Quinazoline Ligands Induce Cancer Cell Death Through Selective STAT3 Inhibition and G-Quadruplex Stabilization

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**Table of contents**

| Section                  | Pages  |
|--------------------------|--------|
| Supporting figures       | 3-21   |
| Supporting tables        | 22-26  |
| Compound synthesis       | 28-119 |
**Figure S1.** Primary screening of synthesized compounds by Taq-polymerase stop assay. (a) Sequence and (b) representative sequencing gel with nonG4 template. (c) Sequence and (d) representative sequencing gel with parallel ribosomal G4 DNA template. The compounds’ names are indicated above each well, at a concentration of 25 µM.
Figure S2. Primary screening of synthesized compounds by Taq-polymerase stop assay. (a) Sequence and (b) representative sequencing gel with hybrid telomeric G4 DNA. (c) Sequence and (d) representative sequencing gel with antiparallel \textit{cdc13}+ promoter G4 DNA template. The compounds’ names are indicated above each well, at a concentration of 25 µM.
Figure S3. Primary screening of the synthesized compounds in a Taq-polymerase stop assay using *S. pombe* with (a) parallel ribosomal G4 DNA, (b) hybrid telomeric G4 DNA, (c) antiparallel *cdc13* promoter G4 DNA, and (d) nonG4 DNA as a control. All graphs represent the mean of two independent experiments ± absolute error. Original representative sequencing gels for a–d are shown in Figures S1 and S2. 25 µM compound was used, and the names of the compounds are indicated below each graph. Arrows indicate the compounds selected for further study.
Figure S4. Dose response of Taq-polymerase stop assay using (a) nonG4 DNA and (b) parallel ribosomal G4 DNA as a template. The 4f and 8g concentrations are indicated above each well.
Figure S5. Dose response of Taq-polymerase stop assay using (a) hybrid telomeric G4 DNA and (b) antiparallel cdc13+ promoter G4 DNA as a template. The 4f and 8g concentrations are indicated above each well.
Figure S6. Dose response of Taq-polymerase stop assay using 5b as the treatment. The concentration of 5b is indicated above each well.
**Figure S7.** (a) sequence of c-MYC Pu24T used as a template in Taq-polymerase stop assay. (b) Denatured polyacrylamide gel with reaction stopped in designated time. c-MYC Pu24T G4 template DNA is labeled on the right side of the gel. c) Quantification of full-length products in b. Black arrow indicates the chosen time for the reaction in figure S8.
Figure S8. (a) Sequence and (b) representative sequencing gels with c-MYC Pu24T G4 DNA template used in Taq-polymerase stop assay treated with 5b, 4f and 8g. Concentration of treatment is indicated above each gel. Guanines forming G4 structures are in bold and underlined in a. The black vertical lines on the side of each gel show the positions of the G-tracts marked in a.
Figure S9. (a) Dose response analyses of Taq-polymerase stop assay of 5b with the different G4 DNA and non-G4 DNA templates used in the primary screen. Original representative sequencing gels are shown in Figure S7. SPR sensorgrams demonstrating the binding of 4f to (b) S. pombe parallel ribosomal G4 DNA, (c) human parallel c-kit G4 DNA, (d) S. pombe hybrid telomeric G4 DNA, and (e) ssDNA. SPR sensorgrams demonstrating the binding of 8g to (f) human c-MYC Pu24T G4 DNA, (g) S. pombe parallel ribosomal G4 DNA, (h) human parallel c-kit G4 DNA, (i) S. pombe hybrid telomeric G4 DNA, and (j) ssDNA.
**Fig. S10. Titration.**

a) UV/vis spectral changes of 10 µM 8g in absence (black line) and presence (blue line) of equimolar concentration c-MYC Pu24T G4 DNA. Red arrow indicates isosbestic point.

b-f) Fluorescence titration analysis of 2 µM 8g with different DNA and RNA molecules. 8g was excited at λ = 305. Titration spectra of representative experiments are shown. Error represents the fitting error of the data. Each binding curve was fitted into data from at least two independent experiments. Data of ssDNA were not fitted.
Figure S11. (a) 1H-NMR spectra showing the imino-region of c-MYC Pu24T in absence (bottom) and presence of a 1:1 compound:DNA ratio of 4f (middle) and 8g (top). (b) Representative binding poses of 8g during MD simulations with the c-MYC Pu24T G4 DNA. The top G4 tetrad (light blue), nucleotides flanking the G4 DNA structure (orange), 8g (ball-stick model), and the potassium ion (central blue sphere) are shown. The binding energies are tabulated in Table S2.
Figure S12. (a) Emission and excitation spectra of 5 μM 8g dissolved in 100% DMSO. (b) 2-photon excitation microscopy imaging of living HeLa cells treated with 50 μM 8g for 10 and 30 min. Confocal microscopy images of HeLa cells treated with 20 μM 8g for 30 min. (d) Quantification of the average fluorescence signal of 8g from (c) in nucleoli and cytoplasm.
Figure S13. Graphs showing the resazurin-based cell viability assay with HeLa cells or HFPs treated for 48 h with the compounds (a) 5b, (b) 4f, and (c) 8g at the indicated concentrations. Data are from the same graphs shown in figures 2a and 2b. Data represent the mean ± SD calculated from three independent replicates. (d) Viability of different cell lines. Cell were treated for 48 hours with 3.3 µM 8g. Data represent average of two independent experiments ± absolute error.
Figure S14. (a) Density plots showing the flow cytometry analysis of HeLa cells stained with propidium iodide and annexin V. Cells were treated for 12 h with 8g at the indicated concentrations. For each treatment, the percentages of living cells (bottom left quarter), cells in early apoptosis (bottom right quarter), cells in late apoptosis (upper right quarter), and necrotic cells (upper left quarter) are indicated. (b) The numbers of BG4-positive dots per cell after 1 h treatment with 8g at the indicated concentrations. Data represent populations of individual cells for each condition of the final experiment, and means ± 2SD are shown. The following numbers of cells were analyzed for each treatment: DMSO only: 119 cells, 8g 5 μM: 104 cells, and 8g 20 μM: 108 cells. Analysis of the data was performed using Welch-corrected two-samples t-tests.
Figure S15. SPR measurements of binding of (a) 4f, (b) 8g, and (c) 8g-tfa to STAT3 protein. Each experiment was run in triplicate.
Figure S16. (a) The full field of confocal microscopy image of Figure 7a. Living *S. pombe* cells were treated with 25 μM 8g or 0.25 % DMSO (-) for 30 min. Dashed area represents zoom in Figure 7a. (b) Schematic overview of the *S. pombe* cell cycle (outer solid line circle) with the corresponding amount of DNA (c) detected in the flow cytometry analysis (inner dotted circle).
Figure S17. Model of action of 4f/8g in cancer cells.
Figure S18. Starting binding modes of 4f for the MD simulations. Eight poses of 4f (stick model) were modeled with c-MYC Pu24T (cartoon model) on the basis of the NMR binding information. MD simulations were performed for all eight complexes. Colors of the guanine bases are based on the three intervals of NMR shift change.
Figure S19. Starting binding modes of 8g for the MD simulations. Four poses of 8g were modeled with c-MYC Pu24T G4 DNA and MD simulations were performed for all four complexes. The top G4 tetrad (light blue), nucleotides flanking the G4 DNA structure (orange), 8g (ball-stick model), and the potassium ion (central blue sphere) are shown.
Table S1: Binding energies and simulation times of the clusters obtained from MD simulations. The average binding energy (kJ/mol) between 4f and c-MYC Pu24T was calculated for the first 50 frames from each cluster with the MM/PBSA method using the g_mmpbsa tool. Standard errors were calculated using the block-averaging method.

| Cluster No. | Simulation Time (ns) | van der Waals Energy | Electrostatic Energy | Polar Solvation Energy | Apolar Solvation Energy | Binding Energy |
|-------------|----------------------|----------------------|----------------------|------------------------|-------------------------|----------------|
| **Intercalating binding modes** | | | | | | |
| 1 | 237.25 | -281 ± 2 | -2 ± 1 | -30 ± 3 | -19 ± 1 | -333 ± 4 |
| 2 | 191.70 | -267 ± 2 | -2 ± 1 | -9 ± 3 | -19 ± 1 | -297 ± 5 |
| 3 | 170.16 | -272 ± 2 | -5 ± 1 | -26 ± 3 | -20 ± 1 | -322 ± 5 |
| 4 | 118.90 | -285 ± 2 | -7 ± 1 | -32 ± 2 | -20 ± 1 | -345 ± 6 |
| 5 | 94.61  | -243 ± 2 | 3 ± 1  | -34 ± 3 | -20 ± 1 | -294 ± 3 |
| 6 | 91.86  | -212 ± 1 | -2 ± 1 | -12 ± 2 | -18 ± 1 | -243 ± 2 |
| 7 | 91.03  | -259 ± 1 | -4 ± 1 | -36 ± 2 | -20 ± 1 | -319 ± 2 |
| 8 | 46.23  | -216 ± 2 | -3 ± 1 | 10 ± 2  | -15 ± 1 | -224 ± 2 |
| **Top binding modes** | | | | | | |
| 1 | 242.69 | -190 ± 9 | 1 ± 1  | 16 ± 5  | -14 ± 2 | -188 ± 14 |
| 2 | 202.28 | -237 ± 1 | -1 ± 1 | 17 ± 2  | -16 ± 1 | -237 ± 3 |
| 3 | 133.37 | -203 ± 5 | -2 ± 1 | 18 ± 1  | -15 ± 1 | -202 ± 5 |
| 4 | 122.40 | -228 ± 1 | 3 ± 1  | 17 ± 2  | -15 ± 1 | -223 ± 2 |
| 5 | 86.20  | -230 ± 2 | 1 ± 1  | 18 ± 2  | -16 ± 1 | -227 ± 3 |
| 6 | 53.13  | -227 ± 2 | 0 ± 1  | 11 ± 2  | -17 ± 1 | -232 ± 2 |
| 7 | 48.83  | -230 ± 2 | 3 ± 1  | 21 ± 2  | -17 ± 1 | -223 ± 3 |
| 8 | 38.71  | -144 ± 3 | 2 ± 1  | 19 ± 3  | -11 ± 1 | -135 ± 5 |
Table S2: Binding energy and simulation time of clusters obtained from MD simulations. Average binding energy (kJ/mol) between 8g and c-MYC Pu24T was calculated for first 50 frames from each cluster using MM/PBSA method by g_mmpbsa tool. Standard error was calculated using block-averaging method.

| Cluster | Van der Waals | Electrostatic | Polar Solvation | Non-polar solvation | Binding Energy | Occurrence (%) |
|---------|---------------|---------------|-----------------|---------------------|---------------|----------------|
| 1       | -235 ± 27     | -3 ± 2        | 22 ± 9          | -16 ± 2             | -232 ± 31     | 49             |
| 2       | -205 ± 28     | -2 ± 2        | 26 ± 22         | -15 ± 2             | -196 ± 40     | 30             |
| 3       | -218 ± 12     | -1 ± 1        | 36 ± 8          | -15 ± 1             | -198 ± 17     | 12             |
| 4       | -216 ± 18     | -9 ± 3        | 69 ± 12         | -16 ± 1             | -171 ± 26     | 9              |
Supplementary table S3. Compound permeability was measured using a Caco-2 cell assay which indicate that both compounds are able to pass the cell membranes. The cut-off Papp values used corresponds to the fraction absorbed in the gut of <20% (Papp value of 0.2 x10-6 cm/s for low permeable compounds), and >80% (Papp of 1.6 x 10-6 cm/s for high permeable compounds). Thus, 4f has a high permeability and 8g a medium permeability and a high efflux ratio. Therefore, 8g will most likely have limited absorption after oral administration and further optimization of this property may be needed.

