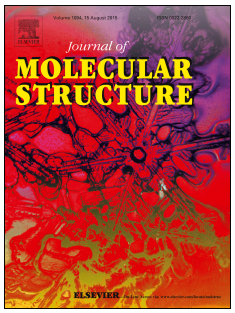

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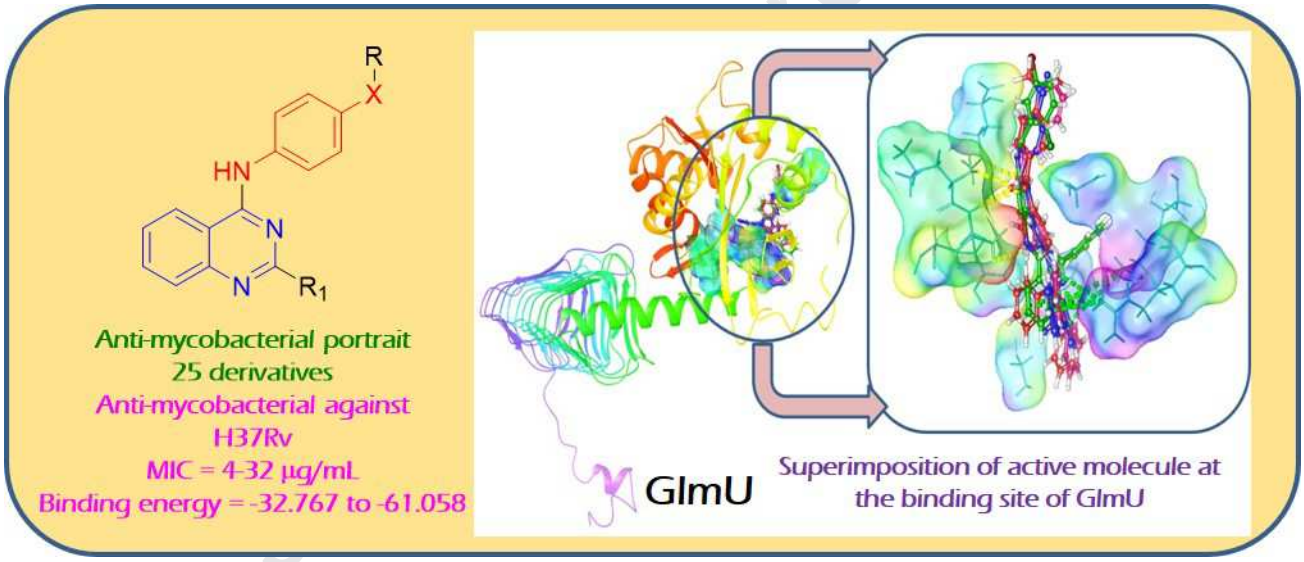

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Abstract: New 2-arylquinazoline benzamide derivatives were synthesised and screened against H37RV strain, compounds displayed specific and potent anti-mycobacterial activity against *Mycobacterium tuberculosis*. **9a**, **9c**, **9d**, **9e**, **9f**, **9h**, **13b**, **17d** and **17e** exhibited selective and good inhibitory activity against *Mycobacterium tuberculosis* with the MIC values range of 4-32 μg/mL. Molecular modelling studies also supports that the active molecules can fit well in the binding pocket of GlmU with good ligand-protein interactions, strong binding energies and satisfactory ADMET properties results (obeys the Lipinski rule of 5). Comprehensively, the studies recommended that these new quinazoline derivatives have the potential to be further develop as prospective anti-mycobacterial leads.

Keywords: 2-arylquinazoline, tuberculosis, minimum inhibitory concentration (MIC), molecular modelling.

1.0 Introduction:

Increased global prevalence and rise in multi-drug resistance status of various infectious disease like tuberculosis fuelled the search for novel antimycobacterial agents (**Figure 1**) [1] acting through different mechanisms to overcome resistance. Tuberculosis is a transmissible disease caused by *Mycobacterium tuberculosis* (Mtb) and recognized to have a high mortality rate globally [2]. According to WHO reports, 10 million cases were reported in 2017 globally, with India having the highest incidence burden [3]. Emergence of drug-resistant TB (DR-TB) is often accompanied with chronic immunosuppressive conditions like HIV and diabetes, thus severely limiting current treatment options. Clinical approval of Bedaquiline (A, **Fig. 1**) [5] after a gap of 40 years has kindled hope for discovering new drugs by consideration of different heterocycles as anti-mycobacterial agents [1]. Quinazoline is one of the versatile scaffold of medicinal importance possessing diverse pharmacological properties such as anti-tubercular [6], antibacterial [7], anticonvulsant [8], anti-HIV [9], antifungal [9], anti-inflammatory, analgesic [10] and anticancer [11] activities. The present work focuses on the exploration of 2-aryl quinazolines as potential antimycobacterial agents. A survey of literature suggests that very few reports exist on quinazoline based compounds as antimycobacterial agents. Pyrazinamide (B, **Fig. 1**) is the front line therapy used to treat tuberculosis. For active tuberculosis, it is often used with other first line drugs like Rifampicin, Isoniazid and Ethambutol [5]. Macozinone (C, **Fig. 1**), a promising fused heterocyclic derivative was identified against drug-susceptible (DS) and drug-resistant (DR) Mtb strains which led to the exploration of different fused heterocycles as antimycobacterials [12]. Wang *et al.* reported 4-(aminopyrazolyl)-substituted quinazolines (D**, Fig. 1**) to possess inhibitory activity against protein kinases (PknA & PknB) of *Mycobacterium tuberculosis* [13]. Tran *et al.* reported 4-aminoquinazolines (E & F, **Fig. 1**), as potent inhibitors of *N*-acetylglucosamine-1-phosphate uridyltransferase (GlmU) of *M. tuberculosis* [14]. Our continued interest in exploration of the potential biological applications of Quinazolines led to the synthesis of 4-anilino-2-phenylquinazolines with various substitution pattern.

