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Synthesis and characterization of a novel series of *N*-acylpiperazinyl-4-anilinoquinazoline derivatives

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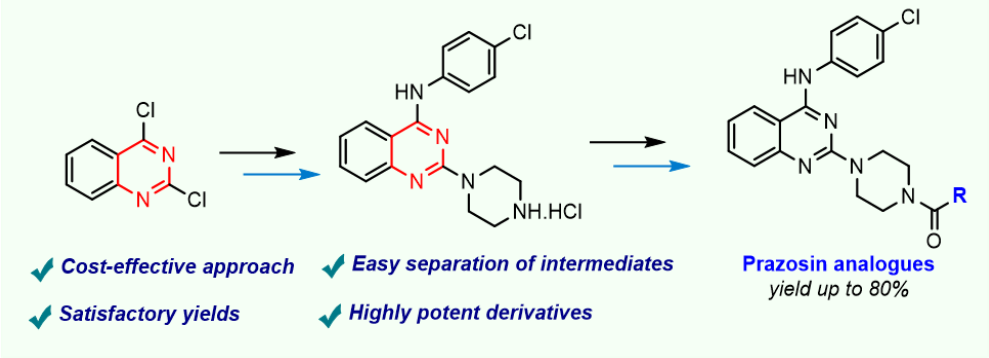
Abstract

Quinazoline is a privileged scaffold in medicinal chemistry, forming the core of numerous clinically important drugs. In this study, a novel series of *N*-acylpiperazinyl-4-anilinoquinazoline derivatives was synthesized starting from 2,4-dichloroquinazoline, via sequential C4 and C2 displacement with 4-chloroaniline and *tert*-butyl piperazine-1-carboxylate, followed by Boc deprotection and HATU-mediated amide coupling with diverse carboxylic acids. The synthesized analogs were characterized by spectroscopic methods. This modular route provides a practical platform for the future design of quinazoline-piperazine hybrid derivatives.



Keywords: Quinazoline; piperazine; anilino quinazoline; HATU-mediated coupling

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Introduction

Heterocyclic compounds constitute one of the most important classes of organic molecules in medicinal chemistry, owing to their widespread presence in natural products, pharmaceuticals, and biologically active agents. Nitrogen-containing organic compounds have attracted considerable attention owing to their diverse biological activities and potential applications in medicinal chemistry.[1-2] Among them, nitrogen-based heterocycles and related compounds in particular played a fundamental role in drug design, since they closely mimicked the structural and electronic features of endogenous biomolecules such as nucleic acid bases, amino acids, and cofactors, which allowed them to interact effectively with a broad range of biological targets.[3-6] Among these scaffolds, quinazoline emerged as a privileged heterocyclic core due to its structural resemblance to purine and pteridine bases and its remarkable versatility across therapeutic areas. Quinazoline derivatives exhibited diverse pharmacological activities including antihypertensive, antitumor, antimicrobial, antiviral, and anti-inflammatory effects.[7-11] Substitution patterns on the quinazoline ring, particularly at the 2- and 4-positions, proved especially consequential for biological activity. Introduction of a piperazine ring at the 2-position gave rise to a well-established class of α1-adrenergic antagonists exemplified by prazosin, terazosin, and doxazosin.[12-14] Installation of an arylamino group at the 4-position defined a distinct pharmacophore central to EGFR tyrosine kinase inhibitors such as gefitinib and vandetanib, where the aniline NH engaged in a critical hydrogen-bonding interaction within the ATP-binding pocket.[15-19] Combining these two structural motifs within a single quinazoline scaffold generated hybrid molecules that merged features of both pharmacophore classes and offered a rational strategy for exploring novel structure-activity relationships. It is this convergence of synthetic accessibility, structural versatility, and multitarget pharmacological potential that established quinazoline as a truly privileged core among heterocyclic molecules, and the rationale for its continued selection as the foundational scaffold in the present study.

Present studies have highlighted diverse pharmacological approaches and their potential therapeutic applications across various disease areas.[20-24] These investigations have further extended the scope of nitrogen-containing molecules and related chemical systems, demonstrating their broad relevance in medicinal chemistry, biological research, diagnostic applications, and therapeutic development.[25-29] In this context, the pharmacological versatility of the quinazoline core was well illustrated by the diverse array of clinically important drugs built upon this scaffold (Fig. 1).[30-33] Prazosin and its analogs doxazosin and terazosin, all sharing a 2-piperazinyl-4-aminoquinazoline core differing only in the piperazine acyl cap, represented a class of selective α1-adrenergic receptor antagonists used in the treatment of hypertension and, in the latter two cases, benign prostatic hyperplasia.

