Asian Journal of Chemistry; Vol. 29, No. 7 (2017), 1434-1440

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20513

Design, Synthesis and Molecular Properties Prediction of Novel Quinazoline Derivatives as Potent Antibacterial Agents

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Received: 12 January 2017; *Accepted*: 7 March 2017; *Published online*: 13 May 2017; AJC-18368

A novel series of compounds were synthesized by C-C bond formation of substituted quinazolinones (**1**) with substituted boronic acids (**2**) to get 2,4-disubstituted quinazoline (**3a-3n**) in good to excellent yields. The structures of the new compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. An antibacterial and antifungal activity screening results showed that compounds 3**b, 3e, 3i** and **3l** possess excellent activity against Gram (+), Gram (-) bacteria (*S. aureus, Klebsiella* species, *P. aeruginosa*) compared to standard drugs. **3l, 3g** and **3n** showed better antifungal activity against *A. nigeri* and *C. albicans* organisms. In this investigation, the target compounds **3a-3n** were subjected to *in silico* molecular properties prediction and drug likeness by employing Molinspiration (Molinspiration, 2014) and MolSoft (MolSoft, 2007) property explorer tool kits for predicting their high oral bioavailability.

Keywords: Antimicrobial activity, Palladium catalyst, Quinazolines.

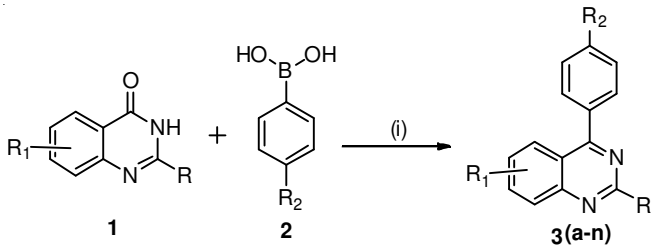
INTRODUCTION

Quinazolines uses in the treatment of inflammatory diseases and particular emphasis on potency specified in the screening assays over the last three decades. There has been considerable interest in the development of preparative methods for the production of quinazolines [1]. This is because quinazolines and their ring-fused derivatives display a broad spectrum of biological activities like antitubercular, analgesic, anti-inflammatory and antibacterial [2]. Heterocyclic chemistry is the largest classical division of medicinal chemistry and display a broad range of industrial and pharmaceutical applications. Additionally, quinazolines have been employed as ligands for benzodiazepine and γ-aminobutyric acid receptors in the CNS systems or as DNA binders. This compound has soporific and sedative action. In last 10 to 15 years of research for medicinal has been characterized by significant advances. In 1968, only two derivatives were used, soporific and anticonvulsant-methaqualone and diuretic quinathazone. By 1980, about 50 kinds of derivatives of this class includes medicinal with different biological actions like 'soporific, sedative, tranquilizing, analgesic, anticonvulsant, antitussive, myorelexant, antirheumatic, hypotensive, antiallergic, bron chodilating, antidiabetic, cholagogue, diuretic, cystatic, antimalarial, spermicidal, *etc*.

Quinazoline derivatives belong to the nitrogen-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anticancer [3-6], anti-inflammation [7,8], antibacterial [9-12], antivirus [13], anticytotoxin [14], antispasm [15], antituberculosis [16], antioxident [17], antimalarial [18], antihypertension [19], antiobesity [20], antipsychotic [21] and antidiabetes [22], *etc*.

Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using developing synthetic methods. The potential applications of the quinazoline derivatives in fields of biology, pesticides and medicine have also been explored. The synthetic methods, either traditional or novel and categorized them into five main classifications, including aza-reaction, microwave-assisted reaction, metal-catalyzed reaction, ultrasound-promoted reaction and phase-transfer catalysis.

Encouraged by the diverse biological activities of quinazoline heterocyclic compounds, an experiment was designed to prepare a new series of quinazoline derivatives. The synthesis of the compounds as per the following and synthetic route was depicted in **Scheme-I** (Fig. 1). The structures



Scheme-I: Reagents and conditions: (i) $Pd(PPh_3)_4$/CuI, NaOEt, 1,4-Dioxane, H_2O, TsCl, reflux, 70 °C, 6 h

of all the synthesized compounds were assigned on the basis of IR, Mass, ^{1}H NMR spectral data analysis. Further these compounds were subjected for antifungal and antibacterial activity.

EXPERIMENTAL

In this investigation chemicals were purchased from local dealer with S.D fine make was used. Chemicals were 99.99 % pure; purity has been checked by thin layer chromatography and melting point. Conventional method has been used for synthesis of quinazoline derivatives. Stirring and reflux method were used for synthesis of quinazoline derivatives **3a-3n**, respectively.

The quinazoline derivatives (**3a-3n**) were synthesized in single step using different reagents and reaction conditions. All the **3a-3n** were obtained in moderate yields. The structure were established by spectral (IR, ^{1}H NMR, ^{13}C NMR and mass) and analytical data.

