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ONE-POT MEDIATED SYNTHESIS OF PYRIMIDINE AND QUINAZOLINE ANNULATED DERIVATIVES OF NITROGEN CONTAINING FIVE MEMBERED RINGS THROUGH THEIR NITRILE DERIVATIVES AS ANTIBACTERIAL AGENTS

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ABSTRACT. Novel five-membered ring (pyrrole, pyrazole and imidazole)-based pyrimidine and quinazoline derivatives were synthesized by one-pot domino approach. This approach has the advantages of high yield, mild reaction conditions and a simple work-up procedure. The structure of the synthesized compound was elucidated by spectroscopy technique and elemental analysis. The synthesized compound were examined for antimicrobial activity against four bacteria (*E. coli*, *S. pyogenes*, *S. aureus*, and *P. aeruginosa*) and two fungi (*C. albicans* and *A. clavatus*) and most of the synthesized compound exhibited moderate to good activity against reference drug ampicillin, ciprofloxacin, norfloxacin, gentamycin, nystatin and griseofulvin, respectively.

KEY WORDS: One-pot, Pyrrole, Pyrazole, Imidazole, Pyrimidine, Quinazoline, Antimicrobial activity

INTRODUCTION

Green methods play a crucial role in synthetic organic chemistry and are thought to be a significant engine of transformation without affecting the environment. The one-pot green approach incorporated distinct features within the "Twelve Principles of Green Chemistry", including simple operation, short reaction time, mild reaction condition and high yield. The one-pot reaction is atom economic, time saving and most notably does not require purification at each step to afford high regio- and stereoselective products. Thus, one-pot strategy has been considered as best method for the preparation of heterocyclic compounds and gaining enormous attention of synthetic organic chemists owing to their eco-friendliness, shorter reaction time, improved selectivity and superior work-up procedures.

Several research articles on the application of one-pot domino approach in chemical synthesis have been published. The one-pot multicomponent reaction is a more pronounced approach for the synthesis of pyrimidine and quinazoline derivatives [1-3].

The ubiquitous presence of heterocyclic systems containing one, two, three and four nitrogen atoms in five-membered ring viz; pyrrole [4-8], pyrazole [9-12], imidazole [13-18], etc. and the privileged systems containing two nitrogen atoms in a six-membered rings viz. pyrimidine [19-25], quinazoline [26-28], in the chemical literature is undoubtedly a result of the diverse biological response that they elicit in combating a wide range of body ailments. Pyrimidine and quinazoline are considered as "privileged structures" in therapeutic chemistry because these nucleus display a vast range of biological activities [29-34].

In COVID-19 scenario, the requirement of new antifungal, antibacterial and immunity-boosting synthetic molecules has been increased throughout the world. The present paper focuses on the incorporation of five membered nitrogen containing heterocyclic motifs (pyrrole, pyrazole, imidazole) onto the privileged pyrimidine and quinazoline nucleus linked to each other through a

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phenyl bridge for their better medicinal utility. The goal is to develop new antibacterial agents with a therapeutic profile and fewer antibacterial resistance tendencies [35-39].

EXPERIMENTAL

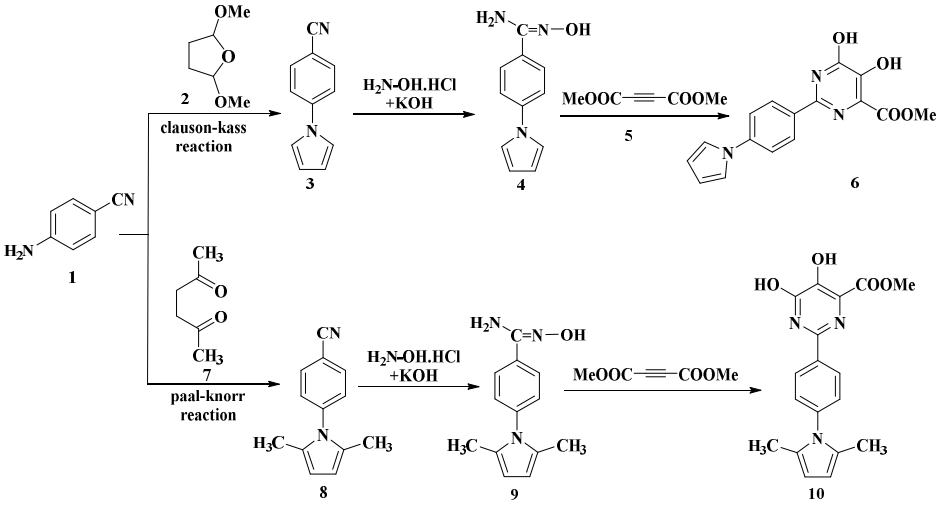
Materials and methods

Chemicals. All high purity reagents, solvents and chemicals were purchased from Sigma Aldrich and TCI (India). The reaction was routinely examined by thin layer chromatography (TLC) on silica pre-coated plates with gradient of solvents. For column chromatography SiO_2 with mesh size 60-120 were used.

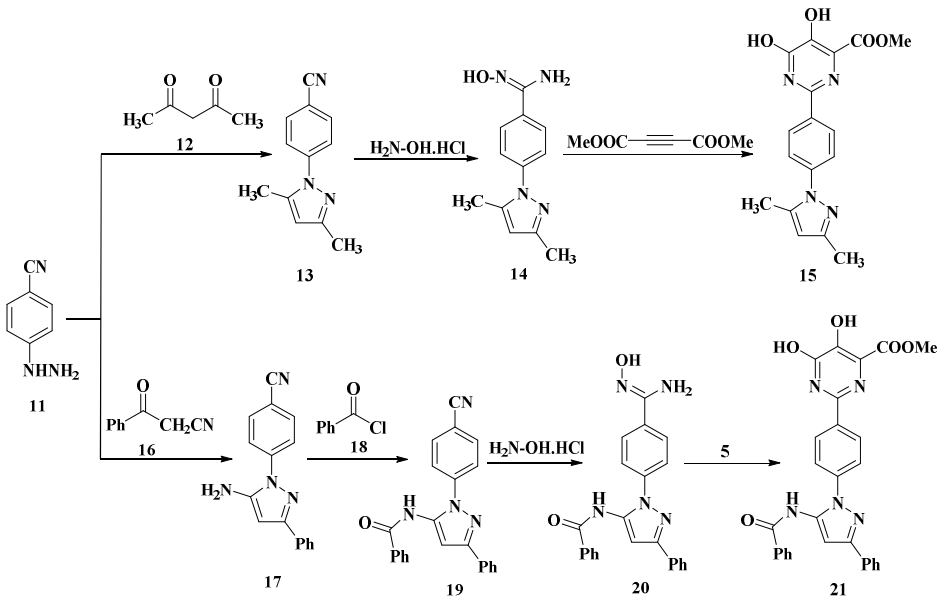
Instrument. The compound melting points were recorded by Buchi melting apparatus. The structure of compounds were confirmed by ^{1}H NMR, ^{13}C NMR by Bruker magnetic spectrometer using 400-MHz. Deuterated solvents were used for analysing the sample, tetramethylsilane was taken as an internal standard and chemical shifts were calculated in ppm. The Agilent carry 660 FTIR spectrophotometer is used to record the IR spectra of neat samples. Mass spectra were recorded on a mass spectrometer using argon/xenon gas by fast atom bombardment (FAB) method.