| Compound | Papp (a-b) x10E-6 cm/s | SD Papp (a-b) | Papp (b-a) x10E-6 cm/s | SD Papp (b-a) | Efflux ratio B/A/A-B |
|----------|------------------------|---------------|------------------------|---------------|---------------------|
| 4f       | 26,6                   | 18,7          | 106,4                  | 8,8           | 4,0                 |
| 8g       | 2,9                    | 0,7           | 118,5                  | 4,8           | 40,5                |

Results summary: Cell line: Caco-2, Passage no: P96, Days in culture: 24, Concentration: 1 µM
### Supplementary table S4

**Oligonucleotides used in the study.**

| Oligonucleotides for Taq stop assay | Name | Sequence (5'-3') | Source | Supplier |
|-------------------------------------|------|-----------------|--------|----------|
| primer TET-ﬂAGAAATTGATATGTCGAGGTTCCG | nonG4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | S. pombe | Eurofins Genomics |
| Parallel ribosomal G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | S. pombe | Eurofins Genomics |
| Hybrid telomeric G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | S. pombe | Eurofins Genomics |
| Antiparallel cdc13' promoter G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | S. pombe | Eurofins Genomics |
| c-MYC Pu24T G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | Human modified | Eurofins Genomics |

| Oligonucleotides for SPR | Name | Sequence (Bio-5'-3') | Source | Supplier |
|-------------------------|------|----------------------|--------|----------|
| Parallel ribosomal G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | S. pombe | Eurofins Genomics |
| Hybrid telomeric G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | S. pombe | Eurofins Genomics |
| c-MYC Pu24T G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | Human modified | Eurofins Genomics |
| ssDNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | Human modified | Eurofins Genomics |

| Oligonucleotides for ﬂuorescence titrations | Name | Sequence (5'-3') | Source | Supplier |
|--------------------------------------------|------|-----------------|--------|----------|
| Parallel ribosomal G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | S. pombe | Eurofins Genomics |
| Hybrid telomeric G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | S. pombe | Eurofins Genomics |
| c-Kit G4 DNA (-Kit87up) | GAGACCGTTCAGGATATGTCGAGGTTCCG | Human modified | Eurofins Genomics |
| ssDNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | Human modified | Eurofins Genomics |

| Oligonucleotide for NMR | Name | Sequence (5'-3') | Source | Supplier |
|----------------------|------|-----------------|--------|----------|
| c-MYC Pu24T G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | Human modified | Eurofins Genomics, Sigma-Aldrich |

| Oligonucleotide for MST | Name | Sequence (Cy5-5'-3') | Source | Supplier |
|------------------------|------|----------------------|--------|----------|
| c-MYC Pu24T G4 DNA | GAGACCGTTCAGGATATGTCGAGGTTCCG | Human modified | Eurofins Genomics |
Supplementary table S5.
Antibodies used in the study.

| Antibody                          | Brand                  | Cat. number | Dilution | Secondary antibody                        | Secondary antibody dilution |
|-----------------------------------|------------------------|-------------|----------|------------------------------------------|----------------------------|
| **Immunoblot**                    |                        |             |          |                                          |                            |
| Mouse anti-pSTAT3 (Tyr705) (B7)   | Santa Cruz Biotechnology | sc-8059     | 1:1000   | Goat anti-mouse IgG (H+L) - HRP          | 1:3000                     |
| Mouse anti-STAT3 (F2)             | Santa Cruz Biotechnology | sc-8019     | 1:1000   | Goat anti-mouse IgG (H+L) - HRP          | 1:3000                     |
| Mouse anti-pSTAT1 (Tyr701) (A-2)  | Santa Cruz Biotechnology | sc-8394     | 1:1000   | Goat anti-mouse IgG (H+L) - HRP          | 1:3000                     |
| Mouse anti-Stat1 alpha p91 (C-111)| Santa Cruz Biotechnology | sc-417      | 1:1000   | Goat anti-mouse IgG (H+L) - HRP          | 1:3000                     |
| Mouse anti-H2A.X (938CT5.1.1)     | Santa Cruz Biotechnology | sc-517336   | 1:1000   | Goat anti-mouse IgG (H+L) - HRP          | 1:3000                     |
| Rabbit anti-γH2A.X                | Cell Signalling         | #2577       | 1:1000   | Goat anti-rabbit IgG (H+L) - HRP         | 1:3000                     |
| Mouse anti-ATM (G-12)             | Santa Cruz Biotechnology | sc-377293   | 1:1000   | Goat anti-mouse IgG (H+L) - HRP          | 1:3000                     |
| Mouse anti-pATM                   | Santa Cruz Biotechnology | sc-47739    | 1:1000   | Goat anti-mouse IgG (H+L) - HRP          | 1:3000                     |
| Mouse anti-PCNA                   | Cell Signalling         | #2586       | 1:1000   | Goat anti-mouse IgG (H+L) - HRP          | 1:5000                     |
| Mouse anti-β-actin                | SIGMA                  | A5441       | 1:10000  | Goat anti-mouse IgG (H+L) - HRP          | 1:10000                    |
| **Immunocytochemistry**           |                        |             |          |                                          |                            |
| anti-DNA G-quadruplex (BG4-FLAG)  | Sigma/Merck            | Mabe 917    | 1:1000   | Rabbit anti-Flag (Cell signaling, Cat. Num 14793) | 1:800                     |
| Antibody | Dilution | Source |
|----------|----------|--------|
| Goat anti-rabbit IgG (H+L) Alexa Fluor 594 (Life Technologies, Cat.num. A11012) | 1:1000 |  |
| DNA fiber immunostaining |  |
| Mouse anti-BrdU Clone B44 (RUO (GMP) | BD Biosciences | BD347580 | 1:1000 | Goat anti-mouse IgG (H+L) Alexa Fluor 647 (Life Technologies, A21235) | 1:1600 |
| Rat anti-BrdU clone BU1/75 (ICRI) For CldU and BrDU detection | ABD Serotec | OBT0030 | 1:1000 | Goat anti-rat IgG Alexa Fluor 568 (Life Technologies, A11077) | 1:1600 |
| Mouse anti-DNA antibody single stranded Clone 16-19 | Sigma Aldrich | MAB3034 | 1:200 | Goat anti-mouse IgG2a (γ2a) Alexa Fluor 488 (Life Technologies, A21131) | 1:1600 |
Compounds synthesis

To improve the hit compounds ability to bind and stabilize G4 DNA structures and to understand which factors that control selectivity and potency, we designed synthetic routes to broadly explore the compounds structure—activity and structure—selectivity relationships. This resulted in a library of forty-seven derivatives that are all based on the initial hit compound 5b, as outlined in Figure 1 and scheme 1-4.

**Figure 1:** Synthesis of various quinazoline-pyrimidine, quinazoline-quinazolinone and pyrimidine-pyrimidine derivatives.

The key intermediates 3a-h were synthesized from commercially available substituted anilines (1a-h) in two steps. In the first step, a modified Skraup synthesis\(^1\) was used to generate the substituted 2,2,4-trimethyl-1,2-dihydroquinolines (2a-h) in 53-78 % yield. In the second step, the 1,2-dihydroquinolines (2a-h) were reacted with 2-cyanoguanidine to give N-(4-methyl-quinazolin-2-yl)-guanidine intermediates (3a-h) in 45-57% yields. Finally, treatment of the intermediates 3a-h with acetylacetone yielded the desired quinazoline-pyrimidine derivatives 4(a, c-f) in 50-65% yield (Scheme 1). Intermediate 3(b, g-h) was not compatible with this method and was therefore synthesized using a different approach starting with the synthesis of 4,6-dimethyl-pyrimidin-2-yl-cyanamide (6) from 2-cyanoguanidine and acetylacetone. Condensation of 6 with 2,2,4-trimethyl-1,2-dihydroquinolines 2(b, g-h) under acidic conditions gave the desired quinazoline-pyrimidine derivatives 4(b, g-h) in 23-31%
yield (Scheme 2). In addition to these derivatives, the condensation of 3a-b with mesityl oxide in DMSO at 100 °C also yielded quinazoline-dihydropyrimidine derivatives (5a-b) (Scheme 1) in 21-26% yield.

The compounds 8 (a-g), 9 (a-f) and 12-17 can exist in two keto and one enolic form as shown in Figure 2.

**Figure 2:** Tautomeric forms of compounds 8 (a-g), 9 (a-f) and 12-17.

**Scheme 1.** Synthesis of various quinazoline-pyrimidine derivatives; Reagents and conditions: i. dry acetone, I$_2$, 1-butyliccatechol, MgSO$_4$, reflux 16-18 h, (53-78 %); ii. 2-cynogunidine, 2M HCl, 100 °C, 0.5 h, (45-57 %); iii. acetylacetone, acetic acid, reflux, 12 h, (51-61 %); iv. mesityl oxide, DMSO, 100 °C, 12 h, (21-26%).
Scheme 2. Synthesis of various quinazoline-pyrimidine derivatives 4(b, g-h); Reagents and conditions: i. 2N NaOH, water, reflux, 16 h, (63%); ii. Dioxane 2 M HCl, 105 °C, 2h, (23-31%).

Condensation of benzalacetone with some of the N-(4-methyl-quinazolin-2-yl)-guanidine derivatives (3a, g) in DMSO has been reported to result in 4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine derivatives (7a, g). However, this method gave us very low yields (19-24%) and, as a consequence, we developed a modified approach using microwave-heating and by varying solvent, temperature, and reaction time. N-(4-methyl-quinazolin-2-yl)-guanidine derivative 3a did not react with benzalacetone when pyridine or tetrahydrofuran was used as solvent and only a very low conversion (10%) was observed in 1,2-dichloroethane when heated by microwaves at 155 °C for 35 min. Instead, polar aprotic solvents worked well; dimethylformamide and dimethylsulfoxide gave the desired 7a in 10% and 12% yield already after 1h at 100 °C, which could be further improved to 53% and 61% yield, respectively, after heating at 155 °C for 35 min. Substituted 4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine derivatives 7a-g was thus synthesized in 50-61% yields starting from 3a-g by using microwave heating at 135 °C for 35 min using DMSO as solvent (Scheme 3).

In order to synthesize quinazoline-quinazoline derivatives, a well-known reaction of different isatoic anhydride with N-(4-methyl-quinazolin-2-yl)-guanidine derivatives (3a-h) was performed under basic conditions to give desired compounds 8(a-g) and 9(a-f) in 60-73% yield (Scheme 3).
Scheme 3. Synthesis of various quinazoline-pyrimidine 7(a-g) and quinazoline-quinazoline derivatives 8(a-g) & 9(a-f). Reagents and conditions: i) DMSO, benzalacetone, 100 °C, 12 h, (19-21%); ii. DMSO, benzalacetone, Microwave, 135 °C, 0.5 h, (50-61%); iii. DMF, different isatoic anhydrides, N,N-diisopropylethylamine, 100 °C, 12 h, (60-73%). * means no reaction.

