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SYNTHESIS, CHARACTERIZATION OF NOVEL QUINAZOLINE DERIVATIVES AND ANTIMICROBIAL SCREENING

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ABSTRACT

A novel series of compounds were synthesised by C-C bond formation of substituted quinazolinones **(1)** with substituted boronic acids **(2)** to get 2,4-disubstituted quinazoline **(3a-3j)** target compounds under mild conditions with good yields. The structures of new compounds were confirmed by IR and ^{1}H NMR and ^{13}C NMR spectral data.

Key words: Quinazolines, Synthesis, Spectral data, Heterocycles.

INTRODUCTION

Hetero cyclic chemistry is a very important branch of organic chemistry accounting for nearly one-third of modern publications. In fact, two thirds of organic compounds are heterocyclic compounds. Heterocyclic chemistry comprises at least half of all organic chemistry research world wide.

Heterocyclic chemistry is the largest classical division of medicinal chemistry and display a broad range of industrial and pharmaceutical applications. Quinazoline (Fig. 1) is a compound made up of two fused six member simple aromatic rings-benzene and pyrimidine rings. It is a yellow coloured compound, found usually in crystalline form. Medicinally, it is used as antimalarial agent. It was first prepared by Gabriel in 1903 and first isolated from the Chinese plant aseru. The development of research on biological activity of quinazoline compounds started, when the compound 2-methyl-1,3-aryl-4-quinazoline derivative was synthesized. This compound has soporific and sedative action. In last 10 to 15 years of research, medicines have been characterized by significant advances. In 1968, only two

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derivatives were used, soporific and anticonvulsant-methaqualone and diuretic quinathazone. By 1980, about 50 kinds of derivatives of this class includes medicines with different biological actions like soporific, sedative, tranquilizing, analgesic, anticonvulsant, antitussive, myorelexant, antirheumatic, hypotensive, anti-allergic, bronchodilating, anti-diabetic, cholagogue, diuretic, cystatic, antimalarial, spermicidal, etc. The search for substances of cardiovascular agents begun in quinazoline derivatives after pharmacological screening of hypotensive activity of quinazoline that have a glycine amide or β-alanine amide residue in 3rd position. But unfortunately due to volume and density of general material on quinazoline derivatives, more specific problem of investigation of cardiovascular agents not has been successfully reflected in some reviews.

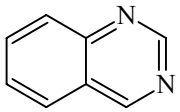


Fig. 1: Quinazoline

Quinazoline derivatives, which 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[1-4], antiinflammation[5,6], antibacterial[7-10], antivirus[11], anti cytotoxin[12], antispasm[13], antituberculosis[14], anti oxidation[15], anti-malarial[16], anti-hypertension[17], anti-obesity[18], antipsychotic[19], anti diabetes[20], etc.

Encouraged by the diverse biological activities of quinazoline heterocyclic compounds, it was decided to prepare a new series of quinazoline derivatives.

The synthetic route was depicted in **Scheme 1**.

The structures of all 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.

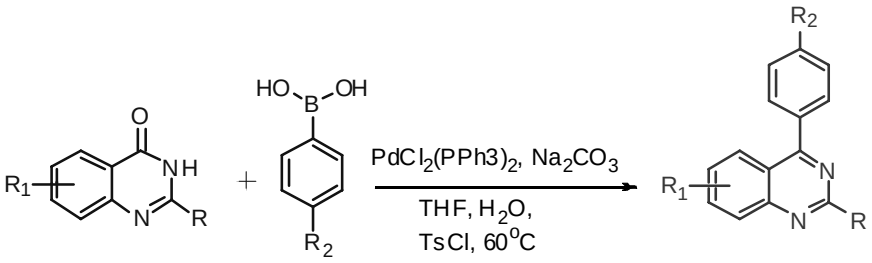
EXPERIMENTAL

Materials and methods

In this investigation, chemicals were purchased from local dealer with S.D. fine make. 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 **3(a-j)**.

The title compounds **3(a-j)** were synthesised in single step using different reagents and reaction conditions, these were obtained in moderate yields. The structures were established by spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) and analytical data.



(1) **(2)** **3(a-j)**

Scheme 1

All 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 solvents were reagent grade. THF was distilled from sodium benzophenoneketyl 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 BrukerAvance spectrometer at 400.1 and 100.6 MHz, for ^{1}H for ^{13}C, respectively, in $CDCl_3$ solution with tetramethylsilane 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 tetramethylsilane (TMS) in the solvent of $CDCl_3$-d 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).

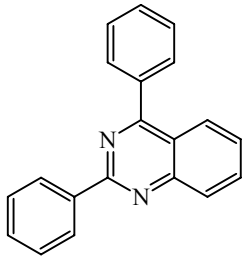
Synthesis of 2, 4-disubstituted quinazolines (3a-j)

The solution of quinazolin-4-ones (1 equiv) in THF (2 mL) was treated with tosyl chloride (1.2 equiv) and Na_2CO_3 (2.5 equiv) at 60^{o}C. After 30 minutes, boronic acid (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv. 5 mol%), and H_2O (0.1 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-j)**.