Synthesis

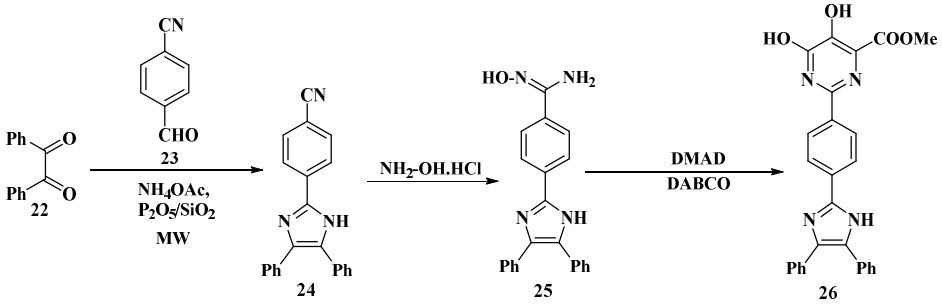
The synthesis of the targeted compound was depicted in Schemes 1-4.



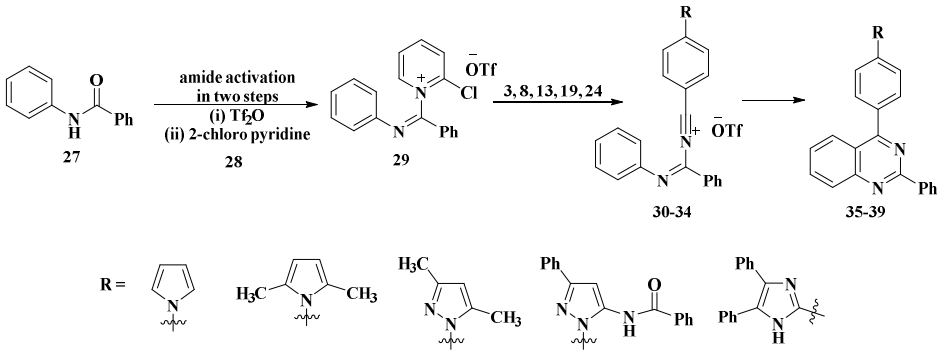
Scheme 1. Synthesis of pyrimidine derivative linked with pyrrole nucleus.



Scheme 2. Synthesis of pyrimidine derivatives linked with pyrazole nucleus.



Scheme 3. Synthesis of pyrimidine derivatives linked with imidazole nucleus.



Scheme 4. Synthesis of pyrrole, pyrazole, imidazole bearing diphenyl-quinazoline derivatives from *N*-phenylbenzamide.

*Synthesis of 4-(1H-pyrrol-1-yl) benzonitrile (**3**)*

4-Aminobenzonitrile (1.8 g, 0.015 mol) was mixed with 2,5-dimethoxytetrahydrofuran (0.99 g, 0.0075 mol) in glacial acetic acid further it was heated to reflux for 2 h at 120 ºC. Completion of reaction mixture was checked by TLC (Hex:EtOH/6:4), after reaction completion acetic acid was distilled and the desired crude was purified by silica column chromatography (15-20% ethylacetate in hexane) to give pure compound 4-(1*H*-pyrrol-1-yl)benzonitrile **3**.

Molecular formula $C_{11}H_8N_2$, yield: 78%, m.p.: 98 °C. IR (KBr, ν/cm^{-1}): 3010, 2918, 2212, 1174. ^{1}H NMR (δ, ppm in DMSO-d$_6$): 7.72 (d, J = 7.3 Hz, 2H), 7.64 (dd, J = 6.5Hz, 2H), 7.55 (dd, J = 6.5 Hz, 2H), 6.36 (d, J = 7.3 Hz, 2H). ^{13}C NMR (δ, ppm in DMSO d$_6$): 140.79, 130.17, 130.15, 121.89, 121.87, 119.12, 118.15, 112.94, 112.45, 112.42. HRMS (ESI) m/z: [M$^+$] calcd for $C_{11}H_8N_2$ 168.1990; found 168.1984. Elemental analysis (calcd/found): C (78.55/78.45); H (4.79/4.75); N (16.66/16.64).

*Synthesis of N-hydroxy-4-(pyrrol-1-yl)benzimidamide (**4**)*

Potassium hydroxide (0.196 g, 0.0035 mol) was added to hydroxyl amine hydrochloride (0.243 g, 0.0034 mol) in distilled water to break the hydrochloride salt. This solution was added to 4-(1*H*-pyrrol-1-yl)benzonitrile (1.2 g, 0.0071 mol) (**3**) in ethanol and the reaction mass was subjected to reflux at 100 ºC for 2 h. The completion of reaction mixture was checked by TLC (Hex:EtOH/8:2). The reaction mass was cooled to RT (Room temperature), then extracted with ethylacetate (3 x 10 mL), combined organic layer was dried with anhydrous magnesium sulfate and concentrated under vaccum to obtain crude product which was purified by flash column chromatography (15-17% ethylaceate in hexane) to yield *N*'-hydroxy-4-(1*H*-pyrrol-1-yl)benzimidamide **4**.

Molecular formula $C_{11}H_{11}N_3O$, yield: 70%, m.p.: 159 °C. IR (KBr, ν/cm^{-1}): 3400, 3332, 1690, 2918, 2212, 1174. ^{1}H NMR (δ, ppm in DMSO-d$_6$): 10.58 (s, 1H), 7.48 (d, J = 6.3 Hz 2H), 7.26 (d, J = 6.73 Hz 2H), 6.33 (d, J = 6.2 Hz, 2H), 6.28 (d, J = 6.4 Hz, 2H), 4.96 (s, 2H). ^{13}C NMR (δ, ppm in DMSO d$_6$): 151.01, 140.71, 125.26, 124.37, 124.33, 122.61, 118.17, 118.15, 112.43, 112.42. HRMS (ESI) m/z: [M$^+$] calcd for $C_{11}H_{11}N_3O$ 201.2290; found 201.2286. Elemental analysis (calcd/found): C (65.66/65.54); H (5.51/5.45); N (20.88/20.84).

