.51 mmol) was added as the solid. The reaction was refluxed under nitrogen gas for overnight. The reaction was checked by TLC and LCMS. Reaction mass was cooled to RT. Then the solvent was evaporated completely under reduced pressure. It gave a black coloured product. It was purified by silica column chromatography (10:90 ethyl acetate: hexane) to obtained the compound tert-butyl 1-(3-(2-methoxyphenyl) quinoxalin-2-yl) pyrrolidin-3-yl carbamate (3a) (4.6 g, 85%).

Yield: 85%; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.42 (s, 9 H, $C(CH_3)_3$), 1.66(m 1HCH_2 pyrrolidine) 2.06 (m, 1H, CH_2) 3.18 (d, 1 H, CH_2), 3.39 (m, 3H OCH_3) 4.11 (m, 1 H, CH), 4.57 (b s, 1H NH) 6.96 (d, 1 H, Ar H), 7.06 (t, 1 H, ArH), 7.53 (m, 1 H, ArH), 7.37-7.45 (m, 3 H, ArH),7.54 (t 1 H ArH) 7.60 (d, 1 H ArH), 7.94 (d, 1 H, Ar H); HPLC-MS: U.V (λ_{max}=215 nm) 100, TIC 93%, Calcd. Av. Mass 420, found. m/z 421.3, 423.3 ($M+H^+$).

Similarly synthetic method was used for the preparation of 3b and 3c compounds

Tert-butyl 1-(3-(3-methoxyphenyl) quinoxalin-2-yl) pyrrolidin-3-yl carbamate (3b)

Yield:81%;^{1}H NMR (300 MHz, $CDCl_3$): δ=1.42 (s, 9 H, $C(CH_3)_3$), 1.79(m 1 H, CH_2 pyrrolidine) 2.11 (m, 1H, CH_2) 3.15 (dd, 1 H, CH_2), 3.40(m, 2 H CH_2) 3.54 (m, 1H , CH), 3.88 (s, 3H, OCH_3), 4.11 (m, 1 H, CH), 4.56 (b s, 1H NH) 6.96 (d, 1 H, Ar H), 7.00-7.26 (m, 2 H, ArH), 7.36-7.44 (m, 2 H, ArH), 7.61 (t, 1 H, ArH),7.78 (d 1H ArH) 7.94 (d, 1 H, Ar H); HPLC-MS: U.V (λ_{max}=215 nm) 100%, TIC 79%, Calcd. Av. Mass 420, found. m/z 365.2, 409.3, 421.3, 423.3 ($M+H^+$).

Tert-butyl 1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-ylcarbamate (3c)

Yield: 75%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.42 (s, 9 H, $C(CH_3)_3$), 1.81 (b 1 H, CH_2 pyrrolidine) 2.10 (m, 1H, CH_2) 3.19 (d, 1 H, CH_2), 3.43 (m, 3H CH_2) 4.14 (b s , 1 H, CH), 4.59 (b s, 1H NH), 7.17 (t, 1 H, ArH), 7.26 (t, 1 H, ArH), 7.32 (m, 2 H, ArH),7.42 (m, 2 H ArH) 7.63 (d, 1 H ArH), 7.95 (d, 1 H, Ar H); HPLC-MS: U.V (λ_{max}=215 nm) 100%, TIC 76%, Calcd. Av. Mass 408, found m/z 409.3, 410.3 ($M+H^+$).

Procedure for synthesis of 4a-c compounds

Synthesis of 1-(3-(2-methoxyphenyl) quinoxalin-2-yl) pyrrolidin-3-amine (4a)

To a solution of tert-butyl 1-(3-(2-methoxyphenyl)quinoxalin-2-yl)pyrrolidin-3-ylcarbamate (3a) (4.6 g, 10.95 mmol) taken in a round bottom flask, dichloroethane (55 ml) was added at room temperature and cooled to 0-5°C. Trifluoro acetic acid (4 times w/v, 18 ml) was slowly added and stirred for 4-6 h at room temperature. The reaction was monitored by HPLC-MS and TLC. When the reaction was complete, the solvent was concentrated *in vacuo*, methanol was added (2 × 50 ml) and evaporated *in vacuo*. The product was dissolved in methanol and basified with 7N ammonia in methanol. The solvent was concentrated *in vacuo* and the product was dissolved in methanol (70 ml). MP-TSOH (13.2 g, 43.80 mmol) 3.3 $mmolg^{-1}$ was added and the reaction mixture shaken at room temperature for overnight. The resin was washed with methanol, and cleaved with 2 N NH_3 in methanol. The solvent was evaporated to get the free based compound:

1-(3-(2-methoxyphenyl) quinoxalin-2-yl) pyrrolidin-3-amine (4a)

(3.3 g, 94% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.74 (b, 3 H, CH, NH_2), 1.98 (b, 1 H, N-CH_2), 3.03 (d, 1 H, CH_2), 3.32 (m, 1 H, CH_2 3.47 (m, 3 H, CH_2) 3.97 (s, 3 H, OCH_3), 6.95 (d, 1 H ArH), 7.01 (t, 1 H, Ar H), 7.32-7.44 (m, 2 H, Ar-H), 7.52 (t, 1 H, Ar-H), 7.75 (d, 1 H, Ar-H), 7.93 (dd, 1 H, Ar-H). HPLC-MS: U.V (λ_{max}=215 nm) 97%, TIC 78%.Calcd. Av. Mass 320, found. m/z 214.1, 255.1, 305.2, 337.2 ($M+H^+$).

1-(3-(3-methoxyphenyl) quinoxalin-2-yl) pyrrolidin-3-amine (4b)

Yield : 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.50 (b, 2 H, NH_2), 2.00 (m, 1 H, N-CH_2), 3.05 (m, 1 H, CH_2), 3.42-3.56 (m, 5 H, CH_2 pyrrolidine), 3.87 (s, 3H, OCH_3), 6.95 (d d, 1 H ArH), 6.99-7.26 (d, 2 H, Ar H), 7.35 (t, 1 H, ArH), 7.75 (d, 1 H, ArH), 7.95 (d, 1 H, ArH). HPLC-MS: U.V (λ_{max}=215 nm) 99%, TIC 92%, Calcd. Av. Mass 320, found. m/z 202.1, 222.6, 304.2, 321.2, 322.2 ($M+H^+$).

1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-amine (4c)

Yield: 93%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.76 (m, 1 H, CH, NH_2), 1.97 (b, 1 H, N-CH_2), 3.25 (d, 2 H, CH_2), 3.41 (m, 1 H, CH_2 3.54-3.64 (m, 2 H, CH_2), 7.15 (t, 1 H, Ar H), 7.22-7.29 (d, 2 H, Ar-H), 7.40 (t, 1 H, Ar-H), 7.45-7.60 (m, 2H, Ar-H), 7.71 (d, 1 H, Ar-H), 7.94 (d, 1 H, Ar-H); HPLC-MS U.V :(λ_{max}=215 nm) 100%, TIC 92%, Calcd. Av. Mass 308, obs. m/z 196.1, 216.6, 309.1, 310.2 ($M+H^+$).

Procedure for synthesis of 5a-d compounds

To a solution of 1-(3-(2-methoxyphenyl) quinoxalin-2-yl) pyrrolidin-3-amine (4a) (45.6 mg, 0.142 mmol) dissolved in dichloroethane (1 ml) was added polymer supported triethyl amine (PL-TEA) (128 mg, 0.45 mmol) in 6 ml vial. The acetyl chloride (18 mg, 0.22 mmol) dissolved in dichloroethane (1 ml) was added to the solution and reaction was shaken overnight. Then polymer methyl isatoic anhydride PL-MIA (2 eq., 0.30 mmol) was added and shaken overnight. The reaction mixture was filtered and the filtrate was evaporated. Then it was dissolved in 1 ml methanol and filtered by micro porous tosic acid (MP-TSOH) (4 eq, 0.60 mmol). After that it was washed with methanol (5 ml) and cleaved with 2 N ammonia (1.5 ml) twice to give the final pure compound (5a). Similar synthetic method applied for synthesis of 5b-d compounds (Figure 1).