All the reactions were carried out under argon in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All the solvents were reagent grade. Tetrahydrofuran was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fitted glass funnel and concentrated with a rotary evaporator (20-30 Torr). Flash chromatography was performed with silica gel (200-300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for ^{1}H NMR, ^{13}C NMR respectively, in $CDCl_3$ solution with tetramethyl silane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethyl silane (TMS) in the solvent

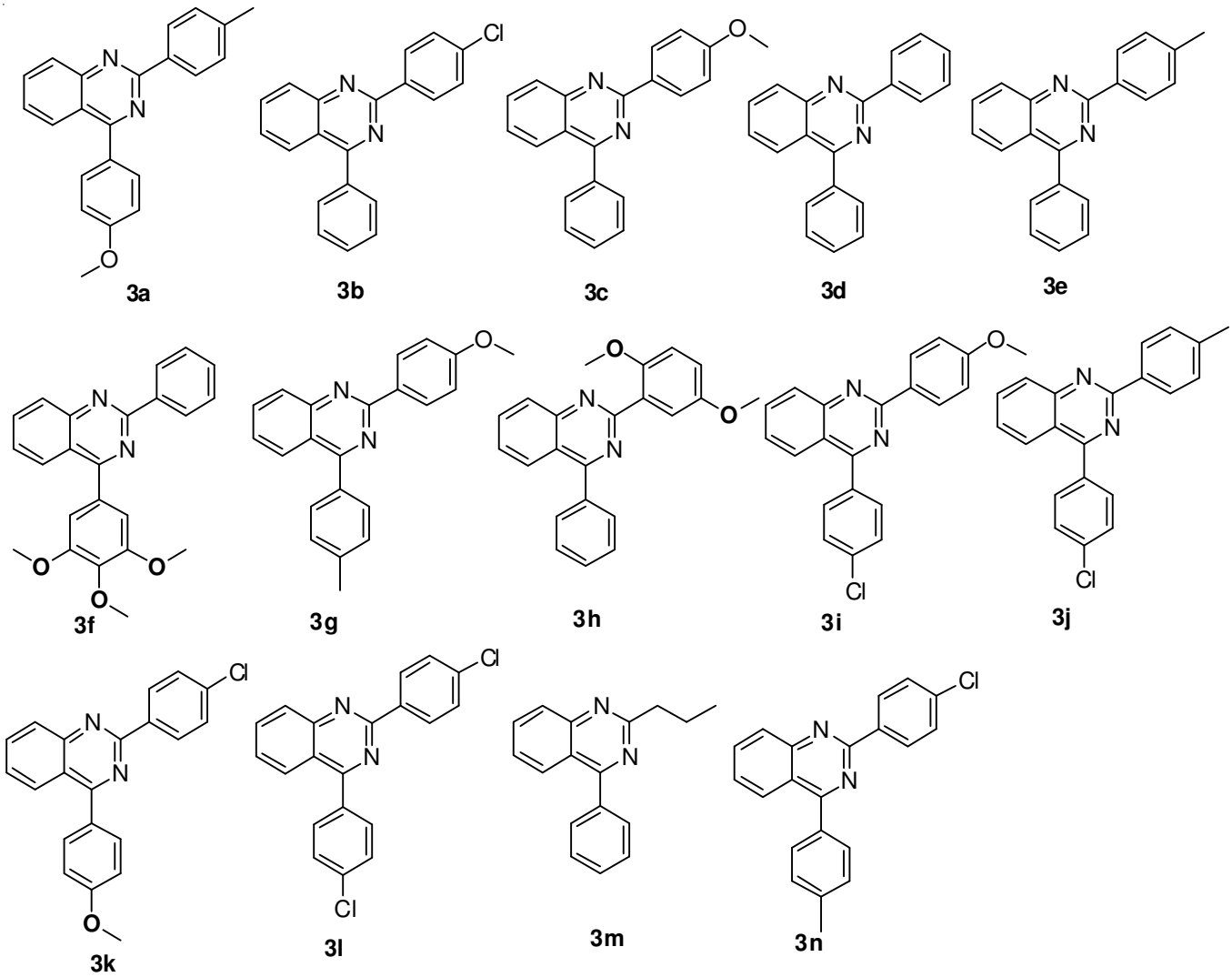


Fig. 1. Synthesise of quinazoline derivatives (**3a-3n**)

of $CDCl_3$ or DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm; ^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm).

Synthesis of 2,4-disubstituted quinazolines (3a-3n): The solution of quinazolin-4-ones (1 eq) in 1,4-dioxane (3 mL) was treated with tosyl chloride (**1.1 eq**) and NaOEt (2.0 eq) at 70 °C. After 20 min, boronic acid (1.25 equiv), $Pd(PPh_3)_4$ (0.05 eq), CuI (0.05 eq) and H_2O (0.5 mL) were added under air atmosphere. After the completion of the reaction as indicated by TLC, the solvent was evaporated and the residue was purified on silica gel to provide the products **3a-3n** (Fig. 1).