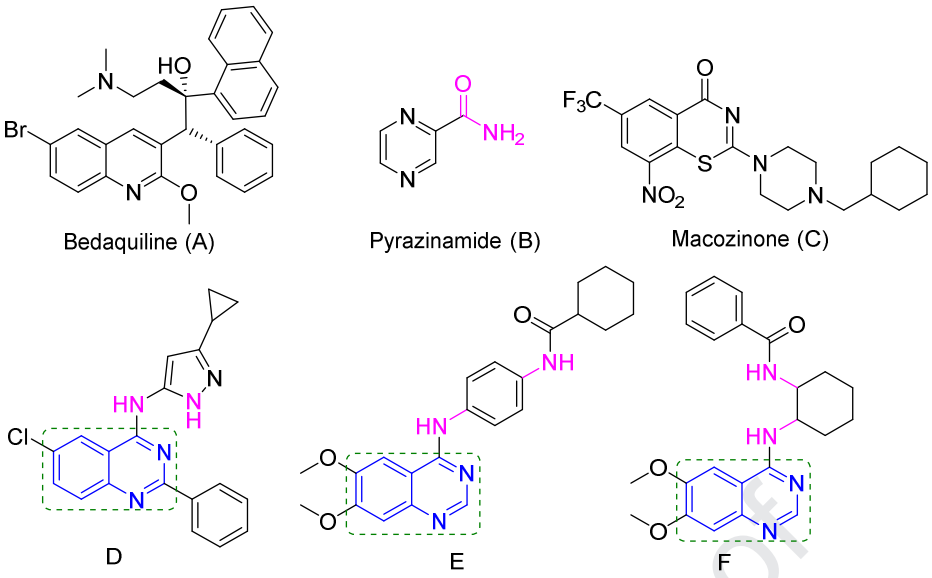


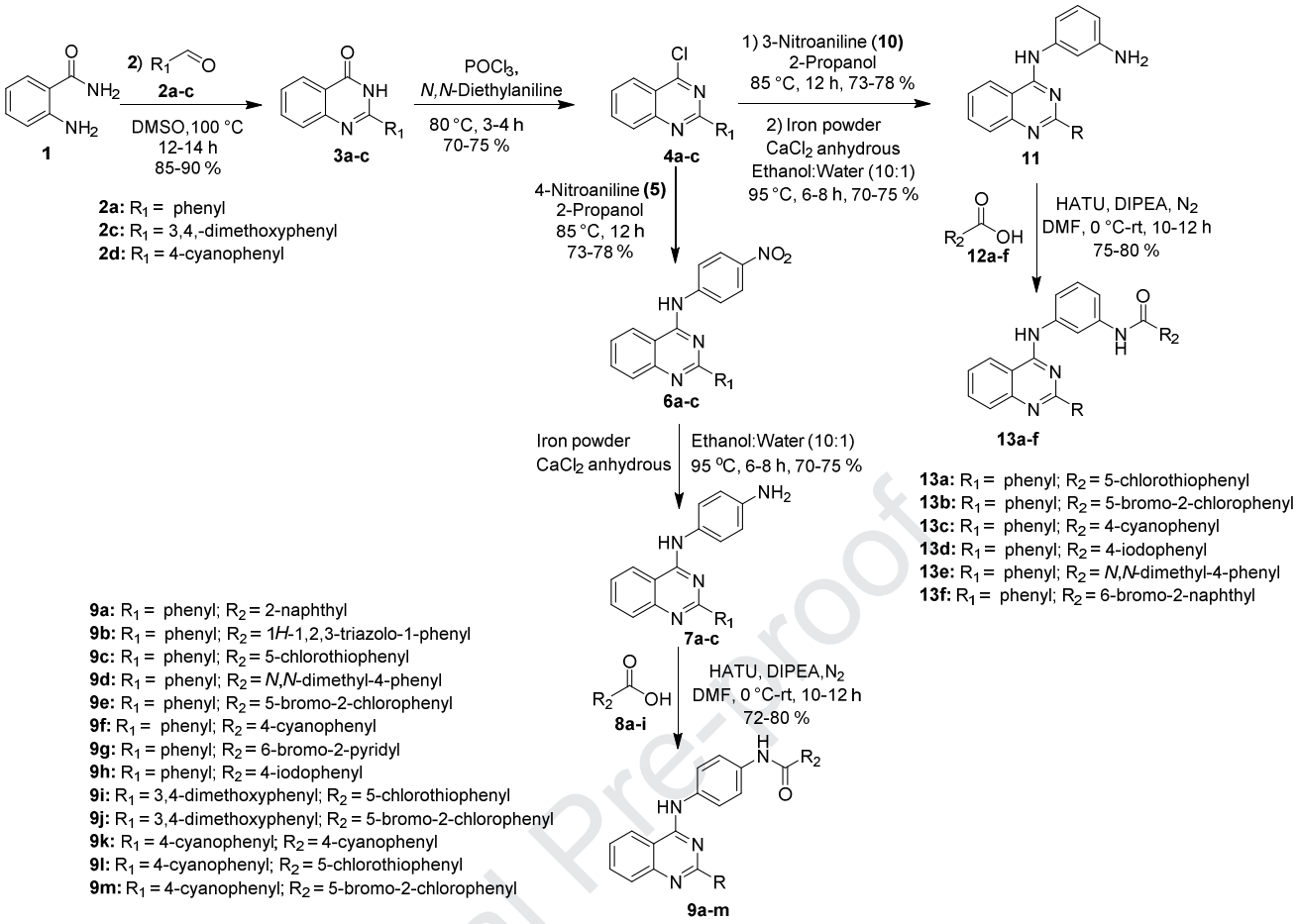
Fig. 1. Approved TB-drugs and Quinazoline derivatives as anti-mycobacterial agents.

2.0 Results and discussion:

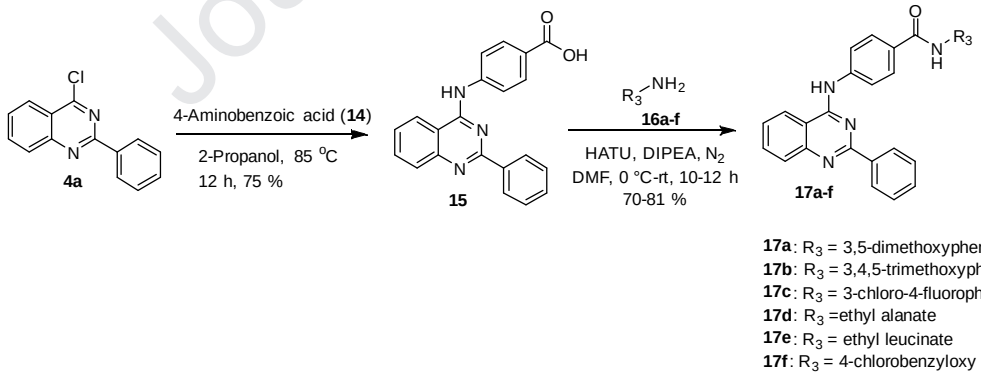
2.1 Chemistry

A series of new 2-arylquinazoline derivatives were synthesized as described in **Schemes 1** & **2**. 2-aminobenzamide **1** was condensed with different substituted aryl aldehydes **2a-c** for about 12-24 h in presence of dimethylsulphoxide to afford 2-arylquinazolinones **3a-c** [15]. These derivatives were treated with phosphorus (V) oxychloride and *N*, *N*-diethyl aniline to provide 2-aryl 4-chloroquinazoline derivatives **4a-c** [15]. The chlorinated derivatives **4a-c** undergo nucleophillic substitution with substituted nitroanilines (**5**&**10**) to obtain *N*-(4/3-nitrophenyl)-2-phenylquinazolin-4-amine **6a-c**. Further, the nitro derivatives were reduced to amine functionality by using iron powder and calcium chloride in presence of ethanol, to afford N^1-(2-phenylquinazolin-4-yl)benzene-1,4-diamine **7a-c** & **11.** Finally, coupling of amines with diverse carboxylic acids **8a-i** & **12a-f** afforded the corresponding amide derivatives **9a-m** and **13a-f** in moderate to excellent yields. Chlorinated derivative **4a** was also treated with 4-aminobenzoic acid **14** to yield 4-((2-phenylquinazolin-4-yl) amino) benzoic acid **15** which was further subjected to amide bond formation with different substituted amines **16a-f** to afford the corresponding amide derivatives **17a-f** in moderate to excellent yields.

Scheme 1. Synthesis of *N*-(4-((2-phenylquinazolin-4/3-yl) amino) phenyl) benzamide derivatives.



Scheme 2. Synthesis of *N*-phenyl-4-((2-phenylquinazolin-4-yl) amino) benzamide derivatives

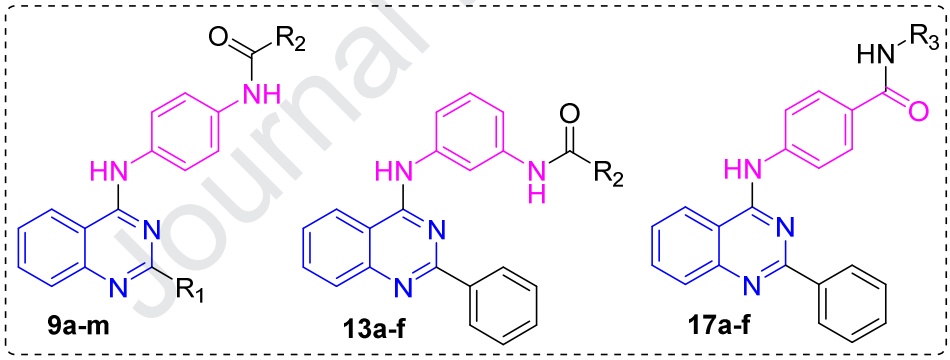


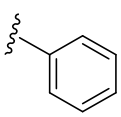
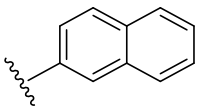
2.2 *In vitro* anti-mycobacterial activity

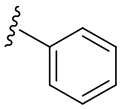
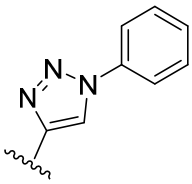
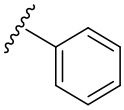
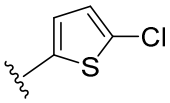
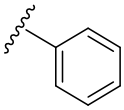
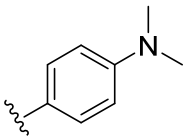
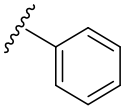
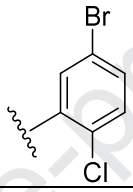
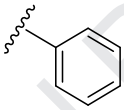
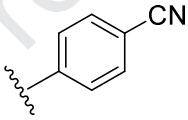
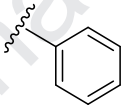
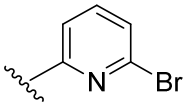
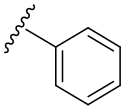
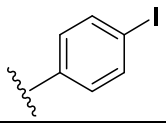
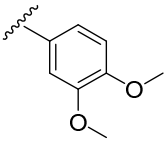
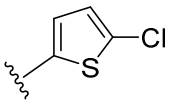
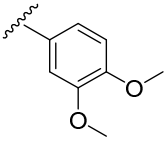
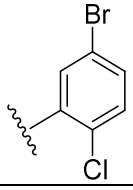
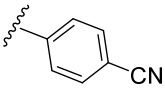
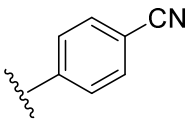
All the newly synthesized 2-aryl quinazoline benzamide derivatives were assessed for their anti-mycobacterial activity against *M. tuberculosis* H37Rv ATCC 27294 (Mtb) using Rifampicin and Isoniazid as reference compounds. The compounds exhibited interesting inhibitory activity in a range of MIC 4-64 μg/mL. The results are tabulated in **Table 1**. In all

