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Research Article

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Synthesis of substituted *N*-aryl pyrollo-quinolines and study of their antimicrobial activities

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ABSTRACT

Substituted N-Aryl Pyrollo-Quinolines was achieved by the reductive isomerisation of (E)-3-(2-nitrobenzylidene)-1-phenylpyrrolidine-2, 5-dione with iron in acetic acid and studied for their biological activity.

Keywords: Pyrroloquinolines, Iron, Reduction, Isomerisation, Cyclization, 2-Nitrobenzaldehyde, Triphenyl -phosphine, Maleimide, antibacterial activity and antifungal activity, MIC.

INTRODUCTION

Polynuclear heterocycles derived from pyrrolo [2, 3-b] quinolines are chemically interesting molecule due to their structural similarity to furo [2, 3-b] quinolines which occur widly in natural biologically active products [1] and shows wide variety of biological activities such as anticancer, analgesic, antipyretic, antihypertensive, anti-MDR, anti-inflammatory, anticonvulsant [2, 3], Blebbistatin (myosin II inhibitor) [4, 5] and PGP-4008 (P-GP-specific MDR modulator) [6, 7]. Pyrrolo [2, 3-b] quinolines represent an important class of compounds and have attracted a great deal of attention in synthetic chemistry. Many synthetic methods for pyrrolo[2,3-b] quinolines have been reported [8-13].We became interested in the less studied pyrrole fused with quinoline core which has more importance in the synthetic organic chemistry due to their broad spectrum of biological as well as pharmacological interest. This scaffold affords a wide range of modulation allowing its chemical structure to fit with a variety of targets involved in tumour progression such as kinase, growth factor receptors or DNA itself. Such types of pyrroloquinoline derivatives are considerably less documented. Here, in this manuscript we report the two step convenient synthesis of N-substituted 1-phenyl-1H-pyrrolo [2, 3-b] quinolin-2(3H)-one from maleimides. Further hetero annulation of N-substituted 1-phenyl-1H-pyrrolo [2, 3-b] quinolin-2(3H)-one is ongoing work in our research group. We intended to develop the convenient synthetic approaches for the synthesis of some new substituted N-Aryl Pyrollo-Quinolines that might be of pharmacological importance.

EXPERIMENTAL SECTION

Melting points were determined on a Gallenkamp melting point apparatus. The ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane (TMS) and multiplicities are given as *s* (singlet), *bs* (broad singlet), *d* (doublet), *t* (triplet), *q* (quartet), or *m* (multiplet). Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer. Mass spectrum was recorded on Shimadzu GC-MS QP 2010A mass spectrometer with an ionization potential of 70 eV. Elemental analyses were performed on Thermo Quest Flash 1112 Series EA analyzer. Reactions were monitored by thin layer chromatography carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light of 254 and 366 nm for detection. Compounds were purified by column chromatography using silica

gel (Merck, 60-120 mesh) and column dimension is 39 x 2 cm^2 and elution volume used was about 200-400 mL for each product.

1) General Procedure for the synthesis of N-Aryl maleimide 1a-h:
Maleic anhydride (2.5g, 25.51 mmol) was added at once with vigorous stirring in the solution of aniline (2.3 mL, 24.31 mmol) in acetic acid (15 mL). It was stirred for another 10 minute while the reaction mixture turned into a suspension. To this reaction mixture concentrated sulphuric acid (5.31 g, 54.20 mmol) was added at once while stirring. The temperature increases by 10^oC and suspension turned into a clear solution. The temperature of reaction mixture was increased to 60^oC and stirred further for 45 minutes. It was allowed to come at room temperature and poured onto crushed ice (80 g). The solid separated was filtered and washed with water. The solid was transferred to the aqueous solution of sodium bicarbonate and stirred for 10 minutes to remove maleanilic acid if present. Then filtered and washed with water and recrystallized in ethanol. Yield: quantitative.

*General Procedure for the one pot synthesis of (E) -3-(2-nitrobenzylidene) -1-phenylpyrrolidine-2, 5-Dione **3a-h**.*
To a solution of compound **1** (1.31 g, 7.01 mmol) in Ethanol (10 ml), was an added portion wise Triphenylphosphine (0.935 g, 7.01 mmol) white solid get separated within 3-5 min, continue the stirring for further 30 min for completion of the reaction (TLC Checked). To this same suspension was added a solution of 2-Nitrobenzaldehyde in ethanol (mL) and stir for 30 min for the reaction completion (TLC Checked). The separated solid was filtered washed with Ethanol, dried and recrystallized from Acetone: DMF=9: 1, to afford the **3a-h** in 94% yield.

*1) (E)-3-(2-nitrobenzylidene)-1-phenylpyrrolidine-2, 5-dione **3a**.*
White solid: mp: 220-222^{0}C , IR (KBr) 1757 (C=O), 1716 (C=O), 1658(C=C), 1565-1525 (NO_2), 1120 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: ^{1}H NMR : 8.16(d, *J*= 6 Hz, 1H, =CH-), 7.88-7.82 (m, *J*= 6.6, 4.5 & 1.5 Hz, 2H, Ar-H), 7.79(t, 1H, Ar-H), 7.71-7.62(m, *J*= 5.1 & 1.5 Hz, 1H, Ar-H), 7.53-7.49(t, *J*= 5.4 & 5.7 Hz, 2H, Ar-H), 7.45-7.41(t, *J*= 5.4 Hz, 1H, Ar-H), 7.36 (t, *J*= 5.4 & 1.5 Hz, 2H, Ar-H), 3.77(d, *J*= 1.5 Hz, 2H, -CH_2): MS (m/z): 307[M^+] : *Anal.* Calcd for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09. Found: C, 66.42; H, 4.07; N, 8.94.