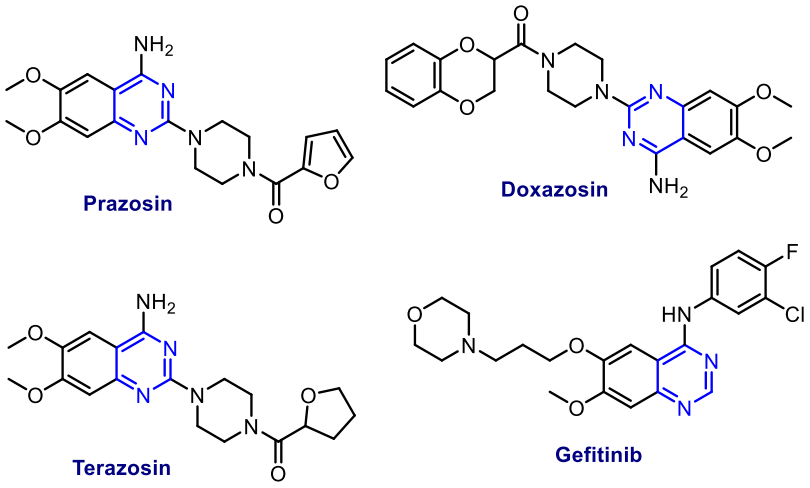

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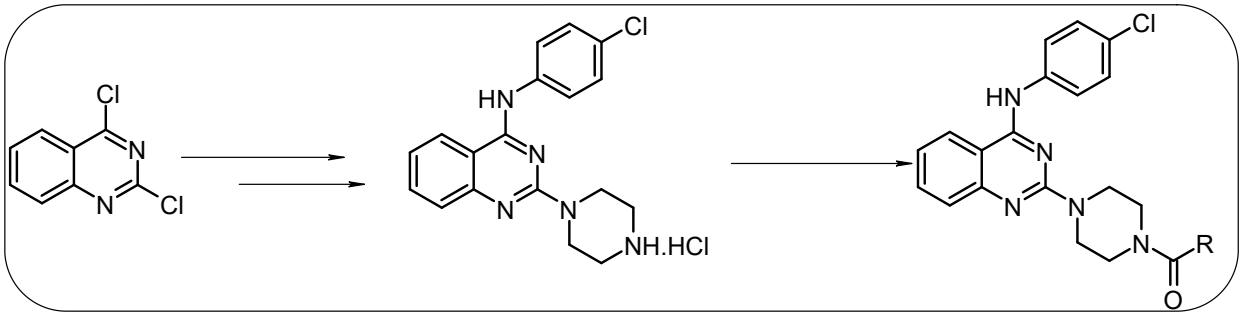
Figure 1. Structures of some clinically important quinazoline-based drugs.

Emerging research has further advanced the exploration of natural products and bioactive molecules, emphasizing their structural diversity, biological activities, and potential therapeutic applications.[34-38] In parallel, the 4-anilinoquinazoline pharmacophore has emerged as an important scaffold in anticancer drug development, giving rise to several epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, including gefitinib and erlotinib, which are established therapies for non-small cell lung cancer (NSCLC). Further structural modifications of this scaffold led to vandetanib, a dual EGFR/VEGFR inhibitor, and afatinib, an irreversible inhibitor of EGFR and HER2, demonstrating its versatility in the development of targeted anticancer agents.[39-43] These examples underscored the remarkable pharmacophoric plasticity of the quinazoline nucleus, wherein subtle changes in substitution at the 2- and 4-positions dictated distinct mechanisms of action, ranging from adrenergic receptor antagonism to kinase inhibition.[44-46] Inspired by this structural versatility, particularly the contrasting bioactivity profiles arising from 2-piperazinyl and 4-arylamino substitution, we sought to synthesize a hybrid quinazoline derivative incorporating both motifs, with the piperazine nitrogen further functionalized as a benzamide, as shown in Scheme 1.



Scheme 1. Synthetic route for the preparation of (4-(4-((4-chlorophenyl)amino)quinazolin-2-yl)piperazin-1-yl) derivative.

Results and Discussion

Considering the immense importance of the quinazoline pharmacophore, the target compound was synthesized through a four-step sequence starting from commercially available 2,4-dichloroquinazoline **1**. Selective displacement of the more electrophilic C4 chlorine was achieved by treatment with 4-chloroaniline **2** in the presence of DIPEA in DMF at 50°C, exploiting the inherent difference in reactivity between the C2 and C4 positions of the 2,4-dichloroquinazoline to afford the 4-arylaminoquinazoline intermediate **3** in 78% yield. The remaining C2 chlorine was subsequently displaced by *tert*-butyl piperazine-1-carboxylate **4** under more forcing conditions (DIPEA, DMF, 120°C, 8 h, see Table 1), installing the Boc-protected piperazine ring and delivering the corresponding intermediate **5** in 75% yield. Boc deprotection was carried out using 4 M HCl in 1,4-dioxane at 0 °C to room temperature, furnishing the free piperazine as its hydrochloride salt **6** in 80% yield. Finally, HATU-mediated amide coupling between the liberated piperazine nitrogen and benzoic acid, performed in the presence of DIPEA in DMF at 0 °C to room temperature over 12 h, furnished the target benzoyl piperazinyl quinazoline **7** in 70–80% yield. This route allowed sequential and regioselective functionalization of both the C2 and C4 positions of the quinazoline core, enabling late-stage installation of the acyl cap on the piperazine nitrogen and providing a flexible platform for generating structurally diverse analogs bearing different aroyl or acyl substituents.