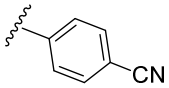
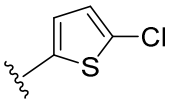
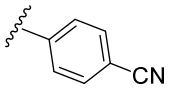
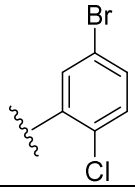
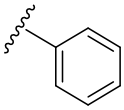
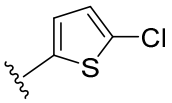
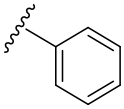
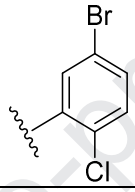
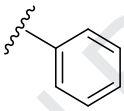
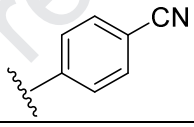
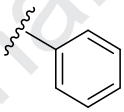
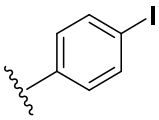
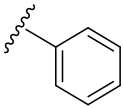
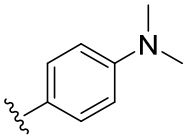
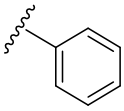
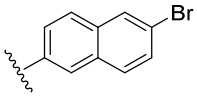
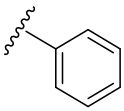
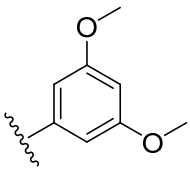
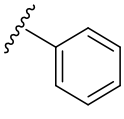
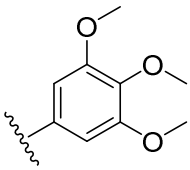
these compounds, the C2-position is maintained as phenyl or substituted phenyls. The compounds exhibited good to moderate activity when the C2 position is phenyl, however, when it is changed to 3,4-dimethoxyphenyl (**9i** - **9j**) or 4-cyanophenyl (**9k** - **9m**) the compounds exhibited loss of activity. Among the synthesized compounds, when the C2-position was substituted with phenyl and C4 was substituted with various differently substituted anilino amines at para position compounds **9a-9m** were obtained. When the substituents on the anilino amines R_2 were varied by different electron withdrawing groups as in 5-bromo-2-chlorophenyl **9e**, 4-cyanophenyl **9f**, 4-*N*,*N*-dimethyl amino phenyl **9d**, 4-iodophenyl **9h** and 5-chlorothiophenyl **9c** derivatives, the compounds exhibited potent inhibitory activities against Mtb H37Rv (MIC ranging from 4-16 μg/mL). When R_2 groups are substituted with bulky group like 2-naphthyl **9a**, the compound has also shown good inhibition against Mtb H37Rv (MIC 16 μg/mL). However, the compound with triazolophenyl **9b** as R_2 was found to be inactive. Further, change of Phenyl at C2-position with 3,4-dimethoxyphenyl (**9i** and **9j**) and 4-cyanophenyl (**9k** to **9m**) resulted in reduction in activity.

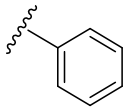
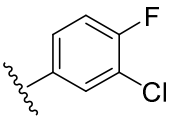
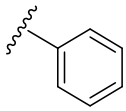
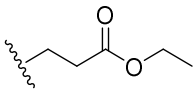
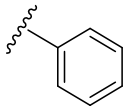
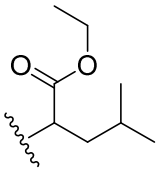
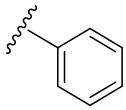
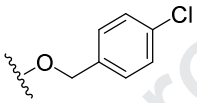
Table 1. MIC (µg/mL) of 2-arylquinazoline based amide derivatives **9a-m, 13a-f & 17a-f**.



S.no	Compound	R_1	R_2/ R_3	*M. tuberculosis* H37Rv ATCC 27294 MIC (µg/mL)
1.	**9a**			**16**

2.	**9b**			>64
3.	**9c**			**16**
4.	**9d**			**8**
5.	**9e**			**4**
6.	**9f**			**4**
7.	**9g**			>64
8.	**9h**			**16**
9.	**9i**			>64
10.	**9j**			>64
11.	**9k**			>64

12.	**9l**			>64
13.	**9m**			>64
14.	**13a**			**64**
15.	**13b**			**32**
16.	**13c**			**64**
17.	**13d**			**64**
18.	**13e**			>64
19.	**13f**			>64
20.	**17a**			>64
21.	**17b**			>64

22.	**17c**			>64
23.	**17d**			**16**
24.	**17e**			**32**
25.	**17f**			>64
26.	**Isoniazid**	-	-	0.03
27.	**Rifampicin**	-	-	0.06

Further, when we changed the substitution on anilino amines from para to meta position, as in 5-chloro-2-thiophenyl **13a,** 5-bromo-2-chlorophenyl **13b**, 4-cyanophenyl **13c** and 4-iodophenyl **13d**, the derivatives showed moderate to good inhibitory activity (MIC 16-64 μg/mL). In further modification, when compounds **17a-f** with reverse amide substitution were tested, they exhibited encouraging results (**17d** and **17e** showed MIC of 16 & 32 μg/mL respectively). In order to assess the broad biological profile of the compounds, the derivatives were also evaluated against ESKAP pathogen panel, the compounds were found to be inactive (supporting information). It was inferred that the synthesized molecules have shown selective inhibition particularly against *Mycobacterium tuberculosis*. The broad Structure Activity Relationships (SAR) derived is presented in **Fig**. **2**.

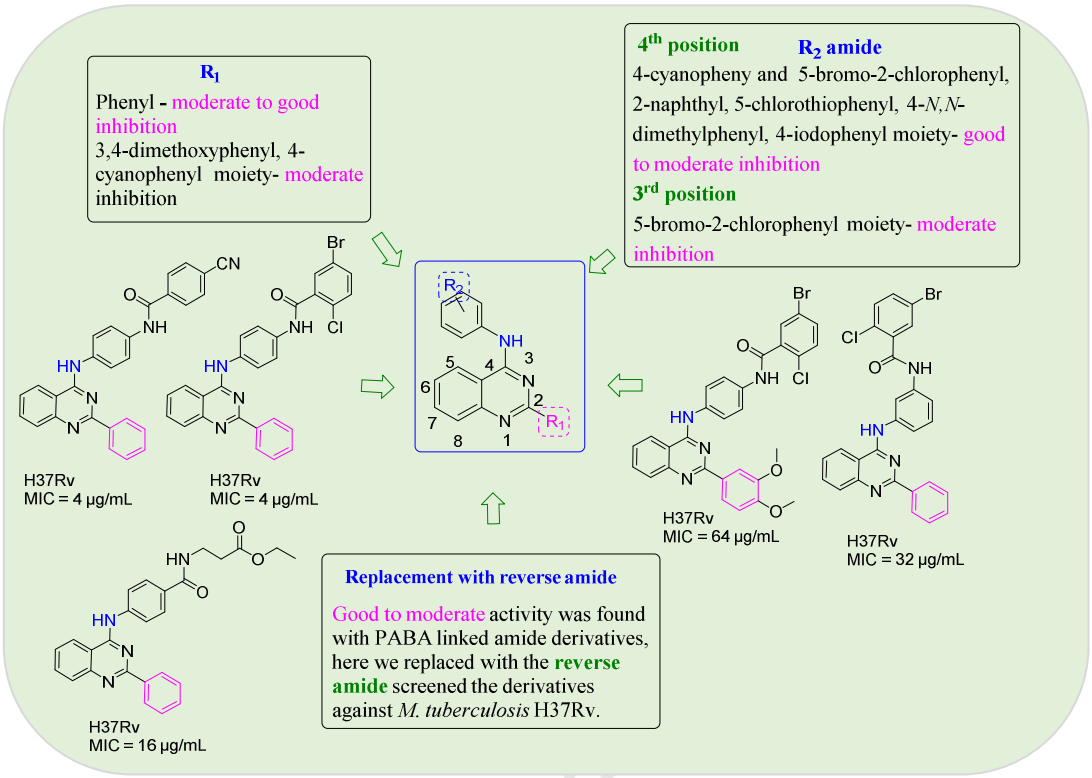


Fig. 2. Structure Activity Relationship (SAR) of new 2-aryl quinazoline derivatives.

3.0 Molecular modelling studies:

As structurally related molecules are reported to exhibit inhibitory activity against Mtb GlmU [16], the newly synthesized molecules were docked against *M. tuberculosis* GlmU crystal structure to determine their inhibitory potential. The 3D crystal co-ordinates of *M. tuberculosis* GlmU were retrieved from the protein data bank (PDB ID: 4K6R). Molecular docking studies were performed for the selected bio-active molecules (**9a**, **9c**, **9d**, **9e**, **9f**, **9h**, **13b**, **17d** and **17e**) of 2-arylquinazoline benzamide derivatives and the best orientations of **9e** and **9f** in to the active-site of GlmU protein is represented in **Fig. 2**. The compound **9e** forms two hydrogen bonding interactions, in which initial one was found at a distance of 2.99 Å, where C=O of **9e** act as an acceptor and NH of Gly15 as a donor and the additional hydrogen bonding interaction was found at a distance of 2.89 Å between aromatic hydrogen of **9e** as a donor and C=O of Glu207 as an acceptor. Besides, five aromatic hydrogen bonding interactions were observed with Leu12, Gln83, Glu166 and Glu207. Further, π-cation interaction was found between nitrogen of Arg19 and Lys26 with aromatic ring of **9e**. Hydrogen bonding interactions of the other potent compound **9f** was found at a distance of 2.62 Å in which C=O of **9f** acts as an acceptor and NH of Gly88 as a donor. The

supplementary hydrogen bonding interaction was found at a distance of 2.76 Å, where C=O of **9f** acts as an acceptor and NH of Leu87 as a donor and 2 aromatic hydrogen bonding interactions were observed with Gln83 and Asp114. Further, π-cation interaction was found between nitrogen of Arg19 and Lys26 with aromatic ring of **9f**, whereas the co-crystal has shown 2 hydrogen bonding interactions with Gln83, i.e. (i) C=O of Gln83 at a distance of 2.04 Å and (ii) the C=O of Gln83 at a distance of 2.76 Å. In our studies we observed that all the active molecules have shown interactions with the key amino acid residues. Further, we observed that all of the active molecules were fitted well in the active binding pocket and interacted with all the amino residues related to the co-crystal.