(5a-1) Yield: 28 mg, 52.8%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.89 (s, 3 H, CH_3), 2.03 (dddd, 1 H, CH_2), 2.25 (dddd, 1 H, CH_2), 3.64 (ddd, 2 H, CH_2), 3.83 (m, 1 H, CH_2), 3.84 (dd, 1 H, CH_2) 3.90 (s, 3 H, O-CH_3), 3.99 (dd, 1 H, N-CH_2), 7.26-7.29 (ddd, 3 H, Ar-H), 7.61-7.65(ddd, 2 H Ar-H), 7.95 (ddd, 1H, Ar-H), 8.12 (ddd, 2 H, Ar-H). HPLC-MS: U.V (λ_{max}=215 nm) 100%, TIC 99%, Calcd. Av. Mass 362, found. m/z 362.2, 364.2 ($M+H^+$).

(5b-1) Yield: 40 mg, 65.5%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.04 (dddd, 1 H, CH_2), 2.26 (dddd 1 H, CH_2), 3.64 (ddd, 1H. CH_2), 3.67 (m, 1H), 3.80 (m, 1 H CH_2), 3.84 (dd, 1 H, CH_2),3.90 (s, 3 H, O-CH_3), 4.01(dd,1H N-CH_2), 7.26-7-34, (m, 8 H, Ar-H) , 7.61 (dt, 1 H, Ar-H), 7.65 (dt, 1 H, Ar-H), 7.95 (ddd, 1 H Ar-H), 8.12 (ddd, 1H Ar-H). HPLC-MS: U.V (λ_{max}=215 nm) 100%, TIC 100%, Calcd. Av. Mass 438, found. m/z 438.2, 439.3 ($M+H^+$).

(5c-1) Yield: 38.5 mg, 71.5%; ^{1}H NMR (300 MHz, $CDCl_3$): δ =1.85 (d, 3 H, CH_3), 2.04 (dddd, 1 H, CH_2), 2.25 (dddd, 1 H, -CH_2), 3.61 (ddd, 1H, CH_2), 3.64 (dd, 1 H, CH_2), 3.82 (dd 1 H, CH), 3.89 (m, 1 H, N-CH_2), 3.90 (s, 3 H, O-CH_3), 4.02 (dd, 1 H, CH_2), 6.09 (d 1 H, C=CH_2), 6.83 (dt, 1 H C=CH_2), 7.26-7.29 (m, 3 H, Ar-H), 7.61 (ddd, 1 H, Ar-H), 7.65 (dt, 1 H, Ar-H), 7.95 (ddd, 1 H, Ar-H), 8.12 (m, 2H Ar-H). HPLC-MS: U.V (λ_{max}=215 nm) 100%, TIC 90%, Calcd. Av. Mass 388.2, found. m/z 388.4, 389.2 ($M+H^+$).

(5d-1) Yield: 42 mg, 68.5%; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.04 (m, 1 H, CH_2), 2.26 (s, 3 H, CH_3-Ar) 2.29 (dddd 1 H, CH_2), 3.64 (ddd, 1H. N-CH_2), 3.90 (s, 3 H, O-CH_3), 3.97 (d,1 H) 4.01(d,1 H N-CH_2), 7.02 (ddd, 1 H Ar-H), 7.08(m, 2 H Ar-H), 7.26-7-34, (m, 4 H, Ar-H) , 7.65 (dt, 1 H, Ar-H), 7.65 (ddd, 1 H, Ar-H), 7.95 (dd, 1 H Ar-H), 8.13 (m, 2 H Ar-H). HPLC-MS: U.V (λ_{max}=215 nm) 100%, TIC 96%, Calcd. Av. Mass 453, found. m/z 453.3, 454.3 ($M+H^+$).

Biological activity

Antibacterial activity

The hole-in-plate bio assay procedure was used for the determination of antibacterial activity. The pure cultures of the microorganisms were inoculated onto Muller-Hilton nutrient broth incubated at temperature of 37°C for 24 h. Using a sterile cork-borer of 5 mm diameter, 4 holes were made into the petri dishes seeded with bacterial culture. Transferred 10, 20, 40 and 80 mg/ml concentrations of samples into the wells. At 37°C of temperature plates were incubated for 18 h. *Staphylococcus aureus and Escherichia coli* were used as the test microorganisms (Table 1). All bacterial cultures were maintained on nutrient agar slants at temperature of 4°C and sub cultured onto nutrient agar broth for 24 h prior to testing. The plates were kept aside for 30 min at room temperature to allow diffusion of the samples, and then incubated at temperature of 37°C for 18 h. After the incubation period, measured the zones of inhibition by using a caliper.

