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Article

Synthesis of Pyrrole Derivatives via Cycloaddition Reaction of Reissert Hydrofluoroborate Salts with α-Bromoacrylamides

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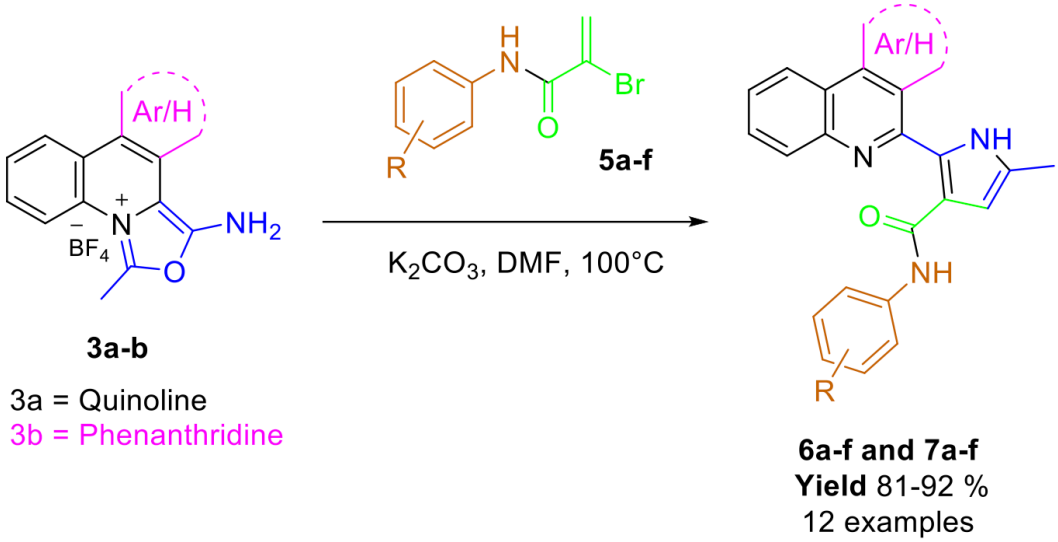
Graphical abstract



Abstract: An investigation of α-bromoacrylamide as a dienophile for the cycloaddition reaction of Reissert hydrofluoroborate salt of quinoline/phenanthridine has been carried out. The optimized condition has been developed for the [4+2] cycloaddition reaction of Reissert hydrofluroborate salt and a-bromoacrylamide by using K_2CO_3 in DMF under moderate temperature to afford highly functionalized pyrrole derivatives (6a-f and 7a-f) in very good to excellent yield. The structures of newly synthesized compounds were established based on FT-IR, Mass, ^1H and ^{13}C NMR spectral techniques. Besides, the structure of compound 7a has been confirmed by 2D NMR experiments (COSY and HSQC).

Keywords: Reissert hydrofluoroborate salt, Pyrrole derivatives, Cycloaddition reaction, α-Bromoacrylamides

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Introduction

A century ago, Reissert compounds were useful for the synthesis of nitrogen contains heterocycles [1-4]. Since the development of Reissert reaction has been exploited to the addition of nitrogen heterocycle with KCN and benzoyl chloride/ acetyl chloride [2, 5, 6], there are several derivatives that have been reported elsewhere from Reissert compounds in different conditions [7]. In addition to Reissert compounds modified to Reissert salts, it is a powerful contrivance for the synthesis of numerous nitrogen-containing heterocycles and enantioselective reactions [8-11].

Reissert salt is a building block for several compounds/reactions, for instance, Reissert-Henze reaction [12, 13], Reissert indole reaction [14, 15], pyrroles [16], alkaloids [17], oxazole [6], enantio-selective reactions [18], asymmetric alkylation [19], olefins [20] etc. Apart from this, pyrrole has been synthesized by Reissert salt with 1,3-dipolarophiles like acetylenes, alkenes and cyclic alkenes under [4+2] cycloaddition reaction via a 1,3-dipolar intermediate [21-23] (I to V, Fig. 1). Pyrrole derivatives are privileged scaffold to examine a wide range of biological activates and drug molecules, including anti-cancer (Obatoclax), anti-microbial, anti-tumor, anti-HIV, NSAID (Tolmetin), etc [24-27].

William McEwen and co-workers reported the mechanistic study of forming pyrrole from different dienophiles such as alkenes, alkynes, ethyl cinnamates, styrenes and stil-benes with Reissert hydrofluoroborate salt under various reaction condition [16, 21, 23]. However, even after several reports yields of corresponding pyrroles were not good due to the reactivity of dienophiles. Hence the exploitation of reactive dienophile is highly required for the cycloaddition reaction of Reissert hydrofluorosalt to afford pyrroles with

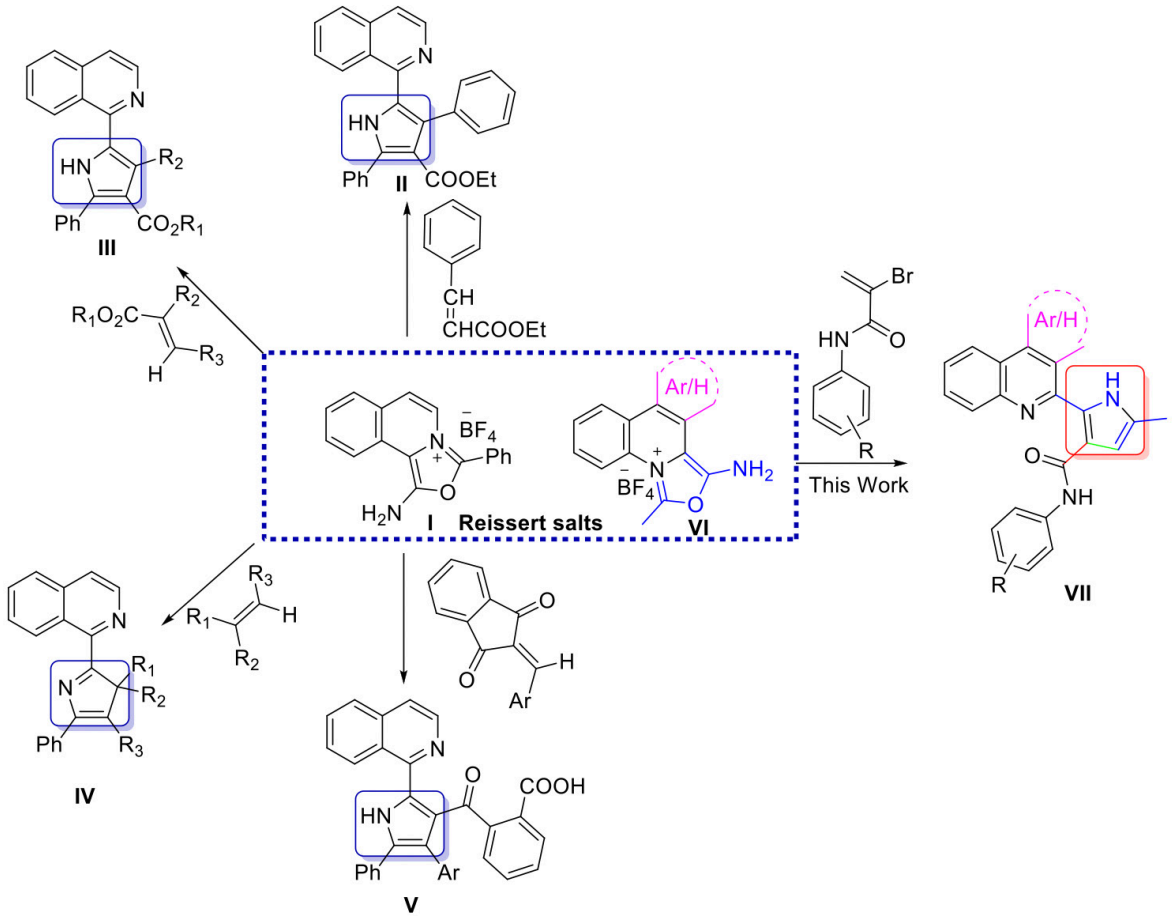


Figure 1. Various methods for the synthesis of pyrroles from Reissert salts

good yields. Therefore, we have investigated the scope of α-Bromoacrylamide as a reactive dienophile for cycloaddition reaction of Reissert hydrofluroborate to afford pyrrole derivatives (VI to VII, Fig. 1) with good to excellent yield.