4-(4-Methoxyphenyl)-2-(*p*-tolyl)quinazoline (3a): Off white solid; yield: 85 %; m.p.: 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.90 (s, 3H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, d, 2H), 7.50 (t, *J* =7.6 Hz) 7.82-7.87 (m, 3H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.57 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 55.5, 114.0, 121.6, 126.6, 127.0, 128.6, 129.1, 129.3, 130.3, 131.8, 133.3, 135.6, 140.6, 152.1, 160.3, 161.2, 167.6; IR (KBr, ν_{max}, cm^{-1}): 3046.94 (ArC-H str), 2924.15, 2860.84 (C-H str), 1608.14, 1540.12, 1481.03 (ArC=C str), 1393.08 (CN str), 1252.46 (C-O-C str); MS/ESI: *m/z* [M+H, 100 %, 327].

2-(4-Chlorophenyl)-4-phenylquinazoline (3b): White solid; yield: 75 %, m.p.: 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.60 (m, 6H), 7.86-7.87 (m, 3H), 8.08 (d, *J* = 8.4 Hz, 1H) 8.12 (d, *J* = 8.4 Hz, 1H), 8.64 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.5, 123.5, 126.6, 127.2, 128.6, 128.7, 128.9, 129.3, 130.6, 131.5, 133.7, 136.1, 138.0, 152.0, 160.2, 167.1; IR (KBr, ν_{max}, cm^{-1}): 3054.9, 2926.2, (ArC-H str), 1612.8, 1506.5 (ArC=C str), 1399.9 (CN str); MS/ESI: *m/z* [M+H, 100 %, 317].

2-(4-Methoxyphenyl)-4-phenylquinazoline (3c): White solid; yield: 90 %; m.p.: 135-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.39-7.44 (m, 4H), 7.75-7.80 (m, 3H), 8.05 (t, *J* = 7.6 Hz, 2H), 8.61 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.4, 112.9, 120.6, 125.7, 125.9, 127.4, 127.6, 128.1, 129.1, 129.4, 130.8, 132.3, 137.3, 151.1, 159.1, 160.2, 166.6. IR (KBr, ν_{max}, cm^{-1}): 3050.81 (ArC-H str), 2925.22, 2857.63 (C-H str), 1608.8, 1537.62, 1413.0 (ArC=C str), 1314.2 (CN str), 1116.6 (C-O-C str); MS/ESI: *m/z* [M+H, 100 %, 313].

2,4-Diphenylquinazoline (3d): White solid; yield: 80 %, m.p.: 122-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.61 (m, 7H), 7.88-7.90 (m, 3H), 8.15 (t, *J* = 8.4 Hz, 2H), 8.69 (dd, *J* = 1.6 Hz, 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.7, 127.0, 128.6, 128.7, 129.2, 129.9, 130.2, 130.5, 133.5, 137.7, 138.3, 152.0, 160.3, 168.3; IR (KBr, ν_{max}, cm^{-1}): 3032.6 2927.60, (ArC-H str), 1634.52, 1530.03 (ArC=C str), 1397.37 (CN str); MS/ESI: *m/z* [M+H, 100 %, 283].

4-Phenyl-2-(*p*-tolyl)quinazoline (3e): White solid; yield: 83 %; m.p.: 189-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.50 (dt, *J* = 0.8, 7.2 Hz, 1H), 7.58-7.60 (m, 3H), 7.84-7.89 (m, 3H), 8.11 (dt, *J* = 0.4, 9.6 Hz, 2H), 8.58 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 121.6, 126.7, 127.0, 128.5, 128.7, 129.1, 129.3, 129.8, 130.2, 133.5, 135.5, 137.8, 140.7, 152.0, 160.4, 168.2; IR (KBr, ν_{max}, cm^{-1}): 3046.2 (ArC-H str), 2926.0, 2858.6 (C-H str), 1602.2, 1525.6, 1476.2 (ArC=C str), 1393.8 (CN str); MS/ESI: *m/z* [M+H, 100 %, 297].

2-Phenyl-4-(3,4,5-trimethoxyphenyl)quinazoline (3f): White solid; yield: 88 %; m.p.: 118-121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.11 (s, 9H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.58-7.63 (m, 3H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.82-7.87 (m, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 8.70 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 122.8, 125.3, 127.2, 128.4, 129.1, 129.8, 130.6, 133.4, 134.9, 138.3, 140.2, 152.6, 160.8, 168.7; IR (KBr, ν_{max}, cm^{-1}): 3034.6 (ArC-H str), 2928.61, 2942.21 (C-H str), 1636.1, 1544.12 (ArC=C str), 1390.42 (CN str), 1115.12 (C-O-C str); MS/ESI: *m/z* [M+H, 100 %, 373].