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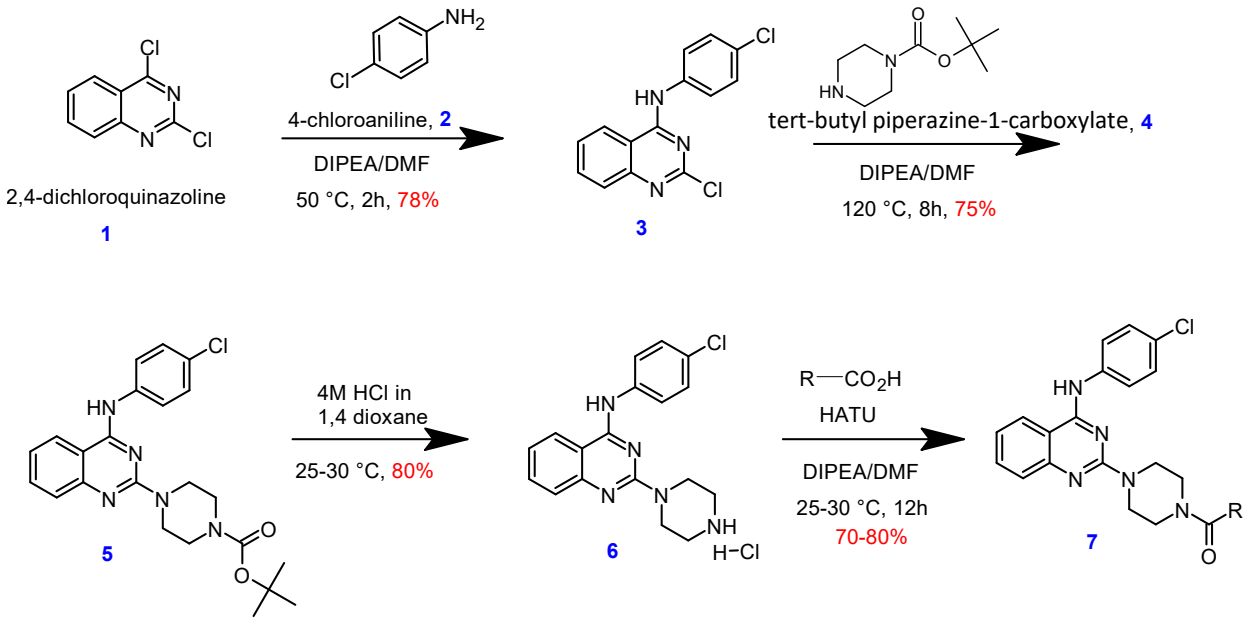
Table 1. Optimization of the temperature to synthesize **4**.

Solvent	Temperature	Yield
DMF	50 °C	10%
DMF	80 °C	50 %
DMF	120 °C	75%



Reagents and conditions*:* (a) 4-chloroaniline, DIPEA, DMF, 50 °C, 2 h, 78%; (b) *tert*-butyl piperazine-1-carboxylate, DIPEA, DMF, 120 °C, 8 h, 75%; (c) 4 M HCl in 1,4-dioxane, 25-30 °C , 80%; (d) Acid substrate, HATU, DIPEA, DMF, 25-30 °C , 12 h, 70–80%.

With the key intermediate **6** in hand, a small library of *N*-acylpiperazine analogs (**7a**–**7k**) was synthesized by coupling the free piperazine nitrogen with a structurally diverse panel of carboxylic acids under HATU/DIPEA-mediated amide coupling conditions, affording the target compounds in good to excellent yields (Scheme 2). This panel was designed to systematically probe the influence of the piperazine acyl cap on the physicochemical properties of the parent anilinoquinazoline scaffold while holding the 4-((4-chlorophenyl)amino)quinazolin-2-yl)piperazine core constant. Simple substituted benzoyl caps bearing varying halogen and methoxy substitution patterns were explored in compounds **7i**, **7j**, and **7k**, incorporating 2,4,6-trifluorobenzoyl, 4-chlorobenzoyl, and 4-fluoro-3-methoxybenzoyl groups, respectively, to assess the effect of electronic variation directly on the aryl ring proximal to the carbonyl. Fused bicyclic and heteroaromatic caps were incorporated in compounds **7b**, **7c**, **7f**, and **7g**, comprising 5-chloro- and 5-fluoro-substituted indole-2-carbonyl groups as well as benzodioxole and difluorobenzodioxole-4-carbonyl systems, introducing additional hydrogen-bond donor or acceptor character alongside increased ring planarity relative to the simple benzoyl analogs. Conformationally restricted cyclopropane-spaced aryl caps were examined in compounds **7e** and **7h**, wherein a cyclopropane ring was interposed between the carbonyl and a para-methoxyphenyl or phenyl group, respectively, with compound **7h** additionally fixing trans stereochemistry across the cyclopropane to probe the effect of defined spatial orientation. An extended polar cap bearing a morpholine-substituted benzoyl group was incorporated in compound **7d** to introduce an additional basic, hydrogen-bond-accepting