*Synthesis of methyl 2-4-pyrrol-1-phenyl-5,6-dihydroxy pyrimidine-4-carboxylate (**6**)*

Amidoxime (**4**) (1.1 g, 0.0054 mol) and dimethylacetylenedicarboxylate (0.7 g, 0.0054 mol) was refluxed in chloroform and then in acidic medium for 14 h, the reaction completion was checked

by TLC (Hex:EtOH/5:5). The solvent chloroform was completely distilled off under vacuo to obtained brown oil, in which xylene was added dropwise and stirred the reaction mass for 16 h at 100 ºC after the reaction completion. Brown colored solid was found in the reaction which were recrystallize with xylene followed by hexane and then dried to obtain pyrrole linked pyrimidine derivatives **6.**

Molecular formula $C_{16}H_{13}N_3O_4$, yield: 22%, m.p.: 154 °C. IR (KBr, ν/cm^{-1}): 3610, 2945, 2253, 1739, 1700. ^{1}H NMR (δ, ppm in DMSO-d_6): 10.28 (s, 1H), 9.25 (s, 1H), 7.77 (d, J = 7.3 Hz, 2H), 7.64 (d, J = 6.9 Hz, 2H), 7.28 (d, J = 6.1 Hz, 2H), 6.33 (d, J = 7.1 Hz, 2H), 3.95 (s, 3H). ^{13}C NMR (δ, ppm in DMSO-d_6): 171.06, 158.30, 154.19, 144.92, 144.57, 141.85, 139.18, 128.17, 128.16, 120.57, 120.56, 118.14, 118.13, 112.43, 112.42, 52.08. HRMS (ESI) m/z: [M$^+$] calcd for $C_{16}H_{13}N_3O_4$ 311.2970; found 311.2967. Elemental analysis (calcd/found): C (61.73/61.69); H (4.21/4.20); N (13.50/13.45).

*Synthesis of 2,5-dimethyl-1-pyrrolyl benzonitrile (**8**)*

4-Amino benzonitrile (1.2 g, 0.0101 mol) was mixed in 50 mL methanol at RT, 2,5-hexanedione (**7**) (2.29 g, 0.02 mol) was added slowly via syringe in the reaction mass, and was stirred for 24 h at RT under acidic condition. Reaction was monitored with TLC plates (Hex:EtOH/8:2). The reaction mixture was extracted with H_2O and ethyl acetate, dried with sodium sulphate, purified by column chromatography (5-8% methanol in DCM) and finally 2,5-dimethyl-1-pyrrolyl benzonitriles was obtained **8**.

Molecular formula $C_{13}H_{12}N_2$, yield: 82%, m.p.: 107 °C. IR (KBr, ν/cm^{-1}): 3012, 2913, 2220, 1218. ^{1}H NMR (δ, ppm in DMSO-d_6): 7.73 (d, J = 7.4 Hz, 4H), 7.64(d, J = 6.3 Hz, 2H), 5.98 (s, 2H), 2.14 (s, 6H). ^{13}C NMR (δ, ppm in DMSO-d_6): 141.50, 130.95, 124.72, 124.71, 124.49, 124.47, 109.23, 109.22, 107.98, 12.41, 12.40. HRMS (ESI) m/z: [M$^+$] calcd for $C_{10}H_9N_3$ 196.2530; found 196.2525. Elemental analysis (calcd/found): C (79.56/79.45); H (6.16/6.12); N (14.27/14.19).

*Synthesis of 2,5-dimethyl-1H-pyrrolyl-hydroxybenzimidamide (**9**)*

Equimolar quantity of potassium hydroxide (0.81 g, 0.01446 mol) and hydroxyl amine hydrochloride (0.98 g, 0.0141 mol) were added in 25 mL of H_2O, this solution was added to the nitrile substrate (**8**) in 25 mL ethanol to ambient temperature. The completion of reaction was checked by TLC (Hex:EtOH/6:4) and reaction mixture was distilled off under *vaccuo* to obtained white solid. Purification was done by crystallization method using chloroform and hexane to achieve 2,5-dimethyl-1*H*-pyrrolyl-hydroxybenzimidamide **9**.

Molecular formula $C_{13}H_{15}N_3O$, yield: 75%, m.p.: 189 °C. IR (KBr, ν/cm^{-1}): 3421, 3179 2358, 1690, 1331. ^{1}H NMR (δ, ppm in $CDCl_3$): 11.09 (s, 1H), 7.95 (d, J = 7.1 Hz, 2H), 7.59 (d, J = 6.3 Hz, 2H), 6.90 (s, 2H), 5.84 (s, 2H), 2.01(s, 6H). ^{13}C NMR (δ, ppm in DMSO-d_6): 151.01, 140.50, 127.90, 125.50, 125.45, 124.49, 109.23, 109.22, 12.41. HRMS (ESI) m/z: [M$^+$] calcd for $C_{13}H_{15}N_3O$ 229.2830; found 229.2825. Elemental analysis (calcd/found): C (68.10/68.05); H (6.59/6.52); N (18.33/18.25).

*Synthesis of methyl 2,5-dimethyl-1H-pyrrol-5,6-dihydroxypyrimidine-4-carboxylate (**10**)*

Amidoxime (0.5 g, 0.0021 mol), dimethylacetylenedicarboxylate (0.782 g, 0.0055 mol) and DABCO catalyst (0.03 g, 0.00035 mol), were dissolved in chloroform and refluxed at 60-65 ºC for 1 h and the reaction completion was monitored by TLC (Hex:EtOH/5:5). After the completion of reaction, the chloroform was evaporated under vacuum till brown color oil was obtained. To this oil addition of 20 mL xylene and then the reaction is refluxed at 140-145 ºC for 10 h. Solids were obtained further filtered and washed with xylene followed by purification with column

chromatography (10-15% ethylacetate in hexane) to obtain brown coloured solid methyl 2,5-dimethyl-1*H*-pyrrolyl-5,6-dihydroxypyrimidine-4-carboxylate **10** in very low yield.

Molecular formula $C_{18}H_{17}N_3O_4$, yield: 17%, m.p.: 211 °C. IR (KBr, ν/cm^{-1}): 3559, 2309, 1744, 1733, 1210. ^{1}H NMR (*δ*, ppm in DMSO-d_6): 15.28 (s, 1H), 12.28 (s, 1H), 8.57 (d, *J* = 6.3 Hz, 2H), 7.19 (d, *J* = 6.4 Hz, 2H), 6.28 (d, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.16 (s, 6H). ^{13}C NMR (δ, ppm in DMSOd_6): 171.06, 158.30, 144.92, 144.57, 144.13, 134.91, 131.09, 124.49, 123.70, 109.23, 52.08, 12.41. HRMS (ESI) m/z: [M$^+$] calcd for $C_{18}H_{17}N_3O_4$, 339.3510; found 339.3506. Elemental analysis (calcd/found): C (63.71/63.65); H (5.05/5.00); N (12.38/12.31).

*Synthesis of 3,5-dimethyl-1-H-pyrazolyl benzonitrile (**13**)*

4-Cyano phenylhydrazine (1.6 g, 0.01201 mol) **11** was mixed with acetyl acetone (1.5 g, 0.0149 mol) **12** in ethanol and methane sulfonic acid was added in catalytic amount to the reaction mixture, further it was condensed at 90 °C for 2 h. The reaction completion was checked by thin layer chromatography (Hex:EtOH/7:3). After completion of reaction, ethanol was distilled under attenuated pressure and the crude product was purified by column chromatography (24-27% ethylacetate in hexane).