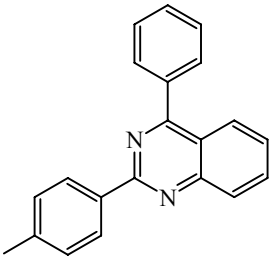
2, 4-Diphenylquinazoline (3a)

Compound **(3a)** was obtained as a white solid; Yield: 80%, mp. 122-123^{o}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, 8.0Hz, 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.



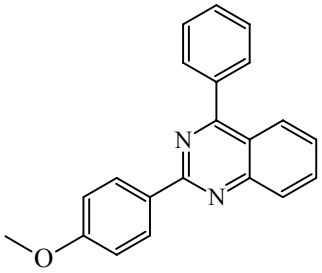
4-Phenyl-2-p-tolyl-quinazoline (3b)

Compound 3b was obtained as a white solid; yield: 88%; mp. 123-124^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.38 (d, J = 7.6 Hz, 2H), 7.48-7.53 (m, 4H), 7.79 (d, J = 8.0 Hz, 2H), 7.83-7.87 (m, 1H), 8.13 (d, J = 8.8 Hz, 1H), 8.69 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 121.7, 126.8, 127.1, 128.5, 128.7, 129.1, 129.3, 130.2, 130.5, 133.4, 134.9, 138.3, 140.2, 152.0, 160.2, 168.3.



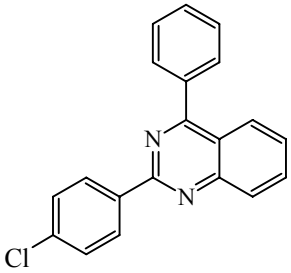
2-(4-Methoxyphenyl)-4-phenyl-quinazoline (3c)

Compound **(3c)** was obtained as a white solid; yield: 90%; mp. 141-142^{0}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.



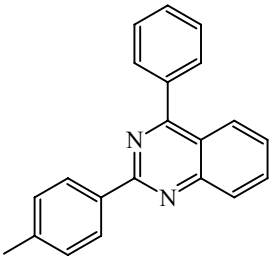
2-(4-Chlorophenyl)-4-phenyl-quinazoline (3d)

Compound **(3d)** was obtained as a white solid; yield: 75%, mp. 139-140^{0}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, $CDCl_3$) δ121.5, 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.



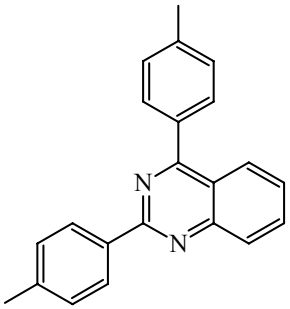
4-Phenyl-2-p-tolyl-quinazoline (3e)

Compound **(3e)** was obtained as a white solid; yield: 83%; mp 189-190^{0}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}CNMR (100 MHz, $CDCl_3$) δ21.6, 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.



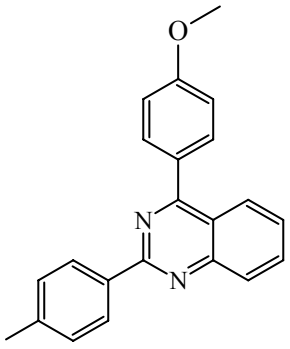
2, 4-Di-p-tolyl-quinazoline (3f)

Compound **(3f)** was obtained as a white solid; yield: 80%, mp. 139-140ć. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.48 (s, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.6 Hz, 2H), 7.50 (dd, J = 7.2, 8.4 Hz, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.84 (dd, J = 6.8, 8.4 Hz, 1H), 8.11 (d, J = 8.8 Hz, 2H), 8.58 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ21.5, 21.6, 121.6, 126.7, 127.1, 128.6, 129.0, 129.2, 129.3, 130.2, 133.3, 134.9, 135.6, 140.1, 140.6, 152.0, 160.3, 168.2.



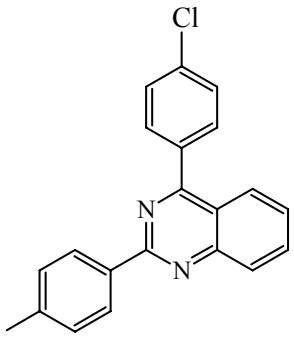
4-(4-Methoxyphenyl)-2-p-tolyl-quinazoline (3g)

Compound **(3g)** was obtained as aoff white solid; yield: 88%; mp. 153-155^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.90 (s, 3H), 7.10 (d, J = 8.4Hz, 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.