Experimental

Materials and methods

All chemicals, solvents and reagents were purchased from Spectrochem, TCI chemicals and Sigma-Aldrich. Reaction progress was monitored by thin-layer chromatography on 0.2 mm precoated aluminium sheet Silica Gel Merck 60 (F254). Melting points of the synthesized compounds were determined by open glass capillary tubes and are uncorrected. Fourier Transform Infra-Red spectra were recorded on (IR Affinity SHIMADZU) FTIR-spectrophotometer using KBr pellets and λ_{max} values were given in cm^{-1}. Proton ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker model 500 MHz or 400 MHz and 125 MHz respectively, DMSO-d_6 and $CDCl_3$ solvents using tetramethylsilane (TMS) as the internal standard. Chemical shift values are given in δ (ppm) scale and the signals are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet) whereas coupling constants (*J*) are expressed in Hz. Mass spectra (ESI-MS) were recorded on SHIMADZU mass spectrometer.

Synthesis of 1-Acetyl-1,2-dihydroquinoline-2-carbonitrile (2a) [28]

To a solution of quinoline (1a, 3.0 g, 23.2 mmol) in DCM (20 mL), trimethylsilyl cyanide (5.8 mL, 46.4 mmol) and a catalytic amount of $AlCl_3$ were added under a nitrogen atmosphere. To this reaction mixture was dropwise added acetyl chloride (2.5 mL, 34.8 mmol). After stirring for 4 hr at rt, the reaction was poured into cold water. The organic layer was separated and washed with water, 5 % sodium hydroxide aqueous solution and water, dried over sodium sulfate and concentrated to dryness in vacuo to give 2a. Yield 88 %; m.p. 92-94°C (lit. 92-93°C).

Following the same synthetic procedure as for 2a, compound 2b was prepared.

Synthesis of 5-Acetyl-5,6-dihydrophenanthridine-6-carbonitrile (2b) [25]

Compound 2b was prepared by using phenanthridine (1b, 1.8 g, 10.0 mmol), trimethylsilyl cyanide (2.5 mL, 20.0 mmol) and acetyl chloride (1.1 mL, 15.0 mmol). Yield 90 %; m.p 170-172°C (lit. 172-174°C); ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 2.22 (s, 3H, $COCH_3$), 7.25 (s, 1H, ArH), 7.45-7.52 (m, 3H, ArH), 7.58 (t, J = 7.6 Hz, 1H, ArH), 7.74 (d, J = 7.2 Hz, 1H, ArH), 7.77 (d, J = 7.5 Hz, 1H, ArH), 8.06-8.07 (m, 2H, ArH); MS m/z (ES+) 249.04 (M+).

Synthesis of 3-Amino-1-methyloxazolo[3,4-*a*] quinolin-10-ium tetrafluoroborate (3a) [22]

Tetrafluoroboric acid (48 %, 3.0 mL,) was dropwise into a solution of 2a (2.5 g, 13.0 mmol) in hot acetic acid (20 mL). The solution was stirred for 30 min at 60-70°C. The mixture was cooled, the orange precipitate was collected by filtration, and the filter cake was washed with ether to give the desired hydrofluoroborate salt 3a. Yield 95 %. m.p 180-182°C (decompose).

Following the same synthetic procedure as for 3a, compound 3b was prepared.

Synthesis of 1-Amino-3-methyloxazolo[3,4-*f*] phenanthridin-4-ium tetrafluoroborate (3b) [25]

Compound 3b was prepared by using 2b (2.0 g, 8.0 mmol), tetrafluoroboric acid (48 %, 3.0 mL) in acetic acid (20 mL). Yield 90 %; m.p 200-202°C; ^{1}H NMR (DMSO-d_6, 400 MHz, δ ppm): 3.24 (s, 3H, CH_3), 7.54 (t, J = 7.4 Hz, 1H, ArH), 7.65 (t, J = 7.2 Hz, 1H, ArH), 7.74 (s, 2H, NH_2), 7.76-7.81 (m, 2H, ArH), 8.02 (d, J = 7.8 Hz, 1H, ArH), 8.24 (d, J = 7.6 Hz, 1H, ArH), 8.47 (d, J = 8.0 Hz, 1H, ArH), 8.63 (d, J = 8.0 Hz, 1H, ArH); MS m/z (ES+) 337.14 (M+).

Synthesis of 2-Bromo-*N*-(4-methoxyphenyl) acrylamide (5a)

To a solution of anisidine (4a, 1 g, 8.0 mmol) in dry THF (25 mL) was added TEA (1.2 mL, 8.8 mmol). To this solution, 2,3-dibromopropionyl chloride (0.93 mL, 8.0 mmol) was added, and the reaction was stirred at 0°C under argon atmosphere for 1 h and then stirred at RT for 3h. The reaction was filtered to remove precipitate

of TEA hydrobromide. The resulting filtrate was evaporated under reduced pressure. The residue was further dissolved in THF (25 mL) and was added TEA (1.2 mL, 8.8 mmol) and stirred for 3 hr at rt. After filtration, the resulting mixture was dried over Na_2SO_4 and solvent was concentrated under vacuo to give the desired product. Yield 90 %; m.p 126-128°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 3.73 (s, 3H, OCH_3), 6.27 (d, *J* = 2.2 Hz, 1H, CH), 6.72 (d, *J* = 2.3 Hz, 1H, CH), 6.91 (d, *J* = 8.7 Hz, 2H, ArH), 7.55 (d, *J* = 8.7 Hz, 2H, ArH), 10.12 (s, 1H, -CONH); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 55.16 (OCH_3), 113.77, 122.05, 125.21, 125.48, 131.25, 155.92, 160.59 (C=O); MS m/z (ES+) 257.25 (M+); Anal. calculated for $C_{10}H_{10}NO_2Br$: C = 46.90; H = 3.94; N = 5.47. Found: C = 46.50; H = 4.00; N = 5.55 %.

Following the same synthetic procedure as for 5a, the following compounds were prepared.

2-Bromo-*N*-phenylacrylamide (5b) [29]
Compound 5b was prepared by using aniline (4b, 0.8 mL, 8.0 mmol), 2,3-dibromopropanoyl chloride (0.93 mL, 8.0 mmol) and TEA (2.4 mL, 17.6 mmol). Yield 91 %; m.p 120-122°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 6.18 (d, *J* = 2.0 Hz, 1H, CH), 6.65 (d, *J* = 2.2 Hz, 1H, CH), 6.93 (t, *J* = 7.5 Hz, 1H, ArH), 7.37 (d, *J* = 8.7 Hz, 2H, ArH), 7.62 (d, *J* = 8.7 Hz, 2H, ArH), 10.13 (s, 1H, -CONH);^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 112.34, 120.16, 125.19, 125.37, 127.48, 131.59, 131.79, 140.08, 161.84 (C=O); MS m/z (ES+) 226.19 (M+); Anal. calculated for C_9H_8NOBr: C = 47.82; H = 3.57; N = 6.20. Found: C = 47.71; H = 3.69; N = 6.48 %.