2-(4-Methoxyphenyl)-4-(*p*-tolyl)quinazoline (3g): Off white solid; yield: 82 %; m.p. 103-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 3.89 (s, 3H), 7.03 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 8.10 (t, *J* = 8.0 Hz, 2H), 8.65 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 55.4, 113.8, 121.5, 126.4, 127.1, 128.9, 129.2, 130.1, 130.3, 130.9, 133.4, 134.9, 140.1, 152.2, 160.0, 161.7, 168.2; IR (KBr, ν_{max}, cm^{-1}): 3046.51 (ArC-H str), 2927.38, 2860.49 (C-H str), 1634.43, 1529.03, (ArC=C str), 1393.43 (CN str), 1113.53 (C-O-C str); MS/ESI: *m/z* [M+H, 100 %, 327].

2-(2,5-Dimethoxyphenyl)-4-phenylquinazoline (3h): Off white solid; yield: 81 %; m.p.: 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 6H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.47-7.52 (m, 3H), 7.85-7.90 (m, 3H), 8.19 (t, *J* = 7.6 Hz, 2H), 8.25 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 112.9, 126.5, 128.1, 128.6, 129.0, 129.8, 130.2, 130.3, 130.7, 133.2, 137.5, 152.2, 160.2, 161.8, 168.6; IR (KBr, ν_{max}, cm^{-1}): 3025.60 (ArC-H str), 2926.15, 2862.35 (C-H str), 1615.10, 1540.12, (ArC=C str), 1398.40 (CN str), 1115.25 (C-O-C str); MS/ESI: *m/z* [M+H, 100 %, 342].

4-(4-Chlorophenyl)-2-(4-methoxyphenyl)quinazoline (3i): Off white solid; yield: 62 %; m.p.: 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.51-7.58 (m, 3H), 7.82-7.86 (m, 3H), 8.03 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H); 8.63 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 113.8, 121.2, 126.6, 126.7, 128.8, 129.0, 130.2, 130.7, 131.5, 133.6, 136.2, 152.1, 160.0, 161.8, 166.9; IR (KBr, ν_{max}, cm^{-1}): 3042.28 (ArC-H str), 2927.26, 2860.28 (C-H str), 1633.38, 1538.14 (ArC=C str), 1392.54 (CN str), 1098.96 (C-O-C str), 816.76 (CCl str); MS/ESI: *m/z* [M+H, 100 %, 347].

4-(4-Chlorophenyl)-2-(*p*-tolyl)quinazoline (3j): Off white solid; yield: 77 %; m.p.: 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.53-7.58 (m, 3H), 7.82-7.87 (m, 3H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.56 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 121.3, 126.5, 126.9, 128.6, 128.8, 129.2, 129.3, 131.5, 133.6, 135.3, 136.1, 136.2, 140.8, 152.0, 160.3, 166.9; IR (KBr, ν_{max}, cm^{-1}): 3042.82, (ArC-H str), 2927.38, 2860.49 (CH str), 1643.43, 1525.12, 1497.26 (ArC=C str), 1393.43 (CN str), 812.00 (CCl str); MS/ESI: *m/z* [M+H, 100 %, 331].

2-(4-Chlorophenyl)-4-(4-methoxyphenyl)quinazoline (3k): Light yellow solid; yield: 71 %; m.p.: 155-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (s, 3H), 7.47-7.61 (m, 5H), 7.86-7.87 (m, 3H), 8.12 (d, *J* = 8.4 Hz, 2H), 8.64 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.7, 127.0, 127.2, 128.6, 128.7, 129.1, 130.0, 130.1, 130.2, 133.7, 136.7, 137.5,

151.9, 159.2, 168.4; IR (KBr, ν_{max}, cm^{-1}): 3038.46, 2927.207, (ArC-H str), 1634.90, 1507.49 (ArC=C str), 1399.81 (CN str), 831.03 (CCl str); MS/ESI: *m/z* [M+H, 100 %, 346].

2,4-*Bis*(4-chlorophenyl)quinazoline (3l): Yellow solid; yield: 64 %; m.p.: 191-193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.57-7.59 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.91 (t, *J* = 6.8 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.62 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.5, 126.6 127.4, 128.7, 128.9, 129.0, 129.2, 129.9, 131.5, 133.9, 135.9, 136.4, 136.5, 151.9, 159.2, 167.1; IR (KBr, ν_{max}, cm^{-1}): 3042.81, 2952.38, (ArC-H str), 1618.30, 1548.62, 1485.12 (ArC=C str), 1389.17 (CN str), 829.06 (CCl str); MS/ESI: *m/z* [M+H, 100 %, 352].