*2) (E)-3-(2-nitrobenzylidene)-1-p-tolylpyrrolidine-2, 5-dione **3b.***
White solid: mp: 197-199 ^{0}C, IR (KBr) 3054 (C-H), 1764 (C=O), 1712 (C=O), 1664 (C=C), 1574-1521 (NO_2), 1384 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: ^{1}H NMR : ^{1}H NMR : 8.18 (d, *J*= 8.1 Hz, 1H, =CH-), 7.89-7.79 (m, *J*= 6.9 & 1.2 Hz, 3H, Ar-H), 7.72-7.67 (t, *J*= 6.9 & 1.2 Hz, 1H, Ar-H), 7.30 (d, , *J*=8.1 Hz, 2H, Ar-H),7.25(d, *J*=8.1 Hz, 2H, Ar-H), 3.89 (s, 2H, -CH_2), 2.38(s, 3H, -CH_3): MS (m/z): 322[M^+]: *Anal.* Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.91; H, 4.49; N, 8.83.

*3) (E)-3-(2-nitrobenzylidene)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione **3c**.*
White solid: mp:212-214 ^{0}C, IR (KBr) 3055(C-H), 1769 (C=O), 1716 (C=O), 1660 (C=C), 1564- 1525 (NO_2), 1380 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: ^{1}H NMR : 8.16 (d, *J*= 8.1 Hz, 1H, =CH), 7.79-7.67 (m, *J*= 6.9 & 1.2 Hz, 3H, Ar-H), 7.64-7.63 (t, *J*= 6.9 & 1.2 Hz, 1H, Ar-H), 7.29 (d, , *J*=8.1 Hz, 2H, Ar-H),6.68(d, *J*=8.1 Hz, 2H, Ar-H), 3.80 (s, 2H, CH_2), 3.49(s, 3H, OCH_3).: MS (m/z): 338[M^+]: *Anal.* Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 64.04; H, 4.33; N, 8.47.

*4) (E)-3-(2-nitrobenzylidene)-1-(4-fluorophenyl) pyrrolidine-2, 5-dione **3d.***
White solid: mp: 210-212 ^{0}C, IR (KBr) 1773 (C=O), 1715 (C=O), 1665 (C=C), 1565-1535 (NO_2), 1361 (C-O), 925 (C-F) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 8.17(d, *J*= 6.8 Hz, 1H,=CH), 7.89(m, 3H, Ar-H), 7.77(d, *J*=6.8 Hz, 2H, Ar-H), 7.73(s, 1H, Ar-H), 7.41 (d, *J*= 6.8 Hz, 2H, Ar-H), 3.78(s, 2H, CH_2): MS (m/z): 326[M^+], 328[M+2]: *Anal.* Calcd for $C_{17}H_{11}FN_2O_4$: C, 62.58; H, 3.40; N, 8.59. Found: C, 62.75; H, 3.28; N, 8.71.

*5) (E)-3-(2-nitrobenzylidene)-1-(3-(trifluoromethyl) phenyl) pyrrolidine-2,5-dione **3e.***
White solid: mp: 186-188^{0}C, IR (KBr) 1770 (C=O), 1716 (C=O), 1560-1532 (NO_2), 1366 (C-O), 629 (C-F) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 8.17 (s, 1H, =CH-), 7.72-7.60 (m, 4H, Ar-H), 7.47-7.29 (m, 4H, Ar-H), 3.68 (s, 2H, CH_2).: MS (m/z): 376 [M^+]: *Anal.* Calcd for $C_{18}H_{11}F_3N_2O_4$: C, 57.45; H, 2.95; N, 7.44. Found: C, 57.63; H, 3.08; N, 7.31.

*6) (E)-3-(2-nitrobenzylidene)-1-(4-chlorophenyl) pyrrolidine-2, 5-dione **3f**.*
White solid: mp: 179-181^{0}C, IR (KBr) 1769 (C=O), 1719 (C=O), 1662 (C=C), 1557-1532 (NO_2), 1358 (C-O), 727 (C-Cl) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 8.15(d, *J*= 6.8 Hz, 1H, =CH-), 7.85(m, 3H, Ar-H), 7.69(s, 1H, Ar-H), 7.59(d, *J*=6.8 Hz, 2H, Ar-H), 7.42(d, *J*= 6.8 Hz, 2H, Ar-H), 3.76(s, 2H, CH_2): MS (m/z): 341[M^+], 343[M+2]: *Anal.* Calcd for $C_{17}H_{11}ClN_2O_4$: C, 59.57; H, 3.23; N, 8.17. Found: C, 59.73; H, 3.39; N, 8.33.