2-Bromo-*N*-(4-nitrophenyl)acrylamide (5c) [30]
Compound 5c was prepared by using 4-nitroaniline (4c, 1.1 g, 8.0 mmol), 2,3-dibromopropanoyl chloride (0.93 mL, 8.0 mmol) and TEA (2.4 mL, 17.6 mmol). Yield 93 %; m.p 128-130°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 6.42 (d, *J* = 2.2 Hz, 1H, CH), 6.77 (d, *J* = 2.5 Hz, 1H, CH), 7.68 (d, *J* = 9.0 Hz, 2H, ArH), 8.06 (d, *J* = 9.0 Hz, 2H, ArH), 10.75 (s, 1H, -CONH); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 118.43, 122.70, 125.72, 126.39, 140.27, 143.61, 161.78 (C=O); MS m/z (ES+) 271.07 (M+). Anal. calculated for $C_9H_7N_2O_3Br$: C = 39.88; H = 2.60; N = 10.33. Found: C = 39.98; H = 2.79; N = 10.21 %.

2-Bromo-*N*-(4-fluorophenyl)acrylamide (5d) [30]
Compound 5d was prepared by using 4-fluoroaniline (4d, 0.8 mL, 8.0 mmol), 2,3-dibromopropanoyl chloride (0.93 mL, 8.0 mmol) and TEA (2.4 mL, 17.6 mmol). Yield 90 %; m.p 60-62°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 6.41 (d, *J* = 2.2 Hz, 1H, CH), 6.76 (d, *J* = 2.5 Hz, 1H, CH), 7.67 (d, *J* = 9.0 Hz, 2H, ArH), 8.07 (d, *J* = 9.0 Hz, 2H, ArH), 10.78 (s, 1H, -CONH); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 118.72, 123.08, 125.38, 126.75, 132.03, 143.73, 161.15; MS m/z (ES+) 244.23 (M+); Anal. calculated for C_9H_7NOBrF: C = 44.29; H = 2.89; N = 5.74. Found: C = 44.43; H = 3.02; N = 5.57 %.

2-Bromo-*N*-(4-chlorophenyl)acrylamide (5e) [30, 31]
Compound 5e was prepared by using 4-chloroaniline (4e, 1.0 g, 8.0 mmol), 2,3-dibromopropanoyl chloride (0.93 mL, 8.0 mmol) and TEA (2.4 mL, 17.6 mmol). Yield 92 %; m.p 90-92°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 6.45 (d, *J* = 2.2 Hz, 1H, CH), 6.70 (d, *J* = 2.5 Hz, 1H, CH), 7.57 (d, *J* = 9.0 Hz, 2H, ArH), 7.91 (d, *J* = 9.0 Hz, 2H, ArH), 10.64 (s, 1H, -CONH); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 118.80, 123.41, 125.84, 126.20, 129.41, 141.94, 161.08; MS m/z (ES+) 260.49 (M+); Anal. calculated for $C_9H_7NOBrCl$: C = 41.49; H = 2.71; N = 5.38. Found: C = 41.68; H = 2.52; N = 5.61 %.

2-Bromo-*N*-(4-(dimethylamino)phenyl)acrylamide (5f) [29]
Compound 5f was prepared by using N^1,N^1-dimethylbenzene-1,4-diamine (4f, 1.1 g, 8.0 mmol), 2,3-dibromopropanoyl chloride (0.93 mL, 8.0 mmol) and TEA (2.4 mL, 17.6 mmol). Yield 85 %; m.p 168-170°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.84 (s, 6H, 2 × CH_3), 6.32 (d, *J* = 2.3 Hz, 1H, CH), 6.59 (d, *J* = 2.6 Hz, 1H, CH), 7.14 (d, *J* = 8.4 Hz, 2H, ArH), 7.67 (d, *J* = 8.4 Hz, 2H, ArH), 10.22 (s, 1H, -CONH); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 40.47, 118.12,

122.94, 125.08, 125.93, 128.85, 141.32, 166.78; MS m/z (ES+) 269.37 (M+); Anal. calculated for $C_{11}H_{13}N_2OBr$: C = 49.09; H = 4.87; N = 10.41. Found: C = 49.42; H = 4.61; N = 10.73 %.

Synthesis of *N*-(4-methoxyphenyl)-5-methyl-2-(quinolin-2-yl)-1*H*-pyrrole-3-carboxamide (6a)

To a solution of Reissert salt of quinoline (3a, 0.5 g, 1.8 mmol) in DMF (10 mL) was added 2-Bromo-*N*-(4-methoxyphenyl)acrylamide (5a, 0.45 g, 1.8 mmol). To this solution, K_2CO_3 (0.362 g, 2.62 mmol) was added, and the reaction was stirred at 100°C for 3 h. On completion, the reaction was poured into ice-cold water and filtered and wash with cold water to get the desired product. The residue was recrystallized from ethanol to give the analytically pure product 6a. Yield 92 %; m.p 268-270°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.34 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 6.54 (d, *J* = 1.9 Hz, 1H, ArH), 6.96 (d, *J* = 9.0 Hz, 2H, ArH), 7.60 (d, *J* = 7.6 Hz, 1H, ArH), 7.64 (d, *J* = 8.9 Hz, 2H, ArH), 7.81 (dt, J_1 = 1.0 Hz, J_2 = 7.3 Hz, 1H, ArH), 7.98-8.0 (m, 2H, ArH), 8.10 (d, *J* = 8.9 Hz, 1H, ArH), 8.46 (d, *J* = 8.9 Hz, 1H, ArH), 11.82 (s, 1H, -CONH), 12.40 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.59 (CH_3), 55.19 (OCH_3), 111.82, 113.95, 120.09, 121.47, 122.07, 126.21, 126.34, 127.18, 127.62, 128.07, 130.57, 130.75, 132.35, 137.28, 146.01, 150.66, 155.30, 162.43 (C=O); IR (KBr): 3400 (N-H amide), 3354 (N-H Ar), 3030 (C-H alkene), 1840 (C-H Ar), 1688 (C=O amide), 1280 (C-N Ar), 1216 (C-O ether), 830 (pera subs.); MS m/z (ES+) 357 (M+); Anal. calculated for $C_{22}H_{19}N_3O_2$: C = 73.93; H = 5.36 N = 11.76. Found: C = 74.31; H = 5.09; N = 11.60 %.

Following the same synthetic procedure as for 6a, the following compounds were prepared.

5-Methyl-*N*-phenyl-2-(quinolin-2-yl)-1*H*-pyrrole-3-carboxamide (6b)

Compound 6b was prepared by using Reissert salt of quinoline (3a, 0.5 g, 1.8 mmol), 2-bromo-*N*-phenylacrylamide (5b, 0.4 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 89 %; m.p 240-242°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.30 (s, 3H, CH_3), 6.49 (d, *J* = 1.7 Hz, 1H, ArH), 6.59 (t, *J* = 7.5 Hz, 2H, ArH), 6.91 (t, *J* = 8 Hz, 1H, ArH), 7.60 (d, *J* = 7.6 Hz, 1H, ArH), 7.67 (d, *J* = 7.6 Hz, 2H, ArH), 7.82 (t, *J* = 8.4 Hz, 1H, ArH), 7.98-8.2 (m, 2H ArH), 7.83 (d, *J* = 7.2 Hz, 2H, ArH), 8.51 (d, *J* = 7.6 Hz, 2H, ArH), 11.72 (s, 1H, -CONH), 12.32 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 13.18 (CH_3), 112.01, 114.22, 119.89, 120.94, 122.16, 126.48, 126.70, 127.20, 127.68, 128.16, 130.50, 130.64, 132.93, 137.46, 145.83, 150.38, 155.10, 162.22 (C=O); IR (KBr): 3390 (N-H amide), 3350 (N-H Ar), 3030 (C-H alkene), 1790 (C-H Ar), 1685 (C=O amide), 1283 (C-N Ar); MS m/z (ES+) 327 (M+); Anal. calculated for $C_{21}H_{17}N_3O$: C = 77.04; H = 5.23 N = 12.84. Found: C = 77.14; H = 5.30; N = 12.61 %.