4-Phenyl-2-propylquinazoline (3m): White solid; yield: 58 %; m.p.: 101-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.6 Hz, 3H), 1.97-2.04 (m, 2H), 3.14 (t, *J* = 8.0 Hz, 2H), 7.50-7.57 (m, 4H), 7.75-7.77 (m, 2H), 7.86 (t, *J* = 8.0 Hz, 1H), 8.03-8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.4, 42.0, 121.2, 126.7, 127.0, 128.3, 128.6, 129.8, 129.9, 133.5, 137.5, 151.4, 167.1, 168.5; IR (KBr, ν_{max}, cm^{-1}): 3036.70, (ArC-H str), 2972.18, 2874.21 (CH str), 1617.40, 1537.19, 1483.73 (ArC=C str), 1399.72 (CN str); MS/ESI: *m/z* [M+H, 100 %, 249].

2-(4-Chlorophenyl)-4-(*p*-tolyl)quinazoline (3n): Yellow solid; yield: 69 %; m.p.: 155-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 7.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.87 (t, *J* = 8.4 Hz, 1H), 8.13 (t, *J* = 8.8 Hz, 9.2 Hz, 2H), 8.64 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 121.8, 127.1, 128.6, 128.7, 129.1, 129.3, 130.0, 130.2, 133.6, 134.8, 136.7, 136.8, 140.3, 151.9, 159.2, 168.4; IR (KBr, ν_{max}, cm^{-1}): 3042.81 (ArC-H str), 2952.38, 2875.46 (C-H str), 1612.15, 1526.45 (ArC=C str), 1378.12 (CN str), 825.78 (CCl str); MS/ESI: *m/z* [M+H, 100 %, 331].

Nutrient broth, nutrient agar and 5 mm diameter antibiotic assay were obtained from Hi-Media Laboratories Limited, India. Barium chloride dihydrate GR, concentrated sulphuric acid GR, dimethyl sulphoxide GR, sodium chloride AR and potassium dichromate were obtained from Ranbaxy Laboratories Ltd, Chemical Division, India. The standard bacterial and fungal strains were procured from National Centre from Cell Science (NCCS), Pune, India. The bacterial included two Gram-positive bacterial isolates *S. aureus* (+ve) and two Gram-negative bacterial isolates *Klebsiella* species and *Pseudomonas aeruginosa* NCCS 2200. The fungal organisms included were *Aspergillus nigeri* NCCS 1196 (AN) and *Candida albicans* NCCS 3471(CA). The bacteria were grown and maintained on nutrient agar (Hi-Media, Mumbai) and were subculture when needed.

Glass wares and apparatus: Glass petridish, glass tubes, beakers, Erlenmeyer flasks, bacterial loop and measuring cylinder were of borosilicate grade. Digital electronics balance (Shankar Scientific Supplies, India), Yorco Horizontal Laminar air flow bench (Yorco sales Pvt. Ltd, New Delhi, India), Ausco incubator, Zone reader (Cintex industrial Corporation, India), hot air oven, autoclave and UV/visible spectrophotometer (Shimadzu corporation, Japan).

Antimicrobial activity: The antibacterial activity of synthesized compounds was studied by the disc diffusion method [23,24] against the following pathogenic organisms. The Gram-positive bacterial screened were *S. aureus* (SA), the Gram-negative bacterial screened were *Klebsiella* species (KS) and *Pseudomonas aeruginosa* NCCS 2200 (PA). The synthesized compounds were used at the concentration of 250 and 500 µg/mL using DMSO as a solvent. The amoxicillin 10 µg/disc and streptomycin 30 µg/disc were used as a standard (Himedia Laboratories Limited, Mumbai).

Disc diffusion method [25,26]: A suspension of *Klebsiella* species (KS) was added to sterile nutrient agar at 45 °C. The mixture was transferred to sterile petridishes to give a depth of 3 to 4 mm and allowed to solidify. Precautions were observed to reduce uniform layer of medium on the plate. Sterile discs 5 mm in diameter (made from whatman filter paper) were immersed in the solutions of synthesized compounds (250 µg/mL) and maintain an untreated control sample for comparison. Leave the plates to stand for 1 h at room temperature as a period of preincubation diffusion to minimize the effects of variations in different time. Then the plates were incubated at 37 °C for 24 h and observed for antibacterial activity. The diameter of the zone of inhibition was measured for each plate in which the zone of inhibition was observed. The average zone of inhibition was calculated and compared with that of standard. A similar procedure was adopted for studying the antibacterial activity against the other organisms.

Antifungal activity: The antifungal activity of synthesized compounds were studied by disc diffusion method against the organisms of *Aspergillus niger* NCCS 1196 (AN) and *Candida albicans* NCCS 3471 (CA). Compounds were treated at the concentrations of 250 µg/mL using DMSO as a solvent. The standard used was ketaconazole 50 µg/mL and griseofulvin 50 µg/mL against both the organisms.