Molecular formula $C_{12}H_{11}N_3$, yield: 85%, m.p.: 102 °C. IR (KBr, ν/cm^{-1}): 2265, 1690, 1654, 1506, 1361. ^{1}H NMR (*δ*, ppm in DMSO): 7.79 (d, *J* = 6.4Hz, 2H), 7.60 (d, *J* = 7.2Hz, 2H), 6.06 (s, 1H), 2.24 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (δ, ppm in DMSO): 150.68, 143.55, 139.85, 133.28, 124.10, 118.57, 110.20, 109.09, 13.65, 13.13. HRMS (ESI) m/z: [M$^+$] calcd for $C_{12}H_{11}N_3$ 197.2410; found 197.2404. Elemental analysis (calcd/found): C (73.07/73.01); H (5.62/5.59); N (21.30/21.28).

*Synthesis of 4-(3,5-dimethyl-1-pyrazolyl)-hydroxybenzimidamide (**14**)*

Potassium hydroxide (2 g, 0.023 mol) was mixed to hydroxyl amine hydrochloride (1.62 g, 0.023 mol) in distilled water to break the hydrochloride salt. This solution was added to **13** (2 g, 0.010 mol) in ethanol and the reaction was subjected to reflux at 100 °C for 2 h. The reaction completion was monitored by TLC with mobile phase (Hex:EtOH/7:3), After the reaction completion, reaction mass was cooled to RT, extracted with ethyl acetate and chloroform, dried with sodium sulfate. The excess solvent was evaporated by rotatory evaporator and purified by column chromatography (17-20% ethylaceate in hexane) to give pure compound **14**.

Molecular formula $C_{12}H_{14}N_4O$, yield: 70%, m.p.: 173 °C. IR (KBr, *ν*/cm^{-1}): 3557, 3345, 2123, 1650, 1243. ^{1}H NMR (*δ*, ppm in DMSO): 11.09 (s, 1H), 7.81 (d, *J* = 6.2 Hz, 2H), 7.47 (d, *J* = 6.1 Hz, 2H), 6.90 (s, 2H), 6.06 (s, 1H), 2.20 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (δ, ppm in DMSO): 151.01, 147.22, 140.31, 139.15, 122.50, 121.94, 109.96, 13.87, 12.28. HRMS (ESI) m/z: [M$^+$] calcd for $C_{12}H_{14}N_3O_4$ 230.2710; found 230.2712. Elemental analysis (calcd/found): C (62.59/62.55); H (6.13/6.08); N (24.33/24.28).

*Synthesis of methyl 3,5-dimethyl(-1-pyrazolyl)-pyrimidine-4-carboxylate(**15**)*

Amidoxime **14**, (0.5 g, 0.00217 mol), dimethylacetylenedicarboxylate (0.77 g, 0.0054 mol) **5** and catalytic amount of DABCO (0.045 g, 0.0004 mol) was mixed in dichloromethane and the reaction mass was refluxed for 2h at 60 °C, the reaction completion was checked by TLC with mobile phase (Hex:EtOH/7:3), on completed dichloromethane was completely distilled off by vacuum to obtain brown oil, which was stirred for 6 h at 105 °C after addition of xylene. Brown colored solid was found after filtration and washing first with xylene followed by hexane to yield crude **15**. Finally, crude product was purified by column chromatography (20-24% ethylaceate in hexane).

Molecular formula $C_{17}H_{16}N_4O_4$, yield: 17%, m.p.: 205 °C. IR (KBr, ν/cm^{-1}): 3517, 3127, 1740, 1685, 1453. ^{1}H NMR (δ, ppm in DMSO): 11.97 (s, 1H), 10.81 (s, 1H), 7.80 (d, J = 7.1 Hz, 2H), 7.77 (d, J = 6.6Hz, 2H), 6.06 (s, 1H), 3.81 (s, 3H), 2.20 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (δ, ppm in DMSO): 171.06, 158.30, 147.22, 144.92, 144.57, 142.45, 139.15, 133.29, 128.62, 122.34, 109.96, 52.08, 13.87, 12.28. HRMS (ESI) m/z: [M$^+$] calcd for $C_{17}H_{16}N_4O_4$ 340.3390; found 340.3385. Elemental analysis (calcd/found): C (60.00/60.01); H (4.74/4.71); N (16.46/16.40).

*Synthesis of 4-cyanophenyl-3-phenyl-1-pyrazol benzamide(**19**)*

4-Cyano phenyl hydrazine (1 g, 0.0751 mol) **11** and benzoylacetonitrile (1.2 g, 0.0082 mol) **16** was mixed without any solvent and heated under stirring for 3 h at 110-120 ºC. The reaction mass was cooled at RT by adding dichloromethane and slowly benzoyl chloride was added **18** (1.86 g, 0.0002 mol) in the reaction mass under N_2 atmosphere. The reaction mixture was well shaken in stirrer for 3 h and completion of reaction was determined by TLC. The reaction mass was extracted in methanol. Then, the filtrate was concentrated to yield desired product **19** which was isolated without further purification.

Molecular formula $C_{23}H_{16}N_4O$, yield: 79%, m.p.: 225 °C. IR (KBr, ν/cm^{-1}): 3217, 3002, 2225, 1641.^{1}H NMR (δ, ppm in DMSO): 10.82 (s, 1H), 8.01-7.38 (m, 14H), 7.08 (s, 1H). ^{13}C NMR (δ, ppm in DMSO): 165.15, 153.12, 142.24, 136.76, 132.84, 132.45, 118.23, 111.37, 99.89. HRMS (ESI) m/z: [M$^+$] calcd for $C_{23}H_{16}N_4O$ 364.4080; found 364.4075. Elemental analysis (calcd/found): C (75.81/75.80); H (4.43/4.40); N (15.38/15.35).

*Synthesis of (Z)-N-(1-(4-(N'-hydroxycarbamimidoyl)phenyl)-3-phenyl-1H-pyrazol-5-yl)benzamide (**20**)*

Potassium hydroxide (2.53 g, 0.030 mol) and hydroxyl amine hydrochloride (1.9 g, 0.0273 mol) 2.044 were added in 50 mL of distilled water, then this solution was mixed to the solution of nitrile substrate **19** in 50 mL ethanol at RT. The reaction mass was heated to 85 ºC for 10 h. The reaction was checked by TLC (Hex:EtOH/7:3). The reaction mass was extracted with DCM and H_2O. The compound containing organic layer was separated and dried by sodium sulfate led to obtain crude white crystalline solid. Purification was done by flash chromatography (20-22% ethylaceate in hexane) to achieve **20**.

Molecular formula $C_{23}H_{19}N_5O_2$, yield: 75%, m.p.: 189 °C. IR (KBr, ν/cm^{-1}): 3643, 3238, 1653, 2362. ^{1}H NMR (δ, ppm in DMSO): 10.82 (s, 1H), 9.74 (s, 1H), 7.92-7.37 (m, 14H), 5.89 (s, 2H) ^{13}C NMR (δ, ppm in DMSO): 166.15, 150.36, 150.08, 139.12, 137.37, 133.15, 126.12, 125.24, 122.75, 101.86. HRMS (ESI) m/z: [M$^+$] calcd for $C_{23}H_{19}N_5O_2$ 397.4380; found 397.4374. Elemental analysis (calcd/found): C (69.51/69.45); H (4.82/4.75); N (17.62/17.56).