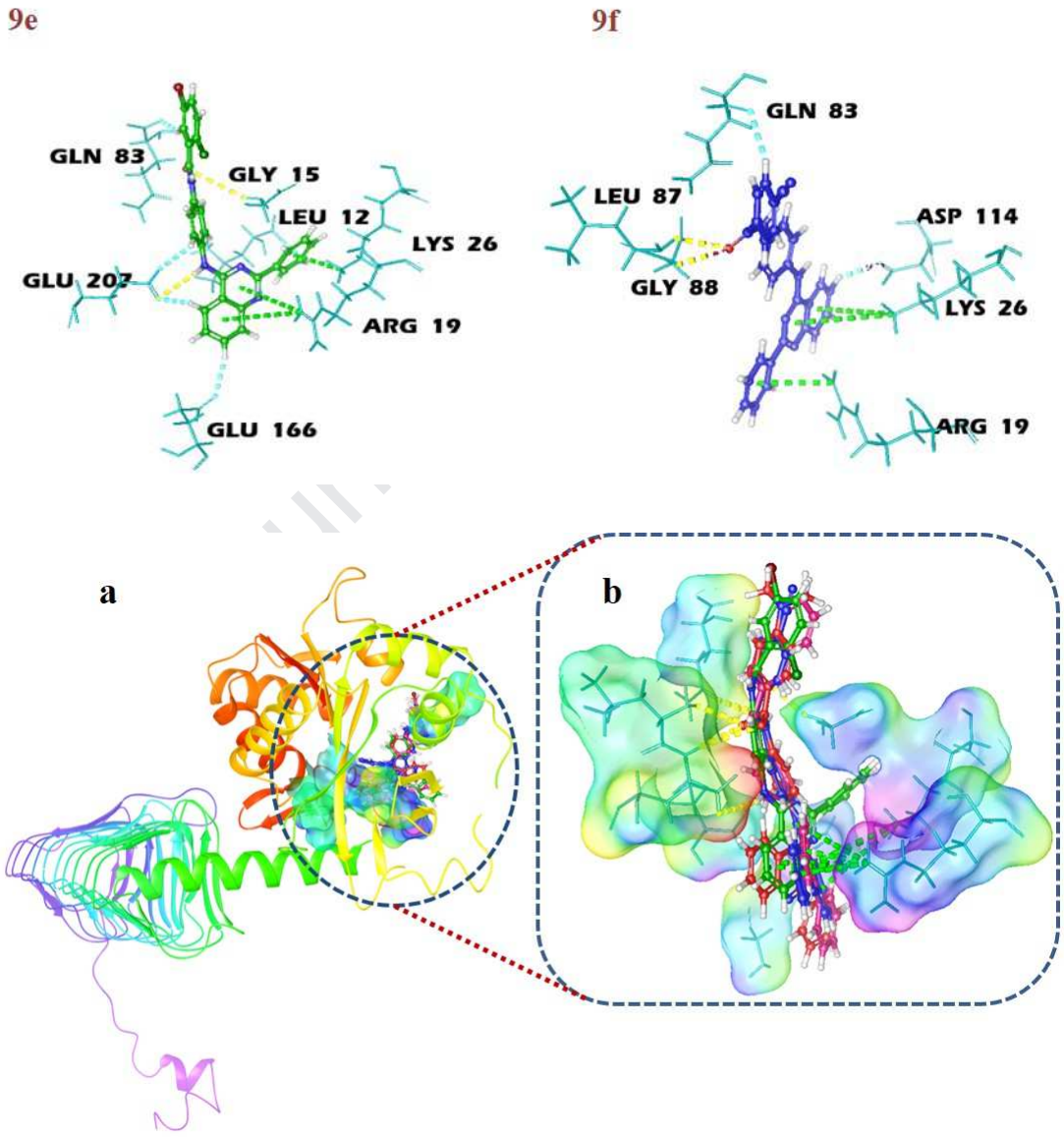


Fig. 3 a) Binding pose of **9e** and **9f** (ball and stick representation) ligand interactions in the active pocket of binding pocket of GlmU (PDB ID: 4K6R). The gold colour lines represent

hydrogen bond interactions, the cyan colour lines imply the aromatic hydrogen bond interactions and green line indicates cation-arene interactions. **b)** Super imposition of **9a**, **9d**, **9e** and **9f** at the binding pocket (binding site indicated in the rainbow colour) of GlmU (PDB ID: 4K6R).

Table 2. Binding energy and ligand interactions of docked molecules (**9a**, **9c**, **9d**, **9e**, **9f**, **9h**, **13b**, **17d** and **17e**).

S.no	Ligand id	Binding Energy (Kcal/mol)	Ligand Interactions		
			H-Bond	π -cation/ π-π stacking	Hydrophobic
1.	**9a**	-51.036	Gln83, Leu87, Gly88	Arg19, Lys26 (π-cation)	Leu12, Ala14, Pro16,Pro86, Leu87, Ala92, Tyr150, Ala182, Val238
2.	**9c**	-37.440	Leu87, Gly88	Tyr209 (π-π)	Ala14, Pro16, Pro86,Leu87, Ala182, Tyr209, Leu210, Val238
3.	**9d**	-45.570	Gln83, Gly88, Asp114,Glu166, Glu207	Arg19 (π-cation)	Leu12, Ala14, Pro16, Pro86, Leu87, Ala92, Tyr150, Tyr209
4.	**9e**	-43.442	Gln83, Gly88, Ser112, Glu166, Glu207	Arg19, Lys26 (π-cation)	Leu12, Ala13, Ala14, Pro16, Val27, Pro86,Leu87, Ala92
5.	**9f**	-49.529	Gln83, Leu87, Gly88, Asp114	Arg19 (π-π)	Leu12, Ala14, Pro16, Pro86,Leu87, Ala92, Tyr150
6.	**9h**	-51.165	Leu87, Gly88	Tyr209 (π-π)	Ala14, Pro16, Ala182, Pro86, Leu87, Tyr150, Tyr209, Val238
7.	**13b**	-54.488	Arg19	-	Leu12, Ala13, Ala14, Pro16, Val27, Pro86, Ala92

8.	**17d**	-61.058	Ala14, Gly15, Gln83	His58 (π-π)	Leu12, Ala13, Ala14, Pro16, Pro86, Ala92
9.	**17e**	-37.289	Lys26	-	Leu12, Ala13, Ala14, Pro16, Val27, Pro86, Leu87, Ala92
10.	**Co-crystal**	-55.550	Gln83	-	Ala14, Pro16, Leu82, Pro86, Leu87, Ala92, Tyr209

3.1 Prime MM/GBSA binding energy calculations

In our studies, we observed that all the active compounds have shown greater binding energies compared to the co-crystal binding energy, calculated by using MM/GBSA tool. The objective of MM/GBSA and docking studies is to explain the potential of the synthesized compounds as inhibitors of GlmU. In our studies, we observed that the synthesized compounds have shown good ligand interactions and binding energies at the binding pocket of GlmU as shown in **Table 2**. The active molecules displayed binding energies ranging from -37.289 to -61.058 kcal/mol in comparison to the co-crystal binding energy -55.550 kcal/mol. Finally, some of the identified ligands confirmed better binding energy compared to the co-crystal, suggesting that the synthesized compounds fit well for inhibiting Mtb GlmU.

3.2 ADMET properties

ADMET properties of the synthesized compounds were calculated using Qikprop program (Qikprop, version 6.5, Schrödinger, LLC, New York, NY, 2014). As can be seen below, the partition coefficient (QPlogPo/w), hydrogen bond donors (donor HB), hydrogen bond acceptors (acceptor HB), molecular weight (mol. Wt.) and percent human oral absorption exhibited satisfactory results. The compounds also followed Lipinski rule of five. ADMET properties for Isoniazid and Rifampicin were also calculated and compared with the results of the synthesized compaunds. The predicted results are shown in **Table 3**.