Next, 4,6-dimethyl-pyrimidin-2-yl-cyanamide (6) was used as starting material to synthesize pyrimidine-pyrimidine and quinazoline-pyrimidine derivatives by reduction with ammonium chloride under refluxing conditions to give 1-(4,6-dimethylpyrimidin-2-yl)guanidine derivative (10) (Scheme 4). Reacting 10 with acetyl acetone or different substituted isatoic anhydrides (obtained through reaction of substituted anthranilic acid with triphosgene) yielded desired pyrimidine-pyrimidine (11) or quinazoline-pyrimidine derivatives 12-17 in 43-57% yields.

Scheme 4. Synthesis of various pyrimidone derivatives; Reagents and conditions: i) Phenol, NH₄Cl, 125 °C, 4 h, (68%); ii. Acetic acid 125 °C, 12 h (64%); iii. Different isatoic anhydrides, DMF, N,N-diisopropylethylamine, 100 °C, 12 h, (43-57%).
Experimental procedure

All analytical grade reagents and solvents were purchased from Sigma-Aldrich, Fluka, or Acros and used as supplied unless stated otherwise. Thin layer chromatography (TLC) was used for monitoring of chemical reactions and performed on aluminium backed silica gel plates (median pore size 60 Å, fluorescent indicator 254 nm) and detected with UV light at 254 and 366 nm. Flash column chromatography was performed using silica gel (0.063–0.200 mesh). Automated flash column chromatography was performed using a Biotage Isolera One system and purchased prepacked silica gel cartridges (Biotage SNAP Cartridge, KP-Sil). Dimethylformamide (DMF) was dried in a solvent drying system (activated molecular sieves in combination with an isocyanate scrubber). $^1$H and $^{13}$C NMR spectra were recorded on Bruker 400 or 600 MHz spectrometers at 298 K and calibrated by using the residual peak of the solvents as the internal standard (DMSO-$d_6$ : $\delta$ H = 2.50 ppm; $\delta$ C = 39.50 ppm and CDCl$_3$ : $\delta$ H = 7.26 ppm; $\delta$ C = 77.02 ppm). The coupling constant values (J) are determined in Hertz. The abbreviations used in NMR data are mentioned as, singlet = s, doublet = d, triplet = t, multiplet = m, double doublet = dd, and broad singlet = brs. LC-MS was conducted on an Agilent 6150 Series Quadrupole LC/MS system. HRMS was performed by using an Agilent 1290 binary LC system connected to an Agilent 6230 Accurate-Mass TOF LC/MS (ESI+); calibrated with an Agilent G1969-85001 ES-TOF Reference Mix containing ammonium trifluoroacetate, purine and hexakis(1H,1H,3H-tetrafluoropropoxy)phosphazine in 90 : 10 acetonitrile : water. Preparatory HPLC was performed with a Gilson instrument using a Nucleodur C18 HTec reversed-phase column (25 cm × 21.5 mm; particle size 5 µm) with H$_2$O/MeCN mixtures as the eluent. Microwave reactions were carried out in an Initiator+ microwave instrument from Biotage, using sealed 0.2–0.5 mL and 10-20 mL process vials. Reaction times refer to irradiation time at the target temperature, not the total irradiation time. The temperature was measured with an IR sensor.

General procedure for the synthesis of 2,2,4-trimethyl-1,2-dihydroquinoline derivatives 2(a-h): The mixture of different anilines 1(a-h) (12.17 mmol) with anhydrous magnesium sulphate (7.3 g, 60.67 mmol) in anhydrous acetone (50 ml) was added to iodine (154mg, 5 mol%) and tert-butylcatechol (61 mg, 3 mol%) and heated to reflux for 12hrs. The progress of reaction was monitored on TLC till consumption of aniline and then reaction mixture was allowed to cool and filtered through a bed of celite. The filtrate solution so obtained was concentrated under reduced pressure to give brown coloured semi-solid material which was
purified through column chromatography over silica in EtOAc (0.5-5%) in heptane to give desired 2,4-trimethyl-1,2-dihydroquinoline derivatives 2(a-h).

**6-Methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (2a):** The title compound (2a) was obtained from the reaction of p-anisidine with acetone as a brown oil in 71% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 6.72 (d, $J$ = 4.0 Hz, 1H), 6.63 (dd, $J$ = 4.0 & 8.0 Hz, 1H), 6.42 (d, $J$ = 4.0 Hz, 1H), 5.39 (s, 1H), 3.76 (s, 3H), 2.00 (s, 3H), 1.26 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 152.03, 137.53, 129.79, 128.54, 122.98, 113.70, 113.51, 110.10, 55.90, 51.73, 30.36, 18.62; ESI MS (m/z): calculated for C$_{13}$H$_{18}$NO (M+H)$^+$: 204.1383, found 204.3.

**7-Methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (2b):** The title compound (2b) was obtained from the reaction of m-anisidine with acetone as a brown oil in 78% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 6.97 (d, $J$ = 8.0 Hz, 1H), 6.20 (dd, $J$ = 8.0 & 4.0 Hz, 1H), 6.01 (d, $J$ = 4.0 Hz, 1H), 5.19 (s, 1H), 3.75 (s, 3H), 1.96 (s, 3H), 1.26 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 160.17, 144.60, 128.21, 125.93, 124.62, 115.36, 115.36, 102.27, 98.59, 55.10, 51.93, 31.08, 18.62; ESI MS (m/z): calculated for C$_{13}$H$_{18}$NO (M+H)$^+$: 204.1383, found 204.2.

**6,7-Dimethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (2c):** The title compound (2c) was obtained from the reaction of 4-aminoveratrole with acetone as a brown oil in 67% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 6.67 (s, 1H), 6.08 (s, 1H), 5.20 (s, 1H), 3.80, 3.81 (2s, 6H), 1.96 (s, 3H), 1.24 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 149.67, 141.01, 134.60, 128.65, 127.98, 114.02, 109.25, 98.16, 57.14, 55.80, 51.81, 30.50, 18.71; ESI MS (m/z): calculated for C$_{14}$H$_{20}$NO$_2$ (M+H)$^+$: 234.1489, found 234.2.

**5,6,7-Trimethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (2d):** The title compound (2d) was obtained from the reaction of 3,4,5-trimethoxyaniline with acetone as a brown oil in 76% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 5.88 (s, 1H), 5.17 (s, 1H), 3.83, 3.79, 377 (3s, 9H), 2.15 (s, 3H), 1.22 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 153.19, 152.01, 141.01, 134.60, 128.65, 127.98, 114.83, 108.61, 93.74, 61.11, 60.97, 55.71, 29.69, 22.14; ESI MS (m/z): calculated for C$_{15}$H$_{22}$NO$_3$ (M+H)$^+$: 264.1594, found 264.2.

**2,2,4-Ttrimethyl-1,2-dihydrobenzo[h]quinolin-7-ol (2e):** The title compound (2e) was obtained from the reaction of 5-aminonaphthalen-1-ol (1e) with acetone as a brown oil in 53% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 7.43 (d, $J$ = 8.0 Hz, 1H), 7.29-7.34 (m, 2H), 7.23 (t, $J$ = 8.0 Hz, 1H), 6.76 (d, $J$ = 8.0 Hz, 1H), 5.36 (s,
1H), 5.21 (brs, 1H), 4.47 (brs, 1H), 2.10 (s, 3H), 1.36 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 153.67, 139.38, 128.51, 126.89, 125.47, 125.60, 124.19, 123.32, 121.25, 114.52, 113.00, 109.06, 108.29, 31.17, 19.29; ESI MS (m/z): calculated for C$_{16}$H$_{18}$NO (M+H)$^+$: 240.1383, found 240.3.

2,2,4-Trimethyl-1,2,7,8,9,10-hexahydrobenzo[h]quinoline (2f): The title compound (2f) was obtained from the reaction of 5,6,7,8-tetrahydro-1-naphthylamine (1f) with acetone as a brown solid in 59% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 6.90 (d, $J = 8.0$ Hz, 1H), 6.42 (d, $J = 8.0$ Hz, 1H), 5.25 (s, 1H), 2.70 (t, 2H, $J = 8.0$ Hz), 2.37 (t, $J = 8.0$ Hz, 2H), 1.98 (s, 3H), 1.83-1.89 (m, 2H), 1.70-1.76 (m, 2H), 1.28 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 140.67, 137.40, 128.88, 126.52, 120.80, 118.83, 118.26, 111.27, 51.73, 31.52, 30.14, 23.58, 23.13, 22.71, 18.82; ESI MS (m/z): calculated for C$_{16}$H$_{22}$N (M+H)$^+$: 228.1747, found 228.3.

2,2,4-Trimethyl-1,2-dihydroquinoline (2g): The title compound (2g) was obtained from the reaction of aniline (1g) with acetone as a brown oil in 68% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 7.07 (d, $J = 4.0$ Hz, 1H), 6.99 (t, $J = 8.0$ Hz, 1H), 6.65 (t, $J = 8.0$ Hz, 1H), 6.45 (d, $J = 4.0$ Hz, 1H), 5.32 (s, 1H), 2.00 (s, 3H), 1.29 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 143.15, 128.56, 128.37, 128.35, 123.62, 121.59, 117.23, 113.00, 51.84, 31.00, 18.61; ESI MS (m/z): calculated for C$_{12}$H$_{16}$N (M+H)$^+$: 174.1277, found 174.3.

4-(2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)morpholine (2h): The title compound (2h) was obtained from the reaction of 4-morpholinoaniline (1h) with acetone as a brown oil in 63% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 6.59-6.62 (m, 2H), 6.40 (d, $J = 8.0$ Hz, 1H), 5.39 (d, $J = 4.0$ Hz, 1H), 5.29 (s, 1H), 3.70 (t, $J = 4.0$ Hz, 4H), 2.89 (t, $J = 4.0$ Hz, 2H), 1.89 (s, 3H), 1.16 (s, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ (ppm): 142.57, 139.07, 129.58, 128.25, 121.37, 117.83, 113.34, 112.94, 66.85, 51.35, 30.84, 18.78; ESI MS (m/z): calculated for C$_{16}$H$_{23}$N$_2$O (M+H)$^+$: 259.1805, found 259.2.