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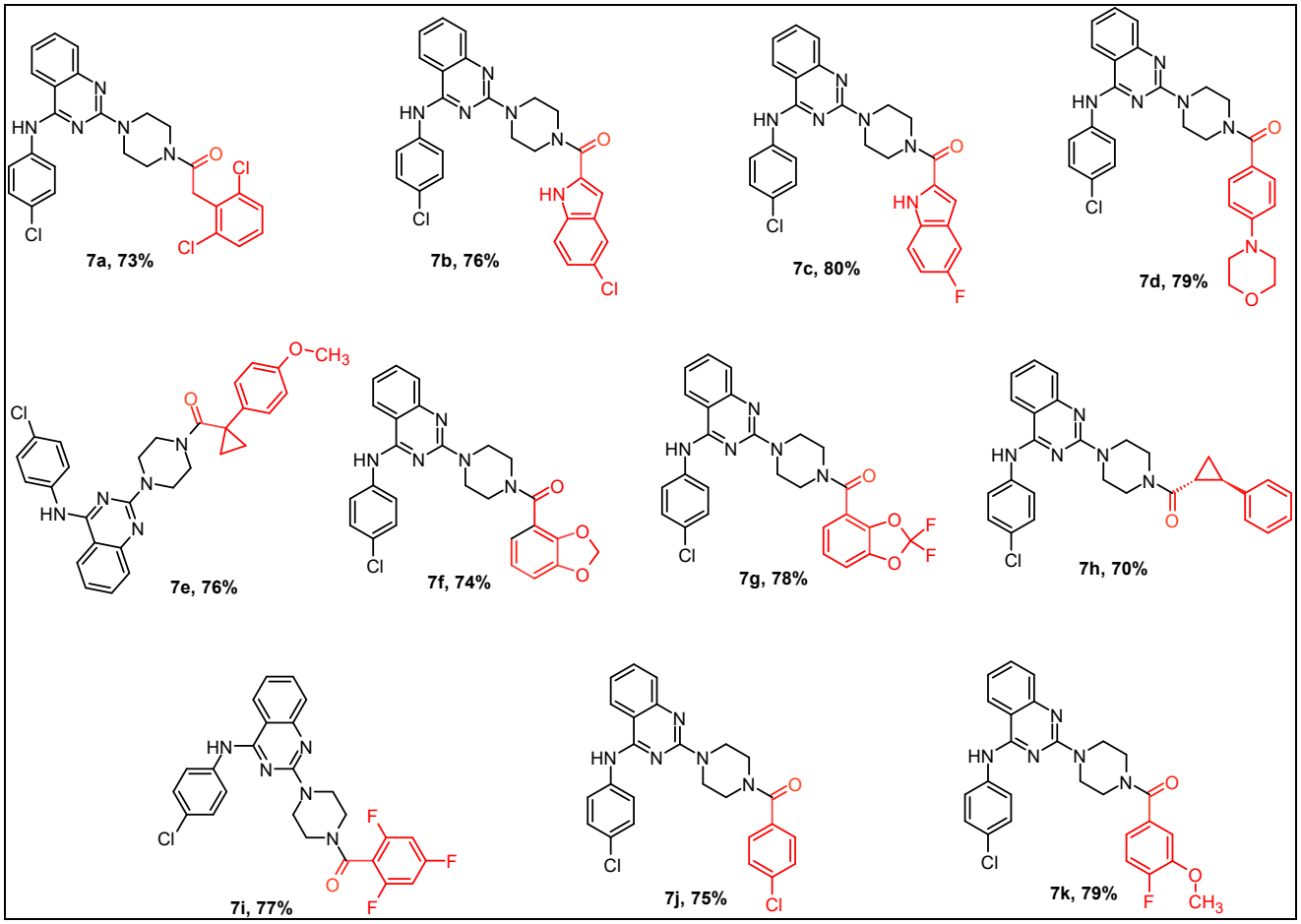
center and improve predicted aqueous solubility, while compound **7a** employed a non-aromatic acetyl spacer bearing a 2,6-dichlorophenyl group, extending the aryl substituent one methylene further from the carbonyl relative to the direct benzoyl analogs. The consistently high yields obtained across this structurally diverse acid panel, ranging from ortho-disubstituted and heteroaromatic to cyclopropane-fused carboxylic acids, indicated that the HATU-mediated coupling step was broadly tolerant of both steric and electronic variation in the acyl donor.



Scheme 2. Synthesis of the N-acylpiperazine analog series (**7a**–**7k**) from intermediate 6. Reagents and conditions: corresponding carboxylic acid, HATU, DIPEA, DMF, 25-30 °C, 12 h.

Conclusions

In summary, a novel series of *N*-acylpiperazinyl-4-anilinoquinazoline derivatives (**7a–7k**) was designed and synthesized through a concise four-step route from commercially available 2,4-dichloroquinazoline, involving sequential displacement of the C4 and C2 chlorines with 4-chloroaniline and *tert*-butyl piperazine-1-carboxylate, followed by Boc deprotection and HATU-mediated amide coupling with a structurally diverse panel of carboxylic acids. This strategy proved efficient and broadly tolerant, delivering all eleven analogs in consistently good yields (70–80%) despite considerable variation in the electronic and steric nature of the acyl coupling partners. The resulting library systematically varied the piperazine *N*-acyl cap while preserving the conserved 4-((4-chlorophenyl)amino)quinazolin-2-yl)piperazine core, providing a structurally diverse analog set suitable for further structure-activity relationship studies. This modular and late-stage diversifiable

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synthetic route may serve as a useful platform for the future design and development of related quinazoline-piperazine hybrid derivatives with potential pharmacological relevance.

Experimental Section

General. All starting materials and commercial reagents were purchased from Alfa Aesar, Sigma-Aldrich, Spectrochem, and TCI. Thin-layer chromatography plates were visualized by exposure to ultraviolet light (UV) with 254 nm of wavelength and then further analyzed using an iodine chamber. Thin-layer chromatography was performed using pre-coated plates. Column chromatography was performed in 120 to 200 mesh size silica gel. The reactions were carried out in a round-bottom flask and a sealed tube. The crude product was examined by SIMADZU GC-MS (Selected Ion Monitoring and all NMR spectra were recorded by Bruker Avance 400 spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz). Chemical shifts for ^{1}H NMR spectra have been reported in parts per million (ppm) from tetramethylsilane, with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm). Similarly,^{13}C NMR spectra have been reported in parts per million (ppm) from tetramethylsilane, with the solvent as the internal standard ($CDCl_3$: δ 77.00 ppm). The ^{1}H NM Rand ^{13}C NMR of the known products were compared with literature reports.

