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# Regioselective addition of Grignard reagents to 2,6-dicyanoanilines and cyclization to new quinazoline derivatives under thermal/microwave irradiation conditions☆

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**Abstract**

Two strategies have been developed for the synthesis of novel quinazoline derivatives. 2,6-Dicyanoanilines were reacted with Grignard reagents followed by cyclization to give two quinazoline regioisomers **2** and **3**. Alternately 2,6-dicyanoanilines on reaction with Grignard reagents gave imine regioisomers **4** and **5**. Each imine regioisomer was separated and independently cyclized to give new quinazoline derivatives **6**, **7** and **8**, **9**, respectively, under different microwave irradiation conditions.


*Keywords:* 2,6-Dicyanoanilines; Regioisomers; Quinazolines; Grignard reagents

## 1. Introduction

The quinazoline nucleus features in many alkaloids and is known to show a wide range of biological activity [1]. A few non-classical quinazoline analogues of folic acid have remarkable antibacterial and antimalarial effects and most prominent is trimetrexate [2]. It is also considered as an anticancer agent and has similar levels of inhibitory potency as methotrexate towards dihydrofolate reductase (DHFR). Prazosin, a quinazoline-based drug, is used as an antihypertensive agent [3]. The prime requirement for any organic molecule to act as a potential drug is low dosage, low toxicity and effective binding to the specific disease causing receptor site with high solubility. In order to target the requirements, specific substituents at appropriate positions of a molecule are desirable. One such group is fluorine [4] or trifluoromethyl [5,6] which, at a strategic position in the molecule, alters the properties of molecule by promoting activity due to high lipid solubility. Previous syntheses of quinazolines are mainly from *o*-aminoketones [7], *o*-aminonitriles [8], enamines via aza Wittig reaction [9], electrocyclic ring closures [10,11] and 1,3-dimethoxybenzenes [12].

Based on the importance of quinazoline derivatives and our continued interest in fluorinated molecules [13], we have selected 2,6-dicyanoanilines (**1**) [14,15], interesting trifunctional intermediates and subjected them to Grignard addition in two ways. One way was addition of Grignard reagents followed by cyclization in a single step to quinazoline derivatives (**2** and **3**). Another way was addition of Grignard reagents to compounds **1** to give imine regioisomers (**4** and **5**). Then, each isomer was separated and independently cyclized to quinazolines **6**, **7** and **8**, **9**, respectively, under microwave irradiation conditions.

## 2. Results and discussion

Unsymmetrical 2,6-dicyanoanilines (**1**) were reacted with various Grignard reagents and the resulted reaction mixture was treated with trifluoroacetic/acetic anhydrides in situ to give quinazoline regioisomers (**2** and **3**) in different proportions. The yields were in the range 60–70%. The main reaction is addition of Grignard reagents to the less hindered nitrile (CN) carbon in preference to highly hindered and followed by cyclization in presence of trifluoroacetic/acetic anhydride resulted two

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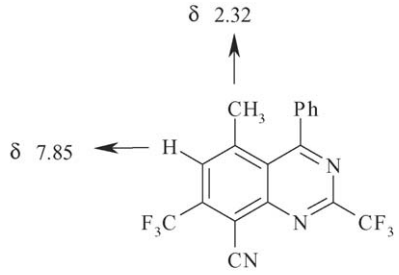
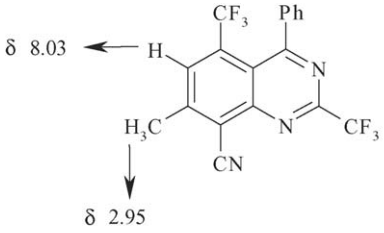
quinazoline regioisomers, as one isomer in major and another isomer in minor depending upon the substituents used. The role of substituents on reaction time, yield and ratio of products formed was established. Thus, the methyl substituent in compound **1** promotes formation of product **2** as the major, whereas the phenyl substituent reverses the formation of products. Regioselectivity is high with phenyl substitution in compound **1** and also in the Grignard reagents. The reaction is schematically drawn in Scheme 1.