*7) (E)-3-(2-nitrobenzylidene)-1-(4-bromophenyl) pyrrolidine-2, 5-dione **3g**.*
White solid: mp: 153-155 ^{0}C, IR (KBr) 1772 (C=O), 1715 (C=O), 1570-1535 (NO_2), 1357 (C-O), 525 (C-Br). cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 8.18 (dd, *J*= 7.2 Hz, 1H, =CH), 8.09 (t, *J*= 2.4 Hz, 1H, Ar-H), 7.74 (dt, *J*= 8 & 0.8 Hz, 1H, Ar-H), 7.62(dt, *J*= 8.8 & 2.4 Hz, 3H, Ar-H), 7.52(d, *J*= 7.6 Hz, 1H, Ar-H), 7.32(d, *J*= 8.8 & 2.4 Hz, 2H, Ar-H), 3.56(d, *J*= 2.4 Hz, 2H, CH_2): MS (m/z): 385[M^+], 387[M+2]: *Anal.* Calcd for $C_{17}H_{11}BrN_2O_4$: C, 60.20; H, 3.27; N, 8.26. Found: C, 60.35; H, 3.44; N, 8.09.

*8) (E)-3-(2-nitrobenzylidene)-1-benzylpyrrolidine-2, 5-dione **3h**.*
White solid: mp:173-175 ^{0}C, IR (KBr) 3053 (CH_2), 1759 (C=O), 1718 (C=O), 1650 (C=C), 1563-1520 (NO_2), 1118 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 8.18(d, *J*= 6 Hz, 1H, =CH), 7.89-7.74 (m, *J*= 6.6, 4.5 & 1.5 Hz, 2H, Ar-H), 7.68(t, 1H, Ar-H), 7.66-7.57(m, *J*= 5.1 & 1.5 Hz, 1H, Ar-H), 7.54-7.43(t, *J*= 5.4 & 5.7 Hz, 2H, Ar-H), 7.34-7.29(t, *J*= 5.4 Hz, 1H, Ar-H), 7.22 (t, *J*= 5.4 & 1.5 Hz, 2H, Ar-H), 4.57 (s, 2H, CH_2), 3.74(d, *J*= 1.5 Hz, 2H, CH_2): MS (m/z): 322[M^+]: *Anal.* Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.23; H, 4.55; N, 8.57.

*General Procedure for the synthesis of (E) -3-(2-aminobenzylidene) -1-phenylpyrrolidine-2, 5-Dione **4a-h**.*
To a stirring solution of compounds 3a-g (1.0 g, 3.4 mmol) in acetic acid (20ml) was added Fe (1.12 g, 20.4 mmol) (200-250 mesh size) and the resultant reaction mixture was heated at 100^{0}C for 10 min, cooled and was filtered through celite and washed with acetic acid, the filtrate was concentrated and poured onto crushed ice, golden yellow solid obtained was filtered and dried. Recrystallized in ethanol (Yield-97%).

*9) (E)-3-(2-aminobenzylidene)-1-phenylpyrrolidine-2,5-dione **4a**.*
Yellow solid: mp:183-185 ^{0}C, IR (KBr) 3444 (NH), 3363 (NH), 1766 (C=O), 1693 (C=O), 1386 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.81 (s, 1H, =CH), 7.52-7.19 (m, 7H, Ar-H), 6.85-6.73 (m, 2H, Ar-H), 4.02 (bs, 2H, -NH_2), 3.69 (d, *J*= 2.4 Hz, 2H, -CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* = 173.2, 169.9, 146.3, 132.0, 1311.4, 130.2, 129.1, 128.6, 128.5, 126.4, 123.2, 119.0, 118.7, 116.6, 34.0: MS (m/z): 279[M^+]: *Anal.* Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.51; H, 4.93; N, 10.24.

*10) (E)-3-(2-aminobenzylidene)-1-p-tolylpyrrolidine-2, 5-dione **4b**.*
Yellow solid: mp:213-215 ^{0}C, IR (KBr) 3444 (-NH), 3363 (-NH), 3242 (-CH), 1766 (C=O), 1695 (C=O), 1631 (C=C), 1382 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.81(s, 1H, =CH), 7.33-7.20(m, 6H, Ar-H), 6.83(t, *J*=7.5 Hz, 1H, Ar-H), 6.77(d, *J*=7.5 Hz, 1H, Ar-H), 4.06(bs, 2H, -NH_2), 3.70(d, *J*=1.8 Hz, 2H, -CH_2), 2.41(s, 3H, -CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.4, 170.1, 146.3, 138.6, 131.4, 130.1, 129.7, 129.3, 128.5, 126.2, 123.2, 119, 118.6, 116.6, 34, 21.2.: MS (m/z): 293[M^+]: *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 74.07; H, 5.65; N, 9.75.

*General Procedure for the synthesis of 1-phenyl-1H-pyrrolo [2, 3-b] quinolin-2 (3H) -one **6a-h**.*
To a stirring solution of compounds 3a-g (2.0 g, 6.8 mmol) in acetic acid (20ml) was added Fe (2.23 g, 40.8 mmol) (>200-250 mesh size) and the resultant reaction mixture was heated at 100^{0}C for 24 hours, and was filtered through celite and washed with acetic acid, the filtrate was concentrated and poured onto crushed ice white solid obtained was filtered and dried. And mixture of product is separated by column chromatography using Hexane: Ethyl acetate as an element to give **6a-h** in 75% and **7a-h** 25%.