Table 3. ADMET properties

Descriptors	**Recommended values**	**9a**	**9c**	**9d**	**9e**	**9f**	**9h**	**13b**	**17d**	**17e**	**Isoniazid**	**Rifampicin**

Molecular weight	130.0–725.0	466.541	456.948	459.549	529.822	441.491	542.378	529.822	440.501	482.581	137.141	820.978
Dipole moment	1.0–12.5	7.028	3.836	9.957	7.522	8.358	4.489	5.767	6.668	2.112	3.32	5.739
Total SASA	300–1000	827.228	775.172	843.619	810.657	804.904	845.794	762.709	786.564	868.952	329.909	983.65
No. of rotatable bonds	0–15	5	5	6	5	6	5	5	8	9	2	24
Donor HB	0.0–6.0	2	2	2	2	2	2	2	1	1.25	3	5
Acceptor HB	2.0–20.0	5	5	6	5	6.5	5	5	6	6.25	4.5	18.65
QP Polarizability	13.0–70.0	56.642	50.375	55.518	53.884	52.682	55.215	52.183	49.948	55.442	14.107	71.616
QP logP o/w	2.0–6.5	6.606	6.074	6.142	6.715	5.052	6.488	6.478	5.444	6.403	-0.646	3.187
QP log BB	−3.0 and 1.2	-0.586	-0.371	-0.696	-0.221	-1.4	-0.846	-0.186	-1.144	-1.06	-0.844	-2.113
Human Oral Absorption	1–3	1	1	1	1	1	1	1	1	1	2	1
Percent Human Oral Absorption	> 80% is high	100	100	100	100	91.88	92.488	100	100	100	66.83	56.518
Rule of Five violations	< 25% is low	1	1	1	2	1	2	2	1	1	0	2

4.0 Conclusion

In conclusion, a series of new 2-arylquinazoline benzamide derivatives were synthesized and evaluated against Mtb H37Rv strains. Compounds **9e** and **9f** exhibited selective and potent anti-mycobacterial activity with MIC value 4 μg/mL. Compounds **9a**, **9c**, **9d**, **9h** and **17d** also showed anti-mycobacterial activity with MIC values in the range of 8-16 μg/mL. Molecular modelling studies conducted suggested that the synthesized compounds act as inhibitors of Mtb GlmU and bind well in the active binding pocket. Mtb GlmU is an important therapeutic target for Mtb. The compounds also showed good ligand-protein interactions, strong binding energies and satisfactory ADMET properties results (obeys the Lipinski rule of 5). With the encouraging results obtained the newly synthesized 2-arylquinazoline benzamide derivatives have shown the potential for further development as promising anti-mycobacterial agents.

5.0 Experimental Section:

5.1 General Methods. All the reagents and solvents were obtained from commercial suppliers and were used without further purification. Analytical thin layer chromatography (TLC) was performed on MERCK pre-coated silica gel 60-F254 (0.5 mm) aluminum plates. Visualization of the spots on TLC plates was achieved by UV light. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 MHz by making a solution of samples in the DMSO-d_6 as solvent using tetramethylsilane (TMS) as the internal standard. Chemical shifts for ^{1}H and ^{13}C are reported in parts per million (ppm) downfield from tetra methyl silane. Spin multiplicities are described as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constant (*J*) values are reported in *hertz* (Hz). HRMS were determined with Agilent QTOF mass spectrometer 6540 series instrument. Wherever required, column chromatography was performed using silica gel (60-120). The reactions wherever anhydrous conditions required are carried under nitrogen positive pressure using freshly distilled solvents. All evaporation of solvents was carried out under reduced pressure using rotary evaporator below 45 ^{o}C. Melting points were determined with an electro thermal digital melting point apparatus IA9100 and are uncorrected. The names of all the compounds given in the experimental section were taken from ChemBioDraw Ultra, Version 12.0.

*5.1.1 Preparation of intermediates **3(a-c)**, **4(a-c), 6(a-c), 11** and **15**.*

Intermediates **3(a-c)**, **4(a-c), 6(a-c), 11** and **15** (**Scheme 1 & 2**) were prepared according to the procedures described in the previously reported methods [15].

*5.1.2 General Experimental Procedure for the Synthesis of piperazine amide derivatives (**9a-m**, **13a-f** and **16a-f**);*

To the mixture of substituted benzoic acids (**8a-i** and **12a-f** 1 mmol) and HATU (1 mmol), DMF (3mL) was added slowly under nitrogen atmosphere. The reaction mixture was then stirred for 20 minutes at 0 ^{o}C, followed by the addition of substituted 2-arylquinazoline (**7a-c**, **11** and **15**, 1 mmol). The reaction mixture was stirred for 20 minutes at room temperature, followed by the addition of DIPEA. Upon completion of the reaction as monitored by TLC, crushed ice was added to the reaction mixture. The resulting solid was then subjected to vacuum filtration; excess of water was used to wash off the insoluble solids to obtain crude powder which was purified using column chromatography (elution with hexane/EtOAc = 7:3). The pure products were collected as white colour solids in good yields.

*5.1.2.1 N-(4-((2-phenylquinazolin-4-yl)amino)phenyl)-2-naphthamide (**9a**)*

Off-white solid; yield 80 %; mp:160–164 °C; FT-IR (cm^{-1}): 3325, 3062, 1650, 1585, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.51 (s, 1H), 9.93 (s, 1H), 8.64 (s, 1H), 8.60 (d, J = 8.3 Hz, 1H), 8.48 (d, J = 6.4 Hz, 2H), 8.12 (d, J = 6.9 Hz, 1H), 8.09 (s, 2H), 8.04 (d, J = 7.1 Hz, 1H), 7.99-7.94 (m, 4H), 7.89 (d, J = 3.8 Hz, 2H), 7.69-7.61 (m, 3H), 7.53 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 165.8, 159.5, 158.3, 150.9, 138.9, 135.6, 135.5, 134.7, 133.6, 132.8, 132.6, 130.7, 129.4, 128.9, 128.6, 128.5, 128.4, 128.1, 127.3, 126.3, 124.9, 123.5, 123.1, 121.0, 114.5; HRMS (ESI): *m/z* calculated for $C_{31}H_{22}N_4O$ 467.1872 found 467.1896 $[M+H]^+$.

*5.1.2.2 1-phenyl-N-(4-((2-phenylquinazolin-4-yl)amino)phenyl)-1H-1,2,3-triazole-4-carboxamide (**9b**)*

Off-white solid; yield 76 %; mp:163–168 °C; FT-IR (cm^{-1}): 3325, 3059, 1650, 1585, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.64 (s, 1H), 9.91 (s, 1H), 9.49 (d, J = 17.0 Hz, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.49-8.89 (m, 2H), 8.04 (d, J = 7.6 Hz, 2H), 7.97 (s, 3H), 7.88 (d, J = 3.8 Hz, 2H), 7.68-7.62 (m, 3H), 7.57-50 (m, 5H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 159.5, 158.4, 158.3, 150.9, 144.3, 138.8, 136.7, 135.7, 134.8, 133.6, 130.7, 130.4, 129.7, 128.8, 128.5, 128.3, 126.3, 125.9, 123.5, 123.1, 121.1, 121.0, 114.4; HRMS (ESI): *m/z* calculated for $C_{29}H_{21}N_7O$ 484.1886 found 484.1904 $[M+H]^+$.

*5.1.2.3 5-chloro-N-(4-((2-phenylquinazolin-4-yl)amino)phenyl)thiophene-2-carboxamide (**9c**)*

White solid; yield 78 %; mp:161–166 °C; FT-IR (cm^{-1}): 3326, 3042, 1656, 1585, 1040, 770; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.40 (s, 1H), 10.02 (s, 1H), 8.58 (d, J = 8.3 Hz, 3H), 7.99-7.87 (m, 7H), 7.82 (s, 2H), 7.69 (s, 2H), 7.30 (s, 1H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 159.5, 159.1, 158.3, 150.9, 139.8, 138.8, 135.8, 134.5, 134.2, 133.6, 130.7, 129.4, 128.8, 128.7, 128.5, 128.4, 126.4, 123.5, 123.2, 121.1, 114.5; HRMS (ESI): *m/z* calculated for $C_{25}H_{17}ClN_4OS$ 457.0890 found 457.0924 $[M+H]^+$.

*5.1.2.4 4-(dimethylamino)-N-(4-((2-phenylquinazolin-4-yl)amino)phenyl)benzamide (**9d**)*

White solid; yield 73 %; mp:163–167 °C; FT-IR (cm^{-1}): 3325, 3059, 1650, 1585, 770, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.91 (d, J = 9.6 Hz, 1H), 8.83 (s, 1H), 8.74 (d, J = 5.8 Hz, 1H), 8.56 (t, J = 6.4 Hz, 1H), 8.47 (d, J = 5.9 Hz, 1H), 8.33 (s, 1H), 8.19–7.98 (m, 2H), 8.00–

7.84 (m, 4H), 7.81–7.43 (m, 4H), 6.99-6.71 (m, 3H), 3.13 (s, 3H), 3.07–2.97 (m, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 166.5, 136.5, 131.9, 131.6, 131.1, 131.0, 130.9, 130.7, 130.5, 130.2, 130.1, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 126.8, 126.4, 122.5, 115.2, 52.8; HRMS (ESI): *m/z* calculated for $C_{29}H_{25}N_5O$ 460.2137 found 460.2160 $[M+H]^+$.