General procedure for the synthesis of 1-(4-methylquinazolin-2-yl)guanidine derivatives (3a-h): To the mixture of 2,2,4-trimethyl-1,2-dihydroquinoline (0.5g, 2.88 mmol) in 1.1 ml of 2M HCl solution, 2-cynoguanidine (0.291 g, 3.64 mmol) was added and heated at 105 °C for 15-40 mins. Upon cooling a precipitation was formed which was collected through filtration. Finally, the precipitate so obtained were sonicated in 5 ml of methanol (20%) and ammonia (20%) in water for 15 min and filtered, washed (1ml of methanol), and dried under vacuum to give pure 1-(4-methylquinazolin-2-yl)guanidine derivatives (3a-h) in 47-55% yield.
1-(6-Methoxy-4-methylquinazolin-2-yl)guanidine (3a): The title compound (3a) was obtained from the reaction of 2a with 2-cyano guanidine as a white solid in 56% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm): 11.08 (s, 1H), 8.85 (brs, 3H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.59 (dd, $J = 4.0$ & 8.0 Hz, 1H), 1-(6-Methoxy-4-methylquinazolin-2-yl)guanidine (3a) 7.44 (d, $J = 4.0$ Hz, 1H), 3.92 (s, 3H), 2.86 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm): 170.81, 157.51, 155.69, 152.18, 144.50, 128.70, 127.68, 122.33, 104.73, 56.33, 22.15; ESI MS (m/z): calculated for C$_{11}$H$_{14}$N$_{3}$O (M+H)$^+$: 232.1193, found 232.2.

1-(7-Methoxy-4-methylquinazolin-2-yl)guanidine (3b): The title compound (3b) was obtained from the reaction of 2b with 2-cyano guanidine as a white solid in 53% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm): 7.98 (d, $J = 8.0$ Hz, 1H), 7.16 (d, $J = 4.0$ Hz, 1H), 7.03 (dd, $J = 4.0$ & 8.0 Hz, 1H), 3.91 (s, 3H), 2.73 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm): 169.02, 164.13, 159.83, 158.40, 152.41, 127.64, 116.76, 115.48, 105.49, 56.12, 21.77; ESI MS (m/z): calculated for C$_{11}$H$_{14}$N$_{3}$O (M+H)$^+$: 232.1193, found 232.2.

1-(6,7-Dimethoxy-4-methylquinazolin-2-yl)guanidine (3c): The title compound (3c) was obtained from the reaction of 2c with 2-cyano guanidine as a white solid in 57% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm): 8.01 (brs, 1H), 7.30 (s, 1H), 7.20 (s, 1H), 3.91, 3.93 (2s, 6H), 2.74 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm): 167.15, 157.93, 156.16, 148.14, 147.42, 115.21, 105.92, 104.17, 56.40, 56.29, 21.88; ESI MS (m/z): calculated for C$_{12}$H$_{16}$N$_{3}$O (M+H)$^+$: 262.1299, found 262.2.

1-(5,6,7-trimethoxy-4-methylquinazolin-2-yl)guanidine (3d): The title compound (3d) was obtained from the reaction of 2d with 2-cyano guanidine as a white solid in 55% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm): 6.95 (s, 1H), 3.92, 3.79 (s, 3H), 2.78 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm): 166.95, 161.80, 159.76, 159.25, 150.53, 149.85, 139.72, 110.48, 102.85, 61.93, 61.53, 56.88, 26.88; ESI MS (m/z): calculated for C$_{13}$H$_{18}$N$_{3}$O$_3$ (M+H)$^+$: 292.1404, found 292.2.

1-(7-Hydroxy-4-methylbenzo[h]quinazolin-2-yl)guanidine (3e): The title compound (3e) was obtained from the reaction of 2e with 2-cyano guanidine as a white solid in 45% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), $\delta$ (ppm): 8.26 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.48 (t, $J = 8.0$ Hz, 1H), 7.14 (d, $J = 8.0$ Hz, 1H), 2.77 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), $\delta$ (ppm): 167.53, 163.45, 159.80, 154.01, 150.09, 130.76, 127.50, 125.87, 120.78, 117.57, 115.97, 114.99, 113.03, 22.31; ESI MS (m/z): calculated for C$_{14}$H$_{14}$N$_{3}$O (M+H)$^+$: 268.1193, found 268.2.
1-(4-Methyl-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-yl)guanidine (3f): The title compound (3f) was obtained from the reaction of 2f with 2-cynoguanidine as a white solid in 54% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 8.27 (brs, 3H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.16 (d, $J = 8.0$ Hz, 1H), 2.92 (t, $J = 8.0$ Hz, 2H), 2.86 (t, $J = 8.0$ Hz, 2H), 2.74 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ (ppm): 170.21, 158.16, 148.48, 143.47, 131.44, 126.68, 122.76, 118.43, 30.25, 24.27, 22.64, 22.54, 21.90; ESI MS (m/z): calculated for C$_{14}$H$_{18}$N$_5$ (M+H)$^+$: 256.1557, found 256.2.

1-(4-Methylquinazolin-2-yl)guanidine (3g): The title compound (3g) was obtained from the reaction of 2g with 2-cynoguanidine as a white solid in 51% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 7.97 (d, $J = 8.0$ Hz, 1H), 7.69 (t, $J = 8.0$ Hz, 1H), 7.57 (d, $J = 8.0$ Hz, 1H), 7.49 (brs, 2H), 7.29 (t, $J = 8.0$ Hz, 1H), 2.73 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ (ppm): 169.58, 161.52, 159.30, 150.13, 134.00, 126.29, 125.98, 123.97, 119.89, 22.00; ESI MS (m/z): calculated for C$_{10}$H$_{12}$N$_5$ (M+H)$^+$: 202.1087, found 202.2.

1-(4-Methyl-6-morpholinoquinazolin-2-yl)guanidine (3h): The title compound (3h) was obtained from the reaction of 2h with 2-cynoguanidine as a white solid in 50% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 7.67 (d, $J = 8.0$ Hz, 1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.19 (s, 1H), 3.78 (t, $J = 4.0$ Hz, 4H), 3.22 (t, $J = 4.0$ Hz, 2H), 2.74 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ (ppm): 168.24, 158.67, 158.30, 147.94, 144.81, 127.23, 126.32, 120.71, 107.07, 65.53, 49.26, 22.06; ESI MS (m/z): calculated for C$_{14}$H$_{19}$N$_6$O (M+H)$^+$: 287.1615, found 287.3.

General procedure for the synthesis of N-(4,6-dimethylpyrimidin-2-yl)-4-methylquinazolin-2-amine derivatives (4a, c-f): The mixture of 1-(4-methylquinazolin-2-yl)guanidine derivatives (4a, c-f) (0.39 mmol) and acetylacetone (0.78 mmol) in acetic acid (0.5 mL) was heated to reflux for 12 hrs. Progress of the reaction was monitored on TLC. On completion, the reaction mixture was basified (pH 8-9) with 28% ammonium hydroxide solution to give a yellow precipitate which was filtered, dried, and purified through column chromatography over silica gel using MeOH (0-2%) and triethylamine (0.2%) in DCM to give desired N-(4,6-dimethylpyrimidin-2-yl)-4-methylquinazolin-2-amine derivatives (4a, c-f) in 50-61% yield.

N-(4,6-Dimethylpyrimidin-2-yl)-6-methoxy-4-methylquinazolin-2-amine (4a) (ECH-69): The title compound (4a) was obtained from the reaction of 3a with acetylacetone as a light yellow solid in 61% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ
N-(4,6-Dimethylpyrimidin-2-yl)-6,7-dimethoxy-4-methylquinazolin-2-amine (4c) (ECH-71): The title compound (4c) was obtained from the reaction of 3c with acetylacetone as a light-yellow solid in 57% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 8.14 (s, 1H), 7.24 (s, 1H), 7.11 (s, 1H), 6.64 (s, 1H), 3.99 (s, 3H), 4.01 (s, 3H), 2.78 (s, 3H), 2.45 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 168.02, 166.60, 158.50, 156.51, 154.07, 148.81, 148.05, 115.89, 113.76, 106.96, 102.74, 56.32, 56.04, 24.15, 21.74; HRMS: (m/z) calcd for C$_{16}$H$_{18}$N$_3$O [M+H]$^+$: 296.1506, found 296.1506.

N-(4,6-dimethylpyrimidin-2-yl)-5,6,7-trimethoxy-4-methylquinazolin-2-amine 2-((4,6-Dimethylpyrimidin-2-yl)amino)-4-methylbenzo[b]quinazolin-7-ol (4d) (ECH-72): The title compound (4d) was obtained from the reaction of 3d with acetylacetone as a light yellow solid in 50% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-d$_6$), δ (ppm): 10.31 (s, 1H), 10.04 (s, 1H), 8.56 (dd, $J = 4.0$ & 8.0 Hz, 1H), 8.00 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 8.0$ Hz, 1H), 7.50 (t, $J = 8.0$ Hz, 1H), 7.16 (dd, $J = 8.0$ Hz, 1H), 6.85 (s, 1H), 2.85 (s, 3H), 2.39 (s, 6H); $^{13}$C NMR (100 MHz, DMSO-d$_6$), δ (ppm): 168.34, 167.51, 159.24, 155.88, 153.79, 150.70, 131.44, 127.70, 125.77, 120.58, 119.18, 117.80, 115.93, 114.06, 113.47, 24.02, 21.95; HRMS: (m/z) calcd for C$_{19}$H$_{18}$N$_3$O [M+H]$^+$: 332.1506, found 332.1506.

2-((4,6-Dimethylpyrimidin-2-yl)amino)-4-methylbenzo[b]quinazolin-7-ol (4e) (ECH-73): The title compound (4e) was obtained from the reaction of 3e with acetylacetone as a light yellow solid in 50% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 7.97 (s, 1H), 7.06 (s, 1H), 6.66 (s, 1H), 4.00 (s, 3H), 3.99 (s, 3H), 3.91 (s, 3H), 2.94 (s, 3H), 2.46 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 168.04, 167.95, 158.94, 158.38, 154.35, 150.26, 150.18, 140.19, 113.92, 111.85, 103.33, 61.13, 61.10, 56.19, 26.26, 24.14; HRMS: (m/z) calcd for C$_{18}$H$_{22}$N$_3$O$_3$ [M+H]$^+$: 356.1717, found 356.1720.

N-(4,6-Dimethylpyrimidin-2-yl)-4-methyl-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-amine (4f) (ECH-74): The title compound (4f) was obtained from the reaction of 3f with acetylacetone as a light yellow solid in 50% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 8.11 (s, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 6.67 (s, 1H), 3.25 (t, $J = 8.0$ Hz, 2H), 2.89 (t, $J = 8.0$ Hz, 2H), 2.83 (s, 3H), 2.47 (s, 6H), 1.86-1.93 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$), δ (ppm): 169.34, 167.80, 158.54, 154.04,
150.24, 142.75, 133.72, 126.47, 121.56, 119.10, 113.65, 30.43, 24.26, 24.11, 22.83, 22.80, 21.78; HRMS: (m/z) calcd for C_{10}H_{22}N_{5} [M+H]^+: 320.1870, found 320.1872.

**Synthesis procedure for synthesis of N-(4,6-dimethylpyrimidin-2-yl)cyanamide (6):**

To the mixture of 2-cyanoguanidine (5g, 59.46 mmol) and acetylacetone (9.2 mL, 89.20 mmol) in water (37 mL), 2.85 mL of 2M of NaOH was added and the reaction mixture was heated at 105 °C for 24 hrs. Progress of the reaction mixture was monitored through TLC. Upon consumption of all starting material, reaction mixture was cooled to room temperature which resulted in precipitation of the product. Filtration and washing of the precipitate with ethanol gave a light-yellow solid in 63% yield. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 12.57 (brs, 1H), 6.64 (s, 1H), 2.31 (s, 6H); \(^13\)C NMR (100 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 167.20, 160.69, 116.25, 110.15, 22.26; ESI MS (m/z): calculated for C\(_7\)H\(_5\)O\(_4\) (M+H): 149.0773, found 149.1.