*Synthesis of methyl 2-(4-(5-benzamido-3-phenyl-1H-pyrazol-1-yl)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate(**21**)*

Amidoxime **20** (0.2 g, 0.0005 mol), dimethylacetylenedicarboxylate (0.178 g, 0.00125 mol) and catalytic amount of DABCO (0.01 g, 0.00008 mol), were dissolved in chloroform and refluxed at 60-65 ºC for 3 h. The completion of reaction was monitored by TLC (Hex:EtOH/7:3). Upon reaction completion the chloroform was evaporated under vacuum till brown color oil was obtained. To this oil 20 ml xylene was mixed and the reaction was refluxed at 140-145 ºC for 10 h. Solids were recrystallizing with xylene followed by hexane to obtain brown colored solid **21**.

Molecular formula $C_{28}H_{21}N_5O_5$, yield: 15%, m.p.: 278 °C. IR (KBr, ν/cm^{-1}): 3624, 3234, 2315, 1735, 1686. ^{1}H NMR (δ, ppm in DMSO): 10.67 (s, 1H), 10.65 (s, 1H), 8.90 (s, 1H), 8.13-7.80 (dd, J = 7.3 Hz, 4H), 8.11-7.38 (m, 11H), 3.83 (s, 3H). ^{13}C NMR (δ, ppm in DMSO): 166.05, 150.66, 137.42, 132.97, 132.52, 122.74, 125.25, 127.42, 102.12, 52.16. HRMS (ESI) m/z: [M$^+$]

calcd for $C_{28}H_{21}N_5O_5$ 507.5060; found 507.5057. Elemental analysis (calcd/found): C (66.27/66.24); H (4.17/4.15); N (13.80/13.75).

*Synthesis of 4,5-diphenyl-1-imidazol-2-yl)benzonitrile (**24**)*

A reaction mixture of benzil (0.8 g, 0.0038 mol), equimolar quantity of 4-cyano benzaldehyde, ammonium acetate (0.99 g, 131.13 mol) and 1 g mixture of P_2O_5/SiO_2, all were mixed in a single neck 100 mL flask and placed in a microwave synthesizer at 50 W, 80-100 ºC for 5-8 min. Then, reaction completion was checked by TLC with mobile phase (Hex:EtOH/6:4). Ethylacetate was added to the reaction mixture and stirring was done for 1 h at 50 ºC. Further, reaction mass was recrystallized with *n*-hexane to obtain pale yellow solids of **24**.

Molecular formula $C_{22}H_{15}N_3$, yield: 82%, m.p.: 275 °C. IR (KBr, ν/cm^{-1}): 3012, 2218, 1436, 1320. ^{1}H NMR (δ, ppm in DMSO): 8.26-7.94 (dd, J = 7.3 Hz, 4H), 7.54-7.33 (m, 10H), 3.38(s, 1H). ^{13}C NMR (δ, ppm in DMSO): 143.66, 138.27, 134.23, 132.78, 128.33, 127.09, 125.48, 118.89, 110.05. HRMS (ESI) m/z: [M$^+$] calcd for $C_{22}H_{15}N_3$ 321.3830; found 321.3828. Elemental analysis (calcd/found): C (82.22/82.20); H (4.70/4.65); N (13.08/13.02).

*Synthesis of (Z)-4-(4,5-diphenyl-1H-imidazol-2yl)-N'-hydroxybenzimidamide (**25**)*

Sodium bicarbonate (1.99 g, 0.0238 mol) was mixed to hydroxyl amine hydrochloride (1.61 g, 0.0233 mol) in distilled water to break the hydrochloride salt. This solution was added to **24** (3 g, 0.0093 mol) in ethanol and reaction mass was subjected to reflux at 100 °C for 2 h. The completion of reaction was checked by TLC (Hex:EtOH/7:3). After the reaction completion, the temperature of reaction mixture was lowered to RT and filtration of reaction mass was done to obtained crude compound. Purification was done by silica flash chromatography (18-20% ethylaceate in hexane) to give pure compound **25**.

Molecular formula $C_{22}H_{18}N_4O$, yield: 77%, m.p.: 254 °C. IR (KBr, ν/cm^{-1}): 3462, 3379, 2253, 1436, 1320. ^{1}H NMR (δ, ppm in DMSO): 13.58 (s, 1H), 11.09 (s, 1H), 8.01 (d, J = 6.1 Hz, 2H), 7.85 (d, J = 7.0 Hz, 2H), 7.47 (d, J = 6.8 Hz, 4H), 7.49 (t, 2H), 7.28 (t, 4H), 6.90 (s, 2H). ^{13}C NMR (δ, ppm in DMSO): 151.01, 145.76, 143.33, 137.58, 133.56, 133.27, 131.36, 130.85, 129.14, 129.12, 129.07, 128.51, 127.93, 127.74, 127.43, 126.89. HRMS (ESI) m/z: [M$^+$] calcd for $C_{22}H_{18}N_4O$ 354.4130; Found 354.4124. Elemental analysis (calcd/found): C (74.56/74.52); H (5.12/5.10); N (15.81/15.75).

*Synthesis of methyl 2-(4-(4,5-diphenyl-1H-imidazol-2yl)phenyl)-5,6-dihydroxypyrimidine-4-carboxylate (**26**)*

Amidoxime **25**, (0.3 g, 0.00084 mol), dimethylacetylenedicarboxylate (0.3 g, 0.00211 mol) and DABCO (0.017 g, 0.00015 mol) was mixed into chloroform and refluxed for 1 h at 60 ºC, the reaction completion was monitored by TLC (Hex:EtOH/7:3). After the completion of reaction, chloroform was distilled off under vacuum to obtain brown oil, in which xylene was added and the reaction mixture was refluxed for 2 h at 100 ºC. The brown colored solid was formed in reaction which were extracted in xylene and then dried to obtain **26**.

Molecular formula $C_{27}H_{20}N_4O_4$, yield: 27%, m.p.: 124 °C. IR (KBr, ν/cm^{-1}): 3432, 3200, 2934, 1696, 1516, 1012. ^{1}H NMR (δ, ppm in DMSO): 12.42 (s, 1H), 10.52 (s, 1H), 8.72 (s, 1H), 7.80 (d, J = 7.0 Hz, 2H), 7.77 (d, J = 7.1 Hz, 2H), 7.60-7.61 (m, 4H), 7.41-7.40 (t, 4H), 7.31-7.30 (t, 2H), 3.91 (s, 3H). ^{13}C NMR (δ, ppm in DMSO-d_6): 171.06, 158.30, 145.76, 144.57, 143.33, 137.58, 137.36, 133.56, 132.24, 132.02, 130.85, 129.14, 129.12, 128.51, 127.93, 127.74, 127.53, 127.43, 52.08. HRMS (ESI) m/z: [M$^+$] calcd for $C_{27}H_{20}N_4O_4$ 464.4810; found 464.4808. Elemental analysis (calcd/found): C (69.82/69.78); H (4.34/4.32); N (12.06/12.01).