5-Methyl-*N*-(4-nitrophenyl)-2-(quinolin-2-yl)-1*H*-pyrrole-3-carboxamide (6c)

Compound 6c was prepared by using Reissert salt of quinoline (3a, 0.5 g, 1.8 mmol), 2-bromo-*N*-(4-nitrophenyl)acrylamide (5c, 0.5 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 86 %; m.p 232-234°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.26 (s, 3H, CH_3), 6.50 (d, J = 2.0 Hz, 1H, ArH), 6.84 (d, *J* = 7.6 Hz, 2H, ArH), 7.48 (d, *J* = 6.8 Hz, 1H, ArH), 7.56 (d, *J* = 7.6 Hz, 2H, ArH), 7.80 (t, *J* = 8.0 Hz, 1H, ArH), 7.93-8.04 (m, 2H, ArH), 8.16 (d, *J* = 7.9 Hz, 1H, ArH), 8.39 (d, *J* = 9.0 Hz, 1H, ArH), 11.86 (s, 1H, -CONH), 12.46 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 13.51 (CH_3), 111.94, 114.05, 120.07, 121.53, 122.10, 126.28, 126.54, 127.07, 127.59, 128.12, 130.48, 130.80, 132.40, 137.05, 146.18, 150.60, 155.49, 161.96 (C=O); IR (KBr): 3385 (N-H amide), 3050 (C-H alkene), 1800 (C-H Ar), 1687 (C=O amide), 1610 (N-H bending) 1296 (C-N Ar), 1530 (N-O of Nitro), 834 (pera subs.); MS m/z (ES+) 372 (M+); Anal. calculated for $C_{21}H_{16}N_4O_3$: C = 67.73; H = 4.33 N = 15.05. Found: C = 67.63; H = 4.46; N = 15.14 %.

***N*-(4-fluorophenyl)-5-methyl-2-(quinolin-2-yl)-1*H*-pyrrole-3-carboxamide (6d)**

Compound 6d was prepared by using Reissert

salt of quinoline (3a, 0.5 g, 1.8 mmol), 2-bromo-*N*-(4-fluorophenyl)acrylamide (5d, 0.45 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol).Yield 90 %; m.p 225-227°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.32 (s, 3H, CH_3), 6.40 (d, *J* = 1.9 Hz, 1H, ArH), 6.78 (d, *J* = 7.8 Hz, 2H, ArH), 7.38 (d, *J* = 7.4 Hz, 1H, ArH), 7.58 (d, *J* = 7.6 Hz, 2H, ArH), 7.68-7.82 (m, 1H, ArH), 7.92-8.21 (m, 2H, ArH), 8.34 (d, *J* = 8.0 Hz, 1H, ArH), 8.53 (d, *J* = 8.2 Hz, 1H, ArH), 11.68 (s, 1H, -CONH), 12.38 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.78 (CH_3), 112.02, 113.90, 120.10, 121.38, 121.98, 126.16, 126.40, 127.24, 127.70, 127.95, 130.52, 130.68, 132.36, 137.28, 146.08, 150.26, 155.32, 162.40 (C=O); IR (KBr): 3410 (N-H amide), 3350 (N-H Ar), 3030 (C-H alkene), 1845 (C-H Ar), 1678 (C=O amide), 1380 (C-F), 1278 (C-N Ar), 835 (pera subs.); MS m/z (ES+) 345 (M+); Anal. calculated for $C_{21}H_{16}N_3OF$: C = 73.03; H = 4.67 N = 12.17. Found: C = 73.19; H = 4.89; N = 12.01 %.

_N_-(4-chlorophenyl)-5-methyl-2-(quinolin-2-yl)-1_H_-pyrrole-3-carboxamide (6e)

Compound 6e was prepared by using Reissert salt of quinoline (3a, 0.5 g, 1.8 mmol), 2-bromo-*N*-(4-chlorophenyl)acrylamide (5e, 0.46 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 83 %; m.p 245-248°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.28 (s, 3H, CH_3), 6. (d, *J* = 1.8 Hz, 1H, ArH), 6.82 (d, *J* = 8.0 Hz, 2H, ArH), 7.56 (d, *J* = 7.6 Hz, 1H, ArH), 7.73 (d, *J* = 7.2 Hz, 2H, ArH), 7.84 (t, *J* = 8.2 Hz, 1H, ArH), 7.96-7.98 (m, 2H, ArH), 8.15 (d, *J* = 8.2 Hz, 1H, ArH), 8.42 (d, *J* = 8.0 Hz, 1H, ArH), 11.80 (s, 1H, -CONH), 12.41 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.90 (CH_3), 112.20, 114.15, 120.32, 121.67, 122.10, 126.04, 126.39, 127.22, 127.73, 128.12, 130.54, 130.85, 132.28, 137.89, 146.06, 150.75, 155.39, 162.46 (C=O); IR (KBr): 3433 (N-H Ar), 3267 (N-H amide), 2968 (C-H alkene), 1645 (C=O amide), 1274 (C-N Ar), 844 (pera subs.), 761 (C-Cl); MS m/z (ES+) 361 (M+); Anal. calculated for $C_{21}H_{16}N_3OCl$: C = 69.71; H = 4.46 N = 11.61. Found: C = 69.52; H = 4.79; N = 11.91 %.

_N_-(4-(dimethylamino)phenyl)-5-methyl-2-(quinolin-2-yl)-1_H_-pyrrole-3-carboxamide (6f)

Compound 6f was prepared by using Reissert salt of quinoline (3a, 0.5 g, 1.8 mmol), 2-bromo-*N*-(4-(dimethylamino)phenyl)acrylamide (5f, 0.5 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 81 %; m.p 260-262°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.30 (s, 3H, CH_3), 2.98 (s, 6H, 2 × CH_3), 6.38 (d, *J* = 2.0 Hz, 1H, ArH), 6.78 (d, *J* = 8.4 Hz, 2H, ArH), 7.47-7.62 (m, 3H, ArH), 7.82 (t, *J* = 8.0 Hz, 1H, ArH), 7.97-7.99 (m, 2H, ArH), 8.21 (d, *J* = 8.2 Hz, 1H, ArH), 8.46 (d, *J* = 8.0 Hz, 1H, ArH), 11.83 (s, 1H, -CONH), 12.45 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.90 (CH_3), 42.47 ($N(CH_3)_2$), 111.90, 113.94, 120.02, 121.74, 122.28, 126.26, 126.79, 127.38, 127.95, 128.49, 130.68, 131.04, 132.90, 146.10, 150.65, 155.37, 162.34 (C=O); IR (KBr): 3398 (N-H amide), 3350 (N-H Ar),3025 (C-H alkene), 1837 (C-H Ar), 1679 (C=O amide), 1276 (C-N Ar), 831 (pera subs.); MS m/z (ES+) 370 (M+); Anal. calculated for $C_{23}H_{22}N_4O$: C = 74.57; H = 5.99 N = 15.12. Found: C = 74.62; H = 6.09; N = 15.29 %.

_N_-(4-methoxyphenyl)-5-methyl-2-(phenanthridin-6-yl)-1_H_-pyrrole-3-carboxamide (7a)

Compound 7a was prepared by using Reissert salt of phenanthridine (3b, 0.6 g, 1.8 mmol), 2-bromo-*N*-(4-methoxyphenyl)acrylamide (5a, 0.45 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 92 %; m.p 290-292°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.33 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 6.60 (d, *J* = 2.6 Hz, 1H, ArH), 6.76 (d, *J* = 8.4 Hz, 2H, ArH), 7.41 (d, *J* = 8.5 Hz, 2H, ArH), 7.69 (t, *J* = 7.4 Hz, 1H, ArH), 7.77 (t, *J* = 7.4 Hz, 1H, ArH), 7.84 (t, *J* = 7.6 Hz, 1H, ArH), 7.92 (t, *J* = 7.6 Hz, 1H, ArH), 8.01 (d, *J* = 8.0 Hz, 1H, ArH), 8.14 (d, *J* = 7.8Hz, 1H, ArH), 8.84-8.9 (m, 2H, ArH), 9.85 (s, 1H, -CONH), 12.20 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.56 (CH_3), 55.07 (OCH_3), 106.71, 113.53, 119.74, 121.15, 122.41, 122.78, 123.48, 125.76, 127.32, 127.61, 128.41, 129.07, 129.30, 129.40, 130.92, 132.28, 132.55, 142.89, 154.52, 154.87, 162.35 (C=O); IR (KBr): 3402 (N-H amide), 3328 (N-H Ar), 3055 (C-H alkene),

1738 (C-H Ar), 1635 (C=O amide), 1307 (C-N Ar), 1202 (C-O ether), 817 (pera subs.) 730 (C-H Ar); MS m/z (ES+) 408 (M+); Anal. calculated for $C_{26}H_{21}N_3O_2$: C = 76.64; H = 5.19 N = 10.31. Found: C = 76.79; H = 5.27; N = 10.49 %.