**General procedure for the synthesis of N-(4,6-dimethylpyrimidin-2-yl)-4-methylquinazolin-2-amine derivatives 4b,4g:**

To the mixture of 2,2,4-trimethyl-1,2-dihydroquinoline 2b,4g (150 mg, 0.86 mmol) and N-(4,6-dimethylpyrimidin-2-yl)cyanamide (6) (128.3 mg, 0.86 mmol) in dioxane (5 mL), 2M HCl (455 µL) was added and the reaction mixture was heated at 105 °C for two hrs. Progress of the reaction mixture was monitored with TLC. Upon consumption of all starting material, reaction mixture was cooled to room temperature, basified with ammonia and concentrated under reduced pressure. Finally, the crude reaction mixture is purified through HPLC in Gilson instrument with acetonitrile (10-70%) and TFA (0.1%) in water system to give required derivatives in 23-31% yield.

**N-(4,6-dimethylpyrimidin-2-yl)-7-methoxy-4-methylquinazolin-2-amine (4b) (ECH-70):**

The title compound (4b) was obtained from the reaction of 2b with 6 as a light yellow solid in 26% yield by following the general procedure. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 8.79 (s, 1H), 7.74 (d, \(J = 8.0\) Hz, 1H), 7.17 (d, \(J = 4.0\) Hz, 1H), 6.91 (dd, \(J = 4.0\) & 8.0 Hz, 1H), 6.58 (s, 1H), 3.84 (s, 3H), 2.71 (s, 3H), 2.39 (s, 6H); \(^13\)C NMR (100 MHz, CDCl\(_3\)), \(\delta\) (ppm): 168.56, 167.95, 163.80, 158.51, 155.33, 153.64, 126.23, 117.17, 116.21, 113.88, 106.17, 55.56, 24.05, 21.44; HRMS: (m/z) calcd for C\(_{16}\)H\(_{18}\)N\(_5\)O [M+H]^+: 296.1506, found 296.1506.

**N-(4,6-Dimethylpyrimidin-2-yl)-4-methylquinazolin-2-amine (4g) (ECH-75):**

The title compound (4g) was obtained from the reaction of 2g with 6 as a light yellow solid in 31% yield by following the general procedure. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 8.10 (brs, 1H), 7.96 (d, \(J = 8.0\) Hz, 1H), 7.89 (d, \(J = 8.0\) Hz, 1H), 7.75 (t, \(J = 8.0\) Hz, 1H), 7.40 (t, \(J = 8.0\) Hz, 1H), 6.68 (s, 1H), 2.87 (s, 3H), 2.48 (s, 6H); \(^13\)C NMR (100 MHz, CDCl\(_3\)), \(\delta\) (ppm):
N-(4,6-dimethylpyrimidin-2-yl)-4-methyl-6-morpholinoquinazolin-2-amine (4h) (ECH-76): The title compound (4h) was obtained from the reaction of 2h with 6 as a yellow solid in 23% yield by following the general procedure. $^1$H NMR (400 MHz, CDCl$_3$), δ (ppm): 8.03 (s, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.54 (dd, $J = 4.0$ & 8.0 Hz, 1H), 7.13 (d, $J = 4.0$ Hz, 1H), 6.65 (s, 1H), 3.91 (t, $J = 4.0$ Hz, 4H), 3.25 (t, $J = 4.0$ Hz, 4H), 2.82 (s, 3H), 2.46 (s, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$), δ (ppm): 168.13, 168.00, 158.48, 153.25, 148.06, 146.66, 128.80, 126.07, 121.68, 113.76, 106.78, 66.84, 49.68, 24.14, 21.84; HRMS: (m/z) calcd for C$_{19}$H$_{23}$N$_6$O [M+H]+: 351.1928, found 351.1930.

General procedure for synthesis of 4-methyl-N-(4,4,6-trimethyl-4,5-dihydropyrimidin-2-yl)quinazolin-2-amine derivatives (5a-b): A mixture of quinazolylguanidine 3a-b (500 mg 2.16 mmol) and mesityl oxide (330 µL, 2.87 mmol) in DMSO (2 ml) was heated at 100 °C for 12 h. Upon consumption of the starting material, the reaction mixture was cooled down to room temperature and poured into ice cold water and extracted with DCM. The organic layer were then dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure to give the crude mixture, which was recrystallized with acetone to give the desired products in 21-26% yield.

6-Methoxy-4-methyl-N-(4,4,6-trimethyl-1,4-dihydropyrimidin-2-yl)quinazolin-2-amine (5a) (ECH-77): The title compound (5a) was obtained from the reaction of 3a with mesityl oxide as a light yellow solid in 21% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-d$_6$), δ (ppm): 9.88 (s, 1H), 7.54-7.55 (m, 1H), 7.40 (d, $J = 4.0$ & 8.0, 1H), 7.31 (d, 1H), 3.88 (s, 3H), 2.73 (s, 3H), 1.72 (s, 2H), 1.32 (s, 6H); ESI MS (m/z): calculated for C$_{11}$H$_{14}$N$_5$O (M+H)+: 311.1746, found 312.19.

7-Methoxy-4-methyl-N-(4,4,6-trimethyl-1,4-dihydropyrimidin-2-yl)quinazolin-2-amine (5b) (ECH-78): The title compound (5b) was obtained from the reaction of 3b with mesityl oxide as a light yellow solid in 26% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-d$_6$), δ (ppm): 9.90 (s, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 6.90-6.93 (m, 2H), 3.90 (s, 3H), 2.65 (s, 3H), 1.78 (s, 2H), 1.33 (s, 6H); ESI MS (m/z): calculated for C$_{11}$H$_{14}$N$_5$O (M+H)+: 311.1746, found 312.21.

General procedure for the synthesis of 4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine 7(a-g): The mixture of 1-(4-methylquinazolin-2-yl)guanidine (100mg, 0.50 mmol) and benzalacetone (80 mg, 0.55 mmol) in DMSO (0.5 ml) was heated in a sealed tube at 155 °C for 35 min using microwaves. The brown colored reaction mixture was then
poured into cold brine and extracted with DCM. The organic layer was dried over anhydrous Na2SO4 and concentrated under reduced pressure. The crude mixture was then purified through column chromatography over silica using MeOH (0-2%) and triethylamine (0.2%) in DCM to give the desired compounds 7(a-g) in 53-61 % yields.

6-Methoxy-4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7a) (ECH-79): The title compound (7a) was obtained from the reaction of 3a with benzalacetone as a yellow solid in 61% yield by following the general procedure. 1H NMR (400 MHz, CDCl3), δ (ppm): 8.18-8.20 (m, 2H), 8.12 (brs, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.45-7.52 (m, 4H), 7.26 (s, 1H), 7.21 (d, J = 4.0 Hz, 1H), 3.94 (s, 3H), 2.88 (s, 3H), 2.59 (s, 3H, CH3); 13C NMR (100 MHz, CDCl3), δ (ppm): 169.07, 168.06, 164.78, 158.82, 156.40, 153.49, 146.93, 137.12, 130.67, 129.39, 128.77, 127.24, 125.92, 121.58, 109.69, 103.10, 55.63, 24.62, 21.92; HRMS: (m/z) calcd for C21H20N5O [M+H]+: 358.1662, found 358.1664.

7-methoxy-4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7b) (ECH-80): The title compound (7b) was obtained from the reaction of 3b with benzalacetone as a yellow solid in 57% yield by following the general procedure. 1H NMR (400 MHz, CDCl3), δ (ppm): 8.16-8.19 (m, 3H), 7.87 (d, J = 8.0 Hz, 1H), 7.48-7.52 (m, 3H), 7.23-7.24 (m, 2H), 7.03 (dd, J = 4.0 & 8.0 Hz, 1H), 3.97 (s, 3H), 2.85 (s, 3H), 2.61 (s, 3H); 13C NMR (100 MHz, CDCl3), δ (ppm): 169.18, 168.65, 164.79, 164.04, 158.72, 155.22, 153.66, 137.04, 130.71, 128.76, 127.23, 126.44, 117.40, 116.37, 109.93, 106.10, 55.65, 24.68, 21.63; HRMS: (m/z) calcd for C21H20N5O [M+H]+: 358.1662, found 358.1659.

6,7-dimethoxy-4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7c) (ECH-81): The title compound (7c) was obtained from the reaction of 3c with benzalacetone as a yellow solid in 60% yield by following the general procedure. 1H NMR (400 MHz, CDCl3), δ (ppm): 8.15-8.18 (m, 3H), 7.48-7.50 (m, 3H), 7.27 (s, 1H), 7.22 (s, 1H), 7.15 (s, 1H), 4.05, 4.02 (2s, 6H), 2.85 (s, 3H), 2.61 (s, 3H, CH3); 13C NMR (100 MHz, CDCl3), δ (ppm): 169.14, 166.52, 164.75, 158.88, 155.72, 154.16, 148.92, 148.15, 137.10, 130.65, 128.74, 127.21, 116.00, 109.67, 106.81, 102.81, 56.29, 56.09, 24.69, 21.81; HRMS: (m/z) calcd for C22H22N5O2 [M+H]+: 388.1768, found 388.1776.

5,6,7-trimethoxy-4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7d) (ECH-82): The title compound (7d) was obtained from the reaction of 3d with benzalacetone as a yellow solid in 55% yield by following the general procedure. 1H NMR (400 MHz, CDCl3), δ (ppm): 8.15-8.18 (m, 3H), 7.48-7.51 (m, 3H), 7.22 (s, 1H), 7.08 (s, 1H), 4.01, 4.02, 3.93 (3s, 9H), 2.99 (s, 3H), 2.59 (s, 3H); 13C NMR (100 MHz, CDCl3), δ (ppm): 169.13, 167.88, 164.73, 159.00, 158.78, 154.48, 150.33, 150.23, 140.23, 137.07, 130.67, 128.73,
127.23, 111.95, 109.77, 103.16, 61.15, 61.13, 56.15, 26.31, 24.67; HRMS: (m/z) calcd for C_{23}H_{24}N_{5}O [M+H]^+: 418.1874, found 418.1876.

4-Methyl-2-((4-methyl-6-phenylpyrimidin-2-yl)amino)benzo[h]quinazolin-7-ol (7e) (ECH-83): The title compound (7e) was obtained from the reaction of 3e with benzalacetone as a yellow solid in 51% yield by following the general procedure. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 8.93 (d, \(J = 8.0\) Hz, 1H), 8.31 (bs, 1H), 8.24-8.27 (m, 2H), 8.05 (d, \(J = 8.0\) Hz, 1H), 7.81 (d, \(J = 8.0\) Hz, 1H), 7.49-7.54 (m, 4H), 7.28 (s, 1H), 7.10 (d, \(J = 8.0\) Hz, 1H), 2.95 (s, 3H), 2.63 (s, 3H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 169.08, 168.46, 163.72, 159.54, 155.88, 153.89, 150.72, 137.21, 131.38, 131.30, 129.17, 128.83, 120.65, 119.35, 117.93, 115.90, 113.56, 109.98, 24.37, 22.01; HRMS: (m/z) calcd for C_{26}H_{20}N_{5}O [M+H]^+: 394.1662, found 394.1657.