*Synthesis of 2-chloro-1-(phenyl(phenylimino)methyl)pyridinium (**29**)*

Benzanilide (2.0 g, 0.0101 mol) (**27**), and 2-chloro pyridine (2.31 g, 0.0203 mol) (**28**) was added in 60 mL dichloromethane. Trifluoromethane sulfonic anhydride (3.12 g, 0.011 mol) in 10 mL was slowly added in the reaction mass at -65 ºC. After addition the reaction mixture was stirred for 15 min and then, the temperature was maintained up to -5 °C. The reaction completion was monitored by TLC (Hex:EtOH/6:4), upon reaction completion the reaction mass was neutralized by adding triethylamine (2.41 g, 0.023 mol) and stirred for 1 h. The pure compound was obtained by flash column chromatography (16-17% ethylaceate in hexane) in yellow colored solids **29**.

Molecular formula $C_{18}H_{14}ClN_2$, yield: 53%, m.p.: 143 °C. IR (KBr, ν/cm^{-1}): 3012, 2312, 1634, 750. ^{1}H NMR (δ, ppm in $CDCl_3$): 8.0-6.0 (m, 13H), 6.94-7.35 (m, 4H). ^{13}C NMR (δ, ppm in $CDCl_3$): 158.35, 142.74, 133.13, 132.76, 131.50, 129.91, 118.57, 110.98, 109.69. HRMS (ESI) m/z: [M^+] calcd for $C_{18}H_{14}ClN_2$ 293.7735; found 293.7734. Elemental analysis (calcd/found): C (73.59/73.55); H (4.80/4.77); N (9.54/9.57).

*General procedure for the synthesis of quinazoline (**35-39**)*

To the mixture of **(29)** (2.0 g, 0.0101 mol) in DCM, substituted nitrile (**3**, **8**, **13**, **19**, **24)** (1.52 g 0.0091 mol) was slowly added in the reaction mass at 0 to -5 °C in 10-15 min and the reaction mass was stirred at 0 °C for 4 h. The completion of reaction was checked by TLC (Hex:EtOH/6:4), upon reaction completion the reaction mass was neutralized by adding triethylamine (2.41 g, 0.023 mol). The derivatives was purified using silica gel flash chromatography (10-12% ethylacetate in hexane) to obtain targeted compound.

*Synthesis of 4-pyrrol-2-phenylquinazoline (**35**)*. Molecular formula $C_{24}H_{17}N_3$, yield: 82%, m.p.: 131 °C. IR (KBr, ν/cm^{-1}): 2945, 2885, 2150, 1653, 1345, 1243.^{1}H NMR (δ, ppm in $CDCl_3$): 8.03 (d, J = 7.3 Hz, 2H), 7.77 (d, J = 7.0 Hz, 2H), 7.74 (t, 2H), 7.66 (d, J = 6.7 Hz, 2H), 7.64 (d, J = 6.3 Hz, 2H), 7.42 (d, J = 7.1 Hz, 2H), 7.35 (t, 1H), 7.28 (d, J = 1.4 Hz, 2H), 6.27 (d, J = 6.2 Hz, 2H). ^{13}C NMR (δ, ppm in $CDCl_3$): 167.42, 165.95, 152.94, 140.98, 136.73, 136.29, 132.22, 131.28, 130.85, 129.11, 128.80, 128.26, 125.91, 124.98, 121.96, 119.96, 118.15, 112.43. HRMS (ESI) m/z: [M^+] calcd for $C_{24}H_{17}N_3$ 347.4210; found 347.4205. Elemental analysis (calcd/found): C (82.97/82.95); H (4.93/4.91); N (12.10/12.06).

*Synthesis of 2,5-dimethyl-1H-pyrrol-2-phenylquinazoline (**36**)*. Molecular formula $C_{25}H_{20}N_4$, yield: 75%, m.p.: 131 °C. IR (KBr, ν/cm^{-1}): 2945, 2885, 2150, 1653, 1345, 1243. ^{1}H NMR (δ, ppm in $CDCl_3$): 8.03 (d, J = 6.1 Hz, 2H), 7.79 (d, J = 7.3 Hz, 2H), 7.66 (t, 2H), 7.62 (t, 2H), 7.42 (t, 2H), 7.35 (t, 1H), 7.24 (dd, J = 7.4 Hz, 2H), 5.09 (d, J = 6.8 Hz, 1H), 2.11 (s, 6H). ^{13}C NMR (δ, ppm in $CDCl_3$): 167.01, 165.95, 152.94, 130.53, 129.11, 128.80, 124.49, 124.46, 122.99, 109.23, 13.42, 12.41. HRMS (ESI) m/z: [M^+] calcd for $C_{25}H_{20}N_4$ 375.4750; found 375.4745. Elemental analysis (calcd/found): C (83.17/83.15); H (5.64/5.62); N (11.19/11.15).

*Synthesis of 3,5-dimethyl-1H-pyrazol-2-phenylquinazoline (**37**)*. Molecular formula $C_{25}H_{20}N_4$, yield: 72%, m.p.: 130 °C. IR (KBr, ν/cm^{-1}): 2945, 2885, 2150, 1653, 1345, 1243.^{1}H NMR (δ, ppm in $CDCl_3$): 8.03 (t, 1H), 7.92 (d, J = 7.1 Hz, 2H), 7.78 (d, J = 6.8 Hz, 2H), 7.74 (t, 3H), 7.65 (s, 1H), 7.54 (t, 2H), 7.42 (d, J = 7.1 Hz, 2H), 6.24 (s, 1H), 2.34 (s, 6H). ^{13}C NMR (δ, ppm in $CDCl_3$): 167.23, 165.95, 139.15, 135.12, 131.28, 129.11, 128.80, 126.56, 125.91, 121.71, 109.96, 13.87, 12.28. HRMS (ESI) m/z: [M^+] calcd for $C_{25}H_{20}N_4$ 376.4630; found 376.4627. Elemental analysis (calcd/found): C (79.76/79.72); H (5.36/5.34); N (14.88/14.85).

*Synthesis of N-(3-phenyl-1-(4-(2-phenylquinazolin-4-yl)phenyl)-1H-pyrazol-5-yl)benzamide (**38**)*. Molecular formula $C_{36}H_{25}N_5O$, yield: 74%, m.p.: 131 °C. IR (KBr, ν/cm^{-1}): 3412, 2945, 2885, 2150, 1653, 1345, 1243. ^{1}H NMR (δ, ppm in $CDCl_3$): 11.70 (s, 1H), 8.25 (d, J = 6.3 Hz,

4H), 7.85 (d, *J* = 7.2 Hz, 4H), 7.80 (d, *J* = 7.4 Hz, 4H), 7.76 (d, *J* = 7.2 Hz, 4H), 7.56 (d, *J* = 6.2 Hz, 2H), 7.47 (s, 1H), 7.40 (d, *J* = 6.4 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.1Hz, 1H). ^{13}C NMR (δ, ppm in $CDCl_3$): 167.00, 165.95, 152.94, 145.76, 143.33, 141.93, 137.58, 136.73, 135.18, 133.17, 132.22, 131.28, 130.85, 129.14, 129.12, 129.11, 128.80, 128.51, 127.93, 127.74, 127.45, 125.91, 124.98, 121.96. HRMS (ESI) m/z: [M^+] calcd for $C_{36}H_{25}N_5O$ 543.6300; found 543.6305. Elemental analysis (calcd/found): C (79.54/79.52); H (4.64/4.62); N (12.88/12.86).