Disc diffusion method: A suspension of *Aspergills niger* NCCS 1196 (AN) was added to a sterile sabouraud dextrose agar at 45 °C. The mixture was transferred to sterile petridishes and allowed to solidify. Sterile discs 5 mm in diameter (made from whatmann filter paper) immersed in the solutions of synthesized compounds and control were placed on the surface of agar medium with forceps and pressed gently to ensure even contact. Leave the plates to stand for 1 h at room temperature as a period of preincubation diffusion to minimize the effects of variation at 37 °C for 13 h and observed for antibacterial activity. The diameters of the zone of inhibition were measured for the plates in which the zone of inhibition was observed. The average zone of inhibition was calculated with that of standard.

RESULTS AND DISCUSSION

The solution of quinazolin-4-ones (1 eq) in 1,4-Dioxane (3 mL) was treated with tosyl chloride (1.1 eq) and NaOEt (2.0 eq) at 70 °C. After 20 min, boronic acid (1.25 eq), $Pd(PPh_3)_4$ (0.05 eq), CuI (0.05 eq) and H_2O (0.5 mL) were added under air atmosphere. The reaction was completed within 2-4 h to afford the corresponding derivative novel quinazoline derivatives (**3a-3n**) in excellent yields as shown in the general **Scheme-I**. To optimize the reaction conditions, we have studied the role of the catalyst $Pd(PPh_3)_4$ using in different mole ratio. The observation shows that 5 % mole equivalent of $Pd(PPh_3)_4$ is sufficient for the completion of reaction. The structures of the

products were identified by their ^{1}H NMR, ^{13}C NMR, IR and mass spectral analysis.

The IR spectrum of the quinazoline derivatives (**3a-3n**) has given stretching vibration at 3010-3060 cm^{-1}, due to the stretching vibration corresponding to Ar-H stretching vibrations. The absorption peak at 2927 cm^{-1} is due to the stretching vibration corresponding to the sp^3 C-H (methyl group). The strong intensity absorption at 1393 cm^{-1} is due to the stretching vibration of C=N stretching in quinazoline, 812 cm^{-1} is due to the stretching vibration of C-Cl bond and 835 cm^{-1} is due to the stretching vibration of C-F bond. Band at 1116.6 cm^{-1} corresponding to C-O-C stretching. It has been observed from chemical structure of compounds **3a-3n** that different pair of protons. The protons of methyl group which is attached to benzene ring appeared as a singlet at $\delta = 2.4$ ppm, the protons of methoxy group appeared as a singlet at $\delta = 3.8$ ppm, the protons attached benzene ring appeared between $\delta = 7.2$-8.2 ppm respectively. The chemical shifts of the final compound carbon vary from $\delta = 175$-21 ppm. The carbon nucleus under the influence of a strong electronegative environment appeared down field, the carbon chemical shift of the methyl group at $\delta = 21.5$ ppm. The carbon chemical shift of the methoxy group at $\delta = 55.5$ ppm.

Biological activity: The results of biological studies of newly synthesized compounds (**8a-8k)** revealed that the compounds possess significant antibacterial and antifungal activities. Additionally the series of compounds were tested to ascertain their antibacterial, antifungal activity and are summarized in Table-1. From the assay it was evident that, some compounds from the series were found to be associated with promising antibacterial and antifungal properties. From antibacterial and antifungal activity screening results, it has been observed that compounds 3**b, 3e, 3i** and **3l** possess excellent activity. The compounds **3b, 3e** and **3l** exhibited best antibacterial activity against *P. aeruginosa* at 29, 26 and 26 mm, respectively. Further, compound **3i, 3e** and **3l** showed good antibacterial activity against *Klebsiella* species values of 28, 26 and 24 mm. Furthermore compounds **3i, 3l, 3g** and **3c** showed moderate *in vitro* antibacterial activity against Gram (+), Gram (-) bacteria (*S. aureus, Klebsiella* species, *P. aeruginosa*). Compounds **3l, 3g** and **3n** in the series show excellent antifungal activity against organism's *A. niger* 18, 16 and 16 mm and **3l, 3g** and **3n** active against *C. albicans* with 17, 16 and 11 mm values, respectively.

***in silico* Molecular properties investigation and prediction of drug-likeness:** Many potential drug candidates do not reach the clinics because of their poor absorption, distribution, metabolism, excretion and toxic liabilities (ADMET) [27]. Good oral bioavailability can be achieved by right balance between partitioning and solubilities. A computational structural sensitivity for predicting the important molecular properties such as hydrophobicity, molecular size, flexibility, toxic liabilities, bioactivity and drug likeness has been studied in order to obtain better analogues of quinazolines.