4-Methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-amine (7f) (ECH-84): The title compound (7f) was obtained from the reaction of 3f with benzalacetone as a yellow solid in 57% yield by following the general procedure. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 8.23-8.25 (m, 2H), 8.19 (bs, 1H), 7.72 (d, \(J = 8.0\) Hz, 1H), 7.49-7.51 (m, 3H), 7.23 (s, 1H), 7.12 (d, \(J = 8.0\) Hz, 1H), 3.38 (t, \(J = 8.0\) Hz, 2H), 2.92 (t, \(J = 8.0\) Hz, 2H), 2.87 (s, 3H), 2.58 (s, 3H), 1.89-1.97 (m, 4H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 169.28, 168.81, 164.85, 158.85, 154.04, 150.31, 142.75, 137.28, 133.72, 130.61, 128.64, 127.39, 126.53, 121.63, 119.14, 109.68, 99.98, 30.48, 24.75, 24.54, 22.87, 22.82, 21.78; HRMS: (m/z) calcd for C_{25}H_{21}N_{6} [M+H]^+: 382.2026, found 382.2031.

4-Methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7g) (ECH-85): The title compound (7g) was obtained from the reaction of 3g with benzalacetone as a yellow solid in 55% yield by following the general procedure. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 8.23 (bs, 1H), 8.19-8.21 (m, 2H), 7.98 (d, \(J = 8.0\) Hz, 1H), 7.93 (d, \(J = 8.0\) Hz, 1H), 7.79 (t, \(J = 8.0\) Hz, 1H), 7.49-7.53 (m, 3H), 7.43 (t, \(J = 8.0\) Hz, 1H), 7.25 (s, 1H), 2.92 (s, 3H), 2.60 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)), \(\delta\) (ppm): 169.92, 169.13, 164.82, 158.69, 154.64, 151.15, 137.05, 133.75, 128.79, 127.92, 127.25, 125.06, 124.68, 121.18, 109.96, 24.61, 21.77; HRMS: (m/z) calcd for C_{20}H_{18}N_{5} [M+H]^+: 328.1557, found 328.1560.

General procedure for the synthesis of 2-((4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one 8(a-g) & 9(a-f): To the mixture of 1-(4-methylquinazolin-2-yl)guanidine derivatives 3(a-f) (100 mg 0.50 mmol) and different isatoic anhydride (97 mg, 0.60 mmol) in anhydrous DMF (1 mL), diisopropyl ethylamine (103 \(\mu\)L, 0.60 mmol) was added and the reaction mixture was heated at 100 °C for 12 hrs. The reaction became a clear solution after stirring for 15 min and reprecipitation of the product appeared after 8 hrs, however, the
reaction was continued until consumption of all starting material. On completion, the reaction mixture was allowed to cool to room temperature. The precipitate was filtered, washed with methanol, and purified through crystallization in methanol to give the desired 2-((4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one 8(a-g) and 9(a-f) in 60-73% yield.

2-((6-Methoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8a) (ECH-86): The title compound (8a) was obtained from the reaction of 3a with isatoic anhydride, as a white solid in 67% yield by following the general procedure. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 13.56 (s, 1H), 10.94 (s, 1H), 8.06 (d, \(J = 8.0\) Hz, 1H), 7.76 (d, \(J = 8.0\) Hz, 1H), 7.72 (t, \(J = 8.0\) Hz, 1H), 7.72 (t, \(J = 8.0\) Hz, 1H), 7.63 (dd, \(J = 4.0\) & 8.0 Hz, 1H), 7.50 (d, \(J = 4.0\) Hz, 1H), 7.48 (d, \(J = 8.0\) Hz, 1H), 7.31 (t, \(J = 8.0\) Hz, 1H), 3.95 (s, 3H), 2.91 (s, 3H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 170.40, 157.10, 154.57, 148.87, 146.98, 134.93, 127.89, 127.40, 126.60, 123.97, 121.59, 119.25, 105.27, 56.34, 22.19; HRMS: (m/z) calcd for C\(_{18}\)H\(_{16}\)N\(_5\)O\(_6\) [M+H]\(^+\): 334.1299, found 334.1305.

2-((7-Methoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8b) (ECH-87): The title compound (8b) was obtained from the reaction of 3b with isatoic anhydride, as a white solid in 63% yield by following the general procedure. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 13.65 (s, 1H), 11.11 (s, 1H), 8.09 (d, \(J = 8.0\) Hz, 1H), 8.05 (dd, \(J = 4.0\) & 8.0 Hz, 1H), 7.72 (t, \(J = 8.0\) Hz, 1H), 7.46 (d, \(J = 8.0\) Hz, 1H), 7.32 (t, \(J = 8.0\) Hz, 1H), 7.13 (d, \(J = 8.0\) Hz, 1H), 7.09 (s, 1H), 3.99 (s, 3H), 2.83 (s, 3H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 170.46, 164.99, 155.94, 151.59, 148.63, 135.05, 128.30, 128.15, 126.62, 124.10, 119.26, 118.02, 115.99, 56.39, 21.85; HRMS: (m/z) calcd for C\(_{18}\)H\(_{16}\)N\(_5\)O\(_6\) [M+H]\(^+\): 334.1295, found 334.1295.

2-((6,7-Dimethoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8c) (ECH-88): The title compound (8c) was obtained from the reaction of 3c with isatoic anhydride, as a white solid in 68% yield by following the general procedure. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 13.64 (brs, 1H), 11.01 (brs, 1H), 8.06 (d, \(J = 8.0\) Hz, 1H), 7.72 (t, \(J = 8.0\) Hz, 1H), 7.43-7.45 (m, 2H), 7.31 (t, \(J = 8.0\) Hz, 1H), 7.13 (s, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 2.85 (s, 3H); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 168.09, 157.10, 154.57, 148.87, 146.98, 134.91, 126.59, 124.59, 123.84, 119.19, 115.81, 105.49, 104.69, 56.66, 56.49, 21.98; HRMS: (m/z) calcd for C\(_{19}\)H\(_{18}\)N\(_5\)O\(_3\) [M+H]\(^+\): 364.1404, found 364.1406.

2-((5,6,7-Trimethoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8d) (ECH-89): The title compound (8d) was obtained from the reaction of 3d with isatoic anhydride, as a white solid in 73% yield by following the general procedure. \(^1\)H NMR (400 MHz, DMSO-
$d_0$, δ (ppm): 13.55 (brs, 1H), 11.09 (brs, 1H), 8.05 (d, $J = 8.0$ Hz, 1H), 7.72 (t, $J = 8.0$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.31 (t, $J = 8.0$ Hz, 1H), 6.97 (s, 1H), 4.04 (s, 3H), 4.00 (s, 3H), 3.84 (s, 3H), 2.93 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 168.77, 160.38, 155.04, 150.49, 148.46, 140.77, 134.91, 126.60, 124.02, 119.27, 111.64, 102.25, 100.08, 61.70, 61.24, 56.88, 26.41; HRMS: (m/z) calcd for C$_{20}$H$_{20}$N$_5$O$_4$ [M+H]$^+$: 394.1510, found 394.1502.

2-((4-Methyl-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-yl)amino)quinazoline-4(1H)-one (8e) (ECH-90): The title compound (8e) was obtained from the reaction of 3f with isatoic anhydride, as a white solid in 67% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 13.83 (brs, 1H), 10.89 (brs, 1H), 8.06 (d, $J = 8.0$ Hz, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.73 (t, $J = 8.0$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.32 (t, $J = 8.0$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 1H), 3.14 (t, $J = 8.0$ Hz, 2H), 2.92 (d, $J = 8.0$ Hz, 2H), 2.86 (s, 3H), 1.95-1.97 (m, 2H), 1.85-1.87 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ (ppm): 171.70, 159.99, 154.93, 147.64, 144.67, 134.89, 131.57, 127.51, 126.54, 124.03, 123.05, 119.36, 118.94, 30.31, 24.35, 22.67, 22.48, 21.94; m/z (ESI MS): HRMS: (m/z) calcd for C$_{21}$H$_{20}$N$_5$O$_4$ [M+H]$^+$: 358.1662, found 358.1653.

2-((4-Methylquinazolin-2-yl)amino)quinazoline-4(1H)-one (8f) (ECH-91): The title compound (8f) was obtained from the reaction of 3g with isatoic anhydride, as a white solid in 63% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 13.70 (brs, 1H), 11.30 (brs, 1H), 8.24 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 7.97 (t, $J = 8.0$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.74 (t, $J = 8.0$ Hz, 1H), 7.59 (t, $J = 8.0$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.34 (s, 1H), 2.93 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 172.14, 165.01, 155.49, 148.89, 135.65, 134.96, 126.70, 126.62, 126.30, 125.98, 124.17, 120.97, 119.39, 22.01; HRMS: (m/z) calcd for C$_{17}$H$_{14}$N$_5$O [M+H]$^+$: 304.1193, found 304.1184.

2-((4-Methyl-6-morpholinoquinazolin-2-yl)amino)quinazoline-4(1H)-one (8g) (ECH-92): The title compound (8g) was obtained from the reaction of 3h with isatoic anhydride, as a yellow solid in 60% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 13.60 (brs, 1H), 10.81 (brs, 1H), 8.06 (d, $J = 8.0$ Hz, 1H), 7.80 (dd, $J = 4.0$ & 8.0 Hz, 1H), 7.71 (t, $J = 8.0$ Hz, 2H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.29-7.32 (m, 2H), 3.80-3.81 (m, 4H), 3.29-3.30 (m, 4H), 2.87 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$), δ (ppm): 169.95, 161.47, 153.60, 148.91, 143.52, 134.87, 127.17, 127.01, 126.59, 123.85, 121.74, 119.22, 107.10, 66.50, 48.99, 22.08; HRMS: (m/z) calcd for C$_{21}$H$_{22}$N$_5$O$_2$ [M+H]$^+$: 389.1721, found 389.1716.
6-Chloro-2-((6-methoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9a) (ECH-93): The title compound (9a) was obtained from the reaction of 3a with 5-chloroisatoic anhydride, as a white solid in 64% yield by following the general procedure. $^1$H NMR (600 MHz, DMSO-$d_6$), δ (ppm): 13.74 (brs, 1H), 11.23 (brs, 1H), 7.96 (s, 1H), 7.71-7.73 (m, 2H), 7.59-7.62 (m, 1H), 7.43-7.48 (m, 2H), 3.93 (s, 3H), 2.90 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 170.36, 157.09, 153.89, 149.04, 144.45, 134.88, 128.26, 128.18, 125.48, 120.46, 118.05, 116.17, 105.38, 56.42, 21.75; HRMS: (m/z) calcd for C$_{19}$H$_{15}$ClN$_5$O$_2$ [M+H]$^+$: 368.0909, found 368.0911.