*11) 1-phenyl-1H-pyrrolo[2,3-b]quinolin-2(3H)-one **6a**.*
White solid: mp:198-200 ^{0}C, IR (KBr) 3058 (CH_2), 1735 (C=O), 1436 (C=N) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.93(s, 1H, =CH-), 7.89(d, *J*= 8.7 Hz, 1H, Ar-H), 7.73(d, *J*= 7.5 Hz, 1H, Ar-H), 7.66-7.54(m, 5H, Ar-H), 7.47-7.41(m, *J*= 7.5 & 8.7 Hz, 2H, Ar-H), 3.81(s, 2H, -CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.6, 157, 146.5, 133.2, 131.4, 129.3, 129, 128.1, 128, 127.5, 126.7, 126.2, 124.8, 119.3, 34.3: MS (m/z): 260[M^+]: *Anal.* Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.60; H, 4.83; N, 10.55.

*12) 1-p-tolyl-1H-pyrrolo[2,3-b]quinolin-2(3H)-one **6b**.*
White solid: mp: 167-169 ^{0}C, IR (KBr) 3057 (CH_2), 1737 (C=O), 1445 (C=N) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.94(s, 1H, =CH), 7.88(d, *J*= 6.3 Hz, 1H, Ar-H), 7.75(d, *J*= 6.0 Hz, 1H, Ar-H), 7.60(t, *J*= 5.1 & 0.9 Hz, 1H, Ar-H), 7.48(d, *J*= 6.0 Hz, 2H, Ar-H), 7.41(t, *J*= 6.3 & 5.1 Hz, 1H, Ar-H), 7.37(d, *J*= 6.0 Hz, 2H, Ar-H), 3.82(d, *J*= 0.9 Hz, 2H, Ar-H), 2.43(s, 3H, CH_3): MS (m/z): 247[M^+]: *Anal.* Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.68; H, 5.25; N, 10.37.

*13) 1-(4-methoxyphenyl)-1H-pyrrolo[2,3-b]quinolin-2(3H)-one **6c**.*
White solid: mp: 141-143 ^{0}C, IR (KBr) 3062 (CH_2), 1737 (C=O), 1432 (C=N) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.92(s, 1H, =CH-), 7.87(d, *J*= 6.3 Hz, 1H, Ar-H), 7.78(d, *J*= 6.0 Hz, 1H, Ar-H), 7.63(t, *J*= 5.1 & 0.9 Hz, 1H, Ar-H), 7.49(d, *J*= 6.0 Hz, 2H, Ar-H), 7.42(t, *J*= 6.3 & 5.1 Hz, 1H, Ar-H), 7.12(d, *J*= 6.0 Hz, 2H, Ar-H), 3.83(d, *J*= 0.9 Hz,

2H, -CH_2), 3.79(s, 3H, -CH_3): MS (m/z): 290[M^+]: *Anal.* Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.64; H, 5.01; N, 9.50.

14) 1-(4-fluorophenyl)-1H-pyrrolo[2,3-b]quinolin-2(3H)-one ***6d***.
White solid: mp: 157-159^{0}C, IR (KBr) 3050 (CH_2), 1713 (C=O), 1645 (C=C), 1450 (C=N) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.87(s, 1H, =CH-), 7.83 (d, *J*= 8.4 Hz, 2H, Ar-H), 7.68 (d, *J*= 8.4 Hz, 2H, Ar-H), 7.57-7.25 (m, 4H, Ar-H), 3.91(d, *J*= 1.2 Hz, 2H, CH_2).: MS (m/z): 278[M^+] 280[M+2]: *Anal.* Calcd for $C_{17}H_{11}FN_2O$: C, 73.37; H, 3.98; N, 10.07. Found: C, 73.52; H, 4.07; N, 9.93.

15) 1-(3-(trifluoromethyl)phenyl)-1H-pyrrolo[2,3-b]quinolin-2(3H)-one ***6e***.
White solid: mp: 173-175^{0}C, IR (KBr) 3083 (CH_2), 1716 (C=O), 1647 (C=C), 1455 (C=N) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.98(s, 1H, =CH-), 7.90 (d, *J*= 8.1 Hz, 1H, Ar-H), 7.78(d, *J*= 7.6 Hz, 1H, Ar-H), 7.67-7.60(m, *J*= 8.4, 2 & 1.2 Hz, 3H, Ar-H), 7.57(d, *J*= 8.4 & 1.2 Hz, 2H, Ar-H), 7.47(t, *J*= 7.2 Hz, 1H, Ar-H), 3.91(d, *J*= 1.2 Hz, 2H, CH_2): MS (m/z): 329[M^+]: *Anal.* Calcd for $C_{18}H_{11}F_3N_2O$: C, 65.85; H, 3.38; N, 8.53. Found: C, 65.68; H, 3.43; N, 8.37.

16) 1-(4-chlorophenyl)-1H-pyrrolo[2,3-b]quinolin-2(3H)-one ***6f***.
White solid: mp: 168-170 ^{0}C, IR (KBr) 2954 (CH_2), 1743 (C=O), 1663 (C=N) 725 (C-Cl) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.97(s, 1H, =CH-), 7.88(d, *J*= 8.1 Hz, 1H, Ar-H), 7.76(d, *J*= 7.6 Hz, 1H, Ar-H), 7.64-7.51(m, *J*= 8.4, 2 & 1.2 Hz, 3H, Ar-H), 7.53(d, *J*= 8.4 & 1.2 Hz, 2H, Ar-H), 7.44(t, *J*= 7.2 Hz, 1H, Ar-H), 3.84(d, *J*= 1.2 Hz, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.3, 156.6, 146.5, 133.5, 131.7, 131.6, 129.5, 129.2, 128.1, 127.9, 127.6, 126.2, 125, 119, 34.2.MS (m/z): 295[M^+] 297[M+2]: *Anal.* Calcd for $C_{17}H_{11}ClN_2O$: C, 69.28; H, 3.76; N, 9.50. Found: C, 69.47; H, 3.83; 9.32.