5-Methyl-2-(phenanthridin-6-yl)-*N*-phenyl-1*H*-pyrrole-3-carboxamide (7b)

Compound 7b was prepared by using Reissert salt of phenanthridine (3b, 0.6 g, 1.8 mmol), 2-bromo-*N*-phenylacrylamide (5b, 0.4 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 89 %; m.p 285-287°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.34 (s, 3H, CH_3), 6.64 (d, *J* = 1.9 Hz, 1H, ArH), 6.94 (t, *J* = 7.4 Hz, 1H, ArH), 7.18 (t, *J* = 6.8 Hz, 2H, ArH), 7.52 (d, *J* = 7.6 Hz, 2H, ArH), 7.69 (dt, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H, ArH), 7.78 (dt, J_1 = 7.6 Hz, J_2 = 1.3 Hz, 1H, ArH), 7.84 (dt, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.92 (dt, J_1 = 7.2 Hz, J_2 = 1.1 Hz, 1H, ArH), 8.01 (d, *J* = 7.9 Hz, 1H, ArH), 8.14-8.16 (m, 1H, ArH), 8.86 (d, *J* = 7.4 Hz, 1H, ArH), 8.89 (d, *J* = 8.4 Hz, 1H, ArH), 9.96 (s, 1H, -CONH), 12.26 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.56 (CH_3), 106.78, 119.57, 119.60, 122.43, 122.71, 123.49, 125.75, 127.37, 127.65, 128.36, 128.39, 128.44, 129.09, 129.32, 129.71, 130.95, 132.29, 139.44, 142.88, 154.48, 162.64 (C=O); IR (KBr): 3410 (N-H amide), 3327 (N-H Ar), 3054 (C-H alkene), 1759 (C-H Ar), 1597 (C=O amide), 1312 (C-N Ar), 825 (pera subs.) 718 (C-H Ar); MS m/z (ES+) 377 (M+); Anal. calculated for $C_{25}H_{19}N_3O$: C = 79.55; H = 5.07 N = 11.13. Found: C = 79.38; H = 5.19; N = 11.26 %.

5-Methyl-*N*-(4-nitrophenyl)-2-(phenanthridin-6-yl)-1*H*-pyrrole-3-carboxamide (7c)

Compound 7c was prepared by using Reissert salt of phenanthridine (3b, 0.6 g, 1.8 mmol), 2-bromo-*N*-(4-nitrophenyl)acrylamide (5c, 0.5 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 89 %; m.p 298-300°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.30 (s, 3H, CH_3), 6.62 (d, *J* = 2.1 Hz, 1H, ArH), 6.80 (d, *J* = 8.0 Hz, 2H, ArH), 7.51 (d, *J* = 8.2 Hz, 2H, ArH), 7.72 (t, *J* = 7.4 Hz, 1H, ArH), 7.76 (t, *J* = 7.6 Hz, 1H, ArH), 7.85 (t, *J* = 7.4 Hz, 1H, ArH), 7.90 (t, *J* = 7.9 Hz, 1H, ArH), 8.03 (d, *J* = 8.0 Hz, 1H, ArH), 8.17 (d, *J* = 8.0 Hz, 1H, ArH), 8.83-8.88 (m, 2H, ArH), 9.86 (s, 1H, -CONH), 12.21 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.60 (CH_3), 106.56, 113.50, 119.73, 121.04, 122.35, 122.80, 123.58, 125.61, 127.08, 127.28, 128.38, 128.86, 129.28, 130.20, 131.90, 132.36, 142.45, 154.12, 154.63, 162.21 (C=O); IR (KBr): 3425 (N-H amide), 3326(N-H Ar), 3032 (C-H alkene), 1666 (C=O amide), 1504 (N-O of Nitro), 1334 (C-N Ar), 825 (pera subs.) 748 (C-H Ar); MS m/z (ES+) 377 (M+); Anal. calculated for $C_{26}H_{21}N_3O_2$: C = 79.55; H = 5.07; N = 11.13. Found: C = 79.38; H = 5.01; N = 11.03 %.

***N*-(4-fluorophenyl)-5-methyl-2-(phenanthridin-6-yl)-1*H*-pyrrole-3-carboxamide (7d)**

Compound 7d was prepared by using Reissert salt of phenanthridine (3b, 0.6 g, 1.8 mmol), 2-bromo-N-(4-fluorophenyl)acrylamide (5d, 0.45 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 92 %; m.p 289-291°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.34 (s, 3H, CH_3), 6.56 (d, *J* = 2.4 Hz, 1H, ArH), 6.81 (d, *J* = 8.0 Hz, 2H, ArH), 7.07 (d, *J* = 7.9 Hz, 2H, ArH), 7.72 (t, *J* = 7.4 Hz, 1H, ArH), 7.75 (t, *J* = 7.2 Hz, 1H, ArH), 7.82 (t, *J* = 8.0 Hz, 1H, ArH), 7.89 (t, *J* = 7.6 Hz, 1H, ArH), 7.98 (d, *J* = 7.8 Hz, 1H, ArH), 8.12 (d, *J* = 7.8 Hz, 1H, ArH), 8.82-8.87 (m, 2H, ArH), 9.82 (s, 1H, -CONH), 12.12 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.56 (CH_3), 106.45, 114.07, 119.58, 122.02, 122.48, 122.70, 123.37, 125.19, 125.73, 127.19, 127.63, 128.32, 128.74, 129.07, 129.38, 129.56, 130.94, 139.53, 142.30, 154.42, 154.81, 162.28 (C=O); IR (KBr): 3410 (N-H amide), 3330 (N-H Ar), 3056 (C-H alkene), 1744 (C-H Ar), 1658 (C=O amide), 1334 (C-N Ar), 827 (pera subs.) 748 (C-H Ar); MS m/z (ES+) 395 (M+); Anal. calculated for $C_{25}H_{18}N_3OF$: C = 75.93; H = 4.59; N = 10.63. Found: C = 76.07; H = 4.71; N = 10.93 %.