Studies were performed and the mean value was calculated. The mean zones of inhibitions were compared by one way analysis of variance. The sample concentrations that exhibited the highest activity were diluted double fold (2:2) with nutrient broth agar in a series of twelve [19-21] test tubes. An aliquot of 1ml of bacterial suspension was inoculated in each tube.

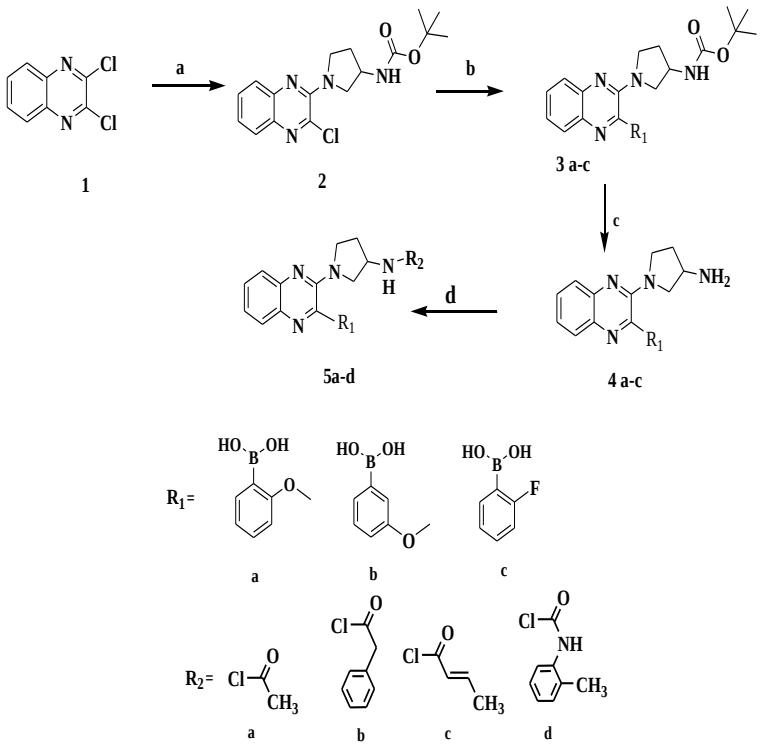
The control tube was inoculated with the same quantity of aqueous sodium benzoate. All tubes were [22,23] incubated at temperatures of 37°C for 24 h. The lowest concentration that not permits any [24,25] visible growth when compared to the control was considered as the Minimum Inhibitory Concentration (MIC).

Antifungal activity

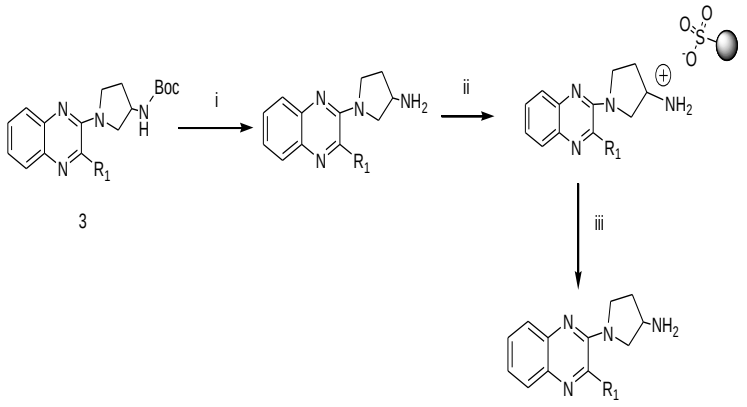
Holes were made into the Petri dishes containing inoculated medium as described by concentrations of 10, 20, 40 and 80 mg/ml samples were transferred into the wells and examined against *Candida albicans* and *Aspergillus niger* (Table 2). At the end of the incubation period diameter [26,27] clear zone around the wells (inhibition diameter) was measured. And four wells per plate against a single microorganism were used.

RESULTS AND DISCUSSION

An improved process for preparing *N*-(1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-yl) derivatives as shown in the synthesis (Scheme 1) which comprises the following steps. In this synthetic route, used inexpensive and commercially readily available polymer supported reagents for the synthesis of *N*-(1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-yl) derivatives.