Synthesis of 2-chloro-*N*-(4-chlorophenyl) quinazolin-4-amine (3). Compound **1** (10 gm, 0.050 mole, 1.0 equiv.) with 4-chloroaniline (7.05 gm,0.055 mole, 1.1 equiv.) in the presence of diisopropylethylamine (DIPEA) (26.1 mL, 0.15 mole, 3 equiv.) in *N, N*-dimethylformamide (DMF) (50 mL, 5 vol.). The reaction mixture was stirred at 50 °C for 2 h, and the progress was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was diluted with water and extracted with Dichloromethane (DCM) (50 mL, 5 vol.). The organic phase was separated, washed with saturated aqueous sodium chloride solution (50 mL, 5 vol.), and concentrated under reduced pressure to afford the desired product as a white solid. The target compound was isolated in (11.3 gm 78% yield).

Synthesis of *tert*-Butyl 4-[4-(4-chloroanilino)quinazolin-2-yl]piperazine-1-carboxylate (5). Compound **3** (10 gm,0.034 mole, 1.0 Eq) with tert-butyl piperazine-1-carboxylate (7.06 gm,0.037 mole, 1.1 Eq) in the presence of diisopropylethylamine (DIPEA) (17.8 mL, 0.102 mole, 3 equiv.) in *N, N*-dimethylformamide (DMF) (50 mL, 5 vol.). The reaction mixture was stirred at 120 °C for 8 h in a sealed vessel, and the progress was monitored by thin-layer chromatography (TLC). Upon completion, the reaction mixture was diluted with water and extracted with dichloromethane (DCM) (50 mL, 5 Vol). The organic phase was separated, washed with saturated aqueous sodium chloride solution (50 mL, 5 Vol), and concentrated under reduced pressure to afford the desired product as a white solid. The target compound was isolated (11.21 gm 75% yield).

***N*-(4-Chlorophenyl)-2-(piperazin-1-yl)quinazolin-4-amine Hydrochloride (6).** Compound **5** (10 gm,0.022 mole, 1.0 Eq) was added to 4 M hydrochloric acid in dioxane (30 ml ,3Vol) at 0-5 °C. Then it was stirred at 25–30 °C. The reaction mixture was stirred for 3 h, and the progress of the reaction was monitored by thin-layer chromatography (TLC). Upon completion, the solvent was removed under reduced pressure, and the resulting residue was triturated with a dichloromethane (DCM)/methyl tert-butyl ether (MTBE) mixture 1:4 (50 mL, 5Vol) to afford the desired hydrochloride as a solid. The isolated solid was dried under vacuum to furnish the desired product in (6.8 gm 80% yield)

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General procedure for the synthesis of novel derivatives, 7a-7k. Compounds **7a-7k were** efficiently prepared from **6** (1.0 Eq) through reaction with the respective acid in DMF (5.0 vol) using DIPEA (3.0 Eq.) & coupling reagent HATU (1.2 eq) for 12 hr at 25–30 °C. Following aqueous workup and extraction with DCM, the desired product was obtained as a solid after solvent removal and purification by column chromatography. Compounds 7a-7k were isolated, demonstrating the effective yield of the synthetic protocol.

2-Chloro-*N*-(4-chlorophenyl)quinazolin-4-amine (3). Off white solid, (Yield 78%) **^{1}H NMR** (500 MHz, DMSO) δ 7.82-7.79 (d, *J* 5.3 Hz, 1H), 7.74-7.73 (dd, *J* 8.1 Hz, *J* 2.3 Hz, 3H), 7.72-7.71 (dd, *J* 8.3 Hz, *J* 2.1 Hz 2H), 7.57-7.54 (dd, *J* 8.1 Hz, *J* 2.3 Hz, 1H), 7.39-7.36 (dd, *J* 8.3 Hz, *J* 2.1 Hz 2H); **^{13}C NMR** (500 MHz, $CDCl_3$) δ 158.50, 157.04, 151.31, 136.04, 134.03, 130.18, 129.19, 129.19, 128.15, 126.96, 122.97, 122.97, 120.67, 113.37; m/z (M + H) calc for $C_{14}H_9Cl_2N_3^+$, 290.2; found 291.20.

***tert*-Butyl 4-[4-[(4-chlorophenyl)amino]quinazolin-2-yl]piperazine-1-carboxylate (5).** Light Yellow solid, (yield 80%) **^{1}H NMR** (500 MHz, DMSO) δ 9.66 (s, 1H), 8.29 (d, *J* 8.3 Hz, 1H), 7.86-7.83 (d, *J* 8.2 Hz, 2H), 7.64-7.60 (dd, *J* 8.3 Hz, *J* 8.2 Hz, 1H), 7.48-7.45 (d, *J* 8.2 Hz, 2H), 7.39-7.38 (d, *J* 8.1 Hz, 1H), 7.23-7.19 (dd, *J* 8.3 Hz, *J* 8.2 Hz 1H), 3.74 (t, 4H), 3.42 (t, 4H), 1.43 (s, 9H); **^{13}C NMR** (500 MHz, DMSO) δ158.44, 154.45, 152.81, 138.81, 133.55, 128.81, 128.81, 127.26, 125.94, 123.89, 123.89, 123.53, 122.00, 111.01, 79.45, 28.57; m/z (M + H) calc for $C_{23}H_{26}ClN_5O_2^+$, 440.9; found 440.9