***N*-(4-chlorophenyl)-5-methyl-2-(phenanthridin-6-yl)-1*H*-pyrrole-3-carboxamide (7e)**

Compound 7e was prepared by using Reissert salt of phenanthridine (3b, 0.6 g, 1.8 mmol), 2-bromo-N-(4-chlorophenyl)acrylamide (5e, 0.46 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 91 %; m.p 287-290°C; ^{1}H NMR (DMSO-d_6, 500

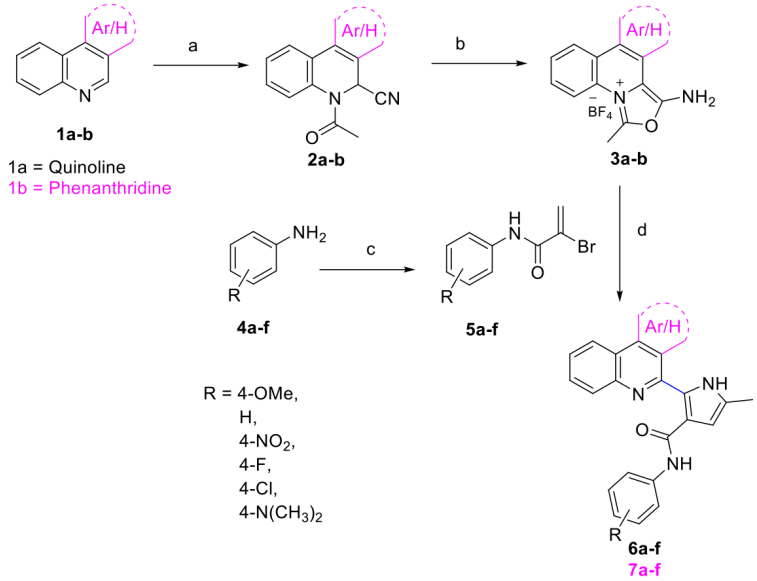
MHz, δ ppm): 2.33 (s, 3H, CH_3), 6.60 (d, J = 2.2 Hz, 1H, ArH), 6.73 (d, J = 8.0 Hz, 2H, ArH), 7.40 (d, J = 8.2 Hz, 2H, ArH), 7.68 (t, J = 7.4 Hz, 1H, ArH), 7.75 (t, J = 7.1 Hz, 1H, ArH), 7.83 (t, J = 7.6 Hz, 1H, ArH), 7.91 (t, J = 8.0 Hz, 1H, ArH), 8.02 (d, J = 8.0 Hz, 1H, ArH), 8.13 (d, J = 7.8 Hz, 1H, ArH), 8.84-8.89 (m, 1H, ArH), 9.83 (s,1H, -CONH), 12.19 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.56 (CH_3), 105.97, 113.17, 118.81, 120.95, 121.33, 122.99, 123.58, 125.70, 127.26, 127.69, 128.32, 129.10, 129.42, 129.53, 130.47, 132.25, 132.65, 141.93, 153.98, 154.51, 161.99 (C=O); IR (KBr): 3408 (N-H amide), 3371 (N-H Ar), 3086 (C-H alkene), 1790 (C-H Ar), 1658 (C=O amide), 1311 (C-N Ar), 840 (pera subs.) 763 (C-Cl), 709 (C-H Ar) MS m/z (ES+) 411 (M+); Anal. calculated for $C_{25}H_{18}N_3OCl$: C = 72.90; H = 4.41; N = 10.20. Found: C = 73.05; H = 4.59; N = 9.98 %.

N-(4-(dimethylamino)phenyl)-5-methyl-2-(phenanthridin-6-yl)-1*H*-pyrrole-3-carboxamide (7f)

Compound 7f was prepared by using Reissert salt of phenanthridine (3b, 0.6 g, 1.8 mmol), 2-bromo-N-(4-(dimethylamino)phenyl)acrylamide (5f, 0.5 g, 1.8 mmol) and K_2CO_3 (0.362 g, 2.62 mmol). Yield 86 %; m.p 304-306°C; ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): 2.33 (s, 3H, CH_3), 3.05 (s, 6H, 2 × CH_3), 6.64 (d, J = 2.3 Hz, 1H, ArH), 7.06 (d, J = 7.3 Hz, 2H, ArH), 7.51 (d, J = 7.6 Hz, 2H, ArH), 7.67 (t, J = 7.4 Hz, 1H, ArH), 7.76 (t, J = 7.6 Hz, 1H, ArH), 7.82 (t, J = 7.5 Hz, 1H, ArH), 7.90 (t, J = 7.2 Hz, 1H, ArH), 8.00 (d, J = 7.8 Hz, 1H, ArH), 8.14 (d, J = 8.1 Hz, 1H, ArH), 8.86 (m, 2H, ArH), 9.95 (s,1H, -CONH), 12.22 (s, 1H, NH of Pyrrole); ^{13}C NMR (DMSO-d_6, 125 MHz, δ ppm): 12.58 (CH_3), 42.84 ($N(CH_3)_2$), 106.79, 113.46, 119.70, 120.92, 121.94, 123.35, 125.87, 127.24, 127.66, 128.49, 129.03, 129.30, 129.46, 131.04, 132.29, 132.68, 143.08, 154.57, 154.82, 162.30 (C=O); IR (KBr): 3433 (N-H amide), 3352 (N-H Ar), 3093 (C-H alkene), 1786 (C-H Ar), 1661 (C=O amide), 1357 (C-N Ar), 833 (pera subs.); MS m/z (ES+) 421 (M+); Anal. calculated for $C_{27}H_{24}N_4O$: C = 77.12; H = 5.75; N = 13.32. Found: C = 77.37; H = 5.56; N = 13.48 %.

Result and discussion

The synthesis of *N*-(substituted)-5-methyl-2-(quinoline/phenanthridine)-1*H*-pyrrole-3-carboxamide derivatives (6a-f & 7a-f) are shown in Scheme 1. Commercially available and cheap quinoline (1a) or phenanthridine (1b) were treated with trimethylsilyl cyanide



Reagent and reaction condition: (a) TMSCN, $AlCl_3$, MDC, CH_3COCl, rt, (b) HBF_4, AcOH, 60°C, (c) 2,3-dibromopropanoyl chloride, TEA in THF 0 °C (d) K_2CO_3, DMF, 100 °C

Scheme 1. Synthesis of highly functionalized pyrrole derivatives (6a-f and 7a-f)

and acyl chloride in dichloromethane (DCM) with the catalytical amount of aluminium chloride ($AlCl_3$) to obtain N-acetyl heterocyclic carbonitrile (2a-b). Which were then converted to Reissert hydrofluoroborate salts (3a-b) by treatment with tetrafluoroboric acid in acetic acid at 60°C to afforded excellent yield (90-95 %). The formation of (3a-b) was ascertained from ^{1}H NMR of 3b, NH_2 protons appeared as a singlet at 7.74 δ (ppm) and its D_2O exchange NMR shows that two protons removed with an exchange of deuterium to confirm the formation of hydrofluoroborate salt. On the other hand, 2-Bromo-*N*-(substituted) acrylamide (5a-f) have been prepared by the reaction between substituted aniline react with 2,3-Dibromopropanoyl chloride in the presence of an organic base to get dienophile (5a-f), a singlet signal at 10.12 δ (ppm) indicate the formation of amide further support it by the value of 160.59 δ (ppm) in ^{13}C NMR to confirm intermediate 5a.

Optimization of cycloaddition reaction of Reissert hydrofluoroborate salt of quinoline 3a as heterodiene and dienophile a-bromoacrylamide 5a was carried out by various base in a polar solvent under Diels-Alder reaction. Among them, we found optimal conditions in K_2CO_3 as base and DMF as a solvent to afforded compound 6a in excellent yield (Table 1).

Having an optimal protocol in our hand, we examined the generality of a method by varying Reissert hydrofluoroborate salts (3a-b) and α-bromoacrylamides (5a-f) under the same reaction condition to afforded highly functionalized pyrrole derivatives (Table 2).