6-Chloro-2-((7-methoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9b) (ECH-94): The title compound (9b) was obtained from the reaction of 3b with 5-chloroisatoic anhydride, as a white solid in 67% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 13.77 (brs, 1H), 11.23 (brs, 1H), 8.09 (d, $J$ = 8.0 Hz, 1H), 7.94 (d, $J$ = 4.0 Hz, 1H), 7.72 (dd, $J$ = 4.0 & 8.0 Hz, 1H), 7.44 (d, $J$ = 8.0 Hz, 1H), 7.13 (dd, $J$ = 4.0 & 8.0 Hz, 1H), 7.06 (s, 1H), 3.99 (s, 3H), 2.82 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 170.43, 160.37, 155.80, 151.72, 148.91, 134.94, 128.26, 128.18, 125.48, 120.46, 118.05, 116.17, 105.38, 56.42, 21.75; HRMS: (m/z) calcd for C$_{18}$H$_{15}$ClN$_5$O$_2$ [M+H]$^+$: 368.0909, found 368.0911.

6-Chloro-2-((6,7-dimethoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9c) (ECH-95): The title compound (9c) was obtained from the reaction of 3c with 5-chloroisatoic anhydride, as a white solid in 63% yield by following the general procedure. $^1$H NMR (600 MHz, DMSO-$d_6$), δ (ppm): 13.68 (brs, 1H), 10.80 (brs, 1H), 7.97 (brs, 1H), 7.70-7.71 (m, 1H), 7.47 (brs, 1H), 7.41 (s, 1H), 7.14 (brs, 1H), 3.94 (s, 3H), 2.89 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 168.10, 160.51, 157.23, 154.39, 149.04, 147.00, 134.88, 127.93, 125.47, 120.30, 115.93, 105.56, 104.79, 56.69, 56.55, 21.94; HRMS: (m/z) calcd for C$_{19}$H$_{15}$ClN$_5$O$_3$ [M+H]$^+$: 398.1014, found 398.1011.

6-Chloro-2-((5,6,7-trimethoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9d) (ECH-96): The title compound (9d) was obtained from the reaction of 3d with 5-chloroisatoic anhydride, as a white solid in 71% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 13.70 (brs, 1H), 11.21 (brs, 1H), 7.97 (d, $J$ = 8.0 Hz, 1H), 7.74 (dd, $J$ = 8.0 Hz, 1H), 7.45 (d, $J$ = 8.0 Hz, 1H), 6.97 (d, $J$ = 8.0 Hz, 1H), 4.04 (s, 1H), 4.00 (s, 1H), 3.85 (s, 3H), 2.97 (s, 3H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 168.85, 160.48, 154.86, 150.50, 148.42, 140.89, 134.95, 125.49, 120.41, 111.76, 102.30, 61.70, 61.25, 56.91, 26.37; HRMS: (m/z) calcd for C$_{20}$H$_{19}$ClN$_5$O$_4$ [M+H]$^+$: 428.1120, found 428.1115.
6-Chloro-2-((4-methyl-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-yl)amino)quinazolin-4(1H)-one (9e) (ECH-97): The title compound (9e) was obtained from the reaction of 3f with 5-chloroisatoic anhydride, as a white solid in 67% yield by following the general procedure. 

1H NMR (600 MHz, DMSO-d6), δ (ppm): 14.08 (brs, 1H), 11.05 (brs, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.71 (dd, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 3.14-3.15 (m, 2H), 2.93 (t, J = 8.0 Hz, 2H), 2.87 (s, 3H), 1.97 (t, J = 8.0 Hz, 2H), 1.88 (t, J = 8.0 Hz, 2H); 13C NMR (150 MHz, DMSO-d6), δ (ppm): 171.79, 158.45, 154.76, 147.59, 144.78, 134.92, 131.62, 128.09, 127.65, 125.42, 123.05, 120.47, 119.04, 30.33, 24.33, 22.66, 22.48, 21.92; HRMS: (m/z) calcd for C21H16ClN5O [M+H]+: 392.1273, found 392.1273.

6-Chloro-2-((4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9f) (ECH-98): The title compound (9f) was obtained from the reaction of 3g with 5-chloroisatoic anhydride, as a white solid in 62% yield by following the general procedure. 

1H NMR (400 MHz, DMSO-d6), δ (ppm): 11.86 (brs, 1H), 10.03 (brs, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.91-7.97 (m, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 2.93 (s, 3H); 13C NMR (150 MHz, DMSO-d6), δ (ppm): 172.09, 159.22, 154.78, 150.02, 149.19, 135.38, 132.08, 130.88, 127.01, 126.54, 126.34, 121.22, 119.37, 118.75, 117.72, 21.88; HRMS: (m/z) calcd for C17H13ClN5O [M+H]+: 338.0803, found 338.0809.

Synthesis procedure for synthesis of 1-(4,6-Dimethylpyrimidin-2-yl)guanidine (10): The mixture of N-(4,6-dimethylpyrimidin-2-yl)cyanamide (6) (8g, 0.054 mol) and ammonium chloride (12g, 0.23 mol) in phenol (25g, 0.27 mol) was heated at 125 °C for 7 hrs. The reaction mixture was then poured into ice water and extracted with ethylacetate, and washed with 2N sodium hydroxide solution. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to give the desired 1-(4,6-dimethylpyrimidin-2-yl)guanidine in 68 % yield. 

1H NMR (400 MHz, DMSO-d6), δ (ppm): 7.03 (brs, 4H), 6.44 (s, 1H), 2.21 (s, 6H); 13C NMR (100 MHz, DMSO-d6), δ (ppm): 166.69, 166.01, 159.61, 110.31, 24.11; ESI MS (m/z) calculated for C7H12N5 (M+H)+: 166.1073, found 166.2.

Synthesis of Bis(4,6-dimethylpyrimidin-2-yl)amine (11) (ECH-99): The mixture of 1-(4,6-dimethylpyrimidin-2-yl)guanidine (198 mg 1.2 mmol) and acetylacetone (242mg, 2.42 mmol) in acetic acid (0.5 mL) was heated at 125 °C for 12 hrs. The progress of the reaction was monitored with TLC. Upon completion, the reaction mixture was allowed to cool to room temperature and was basified with 5 mL of ammonia (28%) in ice cold water to give a precipitate which were filtered and purified through column chromatography over silica using
0.5-1.5% of MeOH in DCM as solvent system to give the desired product in 64% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 7.87 (brs, 1H), 6.64 (s, 2H), 2.43 (s, 12H); \(^13\)C NMR (100 MHz, CDCl\(_3\)), \(\delta\) (ppm): 167.98, 158.33, 113.91, 24.07; HRMS: (\(m/z\)) calcd for C\(_{13}\)H\(_{16}\)N\(_5\) [M+H]\(^+\): 230.1400, found 230.1402.

**General procedure for synthesis of 2-((4,6-dimethylpyrimidin-2-yl)amino)quinazolin-4(1H)-one derivatives 12-17:** To the mixture of 1-((4,6-dimethylpyrimidin-2-yl)guanidine (10) (150 mg, 0.91 mmol) and isatoic anhydride (176 mg, 1.08 mmol) in anhydrous DMF (1.5 mL), diisopropyl ethylamine (188 \(\mu\)L, 1.08 mmol) was added and reaction mixture was heated at 100 °C for 12 hrs. Progress of the reaction mixture was monitored using TLC. Upon completion, the reaction mixture was concentrated under reduced pressure and purified through column chromatography over silica using MeOH (0-2%) and triethylamine (0.2%) in DCM to give the pure 2-((4,6-dimethylpyrimidin-2-yl)amino)quinazolin-4(1H)-one derivatives in 43-57 % yield.

**2-((4,6-Dimethylpyrimidin-2-yl)amino)quinazolin-4(1H)-one (12) (ECH-100):** The title compound (12) was obtained from the reaction of 10 with isatoic anhydride, as a white solid in 57% yield by following the general procedure. \(^1\)H NMR (400 MHz, CDCl\(_3\)), \(\delta\) (ppm): 13.27 (brs, 1H), 9.20 (brs, 1H), 8.23 (dd, \(J = 4.0 & 8.0 \)Hz, 1H), 7.63 (t, \(J = 8.0\) Hz, 1H), 7.50 (dd, \(J = 4.0 & 8.0\) Hz, 1H), 7.29 (t, \(J = 8.0\) Hz, 1H), 6.70 (s, 1H), 2.46 (s, 6H); \(^13\)C NMR (100 MHz, CDCl\(_3\)), \(\delta\) (ppm): 168.25, 161.94, 157.89, 149.74, 147.78, 134.35, 126.71, 125.76, 123.99, 119.39, 114.45, 23.85; HRMS: (\(m/z\)) calcd for C\(_{14}\)H\(_{14}\)N\(_3\)O [M+H]\(^+\): 268.1193, found 268.1195.

**6-Chloro-2-((4,6-dimethylpyrimidin-2-yl)amino)quinazolin-4(1H)-one (13) (ECH-101):** The title compound (13) was obtained from the reaction of 10 with 5-chloroisatoic anhydride, as a white solid in 55% yield by following the general procedure. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 13.47 (brs, 1H), 10.80 (brs, 1H), 7.95 (d, \(J = 4.0 & 8.0\) Hz, 1H), 7.69 (dd, \(J = 4.0 & 8.0\) Hz, 1H), 7.44 (dd, \(J = 8.0\) Hz, 1H), 6.94 (s, 1H), 2.43 (s, 6H); \(^13\)C NMR (150 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 168.12, 160.41, 158.43, 148.93, 134.91, 128.11, 127.81, 125.51, 125.42, 120.33, 114.70, 23.80; HRMS: (\(m/z\)) calcd for C\(_{14}\)H\(_{13}\)ClN\(_3\)O [M+H]\(^+\): 302.0803, found 302.0807.

**2-((4,6-Dimethylpyrimidin-2-yl)amino)-8-methoxyquinazolin-4(1H)-one (14) (ECH-102):** The title compound (14) was obtained from the reaction of 10 with 3-methoxyisatoic anhydride (obtained from the reaction of 2-amino-3-methoxybenzoic acid with triphosgene\(^2\)), as a white solid in 47% yield by following the general procedure. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)), \(\delta\) (ppm): 13.95 (brs, 1H), 10.87 (brs, 1H), 7.59 (d, \(J = 8.0\) Hz, 1H), 7.25-7.32 (m,
2H), 6.97 (s, 1H), 3.99 (s, 3H), 2.46 (s, 6H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 167.94, 160.05, 158.95, 152.52, 147.55, 129.31, 124.16, 119.69, 118.11, 114.58, 56.72, 23.81; HRMS: (m/z) calcd for C$_{15}$H$_{16}$N$_5$O$_2$ [M+H]$^+$: 298.1299, found 298.1292.

2-((4,6-Dimethylpyrimidin-2-yl)amino)-7-methoxyquinazolin-4(1H)-one (15) (ECH-103): The title compound (15) was obtained from the reaction of 10 with 4-methoxyisatoic anhydride (obtained from reaction 2-amino-4-methoxybenzoic acid with triphosgene)$^2$, as a white solid in 50% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 13.19 (brs, 1H), 10.71 (brs, 1H), 7.94 (d, $J$ = 8.0 Hz, 1H), 6.94 (s, 1H), 6.89 (dd, $J$ = 8.0 Hz, 1H), 6.84 (s, 1H), 3.88 (s, 3H), 2.43 (s, 6H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 168.08, 164.73, 160.77, 158.42, 152.67, 148.96, 128.17, 114.56, 113.62, 112.60, 106.85, 56.98, 23.87; HRMS: (m/z) calcd for C$_{15}$H$_{16}$N$_5$O$_2$ [M+H]$^+$: 298.1299, found 298.1299.