***N*-(4-Chlorophenyl)-2-(piperazin-1-yl)quinazolin-4-amine Hydrochloride (6).** Off white solid, (Yield 75%,) **^{1}H NMR** (500 MHz, DMSO) δ 13.55 (bs, 1H), 11.30 (s, 1H), 9.27 (s, 1H), 8.78 (d, *J* 8.3 Hz, 1H), 8.18 (d, *J* 8.2 Hz, 1H), 7.89 (d, *J* 8.3 Hz, 1H), 7.78 (d, *J* 8.2 Hz, 2H), 7.55-7.52 (d, *J* 8.1 Hz, 3H), 4.18 (t, 4H), 3.34 (t, 4H); **^{13}C NMR** (500 MHz, DMSO) 158.63, 152.43, 136.47, 135.88, 130.21, 129.66, 129.09, 126.29, 125.41, 125.12, 118.53, 110.44, 53.73, 42.78, 42.43, 40.49, 18.43, 17.17; m/z (M + H) calc for $C_{18}H_{19}Cl_2N_5^+$, 340.8; found 340.8

1-{4-[4-[(4-Chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}-2-(2,6-dichlorophenyl)ethan-1-one (7a). ^{1}H NMR (500 MHz, DMSO) δ 0.97 (s, 1H), 7.86-7.84 (d, *J* 8.1 Hz, 1H), 7.65-7.62 (d, *J* 8.3, 8.6 Hz, 2H), 7.47-7.45 (t, *J* 8.1Hz, 1H), 7.42-7.40 (dd, *J* 8.1Hz, *J* 8.3Hz, 4H), 7.42-7.40 (d, *J* 8.1Hz, 1H), 7.34-7.30 (d, *J* 8.6 Hz, 1H), 7.24-7.21 (t, *J* 8.6 Hz, 1H), 4.06 (s, 2H), 3.88 (s, 2H), 3.77 (s, 4H), 3.60-3.58 (t, 2H). ^{13}C NMR (500 MHz, DMSO) δ 166.82, 158.41, 152.69, 147.61, 138.80, 135.92, 133.61, 133.57, 129.24, 129.24, 128.79, 128.79, 128.46, 127.3, 127.33, 125.91, 124.05, 123.55, 121.82, 111.10, 45.50, 45.50, 44.50, 44.50, 44.09, 41.91, 36.08. m/z (M + H) calc for $C_{26}H_{22}Cl_3N_5O^+$, 525.0968; found 525.0973.

(5-Chloro-1*H*-indol-2-yl){4-[4-[(4-chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}methanone (7b). ^{1}H NMR (500 MHz, DMSO) δ 11.84 (s, 1H), 9.67 (s, 1H), 8.33-8.31 (d, *J* 8.5 Hz, 1H), 7.88-7.86 (d, *J* 8.1 Hz, 2H), 7.69-7.68 (d, *J* 8.5 Hz, 1H), 7.65-7.64 (t, *J* 8.1 Hz, 1H), 7.47-7.41 (td, *J* 8.5 Hz, *J* 8.1 Hz, 4H), 7.24-7.20 (t, *J* 8.1 Hz, 2H), 6.88-6.87 (s, 1H), 3.89 (t, 8H). ^{13}C NMR (500 MHz, DMSO) δ 162.23, 158.38, 152.66, 138.80, 134.88, 134.86, 133.59, 131.92, 131.66, 128.83, 128.38, 128.35, 127.28, 125.90, 124.72, 124.66, 123.96, 123.89, 123.81, 123.57, 121.83, 120.88, 114.20, 114.15, 111.10, 104.44, 104.26. m/z (M + H) calc for $C_{27}H_{22}Cl_2N_6O^+$, 517.1309; found 517.1294.

{4-[4-[(4-Chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}(5-fluoro-1*H*-indol-2-yl)methanone (7c). ^{1}H NMR (500 MHz, DMSO) δ 11.73 (s, 1H), 9.67 (s, 1H), 8.33-8.31 (d, *J* 8.5 Hz, 1H), 7.88-7.86 (d, *J* 8.1 Hz, 2H), 7.65-7.62 (t, *J* 8.5 Hz, 1H), 7.47-7.37 (td, *J* 8.5 Hz, *J* 8.1 Hz, 5H), 7.24-7.21 (t, *J* 8.1 Hz, 1H), 7.08-7.05 (t, *J* 8.5 Hz, 1H), 6.87 (s, 1H), 3.89 (t, 8H). ^{13}C NMR (500 MHz, DMSO) δ 162.34, 158.53, 158.38, 156.68, 138.80, 133.58, 133.17, 132.16, 131.89, 128.83, 127.44, 127.35, 127.28, 125.89, 123.88, 123.57, 121.82, 113.78, 113.70, 112.64, 112.28, 111.10, 106.08, 105.90, 104.90, 104.72, 104.68. m/z (M + H) calc for $C_{27}H_{22}ClFN_6O^+$, 501.1660; found 501.1590.