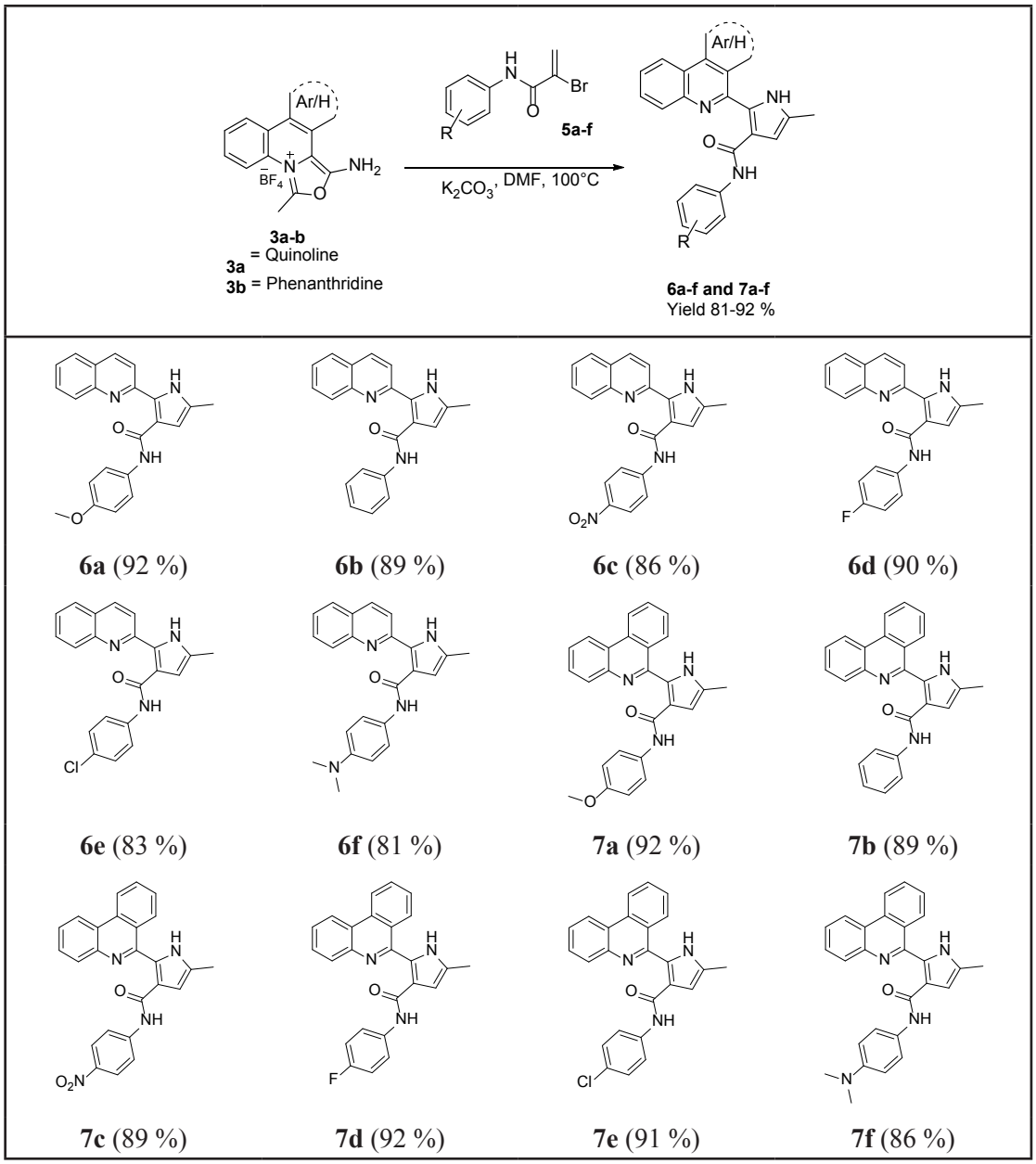
A plausible mechanistic transformation depicted in Scheme 2, were 3a-b react with acrylamide derivatives under [4+2] cycloaddition reaction. Apart from this, bicycle intermediate was form followed by an electron-rich amine group stabilized via cleavage of C-O bond and rearrange to get iminium ion and a ketone group. Under the essential condition, iminium ion was activated and attack on carbonyl carbon to get a substituted pyrrolidine followed by rearrangement and elimination to afforded targeted compounds. The newly synthesized compounds were confirmed by IR, Mass, ^{1}H NMR, and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum of 6a displays two protons at 12.39 and 11.82 δ (ppm) but NMR was recorded with active deuteron; the amidic proton was exchanged by deuterium. It is known that D_2O exchange NMR shows only one proton at 12.84 δ (ppm) which indicates the formation of pyrrole. As final remarks, the regioselective formation of pyrrole has been further confirmed by homonuclear ^{1}H-^{1}H COSY spectrum (Fig. 2) and heteronuclear correlation ^{1}H-^{13}C HSQC spectrum (Fig. 3) of compound 7a. It was a manifest correlation between NH and CH of the pyrrole ring (Fig. 4). Doublet signal at 6.60 δ (ppm) attributed to the presence of pyrrole ring. Besides, long-range coupling between the hydrogen of a nitrogen atom and CH gives spin coupling constant value is 2.6 Hz indicates long-range spin-spin coupling has been observed.

Table 1. Optimization of the reaction condition for the synthesis of *N*-(4-methoxyphenyl)-5-methyl-2-(quinolin-2-yl)-1*H*-pyrrole-3-carboxamide (6a)

Entry	Base [a]	Solvent	Yield (%) [b]	Time (h)
1	Pyridine	Pyridine	15	18
2	KOH	DMF	73	10
3	NaOH	DMF	70	10
4	$CsCO_3$	DMF	69	6
5	Na_2CO_3	DMF	78	5
6	K_2CO_3	DMF	92	3

[a] Reaction condition: condensation of 3a (1.8 mmol) and 5a (1.8 mmol) in the presence of Base (2.62 mmol) in solvent (10.0 mL) at 100°C; [b] Isolated yield of compounds

Table 2. Synthesized pyrrole derivatives (6a-f, 7a-f)

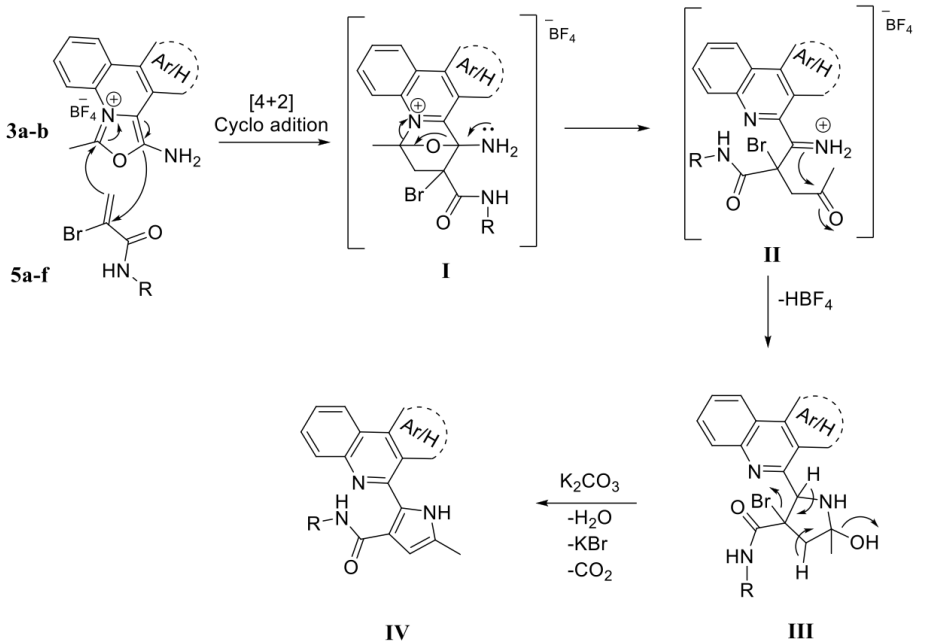


Conclusions

In summary, we have explored the ability of α-bromoacrylamide as a dienophile for the cycloaddition reaction of Reissert hydrofluoroborate salt. We have developed an effi-cient protocol for the synthesis of highly functionalized pyrrole derivatives (6a-f and 7a-f) via cycloaddition reaction of Reissert hydrofluoroborate salt of quinoline/phenan-thridine and α-bromoacrylamides. The reaction smoothly affords the desired cycloaddition product in very good to excellent yields. The present protocol is easy to work up and useful for the facile access of a wide range of structurally diverse pyrrole derivatives.

Supporting information

Representative ^{1}H and ^{13}C NMR, COSY and HSQC of newly synthesized compounds are available in supporting information.