The regioisomers **2** and **3** were separated and identified based on characteristic differences in their $^1$H NMR spectra. In a specific example of **2a** and **3a**, we observed a change in chemical shift of $CH_3$ and C–H proton on C-6 carbon. In **3a** the methyl group as well as C–H proton on C-6 carbon appeared downfield with reference to **2a**. It is attributed to the ortho nitrile (CN) effect on the methyl group and the ortho $CF_3$ group effect on the C-6 proton in line with C-4 phenyl group as a result appeared in downfield in comparison to **2a** isomer. Similar trend is followed in other isomers. The products synthesised are tabulated in Table 1.




**2a**



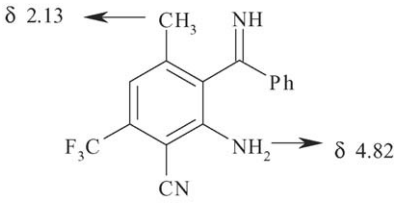

**3a**

The reaction of compound **1** with Grignard reagents followed by aryl aldehydes is further extended in order to obtain 2-arylsubstituted quinazolines; however, in all the cases imine derivatives (**4** and **5**) are exclusively formed. Thus, unsymmetrical 2,6-dicyanoanilines (**1**) on reaction with Grignard reagents gave two imine regioisomers (**4** and **5**). The reaction trend is similar to the first strategy and obtained one of the isomer major and another minor. The regioisomers are with close polarity, separated by column and identified based on spectral data (Scheme 2).

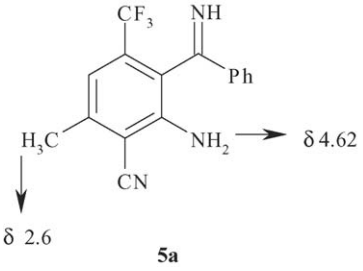
Table 1
Quinazoline regioisomers

| Entry | Product | R | R′ | R″ | Ratio (%) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **2a** | $CH_3$ | Ph | $CF_3$ | 65 | 42 |
| | **3a** | $CH_3$ | Ph | $CF_3$ | 35 | 22 |
| 2 | **2b** | Ph | Ph | $CF_3$ | 28 | 22 |
| | **3b** | Ph | Ph | $CF_3$ | 72 | 56 |
| 3 | **2c** | Ph | Ph | $CH_3$ | 25 | 15 |
| | **3c** | Ph | Ph | $CH_3$ | 75 | 46 |
| 4 | **2d** | Ph | $C_2H_5$ | $CF_3$ | 40 | 23 |
| | **3d** | Ph | $C_2H_5$ | $CF_3$ | 60 | 35 |

The $^1$H NMR spectra of two regioisomers (**4a** and **5a**) show characteristic differences in the chemical shift of $CH_3$ and $NH_2$ signals of one isomer to other isomer are varied due to electronic factors. It depends on mainly two groups, i.e., $CF_3$ and CN. If $CF_3$ and CN are para to each other, the $NH_2$ signal appears more upfield. Similarly, the $CH_3$ signal when it is ortho to CN appeared downfield as in compound **3a** and para to nitrile appeared in upfield. It is presumed that the ortho nitrile has more influence on $CH_3$ than para and as a result the signals for $CH_3$ group appeared in downfield and upfield, respectively (Table 2).