*5.1.2.5 5-bromo-2-chloro-N-(4-((2-phenylquinazolin-4-yl)amino)phenyl)benzamide (**9e**)*

Light brown solid; yield 78 %; mp:160–165 °C; FT-IR (cm^{-1}): 3325, 3060, 1650, 1585, 780, 710, 680, 605; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.92 (s, 1H), 8.59 (d, *J* = 8.4 Hz, 1H), 8.48-8.44 (m, 2H), 7.96 (d, *J* = 8.9 Hz, 2H), 7.91-7.85 (m, 2H), 7.81 (d, *J* = 8.9 Hz, 2H), 7.74 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.66-7.62 (m, 1H), 7.58–7.49 (m, 5H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 163.6, 159.5, 158.3, 150.9, 139.2, 138.8, 135.7, 135.0, 134.2, 133.6, 132.2, 131.9, 130.7, 129.9, 128.9, 128.5, 128.3, 126.4, 123.5, 123.2, 120.5, 120.2, 114.5; HRMS (ESI): *m/z* calculated for $C_{27}H_{18}BrClN_4O$ 529.0431 found 531.0446 $[M+2]^+$.

*5.1.2.6 4-cyano-N-(4-((2-phenylquinazolin-4-yl)amino)phenyl)benzamide (**9f**)*

Light yellow solid; yield 78 %; mp:159–163 °C; FT-IR (cm^{-1}): 3325, 3060, 2230 1650, 1585, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.55 (s, 1H), 9.93 (s, 1H), 8.59 (d, *J* = 8.3 Hz, 1H), 8.46 (dd, *J* = 7.6, 1.8 Hz, 2H), 8.16 (d, *J* = 8.3 Hz, 2H), 8.06 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.9 Hz, 2H), 7.92–7.87 (m, 4H), 7.66-7.62 (m, 1H), 7.53 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 164.4, 159.5, 158.3, 139.5, 138.7, 135.8, 135.0, 133.7, 132.9, 130.7, 129.0, 128.9, 128.8, 128.5, 128.3, 126.4, 123.4, 123.1, 121.0, 118.8, 114.4, 114.2; HRMS (ESI): *m/z* calculated for $C_{28}H_{19}N_5O$ 442.1668 found 442.1694 $[M+1]^+$.

*5.1.2.7 6-bromo-N-(4-((2-phenylquinazolin-4-yl)amino)phenyl)picolinamide (**9g**)*

Brown solid; yield 72 %; mp:161–165 °C; FT-IR (cm^{-1}): 3325, 3060, 1650, 1585, 780, 710, 680; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.56 (s, 1H), 9.92 (s, 1H), 8.97 (s, 1H), 8.59 (d, *J* = 8.2 Hz, 1H), 8.46 (d, *J* = 6.2 Hz, 2H), 8.29 (d, *J* = 6.3 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 2H), 7.87 (t, *J* = 6.0 Hz, 5H), 7.65–7.60 (m, 1H), 7.52 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 163.2, 159.5, 158.3, 150.9, 150.1, 144.6, 139.0, 138.8, 135.9, 134.9, 133.6, 130.7, 128.8, 128.6, 128.5, 128.4, 128.3, 126.3, 123.4, 123.1, 121.0, 114.4 ; HRMS (ESI): *m/z* calculated for $C_{26}H_{18}BrN_5O$ 495.0695 found 497.0646 $[M+2]^+$.

*5.1.2.8 4-iodo-N-(4-((2-phenylquinazolin-4-yl)amino)phenyl)benzamide (**9h**)*

White solid; yield 79 %; mp:163–168 °C; FT-IR (cm^{-1}): 3325, 3060, 1650, 1585, 780, 710, 680; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.36 (s, 1H), 9.90 (s, 1H), 8.59 (d, J = 8.2 Hz, 1H), 8.47 (d, J = 6.0 Hz, 2H), 7.95 (d, J = 8.6 Hz, 4H), 7.90–7.85 (m, 4H), 7.81 (d, J = 8.2 Hz, 2H), 7.65-761 (m, 1H), 7.52 (t, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 159.4, 158.2, 151.1, 141.8, 138.7, 133.8, 130.8, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 127.4, 126.6, 124.9, 123.5, 122.7, 122.3, 114.6, 114.0.; HRMS (ESI): *m/z* calculated for $C_{27}H_{19}IN_4O$ 543.0682 found 543.0710 $[M+H]^+$.

*5.1.2.9 5-chloro-N-(4-((2-(3,4-dimethoxyphenyl)quinazolin-4-yl)amino)phenyl)thiophene-2-carboxamide (**9i**)*

Yellow solid; yield 80 %; mp:158–162 °C; FT-IR (cm^{-1}): 3325, 3060, 1650, 1585, 1245, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.82 (s, 1H), 10.13 (s, 1H), 8.20–7.97 (m, 4H), 7.83 (s, 2H), 7.69 (s, 1H), 7.51 (s, 1H), 7.39 (s, 1H), 6.73 (s, 2H), 6.56 (s, 1H), 5.00 (s, 1H), 3.96–3.79 (m, 6H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 163.6, 163.4, 161.6, 159.2, 152.3, 149.6, 146.0, 139.8, 134.8, 132.8, 132.3, 128.7, 128.1, 127.7, 126.6, 126.2, 122.7, 121.2, 118.8, 115.0, 114.1, 106.3, 99.0, 56.5, 56.0; HRMS (ESI): *m/z* calculated for $C_{27}H_{21}ClN_4O_3S$ 517.1101 found 517.1125 $[M+H]^+$.

*5.1.2.10 5-bromo-2-chloro-N-(4-((2-(3,4-dimethoxyphenyl)quinazolin-4-yl)amino)phenyl)benzamide (**9j**)*

Yellow solid; yield 75 %; mp:158–162 °C; FT-IR (cm^{-1}): 3325, 3060, 1650, 1585, 1245, 780, 710, 605; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.80 (s, 1H), 9.95 (s, 1H), 8.13 (d, J = 6.7 Hz, 1H), 7.84–7.76 (m, 3H), 7.69 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 4.0 Hz, 1H), 6.77–6.66 (m, 2H), 6.55 (d, J = 8.7 Hz, 2H), 4.98 (s, 1H), 3.90 (d, J = 8.3 Hz, 3H), 3.88 (d, J = 11.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 163.4, 161.6, 159.2, 158.5, 152.3, 149.6, 146.0, 140.3, 134.8, 133.5, 132.3, 129.2, 128.6, 128.5, 127.7, 127.5, 126.6, 126.2, 122.8, 121.5, 121.2, 115.1, 114.1, 106.3, 99.0, 56.5, 56.0; HRMS (ESI): *m/z* calculated for $C_{29}H_{22}BrClN_4O_3$ 589. 0642 found 591. 0622 $[M+2]^+$.

*5.1.2.11 4-cyano-N-(4-((2-(4-cyanophenyl)quinazolin-4-yl)amino)phenyl)benzamide (**9k**)*

Light yellow solid; yield 74 %; mp:157–161 °C; FT-IR (cm^{-1}): 3325, 3060, 2230 1650, 1585, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.57 (s, 1H), 10.03 (s, 1H), 8.60 (dd, J = 13.3, 8.4 Hz, 3H), 8.16 (d, J = 8.1 Hz, 2H), 8.06 (d, J = 8.1 Hz, 2H), 8.00 (d, J = 8.2 Hz, 2H),

7.96–7.87 (m, 6H), 7.69 (d, *J* = 4.2 Hz, 1H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 164.4, 158.5, 157.9, 150.6, 143.1, 139.4, 135.5, 135.2, 133.9, 132.9, 128.9, 128.8, 128.8, 128.7, 127.1, 123.5, 123.3, 121.1, 119.3, 118.8, 114.6, 114.2, 112.9; HRMS (ESI): *m/z* calculated for $C_{29}H_{18}N_6O$ 467.1620 found 467.1648 $[M+H]^+$.

*5.1.2.12 5-chloro-N-(4-((2-(4-cyanophenyl)quinazolin-4-yl)amino)phenyl)thiophene-2-carboxamide (**9l**)*

Yellow solid; yield 77 %; mp:159–163 °C; FT-IR (cm^{-1}): 3325, 3060, 2230 1650, 1585, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.64 (s, 1H), 10.02 (s, 1H), 8.63–8.55 (m, 3H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.99-7.89 (m, Hz, 4H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 2.5 Hz, 1H), 7.57-7.51 (m, 1H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 164.4, 158.5, 157.9, 150.6, 143.1, 139.4, 135.5, 135.2, 133.9, 132.9, 128.9, 128.9, 128.8, 128.7, 127.1, 123.5, 123.3, 121.1, 119.3, 118.8, 114.6, 114.2, 112.9; HRMS (ESI): *m/z* calculated for $C_{26}H_{16}ClN_5OS$ 482.0842 found 482.0870 $[M+H]^+$.

*5.1.2.13 5-bromo-2-chloro-N-(4-((2-(4-cyanophenyl)quinazolin-4-yl)amino)phenyl)benzamide (**9m**)*

Yellow solid; yield 72%; mp:159–163 °C; FT-IR (cm^{-1}): 3325, 3060, 2230 1650, 1585, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.64 (s, 1H), 10.02 (s, 1H), 8.65-8.61 (m, 3H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.92 (t, *J* = 5.9 Hz, 4H), 7.82 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 2.5 Hz, 1H), 7.69-7.66 (m, 1H), 7.55-7.51 (m, 1H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 164.6, 158.4, 157.9, 150.6, 143.1, 141.0, 135.4, 135.2, 134.9, 133.9, 132.9, 131.4, 129.1, 128.9, 128.7, 127.1, 123.5, 123.3, 120.5, 120.2, 119.3, 118.0, 114.6, 112.9; HRMS (ESI): *m/z* calculated for $C_{28}H_{17}BrClN_5O$ 554.0383 found 556.0401 $[M+2]^+$.