17) 1-(4-bromophenyl)-1H-pyrrolo[2,3-b]quinolin-2(3H)-one ***6g***.
White solid: mp: 153-155 ^{0}C, IR (KBr) 3058 (CH_2), 1737 (C=O), 1639 (C=C), 1490 (C=N), 825 (C-Br) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.96(s, 1H, =CH-), 7.88 (d, *J*= 8.4 Hz, 1H, Ar-H), 7.76 (d, *J*= 8 Hz, 1H, Ar-H), 7.67(d, *J*= 8.4 Hz, 2H, Ar-H), 7.62(t, *J*= 7.2 Hz, 1H, Ar-H), 7.58(d, *J*= 8.4Hz, 2H, Ar-H), 7.44(t, *J*= 8 Hz, 1H, Ar-H), 3.81(s, 2H, CH_2).MS (m/z): 339[M^+] 341[M+2]: *Anal.* Calcd for $C_{17}H_{11}BrN_2O$: C, 60.20; H, 3.27; N, 8.26. Found: C, 60.35; H, 3.44; N, 8.09.

18) 1-benzyl-1H-pyrrolo[2,3-b]quinolin-2(3H)-one ***6h***.
White solid: mp: 132-134 ^{0}C, IR (KBr) 3034 (-CH_2), 1732 (C=O), 1443 (C=N) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.98(s, 1H, =CH-), 7.84 (d, *J*= 8.4 Hz, 1H, Ar-H), 7.79 (d, *J*= 8 Hz, 1H, Ar-H), 7.64-7.47(m, 5H, Ar-H), 7.43-7.39(m, 2H, Ar-H), 5.27(s, 2H, CH_2), 3.83(s, 2H, CH_2).MS (m/z): 274[M^+]: *Anal.* Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.94; H, 5.32; N, 10.05.

General Procedure for the synthesis of N-(2-((E) -(2,5-dioxo-1-phenylpyrrolidin-3-ylidene) methyl) phenyl) acetamide (7a-h):
Stirring compound **4a-h** (1 g, 3.8 mmol) in acetic anhydride (3 ml) for 5 min and poured the reaction mixture on crushed ice white solid obtained was filtered and dried, crystallized in ethanol (Yield-99%).

19) N-(2-((E)-(2,5-dioxo-1-phenylpyrrolidin-3-ylidene)methyl)phenyl)acetamide ***7a***.
White solid: mp: 178-179^{0}C, IR (KBr) 3238 (-NH), 3029 (-CH_3), 1764 (C=O), 1708 (C=O), 1662 (C=O), 1596 (C=C), 1369 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.86(s, 1H, -NH), 7.78(s, 1H, =CH -), 7.71(d, *J*= 7.5 Hz, 1H, Ar-H), 7.38-7.26(m, 8H, Ar-H), 3.62(s, 2H, -CH_2), 2.10(s, 3H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.8, 169.9, 169.2, 130.1, 137.1, 131.6, 130.8, 130.4, 129, 128.6, 128.1, 126.9, 126.3, 125.5, 124.8, 33.8, 23.8. D_2O: 7.80(s, 1H, =CH-), 7.76(d, *J*= 8.7 Hz, 1H, Ar-H), 7.45-7.21(m, 8H, Ar-H), 3.65(d, *J*= 2.1 Hz, 2H, -CH_2), 2.13(s, 3H, -CH_3).MS (m/z): 320[M^+]: *Anal.* Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24, H, 5.03, N, 8.74. Found: C, 71.41, H, 4.87, N, 8.90.

20) N-(2-((E)-(2,5-dioxo-1-p-tolylpyrrolidin-3-ylidene)methyl)phenyl)acetamide ***7b***.
White solid: mp: 193-195^{0}C, IR (KBr) 3234 (-NH), 1764 (C=O), 1710 (C=O), 1650 (C=O), 1514 (C=C), 1388 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.80(s, 1H, =CH-), 7.56(bs, 1H, -NH), 7.47-7.42(t, *J*=7.2 & 7.5 Hz, 2H, Ar-H), 7.30(m, *J*=8.1 & 7.5 Hz, 5H, Ar-H), 3.67(d, *J*=2.1 Hz, 2H, -CH_2), 2.38(s, 3H, -CH_3), 2.19(s, 3H-CH_3).MS (m/z): 335[M^+]: *Anal.* Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84, H, 5.43, N, 8.38. Found: C, 72.01, H, 5.23, N, 8.49.

21) N-(2-((E)-(1-(4-methoxyphenyl)-2,5-dioxopyrrolidin-3-ylidene)methyl)phenyl)acetamide ***7c***.
White solid: mp: 165-167^{0}C, IR (KBr) 3344 (-NH), 3055 (-CH_3), 1767 (C=O), 1709 (C=O), 1655 (C=O), 1378 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.79(s, 1H, =CH-), 7.57(bs, 1H, -NH), 7.49-7.41(t, *J*=7.2 & 7.5 Hz, 2H, Ar-H), 7.37-7.33(m, 3H, Ar-H), 7.12 (d, *J*=7.5 Hz, 2H, Ar-H), 3.78 (s, 3H, -OCH_3), 3.69(d, *J*=2.1 Hz, 2H, -CH_2), 2.15(s,

3H, -CH_3).MS (m/z): 350[M^+]: *Anal.* Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56, H, 5.18, N, 8.00. Found: C, 68.39, H, 5.35, N, 7.84.