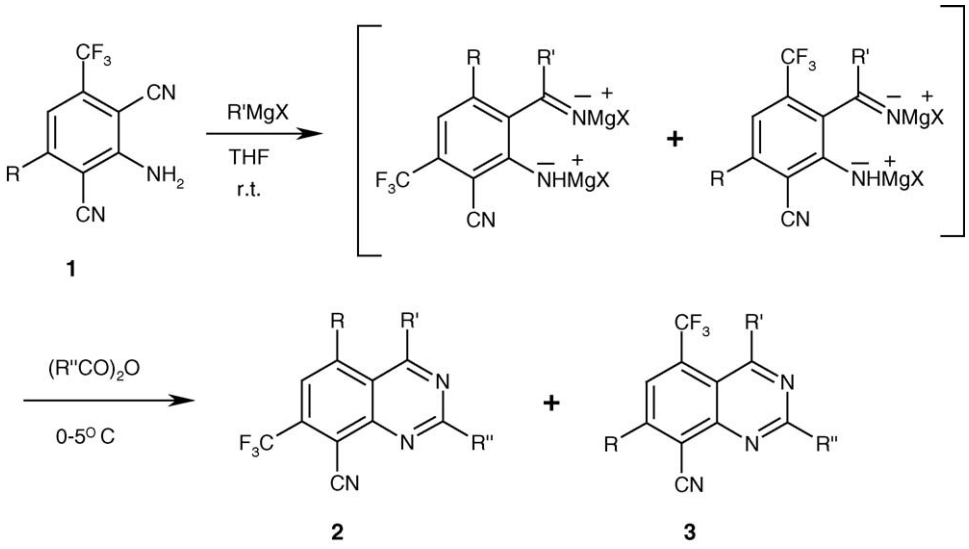

**4a**



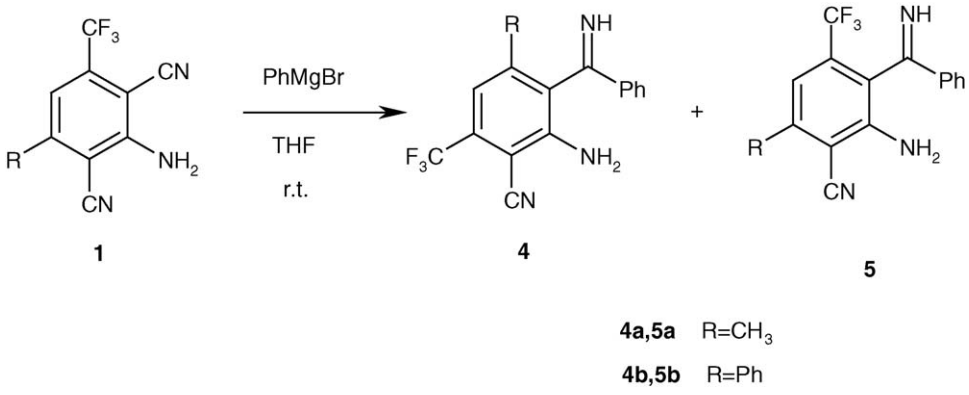

**5a**

In a typical reaction, one of the compounds **4a** was reacted with benzaldehyde in acetic acid under thermal conditions at 110 °C for 4 h to give a number of products. As a result mixture of products **6** and **7** formed in a low yield of 35%. As an alternate method, the same reaction of **4a** with benzaldehyde was conducted under microwave irradiation conditions with 300 W power in 4 min, to give exclusively 1,2-dihydroquinazolines **6a** and no further reaction even at longer time and higher concentration of aldehyde. In contrast with 450 W power of microwave irradiation, quinazoline **7a** was obtained directly. Quinazoline was identified based on spectral data and confirmed by single crystal X-ray analysis (Fig. 1).

Thus, all four compounds **4**–**5** were independently reacted with various aldehydes under two sets of microwave irradiation conditions to obtain 1,2-dihydroquinazolines (**6** and **8**) and quinazolines (**7** and **9**). Thus, the reaction using 300 W microwave irradiation gave exclusively compounds **6** and **8**, whereas with 450 W microwave irradiation gave compounds **7** and **9**. The reaction involved formation of Schiff's base




Scheme 1.




Scheme 2.