Scheme 1: Reagents and conditions: (a)Na_2CO_3/Amine/*t*-BuOH/90°C 76%; (b) $PdCl_2$ (dppf).DCM/toluene: ethanol (2:1)/$NaHCO_3$/boronic acids, 78%; (c) TFA/DCM/RT, MP-TSOH, 90%; (d) R_1COCl, PL-TEA/R_1NCO, 48-82%



Scheme 2: Reagents and conditions: (i) TFA, DCE, 0-5°C to RT, 4-6 h, 7N NH_3/MeOH; (ii) MeOH, MP-TSOH (3.3 mmol/g), 6-8 h; (iii) 2N NH_3/MeOH

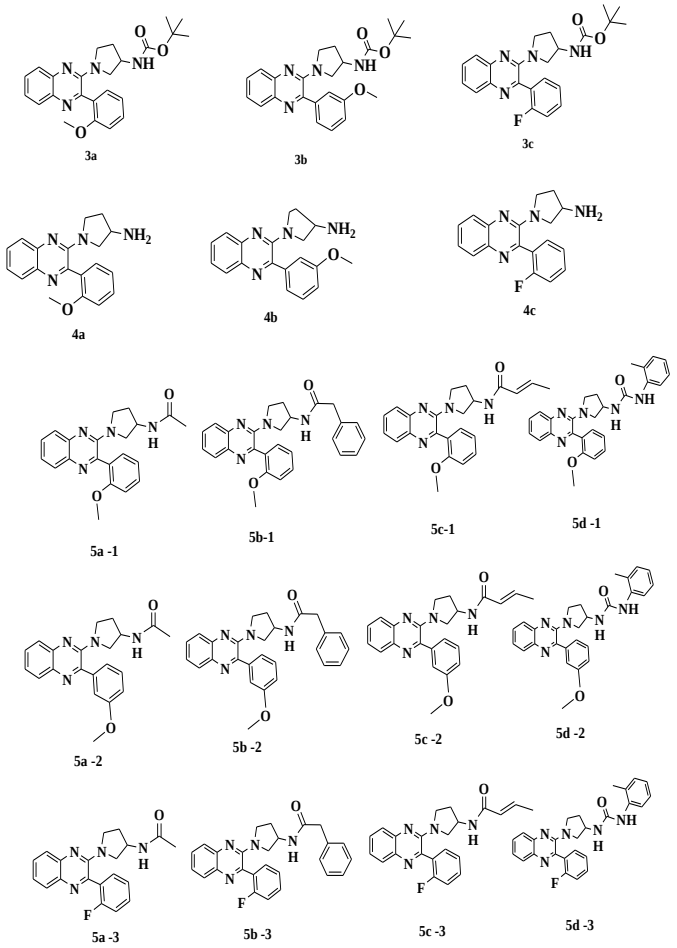


Figure 1: Structures of 5a-d compounds

In the first step 2, 3-dichloroquinoxaline (1) reacted with tert-butyl pyrrolidin-3-ylcarbamate and sodium carbonate in *t*-butanol at 90°C for 6-8 h to formed tert-butyl 1-(3-chloroquinoxalin-2-yl) pyrrolidin-3-yl carbamate (2) with 85% yield by aromatic nucleophilic substituted reaction. While R_1 is introduced by a Suzuki coupling, by treated reacting compound tert-butyl 1-(3-chloroquinoxalin-2-yl) pyrrolidin-3-yl carbamate (2) with 1,1-Bis(diphenylphosphine)ferrocene]dichloropalladium (II) in dichloromethane (Pd(dppf)DCM) in presence of $NaHCO_3$ and finally boronic acids are added in required quantity and heated to 80°C for 6-8 hrs to give tert-butyl 1-(3-(2-fluorophenyl) quinoxalin-2-yl) pyrrolidin-3-ylcarbamate and its related substituted compounds (3a-c) with 85% of yield. The product of 3a-c is purified by column chromatography with yields 77-86%. Then deprotection of the t-butyloxy group obtained by dissolving 3a-c in dichloromethane, treated with triflouroaceticacid (20% v/v) at room temperature and the contents are shaken for 4-6 h to obtain the product 4a-c and it is purified by microporous tosic acid (MP-TSOH) (Scheme 2). Finally R_2 is introduced by a standard capping methodology [28]. The products of 4a-c were dissolved in dichloroethane added with PL-TEA and acid chlorides, and the contents are shaken for 6-8 h at room temperature [29]. The products obtained in both cases are treated with scavengers polymer supported isocyanate (PL-NCO) and polymer supported [30] methylisatoic anhydride (PL-MIA) for untreated starting materials. Finally all compounds (5a-d) are purified by micro porous tosic acid (MP-TSOH).