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{4-[4-[(4-Chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}(4-morpholinophenyl)methanone (7d). ^{1}H NMR (500 MHz, DMSO) δ 9.64 (s, 1H), 8.30 (d, *J* 8.5 Hz, 1H), 7.85-7.84 (d, *J* 8.1 Hz, 2H), 7.64-7.61 (t, *J* 8.5 Hz, 1H), 7.46-7.44 (d, *J* 8.5 Hz, 1H), 7.40-7.39 (d, *J* 8.1 Hz, 1H), 7.37-7.32 (dd, *J* 8.5 Hz, *J* 8.1 Hz, 1H), 7.23-7.22 (d, *J* 9 Hz, 2H), 7.20-7.00 (d, *J* 8.1 Hz, 1H), 6.98-6.96 (d, *J* 9 Hz, 2H), 3.81 (t, 4H), 3.76 (t, 4H), 3.96 (t, 4H), 3.20 (t, 4H). ^{13}C NMR (500 MHz, DMSO) δ 169.97, 158.43, 158.35, 152.36, 138.79, 133.56, 133.56, 129.34, 129.34, 128.82, 128.82, 127.25, 127.25, 125.89, 125.89, 125.79, 123.84, 123.84, 123.54, 123.84, 121.79, 114.27, 114.27, 111.08, 66.47, 66.47, 48.05, 48.05, 44.26. m/z (M + H) calc for $C_{29}H_{29}ClN_6O_2^+$, 529.2114; found 529.2100.

{4-[4-[(4-Chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}[1-(4-methoxyphenyl)cyclopropyl]methanone (7e). ^{1}H NMR (500 MHz, DMSO) δ 9.64 (s, 1H), 8.30-8.28 (d, *J* 8.5 Hz, 1H), 7.82-7.80 (d, *J* 8.1 Hz, 2H), 7.61-7.59 (t, *J* 8.5 Hz, 1H), 7.44-7.43 (d, *J* 8.5 Hz, 1H), 7.37-7.35 (d, *J* 8.1 Hz, 2H), 7.23-7.19 (dd, *J* 8.5 Hz, *J* 8.1 Hz, 1H), 7.15-7.13 (d, *J* 9 Hz, 2H), 7.06-7.05 (d, *J* 8.1 Hz, 1H), 6.87-6.85 (d, *J* 9 Hz, 2H), 6.85-6.85 (t, *J* 8.1 Hz, 1H), 3.73 (s, 3H), 3.71 (t, 4H), 3.56 (t, 4H), 1.30-1.26 (t, 2H), 1.11-1.04 (t, 2H). ^{13}C NMR (500 MHz, DMSO) δ 176.07, 170.59, 158.33, 158.10, 152.51, 138.75, 133.07, 133.07, 132.84, 131.77, 128.79, 127.04, 127.04, 126.95, 126.87, 125.83, 123.86, 123.53, 121.84, 114.52, 113.73, 111.08, 55.84, 43.84, 43.84, 29.37, 29.37, 28.84, 28.84. m/z (M + H) calc for $C_{29}H_{28}ClN_5O_2^+$, 514.2004; found 514.2002.

Benzo[*d*][1,3]dioxol-4-yl{4-[4-[(4-chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}methanone (7f). ^{1}H NMR (500 MHz, DMSO) δ 9.64 (s, 1H), 8.32-8.30 (d, *J* 8.5 Hz, 1H), 7.85-7.84 (d, *J* 8.1 Hz, 2H), 7.64-7.61 (t, *J* 8.5 Hz, 1H), 7.46-7.44 (d, *J* 8.5 Hz, 2H), 7.40-7.39 (d, *J* 8.1 Hz, 1H), 7.24-7.21 (dd, *J* 8.5 Hz, *J* 8.1 Hz, 1H), 7.03-7.01 (d, *J* 9 Hz, 1H), 6.90-6.88 (d, *J* 9 Hz, 2H), 6.10(s, 2H), 3.86 (t, 2H), 3.79 (t, 2H), 3.44 (t, 2H), 3.44 (t, 2H). ^{13}C NMR (500 MHz, DMSO) δ 165.15, 158.37, 152.59, 147.73, 143.96, 138.77, 133.58, 127.27, 125.86, 125.86, 123.84, 123.56, 122.45, 122.45, 122.43, 121.85, 117.58, 111.10, 110.10, 111.00, 101.86, 47.04, 47.04, 44.67, 43.93, 43.93. m/z (M^+ H) calc for $C_{26}H_{22}ClN_5O_3^+$, 488.1484; found 488.1476.

{4-[4-[(4-Chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}(2,2-difluorobenzo[d][1,3]dioxol-4-yl)methanone (7g). ^{1}H NMR (500 MHz, DMSO) δ 9.67 (s, 1H), 8.32-8.30 (d, *J* 8.5 Hz, 1H), 7.84-7.82 (d, *J* 8.1 Hz, 2H), 7.64-7.61 (t, *J* 8.5 Hz, 1H), 7.54-7.53 (d, *J* 8.1 Hz, 1H), 7.44-7.39 (dd, *J* 8.5 Hz, 3H), 7.32-7.29 (t, *J* 8.1 Hz, 2H), 7.22-7.21 (d, *J* 8.5 Hz, 1H), 3.89 (s, 2H), 3.78-3.76 (t, 4H), 3.45-3.33 (t, 2H). ^{13}C NMR (500 MHz, DMSO) δ 163.10, 158.40, 158.34, 152.59, 143.35, 139.54, 138.76, 133.58, 131.49, 128.79, 127.28, 125.89, 125.32, 123.90, 123.85, 123.55, 121.89, 119.25, 111.82, 111.13, 55.37, 47.05, 44.56, 43.83, 42.16, 40.50. m/z (M + H) calc for $C_{26}H_{20}ClF_2N_5O_3^+$, 524.1296; found 524.1277.