*22) N-(2-((E)-(1-(4-fluorophenyl)-2,5-dioxopyrrolidin-3-ylidene)methyl)phenyl)acetamide **7d**.*
White solid: mp: 187-189^{0}C, IR (KBr) 3344 (-NH), 3055 (-CH_3), 1767(C=O), 1709(C=O), 1655(C=O), 1378 (C-F), 1150 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.82(s, 1H, =CH-), 7.78(s, 1H, -NH), 7.53-7.47(m, 4H, Ar-H), 7.32-7.28(m, 4H, Ar-H), 3.71(d, *J*= 2.4 Hz, 2H, -CH_2), 2.26(s, 3H, -CH_3). MS (m/z): 338[M^+]: *Anal.* Calcd for $C_{19}H_{15}FN_2O_3$: C, 67.45; H, 4.47; N, 8.28. Found: C, 67.57; H, 4.61; N, 8.09.

*23) N-(2-((E)-(1-(3-(trifluoromethyl)phenyl)-2,5-dioxopyrrolidin-3-ylidene)methyl)phenyl)acetamide **7e.***
White solid: mp: 190-192 ^{0}C, IR (KBr) 3231 (-NH), 3034 (-CH_3), 1767 (C=O), 1708 (C=O), 1655 (C=O), 1387 (C-F), 1156 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm 7.81 (s, 1H, =CH-), 7.74 (s, 1H, -NH), 7.65-7.45 (m, 4H, Ar-H), 7.29-7.18 (m, 4H, Ar-H), 3.64 (s, 2H, -CH_2), 2.29 (s, 3H, -CH_3). MS (m/z): 388[M^+]: *Anal.* Calcd for $C_{20}H_{15}F_3N_2O_3$: C, 61.86; H, 3.89; N, 7.21. Found: C, 61.96; H, 4.03; N, 7.37.

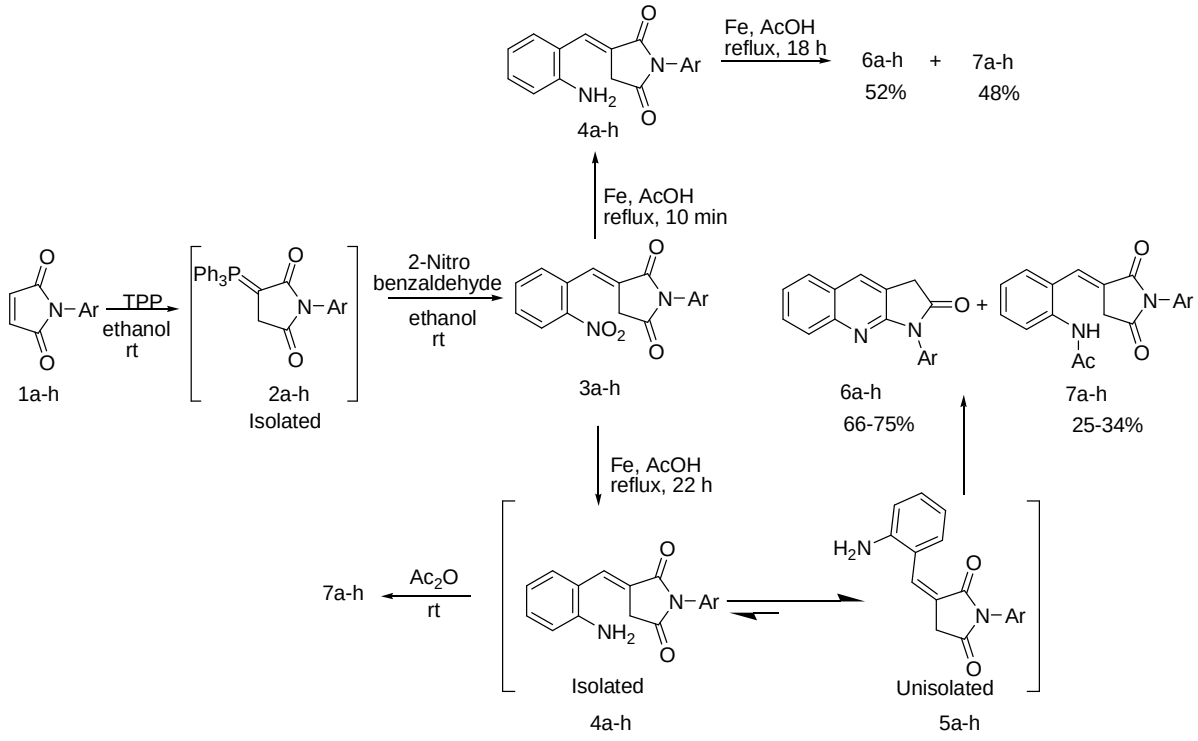
*24) N-(2-((E)-(1-(4-chlorophenyl)-2,5-dioxopyrrolidin-3-ylidene)methyl)phenyl)acetamide **7f**.*
White solid: mp: 177-179 ^{0}C, IR (KBr) 3234 (-NH), 1768 (C=O), 1710 (C=O), 1652 (C=O), 1490 (C=C), 1386 (C-O), 655 (C-Cl) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm. 7.79(s, 1H, =CH-), 7.76(s, 1H, -NH), 7.47-7.43(m, 4H, Ar-H), 7.35-7.24(m, 4H, Ar-H), 3.69(d, *J*= 2.4 Hz, 2H, -CH_2), 2.23(s, 3H, N-CH_3). MS (m/z): 255[M^+] 257[M+2]: *Anal.* Calcd for$C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; N, 7.90. Found: C, 64.19; H, 4.12; N, 8.04.