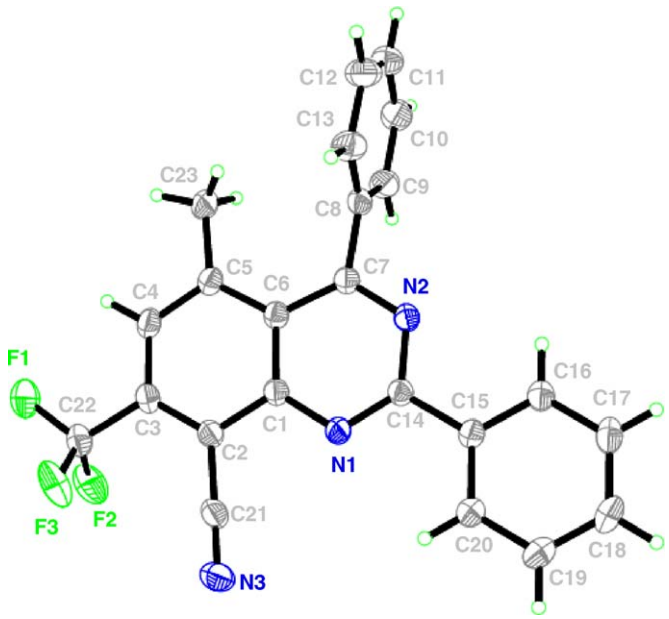


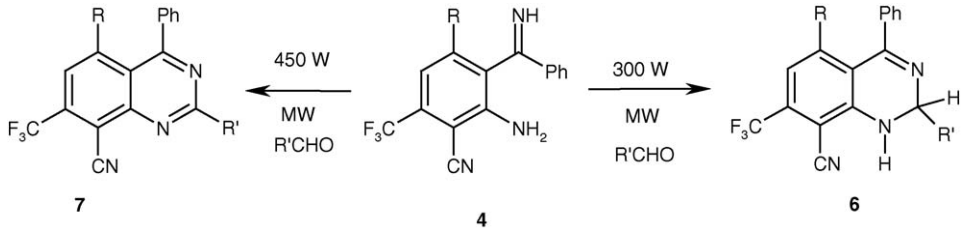

Fig. 1. X-ray crystal structure **7a**. Displacement ellipsoids are drawn at 30% probability level and H atoms are shown as small spheres of arbitrary radii.

Table 2
Imine regioisomers of **4** and **5**

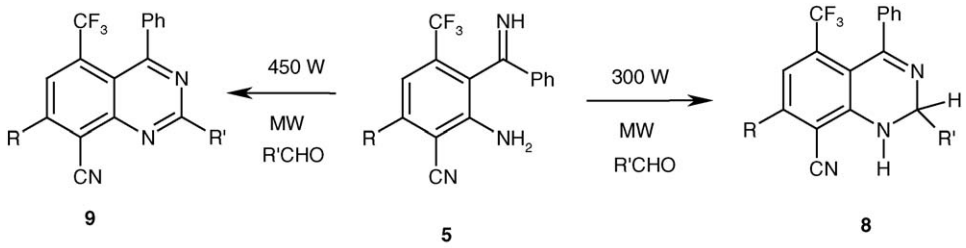
| S. no. | Entry | R | Ratio (%) | Yield (%) |
|---|---|---|---|---|
| 1 | **4a** | $CH_3$ | 75 | 59 |
| | **5a** | $CH_3$ | 25 | 20 |
| 2 | **4b** | Ph | 17 | 15 |
| | **5b** | Ph | 83 | 73 |

Table 3
7-Trifluoromethyl-1,2-dihydroquinazolines (**6**)/quinazolines (**7**)

| S. no. | Entry | R | R′ | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 5 | **6a** | $CH_3$ | Ph | 4 | 62 |
| 6 | **6b** | $CH_3$ | *p*-Cl-$C_6H_4$ | 3 | 63 |
| 7 | **6c** | $CH_3$ | *p*-$CH_3$-$C_6H_4$ | 6 | 55 |
| 8 | **6d** | $CH_3$ | *p*-F-$C_6H_4$ | 3 | 61 |
| 9 | **6e** | Ph | Ph | 4 | 60 |
| 10 | **7a** | $CH_3$ | Ph | 7 | 73 |
| 11 | **7b** | $CH_3$ | *p*-Cl-$C_6H_4$ | 6 | 75 |
| 12 | **7c** | $CH_3$ | *p*-$CH_3$-$C_6H_4$ | 9 | 69 |
| 13 | **7d** | $CH_3$ | *p*-F-$C_6H_4$ | 6 | 70 |
| 14 | **7e** | Ph | Ph | 6 | 70 |




Scheme 3.




Scheme 4.

Table 4
5-Trifluoromethyl-1,2-dihydroquinazolines (**8**)/quinazolines (**9**)

| S. no. | Entry | R | R′ | Time (min) | Yield (%) |
|---|---|---|---|---|---|
| 15 | **8a** | $CH_3$ | Ph | 4 | 65 |
| 16 | **8b** | $CH_3$ | *p*-Cl-$C_6H_4$ | 3 | 64 |
| 17 | **8c** | $CH_3$ | *p*-$CH_3$-$C_6H_4$ | 6 | 59 |
| 18 | **8d** | $CH_3$ | *p*-F-$C_6H_4$ | 3 | 61 |
| 19 | **8e** | Ph | Ph | 4 | 63 |
| 20 | **8f** | Ph | *p*-Cl-$C_6H_4$ | 3 | 65 |
| 21 | **8g** | Ph | *p*-$CH_3$-$C_6H_4$ | 6 | 58 |
| 22 | **9a** | $CH_3$ | Ph | 7 | 83 |
| 23 | **9b** | $CH_3$ | *p*-Cl-$C_6H_4$ | 6 | 82 |
| 24 | **9c** | $CH_3$ | *p*-$CH_3$-$C_6H_4$ | 9 | 78 |
| 25 | **9d** | $CH_3$ | *p*-F-$C_6H_4$ | 6 | 80 |
| 26 | **9e** | Ph | Ph | 7 | 85 |
| 27 | **9f** | Ph | *p*-Cl-$C_6H_4$ | 6 | 88 |
| 28 | **9g** | Ph | *p*-$CH_3$-$C_6H_4$ | 9 | 82 |

followed by cyclization to 1,2-dihydroquinazolines and further to quinazolines.