{4-[4-[(4-Chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}[(1R,2R)-2-phenylcyclopropyl]methanone (7h). ^{1}H NMR (500 MHz, DMSO) δ 9.67 (s, 1H), 8.32-8.30 (d, *J* 8.5 Hz, 1H), 7.84-7.82 (d, *J* 8.1 Hz, 2H), 7.64-7.61 (t, *J* 8.5 Hz, 1H), 7.54-7.53 (d, *J* 8.1 Hz, 1H), 7.44-7.39 (dd, *J* 8.5 Hz, 3H), 7.32-7.29 (t, *J* 8.1 Hz, 2H), 7.22-7.21 (d, *J* 8.5 Hz, 1H), 3.89 (s, 2H), 3.78-3.76 (t, 4H), 3.45-3.33 (t, 2H). ^{13}C NMR (500 MHz, DMSO) δ 163.10, 158.40, 158.34, 152.59, 143.35, 139.54, 138.76, 133.58, 131.49, 128.79, 127.28, 125.89, 125.32, 123.90, 123.85, 123.55, 121.89, 119.25, 111.82, 111.13, 55.37, 47.05, 44.56, 43.83, 42.16, 40.50. m/z (M + H) calc for $C_{28}H_{26}ClN_5O^+$, 484.1899; found 484.1887.

{4-[4-[(4-Chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}(2,4,6-trifluorophenyl)methanone (7i). ^{1}H NMR (500 MHz, DMSO) δ 9.68 (s, 1H), 8.32-8.30 (d, *J* 8.5 Hz, 1H), 7.83-7.82 (d, *J* 8.1 Hz, 2H), 7.64-7.61 (t, *J* 8.5 Hz, 1H), 7.44-7.41 (d, *J* 8.1 Hz, 2H), 7.39-7.35 (dd, *J* 8.5 Hz, 3H), 7.24-7.21 (d, *J* 8.5 Hz, 1H), 3.87 (s, 2H), 3.78-3.74 (t, 4H), 3.41-3.39 (t, 2H). ^{13}C NMR (500 MHz, DMSO) δ 164.09, 162.11, 160.05,159.83, 158.89,158.41,158.26,

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158.07, 157.98, 157.95, 152.56, 138.72, 1333.59, 128.81, 127.31, 125.89, 123.95, 123.55, 121.94,1 11.15, 102.17, 101.96, 101.72, 46.71, 44.69, 43.9, 41.98. m/z (M + H) calc for $C_{25}H_{19}ClF_3N_5O^+$, 498.1303; found 498.1286.

(4-Chlorophenyl){4-[4-[(4-chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}methanone (7j). ^{1}H NMR (500 MHz, DMSO) δ 9.66 (s, 1H), 8.32-8.31 (d, *J* 8.5 Hz, 1H), 7.84-7.82 (d, *J* 8.1 Hz, 2H), 7.63-7.61 (t, *J* 8.5 Hz, 1H), 7.58-7.55 (dd, *J* 8.5 Hz, 3H), 7.53-7.52(d, *J* 8.1 Hz, 2H), 7.50-7.48 (dd, *J* 8.5 Hz, 3H), 7.24-7.21 (d, *J* 8.5 Hz, 1H), 3.87 (s, 2H), 3.87-3.72 (t, 6H), 3.41-3.39 (t, 2H). ^{13}C NMR (500 MHz, DMSO) δ m/z (M + H) calc for $C_{25}H_{21}Cl_2N_5O^+$, 478.1198; found 478.1195.

{4-[4-[(4-Chlorophenyl)amino]quinazolin-2-yl]piperazin-1-yl}(4-fluoro-3-methoxyphenyl)methanone (7k). ^{1}H NMR (500 MHz, DMSO) δ 9.64 (s, 1H), 8.30-8.29 (d, *J* 8.5 Hz, 1H), 7.84-7.82 (d, *J* 8.1 Hz, 2H), 7.63-7.60 (t, *J* 8.5 Hz, 1H), 7.44-7.38 (d, *J* 8.1 Hz, 2H), 7.23-7.20 (d, *J* 8.5 Hz, 1H), 7.15-7.13 (dd, *J* 8.5 Hz, 1H),6.86-6.81 (ddd, *J* 8.0 , 3H), 3.86 (s, 2H), 3.78-3.70 (t, 3H), 3.33- (t, 4H), 3.27(s.1H), 2.22(s,1H) ^{13}C NMR (500 MHz, DMSO) δ 169.33, 159.71, 158.42, 158.36,152.62, 138.44, 136.56, 129.15, 128.82, 127.85, 127.25, 125.90, 123.82, 123.54, 121.83, 116.00, 111.66, 111.10, 55.55, 46.83, 44.62, 44.04, 41.49,19.43m/z (M + H) calc for $C_{26}H_{23}ClN_5O_2^+$, 473.1613; found 473.1629.

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Supplementary Material

Please see the supplementary information file for copies of the proton and carbon NMR spectra.

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