*25) N-(2-((E)-(1-(4-bromophenyl)-2, 5-dioxopyrrolidin-3-ylidene)methyl)phenyl)acetamide **7g**.*
White solid: mp: 189-191 ^{0}C, IR 3234 (-NH), 3014 (-CH_3), 1766 (C=O), 1708 (C=O), 1654 (C=O), 1490 (C=C), 1176 (C-O), 763 (C-Br). (KBr) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.76(s, 1H, =CH-), 7.72(s, 1H, -NH), 7.48-7.45(m, 4H, Ar-H), 7.37-7.27(m, 4H, Ar-H), 3.72(d, *J*= 2.4 Hz, 2H, -CH_2), 2.25(s, 3H, -CH_3). MS (m/z): 397[M^+], 399 [M+H]: *Anal.* Calcd for $C_{19}H_{15}BrN_2O_3$: C, 57.16; H, 3.79; N, 7.02. Found: C, 57.33; H, 3.92; N, 6.87.

*26) N-(2-((E)-(1-benzyl-2, 5-dioxopyrrolidin-3-ylidene)methyl)phenyl)acetamide **7h**.*
White solid: mp:210-212 ^{0}C, IR (KBr) 3268 (-NH), 3034 (-CH_3), 1770 (C=O), 1712 (C=O), 1655 (C=O), 1390 (C-O) cm^{-1}: ^{1}H NMR ($CDCl_3$) δ ppm: 7.77(s, 1H, =CH-), 7.73(s, 1H, -NH), 7.50-7.43(m, 4H, Ar-H), 7.39-7.31(m, 4H, Ar-H), 4.37 (s, 2H, -CH_2), 3.78 (s, 2H, -CH_2), 2.26 (s, 3H, -CH_3). MS (m/z): 334[M^+]: *Anal.* Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.65; H, 5.59; N, 8.51.

RESULTS AND DISCUSSION

N-aryl Maleimides (**1a-h**) are an important framework in many biological active synthetic as well as natural products which was synthesized by the reaction between aniline and Maleic anhydride in acetic acid in the presence of concentrated sulphuric acid, one pot reaction reported recently by our group [14] in quantitative yield. The reaction of Triphenylphosphine (TPP) with maleimide in ethanol at room temperature furnished the Triphenylphosphine (TPP) -Maleimide adducts **2a-h** as an intermediate also in quantitative yield. Previously [15], synthesis of such types of Wittig adduct was reported in acetic acid, THF, acetone as solvent and at refuxing temperature, here in this manuscript we use the ethanol as a reaction solvent gives highly pure and quantitative yield of product **2a-h**. Triphenylphosphine (TPP) -Maleimide adduct on reaction with 2-Nitrobenzaldeyde in ethanol gives the (*E*) -3-(2-nitrobenzylidene) -1-phenylpyrrolidine-2, 5-Dione **3a-h** selectively [16and Ref. Cited their in] and side product Triphenylphosphineoxide (TPP=O) is soluble in ethanol and easily removed by washing the compound with ethanol during compound isolation. Also (*E*) -3-(2-nitrobenzylidene) -1-phenylpyrrolidine-2, 5-Dione **3a-h** was prepared by one pot synthesis from maleimides, in quantitative yield. Reduction of (*E*) -3-(2-nitrobenzylidene) -1-phenylpyrrolidine-2,5-Dione in Fe (250-300 mesh) acetic acid at 100^{0}C for 24 hours furnishes the mixture of products which on separation by column chromatography(Hexane:Ethylacetate, 9:1) gives cyclized 1-phenyl-1H-pyrrolo [2,3-b] quinolin-2 (3H) -one **6a-h** and N-(2-((*E*) -(2,5-dioxo-1-phenylpyrrolidin-3-ylidene) methyl) phenyl) acetamide **7a-h** (Scheme-1). Reaction mechanism shows that reduction of the Nitro group of compound **3a-h** followed by the isomerization of exocyclic double of compound **4a-h** (*E*) -3-(2-aminobenzylidene) -1-phenylpyrrolidine-2,5-dione bond to **5a-h** (*Z*) -3-(2-aminobenzylidene) -1-phenylpyrrolidine-2,5-dione, in compound **5a-h** the amino group is close proximity to the imide carbonyl carbon which on S_N2 reaction release the ring strain instead the opening of the pyrrole ring and undergoes cyclization to give the compound **6a-h** in 75% conversion, while the non-isomerized compound **4a-h** undergoes acylation with acetic acid under reflux condition in 25%. Also reaction of compound **4a-h** with acetic anhydride at room temperature afford the compound **7a-h** which was confirmed by TLC and physical constants and also spectroscopic analysis.