*Synthesis of 4,5-diphenyl-1H-imidazol-2-phenylquinazoline (**39**)*. Molecular formula $C_{35}H_{24}N_4$, yield: 72%, m.p.: 135 °C. IR (KBr, *v*/cm^{-1}): 2945, 2885, 2150, 1653, 1345. ^{1}H NMR (*δ*, ppm in $CDCl_3$): 11.70 (s, 1H), 8.25 (d, *J* = 6.4 Hz, 4H), 7.85 (d, *J* = 7.3 Hz, 4H), 7.80 (d, *J* = 6.1 Hz, 4H), 7.76 (d, *J* = 5.6 Hz, 4H), 7.56 (d, *J* = 6.4 Hz, 2H), 7.48 (s, 1H), 7.40 (d, *J* = 7.1 Hz, 2H), 7.33 (d, *J* = 7.4 Hz, 2H). ^{13}C NMR (δ, ppm in $CDCl_3$): 167.00, 165.95, 152.94, 145.76, 143.33, 141.93, 137.58, 136.73, 135.18, 133.17, 132.22, 131.28, 130.85, 129.14, 129.12, 129.11, 128.80, 128.51, 127.93, 127.74, 127.45, 125.91, 124.98, 121.96. HRMS (ESI) m/z: [M^+] calcd for $C_{35}H_{24}N_4$ 500.6050; found 500.6045. Elemental analysis (calcd/found): C (83.98/83.95); H (4.83/4.82); N (11.19/11.15).

Antibacterial activity

The antimicrobial activity of the compound was evaluated against *E. coli* [MTCC 433], P. aeruginosa [MTCC 424], S. pyogenes [MTCC 2645], S.aureus [MTCC 9886], *C. albicans* [MTCC 7315] *and A. clavatus* [MTCC 1323] using nutrient broth dilution method. The serial dilutions of synthesized compound in nutrient broth were taken and their pH was adjusted in the range of 7.2-7.4. The test bacterium's standardised suspension was incubated and inoculated at 37 °C for 24 hours.

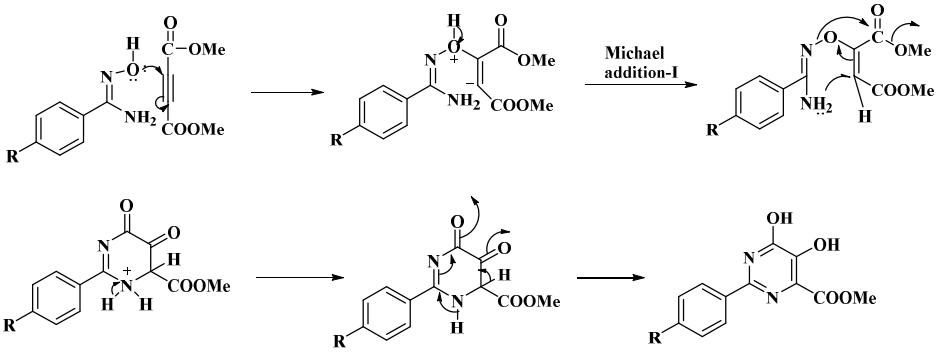
RESULTS AND DISCUSSION

Chemistry

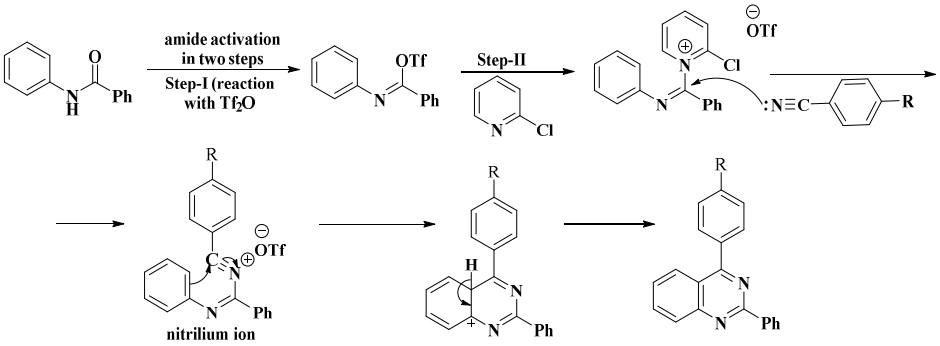
The nitrile bearing pyrrole (**3**, **8**), pyrazole (**13**, **19**) and imidazole (**24**) were synthesized from 4-amino benzonitrile (**1**), 4-cyano phenyl hydrazine (**11**) and benzyl (**22**), respectively. The nitrile bearing intermediate **3**, **8**, **13**, **19**, **24** were reacted with hydroxyl amine hydrochloride to yield **4**, **9**, **14**, **20** and **25**, respectively, which on cyclocondensation with dimethyl acetylene dicarboxylate (DMAD) **5** in a domino click fashion to synthesize the target molecule **6**, **10**, **15**, **21** and **26** respectively (Scheme 1, 2 and 3) and mechanism is shown in Scheme 5.

The synthesized compound (**4**) was affirmed by the appearance of peak at 3600 cm^{-1} (O-H group) and 3410 cm^{-1}(N-H group) in the IR spectrum. Further, the structure of compound (**4**) was ascertained by the presence of additional peak at δ 9.68 and δ 5.88, which may be attributed to the presence of –OH and –NH_2 respectively of amidoxime group. The appearance of peak at 1700 cm^{-1} and 1646 cm^{-1} (C-O, stretching) affirmed the formation of (**6**) from (**4**). The synthesis of a pyrimidine ring in (**6**) was assured by one upfield at δ 3.36 for three proton of methyl ester group and sharp singlet at δ 8.01 for one proton of OH group. The presence of 2913 cm^{-1} peak (C-H Str, aliphatic) along with peak at 1218 cm^{-1} (C-N bending) ascertained the formation of (**8**). The IR spectrum of (**9**) revealed presence of Fermi resonance peak of -NH_2 group at 3475-3392 cm^{-1} and appearance of peak at 1739-1833 cm^{-1} (-COOMe) due to the coupled vibration confirmed the formation of (**10**). The ^{1}H NMR of (**8**) signifies the presence of six methyl protons which appeared in the form of sharp singlet at δ 2.45 and the formation of (**9**) was confirmed through the sharp downfield singlet at δ 9.77 which represents the presence of –OH of amidoxime. Finally the formation of (**10**) was ascertained by the appearance of additional sharp singlet of methyl ester at δ 3.87 in its ^{1}H NMR spectra. Similarly, the structures of synthesized compounds **15**, **21** and **26** was confirmed.