The yields of quinazoline products are comparatively higher than the 1,2-dihydroquinazolines. Each set of reactions and products formed has been schematically drawn in Scheme 3, Table 3 and Scheme 4, Table 4.

## 3. Conclusion

In conclusion, two strategies have been developed to synthesise quinazoline derivatives. One of the strategies is the regioselective addition of Grignard reagents followed by cyclization under thermal conditions and another is isolation of imine followed by cyclization under microwave irradiation conditions. Both strategies provide useful route to different quinazolines.

## 4. Experimental

$^1$H NMR spectra were recorded in $CDCl_3$ on Bruker AV 300 and Unity 400 spectrometers, chemical shifts are reported in ppm relative to 0 for TMS. Melting points were recorded on VMP-AM melting point apparatus and are uncorrected. Elemental analyses were carried out on Elemental Vario EL (Germany) apparatus. IR spectra were recorded on FT-IR Schimadzu Perkin-Elmer 1310 infrared spectrometer. Electron impact (EI) and chemical ionization mass spectra (CIMS) were recorded on VG 7070 H ev instrument at 70 ev. During usual workup, all organic extracts were dried over $Na_2SO_4$ and evaporated. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 $F_{254}$ (Merck); spots were visualized with UV light. Merck silica gel (100–200 mesh) was used for chromatography.

### 4.1. General procedure

#### 4.1.1. 2-Trifluoromethyl/methyl-4-phenyl/ethyl-5-methyl/phenyl-7-trifluoromethyl-quinazoline-8-carbonitrile (2), 2-trifluoromethyl/methyl-4-phenyl/ethyl-5-trifluoro methyl-7-methyl/phenyl-quinazoline-8-carbonitrile (3)

2,6-Dicyanoanilines **1** (1 mmol) dissolved in dry THF (2 mL) and added dropwise to a well-stirred solution of RMgBr (alkyl/aryl bromide, 2 mmol and magnesium, 2 mmol) in THF (2 mL) at 0 °C. After complete addition, the reaction mixture was further stirred at room temperature for 1 h; trifluoroacetic anhydride/acetic anhydride (1 mL) in THF (3 mL) was added dropwise under cooling (0–5 °C). The reaction mixture was slowly brought to room temperature and stirred for 2 h. The THF was removed, residue was cooled to 5 °C and quenched with $NH_4Cl$ solution, then stirred for 0.5 h, and the residue was extracted with ether. The ether layer was washed with water

until washings were neutral to pH and dried over $Na_2SO_4$. The solvent was evaporated in vacuum and the residue was purified through column chromatography using silica gel (100–200 mesh) in *n*-hexane:chloroform (70:30) as eluents, to give title compounds of good purity.

#### *4.1.2. 5-Methyl-4-phenyl-2,7-bis(trifluoromethyl)quinazoline-8-carbonitrile (**2a**)*

Yield: 160 mg (42%), a pale yellow solid, mp: 149 °C. IR (KBr) ($cm^{-1}$): 2238, 1568 and 1470. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.32 (s, 3H, $CH_3$), 7.5–7.63 (m, 5H, aromatic), 7.85 (s, 1H, aromatic-H). MS: *m/z* (%) 382 ($M^+$, 51). Anal. Calcd for $C_{18}H_9F_6N_3$: C, 56.70; H, 2.38; N, 11.02. Found: C, 56.91; H, 2.56; N, 10.78%.