6-Bromo-2-((4,6-dimethylpyrimidin-2-yl)amino)quinazolin-4(1H)-one (16) (ECH-104): The title compound (16) was obtained from the reaction of 10 with 5-bromoisatoic anhydride as a white solid in 45% yield by following the general procedure. $^1$H NMR (400 MHz, DMSO-$d_6$), δ (ppm): 13.50 (brs, 1H), 10.91 (brs, 1H), 8.10 (d, $J$ = 8.0 Hz, 1H), 7.83 (d, $J$ = 8.0 Hz, 1H), 7.39 (d, $J$ = 8.0 Hz, 1H), 6.97 (s, 1H), 2.44 (s, 6H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 168.15, 160.47, 158.42, 149.12, 137.64, 128.56, 127.76, 120.80, 115.88, 114.75, 23.82; HRMS: (m/z) calcd for C$_{15}$H$_{16}$BrN$_5$O [M+H]$^+$: 346.0298, found 346.0297.

2-((4,6-Dimethylpyrimidin-2-yl)amino)-6,7-difluoroquinazolin-4(1H)-one (17) (ECH-105): The title compound (17) was obtained from the reaction of 10 with 4,5-difluoroisatoic anhydride (obtained from reaction 2-amino-4,5-difluorobenzoic acid with triphosgene)$^2$, as a white solid in 43% yield by following the general procedure.$^1$H NMR (600 MHz, DMSO-$d_6$), δ (ppm): 13.50 (brs, 1H), 10.85 (brs, 1H), 7.89-7.92 (m, 1H), 7.37-7.40 (m, 1H), 6.97 (s, 1H), 2.45 (s, 6H); $^{13}$C NMR (150 MHz, DMSO-$d_6$), δ (ppm): 168.16, 160.13, 158.38, 155.49 (d $J_{C,F}$ = 60 Hz), 153.81 (d $J_{C,F}$ = 60 Hz), 149.33, 148.01 (d, $J_{C,F}$ = 60 Hz), 146.39 (d, $J_{C,F}$ = 54 Hz), 115.94 (d, $J_{C,F}$ = 24 Hz), 114.77, 113.89 39 (d, $J_{C,F}$ = 78 Hz), 23.80; HRMS: (m/z) calcd for C$_{14}$H$_{11}$F$_2$NaN$_5$O [M+Na]$^+$: 326.0823, found 326.0826.
$^1$H and $^{13}$C NMR of 6-methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (2a).
$^1$H and $^{13}$C NMR of 7-methoxy-2,2,4-trimethyl-1,2-dihydroquinoline (2b).
$^1$H and $^{13}$C NMR of 6,7-dimethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (2c).
$^1$H and $^{13}$C NMR of 5,6,7-trimethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (2d).
$^1$H (CDCl$_3$) and $^{13}$C (DMSO-d$_6$) NMR of 2,2,4-trimethyl-1,2-dihydrobenzo[h]quinolin-7-ol (2e).
$^1$H and $^{13}$C NMR of 2,2,4-trimethyl-1,2,7,8,9,10-hexahydrobenzo[\textit{h}]quinoline (2f).
$^1$H and $^{13}$C NMR of 2,2,4-trimethyl-1,2-dihydroquinoline (2g)
$^1$H and $^{13}$C NMR of 4-(2,2,4-trimethyl-1,2-dihydroquinolin-6-yl)morpholine (2h).
$^1$H and $^{13}$C NMR of 1-(6-methoxy-4-methylquinazolin-2-yl)guanidine (3a).
$^1$H and $^{13}$C NMR of 1-(7-methoxy-4-methylquinazolin-2-yl)guanidine (3b).
$^1$H and $^{13}$C NMR of 1-(6,7-dimethoxy-4-methylquinazolin-2-yl)guanidine (3c).
$^1$H and $^{13}$C NMR of 1-(5,6,7-trimethoxy-4-methylquinazolin-2-yl)guanidine (3d).
$^1$H and $^{13}$C NMR of 1-(7-hydroxy-4-methylbenzo[h]quinazolin-2-yl)guanidine (3e).
$^1$H and $^{13}$C NMR of 1-(4-methyl-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-yl)guanidine (3f).
1H and 13C NMR of 1-(4-methylquinazolin-2-yl)guanidine (3g).
$^{1}$H and $^{13}$C NMR of 1-(4-methyl-6-morpholinoquinazolin-2-yl)guanidine (3h).
$^1$H and $^{13}$C NMR of $N$-(4,6-dimethylpyrimidin-2-yl)-6-methoxy-4-methylquinazolin-2-amine (4a).
$^1$H and $^{13}$C NMR of $N$-(4,6-dimethylpyrimidin-2-yl)-6,7-dimethoxy-4-methylquinazolin-2-amine (4c).
$^1$H and $^{13}$C NMR of 2-((4,6-dimethylpyrimidin-2-yl)amino)-4-methylbenzo[h]quinazolin-7-ol (4d).
$^1$H and $^{13}$C NMR of N-(4,6-dimethylpyrimidin-2-yl)-5,6,7-trimethoxy-4-methylquinazolin-2-amine (4e).
$^1$H and $^{13}$C NMR of $N$-(4,6-dimethylpyrimidin-2-yl)-4-methyl-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-amine (4f).
$^1$H and $^{13}$C NMR of $N$-(4,6-dimethylpyrimidin-2-yl)cyanamide (6).
$^1$H and $^{13}$C NMR of $N$-(4,6-dimethylpyrimidin-2-yl)-7-methoxy-4-methylquinazolin-2-amine (4b).
$^1$H and $^1$C NMR of $N$-(4,6-dimethylpyrimidin-2-yl)-4-methylquinazolin-2-amine (4g).
$^1$H and $^{13}$C NMR of $N$-(4,6-dimethylpyrimidin-2-yl)-4-methyl-6-morpholinoquinazolin-2-amine (4h).
$^1$H NMR of 6-methoxy-4-methyl-N-(4,4,6-trimethyl-1,4-dihydropyrimidin-2-yl)quinazolin-2-amine (5a).

$^1$H NMR of 7-methoxy-4-methyl-N-(4,4,6-trimethyl-1,4-dihydropyrimidin-2-yl)quinazolin-2-amine (5b).
$^1$H and $^{13}$C NMR of 6-methoxy-4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7a).
$^1$H and $^{13}$C NMR of 7-methoxy-4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7b).
$^1$H and $^{13}$C NMR of 6,7-dimethoxy-4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7c).
$^1$H and $^{13}$C NMR of 5,6,7-trimethoxy-4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7d).
$^1$H and $^{13}$C NMR of 4-methyl-2-((4-methyl-6-phenylpyrimidin-2-yl)amino)benzo[h]quinazolin-7-ol (7e).
$^1$H and $^1$C NMR of 4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-amine (7f).
$^1$H and $^13$C NMR of 4-methyl-N-(4-methyl-6-phenylpyrimidin-2-yl)quinazolin-2-amine (7g)
$^1$H and $^{13}$C NMR of 2-((6-methoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8a).
$^1$H and $^{13}$C NMR of 2-((7-methoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8b).
$^1$H and $^{13}$C NMR of 2-((6,7-dimethoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8c).
$^1$H and $^{13}$C NMR of 2-((5,6,7-trimethoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8d)
$^1$H and $^{13}$C NMR of 2-((4-methyl-7,8,9,10-tetrahydrobenzo[h]quinazolin-2-yl)amino)quinazolin-4(1H)-one (8e).
$^1$H and $^{13}$C NMR of 2-((4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (8f).
$^1$H and $^{13}$C NMR of 2-((4-methyl-6-morphinoquinazolin-2-yl)amino)quinazolin-4(1H)-one (8g).
$^1$H and $^{13}$C NMR of 6-chloro-2-((6-methoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9a).
$^1$H and $^{13}$C NMR of 6-chloro-2-((7-methoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9b).
$^1$H and $^{13}$C NMR of 6-chloro-2-((6,7-dimethoxy-4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9c).
$^1$H and $^13$C NMR of 6-chloro-2-(5,6,7-trimethoxy-4-methylquinazolin-2-yl)aminoquinazolin-4(1H)-one (9d).
$^{1}H$ and $^{13}C$ NMR of 6-chloro-2-((4'-methyl-7,8,9,10-tetrahydrobenzo[h]quinazolin-4-yl)amino)quinazolin-4(1H)-one (9e).
$^1$H and $^{13}$C NMR of 6-chloro-2-((4-methylquinazolin-2-yl)amino)quinazolin-4(1H)-one (9f).
$^1$H and $^{13}$C NMR of 1-(4,6-dimethylpyrimidin-2-yl)guanidine (10).
$^1$H and $^{13}$C NMR of bis(4,6-dimethylpyrimidin-2-yl)amine (11).
$^1$H and $^{13}$C NMR of 2-((4,6-dimethylpyrimidin-2-yl)amino)quinazolin-4(1H)-one (12).
$^1$H and $^{13}$C NMR of 6-chloro-2-((4,6-dimethylpyrimidin-2-yl)amino)quinazolin-4(1H)-one (13).
$^1$H and $^{13}$C NMR of 2-((4,6-dimethylpyrimidin-2-yl)amino)-8-methoxyquinazolin-4(1H)-one (14).
$^1$H and $^{13}$C NMR of 2-((4,6-dimethylpyrimidin-2-yl)amino)-7-methoxyquinazolin-4(1$H$)-one (15)
$^1$H and $^{13}$C NMR of 6-bromo-2-((4,6-dimethylpyrimidin-2-yl)amino)quinazolin-4(1H)-one (16).
$^1$H and $^{13}$C NMR of 2-((4,6-dimethylpyrimidin-2-yl)amino)-6,7-difluoroquinazolin-4(1H)-one (17).
HRMS Spectral Data:

HRMS Spectra of 4a.

HRMS Spectra of 4b.
HRMS Spectra of 4c.

HRMS Spectra of 4d.
HRMS Spectra of 4e.

HRMS Spectra of 4f.
HRMS Spectra of 4g.

HRMS Spectra of 7a.
HRMS Spectra of 7b.

HRMS spectra of 7c.
HRMS spectra of 7d.

HRMS spectra of 7e.
HRMS spectra of **7f**.

HRMS spectra of **7g**.
HRMS spectra of 8a.

HRMS spectra of 8b.
HRMS spectra of 8c.

HRMS spectra of 8d.
HRMS spectra of 8e.

HRMS spectra of 8f.
HRMS spectra of 8g.

HRMS spectra of 9a.
HRMS spectra of 9b.

HRMS spectra of 9c.
HRMS spectra of 9d.

HRMS spectra of 9e.
HRMS Spectra of 9f.

HRMS Spectra of 11.
HRMS spectra of 12.

HRMS Spectra of 13.
HRMS Spectra of 14.

HRMS Spectra of 15.
HRMS Spectra of **16**.

HRMS Spectra of **17**.
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