Another one pot pioneering reaction deals with the activation of less active *N*-aryl amide like benzanilide (**27**). The amide was activated in two steps, firstly reacted with Tf_2O and secondly reacted with 2-chloropyridine. The activated benzanilide (**29**) was now ready to couple with substituted nitrile **3**, **8**, **13**, **19**, **24**. The synthesized nitrilium (**30-34**) undergo cyclocondensation with the π-electron system of benzene ring to yield the quinazoline nucleus in a single step **35-39** depicted in Scheme 4 and mechanism shown in Scheme 6.



Scheme 5. Plausible mechanism for the formation of pyrimidine derivatives.



Scheme 6. Plausible mechanism for the formation of quinazoline derivatives.

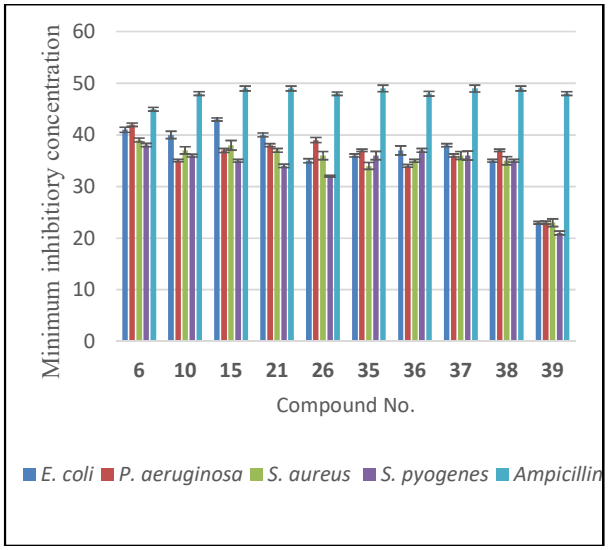
Antimicrobial activity

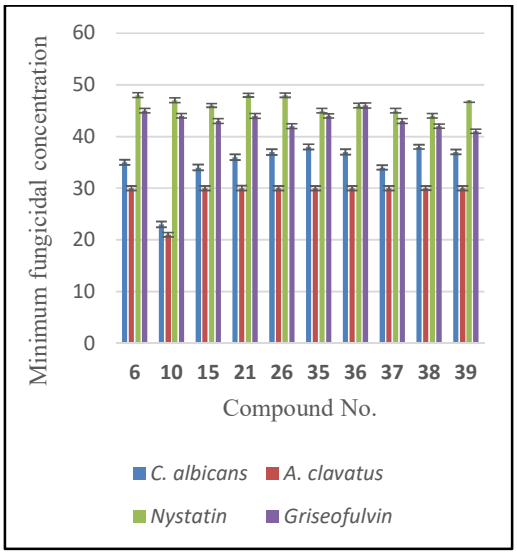
The synthesized derivatives were examined for antibacterial and antifungal activity. The antibacterial activity of the synthesized compound was screened against the gram negative bacteria *E. coli*, *P. aeruginosa* and gram positive bacteria *S. pyogenes* and *S. aureus*. The derivatives were also screened for antifungal activity against *C. albicans* and *A. clavatus*. The microbroth dilution method was used for the determination of MIC, MBC and MFC. Among all the ten synthetically derived compounds, compound **39** showed maximum antibacterial potential against all tested bacterial pathogens with a zone of inhibition of 23, 20, 23 and 20 mm against *S. pyogenes*, *S. aureus*, *E. coli* and *P. aeruginosa*, respectively, at the concentration of 250 μg/mL while derivatives **10** and **21** both showed maximum antifungal potential with zone of inhibition of 23 and 22 mm against *C. albicans* and *A. clavatus*, respectively (Table 1).

Table 1. Antimicrobial screening results of synthesized compounds.

Compound No.	MIC (µg/mL)					
	Bacteria				Fungi	
	S. pyogenes	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. clavatus*
6	45	46	45	46	75	75
10	42	43	42	43	24	24
15	43	45	43	45	75	26
21	41	40	41	40	23	22
26	39	38	39	38	75	75
35	36	42	36	42	75	25
36	34	44	34	44	76	24
37	33	32	33	32	65	53
38	32	34	32	34	60	54
39	23	20	23	20	45	56
Ampicillin	50	25	50	50	-	-
Nystatin	-	-	-	-	50	25

The compound **39** also displayed least MBC against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* which was comparable to reference drugs ampicillin, ciprofloxacin, norfloxacin and gentamycin revealing its potent antibacterial activity. While each of the synthesized compound exhibited different MFC values against each of the tested fungal pathogens revealing their moderate antifungal activity when compared to standard drugs nystatin and griseofulvin.





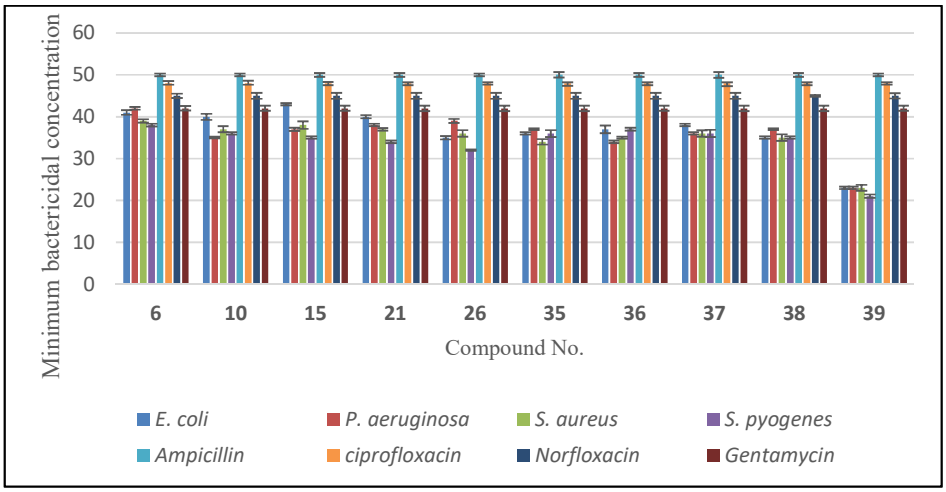


Figure 1. MIC, MFC and MBC of the synthesized compounds.

CONCLUSION

The novel and efficient methodologies were described for the preparation of pyrimidine and quinazoline derivatives using a one-pot domino approach. Compound **39** showed maximum antibacterial potential against the bacterial pathogens with a zone of inhibition of 23 mm, 20 mm, 23 mm and 20 mm against *P. aeruginosa*, *S. pyogenes*, *E. coli*, *S. aureus*, respectively, at a concentration of 250 µg/mL while compound 10 exhibited potential antifungal activity against *C. albicans* and *A. clavatus*. This work exploited a synthesis of various pyrimidine and quinazoline

derivatives as novel antibacterial agent. This approach shed light on the further development of pyrimidine and quinazoline derivatives against microbial infections.

The findings of the present study are promising, however attaining the same extent of response in *in vitro* and *in vivo* studies would be a great challenge to the investigators. Thus, further efforts are required to conduct in depth *in vitro* and *in vivo* studies to establish the safety and efficacy of these compounds for their future development in clinical practice.

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