Table 1: Antibacterial activities of ligands and their transitions metal complexes (Zone of inhibition in mm)

Compound	Zone of inhibition in mm			
	Escherichia coli **(40 mg/ml)**	***Escherichia coli*** **(80 mg/ml)**	***Staphylococcus aureus* (40 mg/ml)**	***Staphylococcus aureus*** **(80 mg/ml)**
5a	14	17	12	14
5b	16	20	12	13
5c	13	15	11	15
5d	15	18	13	16

Table 2: Antifungal activities of ligands and their transitions metal complexes (Zone of inhibition in mm)

Compound	Zone of inhibition in mm			
	Aspergillus niger **(40 mg/ml)**	***Aspergillus niger*** **(80 mg/ml)**	***Candida albicans*** **(40 mg/ml)**	***Candida albicans*** **(40 mg/ml)**
5a	12	16	12	14
5b	14	18	10	14
5c	13	15	12	14
5d	14	17	14	15

Compounds (5a-d) were evaluated for anti-bacterial and anti-fungal activity. 5b and 5d compound showed better activity compared with other 5a-5c compounds. Purity and yields of products 4 and 5 are significantly enhanced by polymer scavengers MP-TSOH; PL-NCO and PL-MIA. The present method relates to a novel, cost effective and industrially viable process. Thus the process described is high purity by using polymer supported reagents. In comparison with previously reported synthetic strategies, this novel approach is believed to be the shortest and the most efficient synthetic route to date.

CONCLUSION

Quinoxaline pyrrolidine derivatives (5a-d) were successfully synthesized from 2, 3-dichloroquinoxaline. In this synthetic route, initially from 2, 3-dichloroquinoxaline, one chlorine atom is substituted by tert-butyl pyrrolidin-3-ylcarbamate through aromatic nucleophilic substituted reaction and other is with aryl group (R_1) derivatives (substituted phenyl boronic acids) via Suzuki coupling reaction then formed free base (4a-c) compounds, Purified by the MP-tosic acid. The amidation of 4a-c compounds by using different acid chlorides to obtained pyrrolidine derivatives (5a-d). Purity and yields of products 4 and 5 are significantly enhanced by polymer scavengers MP-TSOH; PL-NCO and PL-MIA. Compounds (5a-d) are evaluated for anti-bacterial and anti-fungal activity. 5b and 5d compound show better activity compared with other compounds. The present method relates to a novel, cost effective and industrially viable process. Thus the process described is high purity and quantity of the yield. In comparison with previously reported synthetic strategies, this novel approach is believed to be the shortest and the most efficient synthetic route to date.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