*5.1.2.14 5-chloro-N-(3-((2-phenylquinazolin-4-yl)amino)phenyl)thiophene-2-carboxamide (**13a**)*

White solid; yield 81 %; mp:160–164 °C; FT-IR (cm^{-1}): 3326, 3042, 1656, 1585, 1040, 770; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.40 (s, 1H), 10.02 (s, 1H), 8.69–8.45 (m, 3H), 8.06–7.78 (m, 9H), 7.72–7.47 (m, 2H), 7.30 (s, 1H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 164.6, 158.4, 157.9, 150.6, 143.1, 141.0, 135.4, 135.3, 134.9, 133.9, 132.9, 131.4, 129.1, 128.9, 128.7, 127.1, 123.5, 123.3, 120.2, 119.3, 118.0, 114.6, 112.9; HRMS (ESI): *m/z* calculated for $C_{25}H_{17}ClN_4OS$ 457.0890 found 457.0924 $[M+H]^+$.

*5.1.2.15 5-bromo-2-chloro-N-(3-((2-phenylquinazolin-4-yl)amino)phenyl)benzamide (**13b**)*

Brown solid; yield 75 %; mp:159–163 °C; FT-IR (cm^{-1}): 3325, 3060, 1650, 1585, 780, 710, 680, 605; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.63 (s, 1H), 9.99-9.91 (m, 1H), 8.58 (t, J = 10.8 Hz, 1H), 8.49-8.41 (m, 2H), 7.99-7.89 (m, 2H), 7.89-7.82 (m, 3H), 7.81 (d, J = 8.9 Hz, 2H), 7.79-7.89 (m, 1H), 7.65-7.61 (m, 1H), 7.58–7.50 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.6, 160.3, 152.8, 149.2, 139.7, 137.3, 135.1, 133.8, 131.7, 129.4, 127.8, 127.5, 127.1, 126.4, 124.4, 124.1, 123.5, 123.1, 122.3, 121.5, 120.4, 120.2, 117.1, 112.9, 104.6; HRMS (ESI): *m/z* calculated for $C_{27}H_{18}BrClN_4O$ 529.0431 found 531.0446 $[M+2]^+$.

*5.1.2.16 4-cyano-N-(3-((2-phenylquinazolin-4-yl)amino)phenyl)benzamide (**13c**)*

Light yellow solid; yield 76 %; mp:159–163 °C; FT-IR (cm^{-1}): 3325, 3060, 2230 1650, 1585, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.56 (s, 1H), 9.92 (s, 1H), 8.97 (s, 1H), 8.59 (d, J = 8.2 Hz, 1H), 8.46 (d, J = 6.2 Hz, 2H), 8.33–8.23 (m, 1H), 7.97 (d, J = 8.7 Hz, 2H), 7.89-7.78 (m, 5H), 7.75–7.32 (m, 5H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 164.4, 158.5, 157.9, 150.6, 143.1, 139.4, 135.5, 135.2, 133.9, 132.9, 128.9, 128.8, 128.7, 128.4, 127.1, 123.5, 123.3, 121.2, 121.1, 119.3, 118.8, 114.6, 114.2, 112.9; HRMS (ESI): *m/z* calculated for $C_{28}H_{19}N_5O$ 442.1668 found 442.1694 $[M+H]^+$.

*5.1.2.17 4-iodo-N-(3-((2-phenylquinazolin-4-yl)amino)phenyl)benzamide (**13d**)*

White solid; yield 82 %; mp:163–168 °C; FT-IR (cm^{-1}): 3325, 3060, 1650, 1585, 780, 710, 680; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.36 (s, 1H), 9.90 (s, 1H), 8.59 (d, J = 8.2 Hz, 1H), 8.53–8.43 (m, 2H), 7.99-7.93 (m, 4H), 7.92–7.84 (m, 4H), 7.81 (d, J = 8.2 Hz, 2H), 7.67–7.50 (m, 4H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 163.2, 159.5, 158.3, 150.9, 150.1, 144.6, 139.1, 139.0, 138.8, 135.9, 134.9, 133.6, 130.7, 128.8, 128.7, 128.6, 128.4, 128.3, 126.3, 123.4, 123.1, 121.0, 114.4; HRMS (ESI): *m/z* calculated for $C_{27}H_{19}IN_4O$ 543.0682 found 543.0710 $[M+H]^+$.

*5.1.2.18 4-(dimethylamino)-N-(3-((2-phenylquinazolin-4-yl)amino)phenyl)benzamide (**13e**)*

White solid; yield 79%; mp:158–162 °C; FT-IR (cm^{-1}): 3325, 3059, 1650, 1585, 770, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.91 (d, 1H), 8.93–8.51 (m, 3H), 8.47 (d, J = 5.9 Hz, 1H), 8.09-8.01 (m, 2H), 7.97–7.76 (m, 5H), 7.76–7.58 (m, 2H), 7.52 (s, 2H), 7.15 (s, 1H), 6.92–6.88 (m, 1H), 6.79-7.68 (m, 1H), 3.13 (s, 3H), 3.08–2.96 (m, 3H); ^{13}C NMR (125 MHz,

DMSO- d_6): δ 166.5, 136.5, 131.9, 131.8, 131.6, 131.1, 131.0, 130.9, 130.7, 130.5, 130.2, 130.1, 128.9, 128.7, 128.6, 128.4, 128.1, 127.9, 127.8, 126.8, 126.4, 122.5, 115.2, 52.8; HRMS (ESI): m/z calculated for $C_{29}H_{25}N_5O$ 460.2137 found 460.2160 [M+H] +.

*5.1.2.19 6-bromo-N-(3-((2-phenylquinazolin-4-yl)amino)phenyl)-2-naphthamide (**13f**)*

Light brown solid; Yield 81 %; mp: 163-168 ^oC; FT-IR (cm^{-1}): 3325, 3062, 1650, 1585, 780, 710; ^1H NMR (500 MHz, DMSO-d_6): δ 10.58 (s, 1H), 9.97 (s, 1H), 8.71-8.61 (m, 4H), 8.55 (s, 1H), 8.32 (s, 1H), 8.15–8.09 (m, 3H), 8.03 (d, *J* = 5.9 Hz, 2H), 7.90 (s, 2H), 7.75 (d, *J* = 15.6 Hz, 2H), 7.64 (s, 1H), 7.49 (s, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 165.8, 159.5, 158.3, 150.9, 138.9, 135.6, 135.5, 134.7, 134.7, 133.6, 132.8, 132.8, 132.6, 130.7, 129.7, 129.4, 128.9, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.3, 126.3, 124.9, 123.5, 123.1, 121.0, 114.5; HRMS (ESI): m/z calculated for $C_{31}H_{21}BrN_4O$ 545.0977 found 542.0966 [M+2] +.

*5.1.2.20 N-(3,5-dimethoxyphenyl)-4-((2-phenylquinazolin-4-yl)amino)benzamide (**17a**)*

White solid; Yield 78 %; mp: 165-169 ^oC; FT-IR (cm^{-1}): 3320, 3053, 1645, 1582, 780, 710; ^1H NMR (500 MHz, DMSO-d_6): δ 10.14 (s, 1H), 10.10 (s, 1H), 8.65 (d, *J* = 8.2 Hz, 1H), 8.51 (d, *J* = 6.8 Hz, 2H), 8.22 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 8.4 Hz, 2H), 7.93 (s, 2H), 7.68 (s, 1H), 7.56 (d, *J* = 7.3 Hz, 3H), 7.15 (s, 2H), 6.28 (s, 1H), 3.77 (s, 6H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 165.4, 160.8, 159.4, 158.2, 151.1, 143.1, 141.5, 138.6, 130.9, 129.6, 129.0, 128.8, 128.7, 128.4, 126.6, 123.6, 121.3, 114.6, 99.0, 96.1, 55.6; HRMS (ESI): m/z calculated for $C_{29}H_{24}N_4O_3$ 477.1927 found 477.1960 [M+H] +.

*5.1.2.21 4-((2-phenylquinazolin-4-yl)amino)-N-(3,4,5-trimethoxyphenyl)benzamide (**17b**)*

White solid; Yield 77 %; mp: 163-167 ^oC; FT-IR (cm^{-1}): 3320, 3053, 1645, 1582, 780, 710; ^1H NMR (500 MHz, DMSO-d_6): δ 10.48 (s, 1H), 10.13 (s, 1H), 8.63 (d, *J* = 8.3 Hz, 1H), 8.30 (s, 1H), 8.26 (d, *J* = 8.8 Hz, 2H), 8.18-8.10 (m, 3H), 7.93 (t, *J* = 7.0 Hz, 2H), 7.86 (s, 2H), 7.73–7.52 (m, 3H), 7.47 (d, *J* = 7.7 Hz, 1H), 3.94 (s, 6H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 165.7, 158.8, 158.0, 153.3, 152.7, 151.1, 143.4, 140.6, 140.2, 133.9, 130.3, 129.2, 128.7, 128.6, 126.5, 124.2, 123.5, 121.5, 116.8, 114.4, 105.6, 60.6, 56.2; HRMS (ESI): m/z calculated for $C_{30}H_{26}N_4O_4$ 507.2032 found 407.2060 [M+H] +.