Scheme 2. A plausible mechanism for the formation of Pyrrole derivatives

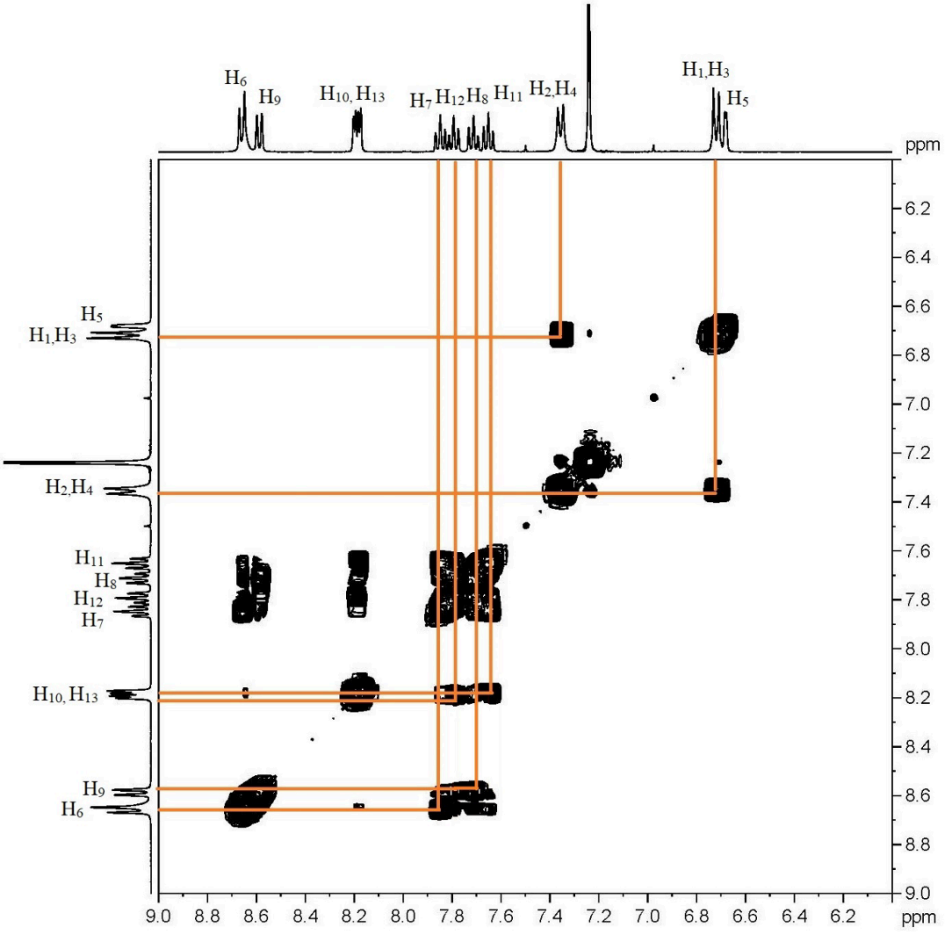


Figure 2. 1H-1H COSY NMR spectrum of compound 7a

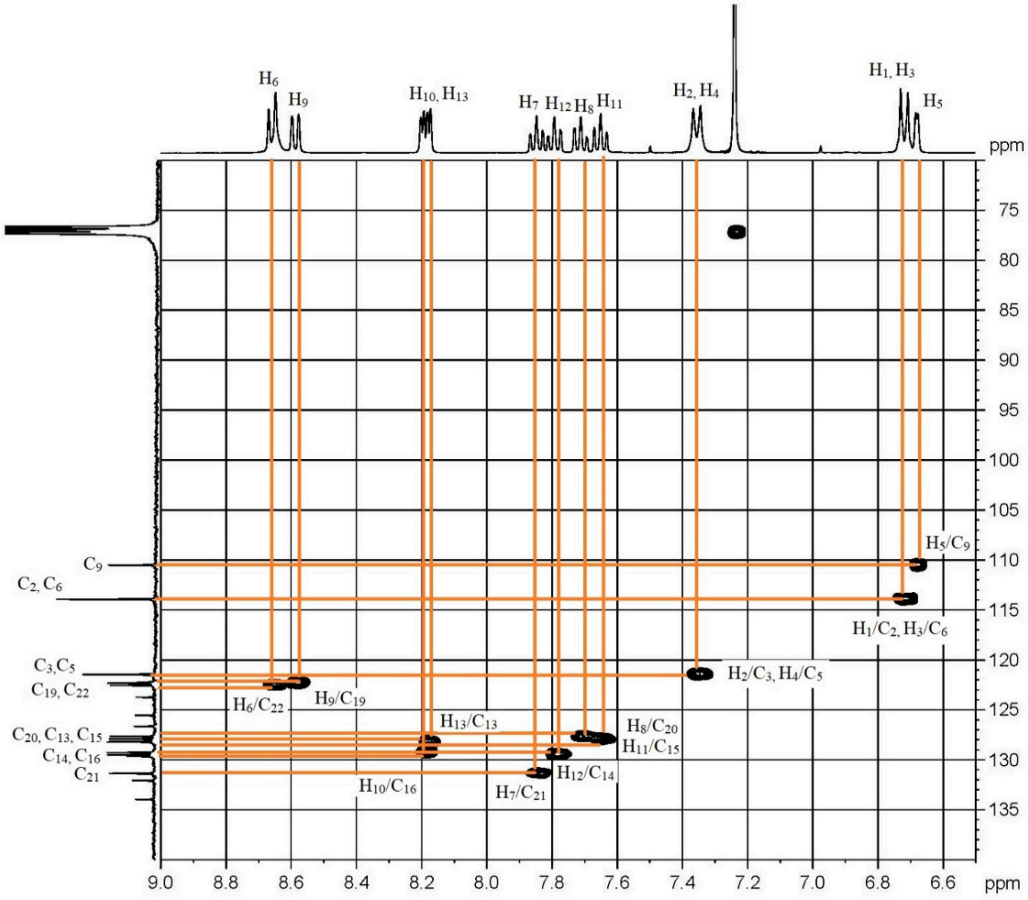


Figure 3. HSQC NMR spectrum of compound 7a

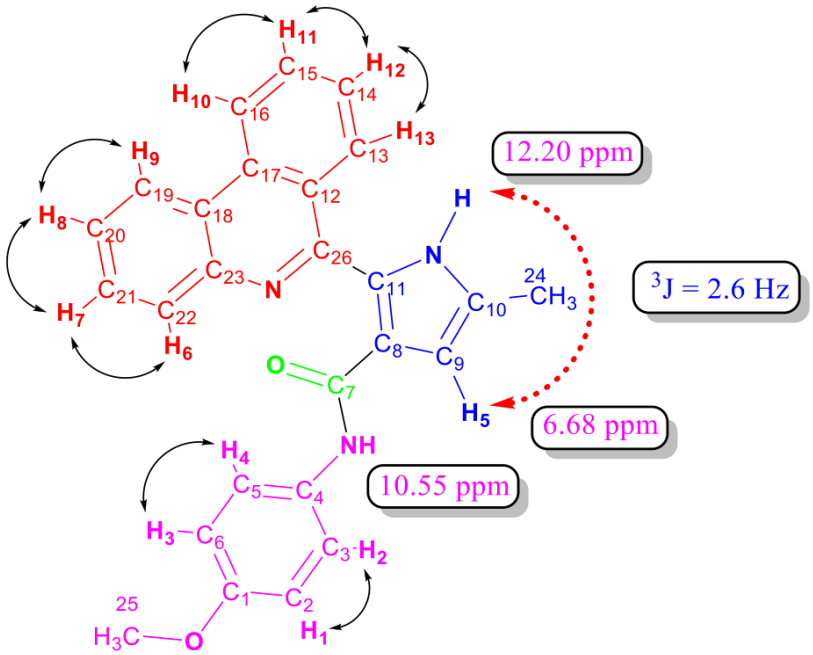


Figure 4. Structure of compound 7a with COSY and HSQC correlation

Acknowledgment

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