REFERENCES

[1] K.R. Justin Thomas, M. Velusamy, J.T. Lin, C.H. Chuen, Y.T. Tao, *Chem. Mater*., **2005**, 17, 1860-1866.
[2] C.W. Lindsley, Z. Zhao, W.H. Leister, R.G. Robinson, S.F. Barnett, D. Defeo-Jones, R.E. Jones, G.D. Hartman, J.R. Huff, H.E. Huber, M.E. Duggan, *Bioorg. Med. Chem. Lett*., **2005**, 15, 761-764.
[3] K. Ajit Parhi, Yongzheng Zhang, W. Kurt Saionz, Padmanava Pradhan, *Bioorg. Med. Chem. Lett.*, **2013**, 23(17), 4968-4974.
[4] Umesh P. Tarpada, Bhautik B Thummar., Dipak K Rava, *Arabian J. Chem*., **2013**.
[5] A.R. Choudhury, K. Nagarajan, T.N. Guru Row, *Cryst. Eng*., **2003**, 6(3), 145-152.
[6] D.G. Hartman, D.R. Hartman, J.E. Schwering, W.S. Saari, E.L. Engelhardt, R.N. Jones, P. Wardman, E.M. Watts, M. Woodcock, *J. Med. Chem.*, **1984**, 27, 1634.
[7] W.B. Hugo, A.D. Russel, Blackwell, **1983**, 167.
[8] A. Hasaninejada, A. Zareb, M.R. Mohammadizadeha, Z. Karamia, *J. Iran. Chem. Soc*., **2009**, 6(1) 153.
[9] R.A. Batey, V. Santhakumar, C. Yoshina-Ishii, S.D. Taylor, *Tetrahedr. Lett*., **1998**, 39, 6267.
[10] S. Bhattacharyya, *Curr. Opin. Drug Discov. Dev*., **2004**, 7(6), 752-764.
[11] A.K. Gosh, W.J. Thompson, K.M. Holloway, S.P. McKee, T.T. Duong, Y.H. Lee, M.P. Munson, A.M. Smith, J.M. Wai, L.P. Darke, J.A. Zugay, E.A. Emini, W.A. Schleif, R.J. Huff, S. P. Anderson, *J. Med. Chem*., **1993**, 36, 2300.
[12] G. Fabiola Felcy, D, Lakshminarasimhan, P. Vasantha, N. Kuppuswamy, *Curr. Sci*., **2001**, 80(1), 26-34.
[13] T. Mizuno, W.H. Wei, L.R. Eller, J.L. Sessler, *J. Am. Chem. Soc.*, **2000**, 124, 1134-1135.
[14] W. He, M.R. Myers, Hanney, *Bioorg. Med. Chem. Lett*., **2003**, 13, 3097-3100.
[15] L.E. Seitz, W.J. Suling, R.C. Reynolds, *J. Med. Chem*., **2002**, 45, 5604-5606.
[16] B. Tarallo, A.J. Costa-Fillo, E. Vieira, A. Monge, C.Q. Leite, F. Pavan, G. Borthagaray, D. Gambino, M. Torrel, *J. Argent. Chem. Soc.*, **2009**, 97(1), 80.
[17] H.C. Shen, M.J. Szymonifka, D. Karbanda, Q. Deng, E. Carballo-Jane, K.K. Wu, T. Wu, K. Cheng, N. Ren, T. Cai, A.K. Taggart, J. Wang, X. Tong, M.G. Waters, M.L. Hammond, J.R. Tata, S.L. Colletti, *Bioorg. Med. Chem. Lett*., **2007**, 17, 6723.
[18] S. Tunaru, J. Kero, A. Schaub, C. Wufka, A. Blaukat, K. Pfeffer, S. Offermanns, *Nat. Med*., **2003**, 9, 352.
[19] R. Altschul, A. Hoffer, J.D. Stephen, *Arch. Biochem*., **1955**, 54, 558-559.
[20] L.A. Carlson, *J. Int. Med.*, **2005**, 258, 94-114.
[21] A.M. Gotto, *Circulation*., **2001**, 103, 2213-2218.
[22] S. Offermanns, *Trends Pharmacol. Sci*., **2006**, 27, 384-390.
[23] Coronary Drug Project. *J. Am. Med. Assoc*., **1975**, 231, 360-381.
[24] P.L. Canner, K.G. Berge, N.K. Wenger, J. Stamler, L. Friedman, R.J. Prineas, W. Friedewald, *J. Am. Coll. Cardiol*., **1986**, 8, 1245-1255.
[25] K.G. Berge, P.L. Canner, *Eur. J. Clin. Pharmacol*., **1991**, 40(1), S49-S51.
[26] G.A. Goldsmith, S. Cordill, *Am. J. Med. Sci*., **1943**, 205, 204-208.
[27] A.J. Vlientick, L. Vanhoof, J. Totte, A. Lasure, D. Vandenberghe, P.C. Rwangabo, J. Mvukiyumwami, J, *J. Ethnopharmacol.*, **1995**, 46, 31-47.
[28] C.A. Whistler, L.S. Pierson, *J. Bacterial*., **2003**, 185, 3718.
[29] D.R. Schmidt, A.L. Smenton, S. Raghavan, H.C. Shen, F. Ding, E. Carballo-Jane, S. Luell, T. Ciecko, T.G. Holt, M.S. Wolff, A.K.P. Taggart, L.C. Wilsie, M.L. Krsmanovic, N. Ren, D. Blom, K. Cheng, P.E. McCann, M.G. Waters, J.R. Tata, S.L. Colletti, *Bioorg. Med. Chem. Lett.*, **2010**, 20, 3426.
[30] H.C. Shen, S.L. Colletti, *Expert Opin. Ther*., **2009**, 19, 957.