Molinspiration calculations: Lipinski's rule of five [28] which is generally used by pharmaceutical chemists for screening the potentiality of drug like candidates states that a molecule is orally active if the (i) molecular weight is under 500 da; (ii) calculated octanol/water partition coefficient (log P) ≤ 5; (iii) number of hydrogen bond acceptors ≤ 10; (d) number of hydrogen bond donors ≤ 5. The method used by molinspiration [29] is very robust and is based on the sum of fragment contributions and handles most of the organometallic and organic molecules. Present results (Table-2) indicate that the quinazoline derivatives **3a-3n** under study presented lipophilicities (log P) varied in the range of 0.94 to 2.21 suggesting their better permeability across cell membranes. Number of hydrogen bond acceptors and number of hydrogen bond donors in the products **3a-3n** were in accordance with the rule *i.e.*, less than 10 and 5 respectively. Hydrogen bonding is considered to be an important parameter for describing the permeability of drugs [30] number of rotable bonds (nrotb) is an important parameter for molecular flexibility and conformational change for binding to the receptors and should be in the range of ≤ 10 [31] and the compounds **3a-3n** under study exhibited nrotb

TABLE-1
ANTIMICROBIAL EVALUATION OF NOVEL COMPOUNDS (**3a-3n**);
DIAMETER OF ZONE OF INHIBITION (mm) AT CONCENTRATION OF 1.0 mg/50 µL

Compd. No.	Antibacterial activity			Antifungal activity	
	S. aureus (+ve)	*Klebsiella* species (-ve)	*P. aeruginosa* (-ve)	*A. niger*	*C. albicans*
3a	18 ± 0.3	16 ± 0.1	13 ± 0.2	11 ± 0.2	10 ± 0.1
3b	20 ± 0.1	17 ± 0.3	18 ± 0.1	08 ± 0.1	07 ± 0.3
3c	19 ± 0.4	21 ± 0.1	25 ± 0.3	19 ± 0.2	NZ
3d	19 ± 0.2	NZ	21 ± 0.1	14 ± 0.2	NZ
3e	22 ± 0.4	26 ± 0.1	26 ± 0.2	12 ± 0.4	10 ± 0.3
3f	18 ± 0.4	15 ± 0.4	NZ	15 ± 0.1	16 ± 0.1
3g	21 ± 0.3	22 ± 0.1	25 ± 0.2	16 ± 0.2	14 ± 0.4
3h	14 ± 0.1	21 ± 0.3	NZ	09 ± 0.3	08 ± 0.1
3i	26 ± 0.2	28 ± 0.1	29 ± 0.1	14 ± 0.2	10 ± 0.2
3j	15 ± 0.3	14 ± 0.2	NZ	11 ± 0.4	09 ± 0.2
3k	7 ± 0.4	17 ± 0.1	15 ± 0.2	12 ± 0.2	10 ± 0.3
3l	21 ± 0.1	24 ± 0.3	26 ± 0.3	18 ± 0.1	17 ± 0.1
3m	18 ± 0.1	22 ± 0.1	14 ± 0.4	NZ	NZ
3n	14 ± 0.2	12 ± 0.4	10 ± 0.2	16 ± 0.1	11 ± 0.4
Fluconazole	22 ± 0.1	20 ± 0.2	23 ± 0.3	NZ	NZ
Moxifloxacin	24 ± 0.3	31 ± 0.1	28 ± 0.2	NZ	NZ
Luliconazole	NZ	NZ	NZ	22 ± 0.2	25 ± 0.1

NZ: no zone of inhibition, Data are means (n = 3) ± Standard deviation of three replicates.

with in the said range. Molecular weights of all the quinazoline derivatives was found to be less than 500 and thus these molecules are anticipated to be easily transported, diffused and absorbed as compared to large molecules. Volume, percentage of absorption (%ABS), for the compounds **3a-3n** are presented in Table-2. Molecular polar surface area (PSA) contributed by the sum of polar atoms such as oxygen, nitrogen and attached hydrogens is calculated by Ertl *et al.* [32] methodology and is believed to be a very useful descriptor for drug absorption and transportation properties apart from intestinal absorption, bioavailability, human intestinal epithelial adenocarcinoma (Caco-2) cells permeability and blood-brain barrier (BBB) penetration. Percentage of absorption and is calculated by the expression: %ABS = 109-0.345*PSA. PSA and volume are inversely related to %ABS. PSA and log P are considered to be the two most important parameters for predicting oral bioavailability of a drug though not sufficient criteria [33] TPSA is very much correlated with the hydrogen bonding of a molecule and is associated with the transport properties of drug across the membranes, prediction in the BBB and intestinal crossing. Molecules with TPSA/PSA in the range ≤ 160 $Å^2$ have good intestinal absorption and ≤ 60 $Å^2$ has BBB penetration [34]. For the analyzed series all the derivatives have come out to be best intestinal absorbers. Compounds **3a-3n** obeyed the rule of five suggesting their drug likeness. The bioactivity scores of the synthesized analogues for drug targets were also predicted by molinspiration and are presented in Table-3 by means of numerical assignment. A molecule having bioactivity score more than 0.00 is most likely to exhibit considerable biological activities, while values -0.50 to 0.00 are excepted to be moderately active and if score is less than -0.50 it is presumed to be inactive.