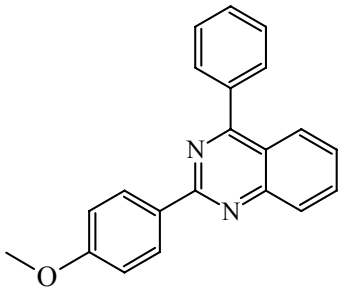
4-(4-Chlorophenyl)-2-p-tolyl-quinazoline (3h)

Compound **(3h)** was obtained as aoff white solid; yield: 78%; mp. 150-151°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.



2-(4-Methoxyphenyl)-4-phenyl-quinazoline (3i)

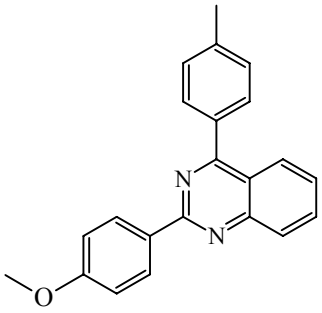
Compound **(3i)** was obtained as a off white solid; yield: 82%; mp 165-166^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.03 (d, J = 8.8 Hz, 2H), 7.49 (t, J = 8.0 Hz, 1H), 7.57-7.59 (m, 3H), 7.82-7.88 (m, 3H), 8.09 (t, J = 7.6 Hz, 2H), 8.65 (d, J = 8.8 Hz, 2H); ^{13}CNMR (100 MHz, $CDCl_3$) δ55.4, 113.8, 121.4, 126.5, 127.0, 128.5, 128.9, 129.8, 130.2, 130.3, 130.9, 133.4, 137.8, 152.1, 160.0, 161.7, 168.1.



2-(4-Methoxyphenyl)-4-p-tolyl-quinazoline (3j)

Compound **(3j)** was obtained as a off white solid; yield: 82%; mp. 110-111^{0}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.



Biological activity

Antibacterial activity

For antimicrobial screening, the samples of synthesized compounds **(3a-j)** for antimicrobial activity were prepared at concentration 40 μg/mL in DMSO solvent. In case of antibacterial activity, the plates were incubated at 37°C for 24 hours and for antifungal activity the plates were incubated at 30°C for 48 hours. The antibacterial activity was checked against Gram positive bacteria *Staphylococcus aureus* (*S. aureus*) and *Bacillus subtilis* (*B. subtilis*), Gram negative bacteria *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Escherichia coli* (*E. coli*). The antifungal activity was checked against fungi *Aspergillus niger* (*A. niger*) and *Candida albicans* (*C. albicans*). The results were compared with standard drugs Sparfloxacin, Benzyl penicillin and Fluconazole. The quinazoline derivates containing core structure with flouro and methyl (3 g) and –F (3 h) showed more activity than other substituent's 3g > 3h > 3i > 3j > 3f > 3d > 3b > 3a > 3c > 3e.

Table 4: *In vitro* antibacterial and antifungal activities of the synthesized compounds (3a-j)

Compound	Anti-bacterial activity (Zone if inhibition in mm)		Anti-fungal activity (Zone if inhibition in mm)			
	S. aureus	***B. subtilis***	***P. aeruginosa***	***E. coli***	***A. niger***	***C. albicans***
3a	12	11	07	11	23	19
3b	12	16	10	14	09	12

Cont…

Compound	Anti-bacterial activity (Zone if inhibition in mm)		Anti-fungal activity (Zone if inhibition in mm)			
	S. aureus	***B. subtilis***	***P. aeruginosa***	***E. coli***	***A. niger***	***C. albicans***
3c	10	28	17	21	14	12
3d	13	17	30	13	11	18
3e	10	19	09	09	12	16
3f	16	12	13	11	10	18
3g	23	13	18	15	18	10
3h	19	10	12	11	17	15
3i	18	16	08	08	17	09
3j	16	12	13	11	10	18
Sparfloxacin	**24**	**25**	**25**	**22**	**---**	**---**
Benzyl penicillin	**18**	**17**	**16**	**16**	**---**	**---**
Fluconazole	**---**	**---**	**---**	**---**	**22**	**20**

RESULTS AND DISCUSSION

Quinazolin-4-ones (1 equiv) in THF (2 mL) was treated with tosyl chloride (1.2 equiv) and Na_2CO_3 (2.5 equiv) at 60^oC. After 30 minutes, boronic acid (1.2 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv. 5 mol%), and H_2O (0.1 mL) were added under air atmosphere. The reaction was completed within 2-4 hrs to afford the corresponding derivative novel quinazoline derivatives **(3a-j)** in excellent yields as shown in the general Scheme 1. To optimize the reaction conditions, the role of the catalyst $Pd(PPh_3)_2Cl_2$ was studied using in different mole ratio. The observation shows that 5% mole equivalent of $Pd(PPh_3)_2Cl_2$ is sufficient for the completion of reaction. The structures of the products were identified by their ^1H & ^{13}C NMR, IR and mass spectral analysis.

CONCLUSION

All these reactions are very 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 arylboronic acids in the presence of TsCl leading to 4-arylquinazolines in good to excellent yields.

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