6a)Ar=C_6H_5, 6b)Ar=4-$CH_3C_6H_4$, 6c)Ar=Ar= 4-$OCH_3C_6H_4$, 6d)Ar= 4-FC_6H_4, 6e)Ar= 3-$CF_3C_6H_4$, 6f) 4-ClC_6H_4, 6g)Ar= 4-BrC_6H_4, 6h)Ar=$CH_2C_6H_5$

Scheme-1

It was noted that, during the synthesis of compound **6a-h**and **7a-h** if the substituent present on N-aromatic ring show the effect on reaction time and yield. Thus, the substituent at present para position is the electron donating then the reaction rate is high and also yield is high. Similarly if the substituent at ring is the electron withdrawing at para position then the reaction rate is slow and also yields.

Table-1: Optimization of time and yield of synthesized compounds 6a-hand 7a-h

Comp.No. 6 and 7	Time (h)	Yield(%)	
		6	7
a	20	73	27
b	19	72	28
c	16	75	25
d	22	66	34
e	20	68	32
f	19	69	31
g	20	70	30
h	20	71	29

Biological Assay

The antimicrobial activity of the synthesized compounds was evaluated by the agar cup plate method. The antibacterial and antifungal assays were performed in Muller-Hinton broth and Czapek Dox broth respectively. Evaluation was performed using the bacteria reseeded in broth for 24 h at 37 ^oC, and the fungi were reseeded in broth for 48 h at 25 ^oC. The antibacterial activity of tested samples was studied against one Gram positive bacteria *Bacillus subtilis* NCIM 2250, one Gram negative bacteria *Escherichia Coli* ATCC 25922 while *Candida albicans* MTCC 277, *Candida tropicalis* MTCC 184, *Aspergillus niger* MCIM 545 and *Aspergillus clavatus* MTCC 1323 were used as standard fungal strain. The compounds were diluted in DMF with required concentration for bioassay. DMF was also loaded as control. Streptomycin and griseofluvin was used as standard to evaluate the potency of the tested compounds under same conditions. The zone of inhibition was determined from the diameter of the zone of inhibition using caliper. Each inhibition zone was measured three times to get average value. The minimum inhibitory concentration (MIC) values were determined on MH agar plates by pouring the molted agar in Petri dishes according to National Committee for Clinical Laboratory Standards (NCCLS, M7-A5 January 2000), containing the following concentrations (mg/mL): 0 (control), 5, 10, 15, 20, 30, 40. The MIC was defined as the lowest concentration tested samples showing no visible bacterial growth after 24 h incubation period at 37^oC.

Antimicrobial Activity

In vitro antibacterial and antifungal activity of all newly synthesized compounds was screened by considering zone of inhibition of growth. The synthesized compounds (**6a-h)** were screened with their different concentrations along with standard antibiotics such as Streptomycin (5 µg/mL) and Griseofluvin (5 µg/mL) (Table-2). The results showed that compounds (**6a, 6b, 6c and 6h**) had very low antimicrobial activity while compounds (**6d-g**) showed excellent antibacterial and antifungal activity with MIC value in between (10 and 15 µg/mL).

From the data it is clear that antimicrobial activity of the compounds (**6d-g**) influences by changing the substituent's on the aromatic ring. Compound 6d having fluorine substituent while, 6e having trifluoro, 6f having chloro, 6g having bromo substituent. Hence, F, Cl, Br and CF_3 substituent's was showed consistently excellent antimicrobial activity against antibacterial and antifungal strains.

Table-2 Antibacterial and antifungal activity of compounds (6a-h)

Entry	*Bacillus subtilis* NCIM 2250	*Escherichia Coli* ATCC 25922	*Candida albicans* MTCC 277	*Candida tropicalis* MTCC 184	*Aspergillus niger* MCIM 545	*Aspergillus clavatus* MTCC 1323
	ZI[a] (MIC)[b]	ZI (MIC)	ZI (MIC)	ZI (MIC)	ZI (MIC)	ZI (MIC)
6a	17.1(25)	17.3(20)	-	13.7(20)	-	15.3(20)
6b	16.1(20)	14.2(20)	13.5(20)	16.2(20)	17.2(20)	16.0(20)
6c	14.1 (20)	15.1(20)	16.4(20)	16.8(20)	14.4(20)	12.4(20)
6d	**14.6(10)**	**15.3(10)**	**13.8(10)**	**14.7(10)**	**15.2(10)**	**13.1(10)**
6e	**14.1 (10)**	**17.1(10)**	**16.8(10)**	**13.4(15)**	**17.1(10)**	**13.1(10)**
6f	**15.2(10)**	**14.8(15)**	**12.4(10)**	**13.2(15)**	**16.9(15)**	**15.3(15)**
6g	**17.2(15)**	**16.6(15)**	**18.7(15)**	**15.2(20)**	**12.4(15)**	**16.4(15)**
6h	16.1(20)	15.1(20)	14.1(20)	15.3(20)	15.5(20)	14.8(20)
Strept.	16.2(05)	16.4(05)	n.t.[c]	n.t.	n.t.	n.t.
Gris.	n.t.	n.t.	16.8(05)	17.3(05)	16.9(05)	17.6(05)

Bold values indicates better results ; [a]Zone of inhibition in mm.; [b]Minimum inhibitory concentration in µg/ml.; [c]n.t. not tested

CONCLUSION

We synthesized new N-Aryl Pyrrolo Quinolines by the reductive isomerisation of (*E*)-3-(2-nitrobenzylidene)-1-phenylpyrrolidine-2, 5-dione with iron in acetic acid. The result from biological activity study proved that **6d-g** showed good antibacterial as well as antifungal activity.

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