Conclusion

All these reactions are easy to carry out giving high yield. An efficient route to 4-arylquinazolines *via* arylation of quinazolin-4-ones under mild condition is described. The reaction is carried out by the palladium catalyzed coupling of quinazolin-4-ones with aryl boronic acids in the presence of TsCl leading to 4-arylquinazolines in good to excellent yields. From antibacterial and antifungal activity screening results, it has been observed that compounds **3b, 3e, 3i** and **3l** possess excellent activity against Gram (+), Gram (-) bacteria (*S. aureus, Klebsiella* species, *P. aeruginosa*) compared to standard drugs. **3l, 3g**

TABLE-2
MOLINSPIRATION CALCULATIONS OF TARGET COMPOUNDS (**3a-3n**)

Compd.	milog P	TPSA	Abs (%)	N atoms	MW	nON	nOHNH	N violations	Nrotb	Volume
3a	5.83	35.02	96.9181	25	326.40	3	0	1	3	304.65
3b	6.00	25.78	100.1059	23	316.79	2	0	1	2	276.08
3c	5.38	35.02	96.9181	24	312.37	3	0	1	3	288.08
3d	5.33	25.78	100.1059	22	282.35	2	0	1	2	262.54
3e	5.77	25.78	100.1059	23	296.37	2	0	1	2	279.10
3f	4.96	53.49	90.5459	28	372.42	5	0	0	5	339.18
3g	5.83	35.02	96.9181	25	326.40	3	0	1	3	304.65
3h	5.37	44.25	93.7337	26	342.40	4	0	1	4	313.63
3i	6.06	35.02	96.9181	25	346.82	3	0	1	3	301.62
3j	6.45	25.78	100.1059	24	330.82	2	0	1	2	292.64
3k	6.06	35.02	96.9181	25	346.82	3	0	1	3	301.62
3l	6.68	25.78	100.1059	24	351.24	2	0	1	2	289.61
3m	4.37	25.78	100.1059	19	248.33	2	0	0	3	241.30
3n	6.45	25.78	100.1059	24	330.82	2	0	1	2	292.64
Fluconazole	-0.12	81.66	80.8273	22	306.28	7	1	0	5	248.96
Moxifloxacin	-0.70	74.57	83.27335	24	331.35	6	2	0	3	285.46

TABLE-3
BIOACTIVITY SCORES FOR THE DESIGNED MOLECULES **3a-3n**

Entry	GPCRL	ICM	KI	NRL	PI	EI	HBA	HBD	Drug-likeness
3a	0.04	-0.30	0.13	0.10	-0.35	0.04	3	0	0.12
3b	0.14	-0.17	0.21	0.13	-0.33	0.13	2	0	-0.11
3c	0.09	-0.24	0.18	0.14	-0.31	0.10	3	0	0.27
3d	0.13	-0.17	0.23	0.14	-0.32	0.17	2	0	-0.38
3e	0.09	-0.24	0.18	0.12	-0.34	0.10	2	0	-0.11
3f	0.05	-0.22	0.20	0.03	-0.31	0.10	5	0	0.19
3g	0.04	-0.30	0.13	0.10	-0.35	0.04	3	0	0.12
3h	0.07	-0.25	0.17	0.14	-0.30	0.14	4	0	-0.03
3i	0.08	-0.24	0.15	0.11	-0.34	0.06	3	0	0.51
3j	0.09	-0.24	0.15	0.10	-0.36	0.06	2	0	0.14
3k	0.08	-0.24	0.15	0.11	-0.34	0.06	3	0	0.51
3l	0.14	-0.16	0.21	0.13	-0.29	0.12	2	0	0.17
3m	0.14	0.01	0.06	0.08	-0.50	0.21	2	0	0.26
3n	0.09	-0.24	0.15	0.10	-0.36	0.06	2	0	0.14
Fluconazole	0.04	0.01	-0.09	-0.23	-0.09	0.03	6	1	0.68
Moxifloxacin	0.12	-0.04	-0.07	-0.19	-0.21	0.28	4	2	0.93

and **3n** showed better antifungal activity against *A. niger*, *C. albicans* organism's. Moreover, the target compounds **3a-3n** were subjected to *in silico* molecular properties prediction and better drug likeness score (0.27) by employing Molinspiration and MolSoft property explorer toolkits for predicting their high oral bioavailability.

ACKNOWLEDGEMENTS

One of the authors, Eswararao SV, is thankful to Sreeni Labs Pvt. Ltd. Hyderabad, India for constant encouragement and thankful to Dr. Sreenivasareddy Mundla for this support.

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