*5.1.2.22 N-(3-chloro-4-fluorophenyl)-4-((2-phenylquinazolin-4-yl)amino)benzamide (**17c**)*

White solid; Yield 70 %; mp: 157-161 ^{o}C; FT-IR (cm^{-1}): 3320, 3053, 1645, 1582, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.37 (s, 1H), 10.14 (s, 1H), 8.64 (t, J = 8.2 Hz, 1H), 8.50 (t, J = 7.5 Hz, 2H), 8.39–8.18 (m, 2H), 8.18–8.00 (m, 3H), 7.93 (d, J = 2.8 Hz, 2H), 7.90–7.76 (m, 1H), 7.75–7.66 (m, 1H), 7.55 (t, J = 9.1 Hz, 3H), 7.44 (t, J = 9.1 Hz, 1H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 162.7, 159.3, 158.3, 152.8, 135.0, 134.1, 133.2, 131.8, 131.1, 129.0, 128.4, 128.2, 128.1, 127.8, 127.0, 126.8, 126.3, 124.1, 123.6, 122.5, 122.4, 121.4, 114.5; HRMS (ESI): m/z calculated for $C_{27}H_{18}ClFN_4O$ 469.1231 found 469.1250 [M+H] +.

*5.1.2.23 Ethyl 3-(4-((2-phenylquinazolin-4-yl)amino)benzamido)propanoate (**17d**)*

White solid; Yield 80 %; mp: 155-159 ^{o}C; FT-IR (cm^{-1}): 3320, 3053, 1645, 1582, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.04 (s, 1H), 8.62 (d, J = 8.1 Hz, 1H), 8.58–8.39 (m, 3H), 8.13 (d, J = 8.0 Hz, 2H), 8.03–7.85 (m, 4H), 7.66 (s, 1H), 7.54 (s, 3H), 4.10 (d, J = 7.0 Hz, 2H), 3.54 (d, J = 5.6 Hz, 2H), 2.62 (s, 2H), 1.22-1.17 (m, 3H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 171.8, 166.3, 159.4, 158.2, 151.0, 142.6, 138.6, 133.9, 130.8, 129.3, 128.9, 128.6, 128.3, 128.2, 126.6, 123.5, 121.4, 114.5, 60.4, 36.0, 34.3, 14.5; HRMS (ESI): m/z calculated for $C_{26}H_{24}N_4O_3$ 441.1927 found 441.1960 [M+H] +.

*5.1.2.24 Ethyl (4-((2-phenylquinazolin-4-yl)amino)benzoyl)leucinate (**17e**)*

White solid; Yield 79 %; mp: 152-156 ^{o}C; FT-IR (cm^{-1}): 3320, 3053, 1645, 1582, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.07 (d, J = 12.4 Hz, 1H), 8.69-8.60 (m, 2H), 8.49 (d, J = 6.8 Hz, 1H), 8.16 (d, J = 8.1 Hz, 2H), 8.07–7.96 (m, 2H), 7.91 (s, 2H), 7.84 (s, 1H), 7.66 (s, 2H), 4.55 (s, 1H), 3.88-3.81 (m, 2H), 3.68 (s, 1H), 3.48 (s, 3H), 1.86-1.65 (m, 3H), 1.13-0.93 (m, 6H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 173.7, 166.5, 159.4, 158.2, 153.3, 151.0, 142.9, 138.6, 133.9, 130.8, 128.9, 128.6, 128.3, 126.6, 123.5, 121.6, 121.3, 114.5, 56.2, 52.3, 51.4, 24.9, 23.3, 21.6; HRMS (ESI): m/z calculated for $C_{29}H_{30}N_4O_3$ 483.2396 found 483.2426 [M+H] +.

*5.1.2.25 N-((4-chlorobenzyl)oxy)-4-((2-phenylquinazolin-4-yl)amino)benzamide (**17f**)*

White solid; Yield 8 %; mp: 152-156 ^{o}C; FT-IR (cm^{-1}): 3320, 3053, 1645, 1582, 1550, 780, 710; ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.75 (s, 1H), 10.06 (s, 1H), 8.62 (d, J = 8.4 Hz, 1H), 8.50-8.46 (m, 2H), 8.14 (d, J = 8.7 Hz, 2H), 7.96-7.91 (m, 4H), 7.69–7.64 (m, 1H), 7.55 (t, J = 6.1 Hz, 3H), 7.50 (d, J = 6.9 Hz, 2H), 7.45-7.37 (m, 3H), 4.97 (s, 2H); ^{13}C NMR (125 MHz, DMSO- d_6): δ 159.4, 158.2, 151.1, 143.0, 138.6, 136.5, 133.9, 130.9, 129.3, 128.9,

128.8, 128.7, 128.4, 128.2, 127.2, 126.6, 123.6, 121.5, 114.5, 77.5; HRMS (ESI): m/z calculated for $C_{28}H_{21}ClN_4O_2$ 481.1431 found 481.1456 [M+H] +.

5.2 Antibiotic susceptibility testing against ESKAP pathogen panel

Antibiotic susceptibility testing was carried out on the newly synthesized compounds by determining the Minimum Inhibitory Concentration (MIC) with reference to the standard CLSI guidelines [17, 18]. MIC is defined as the minimum concentration of compound at which visible bacterial growth is inhibited. Bacterial cultures were grown in Mueller-Hinton cation supplemented broth (CA-MHB). Optical density (OD_{600}) of the cultures was measured, followed by dilution for ~10^6 cfu/mL. This inoculum was added into a series of test wells in a microtitre plate that contained various concentrations of compound under test ranging from 64-0.03 μg/mL. Controls i.e., cells alone and media alone (without compound+cells) and levofloxacin used as a reference standard. Plates were incubated at 37 °C for 16-18 h followed by observations of MIC values by the absence or presence of visible growth. For each compound, MIC determinations were performed independently thrice using duplicate samples each time.

5.3 Antibiotic susceptibility testing against pathogenic mycobacteria

Antimycobacterial susceptibility testing was carried out on the newly synthesized compounds by using broth micro dilution assay [19]. 1g/100 mL stock solutions of test and control compounds were prepared in DMSO and stored in −20 °C. Mycobacterial cultures were inoculated in Middlebrook 7H9 enriched (Difco, Becton, NJ, USA) media supplemented with 10% ADC-Tween-80 (Bovine Serum Albumin, Dextrose, 0.2% glycerol and 0.05% Tween-80) and OD_{600} of the cultures was measured, followed by dilution to achieve ~10^6 cfu/mL [20]. The newly synthesized compounds were tested from 0.0064–0.00005 g/100 mL in two-fold serial diluted fashion with 2.5 µL of each concentration added per well of a 96-well round bottom microtitre plate. Later, 97.5 µL of bacterial suspension was added to each well containing the test compound along with appropriate controls. Presto blue (Thermo Fisher, USA) resazurin-based dye was used for the visualized identification of active compounds. MIC of active compound was determined as lowest concentration of compound that inhibited visible growth after incubation period. For each compound, MIC determinations were replicated thrice using duplicate samples. The MIC plates were incubated at 37 °C for 7 days for Mtb.

5.4 Molecular docking:

The crystal co-ordinates of Glmu were retrieved from the protein data bank (PDB ID: 4K6R). The 3D structure of ligands was drawn on Maestro Molecule Builder of of Schrödinger suite 2015-4.9 version 10.4. The molecules were optimized using OPLS_2005 force field in LigPrep 3.6 module of Schrödinger suite 2015-4.9. Docking procedure [21] was performed according to the default settings implemented in maestro software, version 10.4 and the ligands was docked into the binding site of GlmU (PDB ID: 4K6R).

5.4.1 Binding energy calculations for Active molecules with binding site of GlmU

The MM/GBSA (Molecular mechanics/generalized born surface area) analysis was used to calculate ligand-binding energies based on docking complex, using the MM/GBSA technology available in Prime module of Schrodinger software [22]. We performed binding energy calculations of docked complexes of GlmU with the active molecules and the results were depicted in **Table 2**.

Conflicts of interest

The authors declare no conflicts of interest.

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Synthesis, biological evaluation and molecular modelling insights of 2-arylquinazoline benzamide derivatives as anti-tubercular agents

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Highlights:

1. New 2-arylquinazoline aminobenzamide derivatives were synthesized successfully, with simple reaction conditions.
2. A series of 25 molecules were screened against *Mycobacterium tuberculosis* $H_{37}R_V$ strain for the anti-mycobacterial activity.
3. **9a**, **9c**, **9d**, **9e**, **9f**, **9h**, **13b**, **17d** and **17e** displayed potent and specific anti-mycobacterial activity against *Mycobacterium tuberculosis* with MIC values in range of 4-32 μg/mL.
4. 2 molecules (**9e** and **9f**) identified as potent leads, with the minimum inhibitory concentration of 4 μg/mL, respectively.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflicts of interest

The authors declare no conflicts of interest.