#### *4.1.3. 7-Methyl-4-phenyl-2,5-bis(trifluoromethyl)quinazoline-8-carbonitrile (**3a**)*

Yield: 80 mg (22%), a pale yellow solid, mp: 162 °C. IR (KBr) ($cm^{-1}$): 3384, 2930, 2220, 1545 and 1476. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.95 (s, 3H, $CH_3$), 7.47–7.6 (m, 5H, aromatic), 8.03 (s, 1H, aromatic-H). MS: *m/z* (%) 382 ($M^+$, 34). Anal. Calcd for $C_{18}H_9F_6N_3$: C, 56.70; H, 2.38; N, 11.02. Found: C, 56.49; H, 2.19; N, 11.20%.

#### *4.1.4. 4,5-Diphenyl-2,7-bis(trifluoromethyl)quinazoline-8-carbonitrile (**2b**)*

Yield: 0.1 mg (22%), a pale yellow solid, mp: 125 °C. IR (KBr) ($cm^{-1}$): 3442, 2973, 2228, 1558 and 1449. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.52–7.7 (m, 8H, aromatic), 7.81–7.89 (m, 2H, aromatic), 8.32 (s, 1H, aromatic-H). MS: *m/z* (%) 444 ($M^+$, 50). Anal. Calcd for $C_{23}H_{11}F_6N_3$: C, 62.31; H, 2.51; N, 9.48. Found: C, 62.57; H, 2.30; N, 9.32%.

#### *4.1.5. 4,7-Diphenyl-2,5-bis(trifluoromethyl)quinazoline-8-carbonitrile (**3b**)*

Yield: 250 mg (56%), a pale yellow solid, mp: 132 °C. IR (KBr) ($cm^{-1}$): 3440, 2979, 2232, 1569 and 1458. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.1–7.22 (m, 8H, aromatic), 7.35–7.42 (m, 2H, aromatic), 8.12 (s, 1H, aromatic-H). MS: *m/z* (%) 444 ($M^+$, 53). Anal. Calcd for $C_{23}H_{11}F_6N_3$: C, 62.31; H, 2.51; N, 9.48. Found: C, 62.13; H, 2.76; N, 9.18%.

#### *4.1.6. 2-Methyl-4,5-diphenyl-7-trifluoromethyl-quinazoline-8-carbonitrile (**2c**)*

Yield: 60 mg (15%), a pale yellow solid, mp: 120 °C. IR (KBr) ($cm^{-1}$): 3440, 2976, 2227, 1569 and 1449. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.01 (s, 3H, $CH_3$), 7.46–7.52 (m, 5H, aromatic), 7.59–7.63 (m, 3H, aromatic), 7.75–7.79 (m, 2H, aromatic), 8.04 (s, 1H, aromatic-H). MS: *m/z* (%) 390 ($M^+$, 36). Anal. Calcd for $C_{23}H_{14}F_3N_3$: C, 70.95; H, 3.62; N, 10.79. Found: C, 71.18; H, 3.46; N, 10.96%.

#### *4.1.7. 2-Methyl-4,7-diphenyl-5-trifluoromethyl-quinazoline-8-carbonitrile (**3c**)*

Yield: 180 mg (46%), a pale yellow solid, mp: 111 °C. IR (KBr) ($cm^{-1}$): 3446, 2956, 2231, 1562 and 1437. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.05 (s, 3H, $CH_3$), 7.0–7.12 (m, 8H, aromatic), 7.2–7.28 (m, 2H, aromatic), 7.32 (s, 1H, aromatic-H). MS: *m/z* (%) 390 ($M^+$, 54). Anal. Calcd for $C_{23}H_{14}F_3N_3$: C, 70.95; H, 3.62; N, 10.79. Found: C, 71.13; H, 3.84; N, 10.55%.

#### *4.1.8. 4-Ethyl-5-phenyl-2,7-bis(trifluoromethyl)quinazoline-8-carbonitrile (**2d**)*

Yield: 90 mg (23%), a pale yellow solid, mp: 138 °C. IR (KBr) ($cm^{-1}$): 3450, 2942, 2239, 1601, 1562 and 1140. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.4 (t, 3H, $CH_3$), 3.5 (q, 2H, $CH_2$), 7.5–7.58 (m, 3H, aromatic), 7.6–7.7 (m, 2H, aromatic), 8.2 (s, 1H, aromatic-H). MS: *m/z* (%) 396 ($M^+$, 61). Anal. Calcd for $C_{19}H_{11}F_6N_3$: C, 57.73; H, 2.80; N, 10.63. Found: C, 57.57; H, 2.59; N, 10.81%.

#### *4.1.9. 4-Ethyl-7-phenyl-2,5-bis(trifluoromethyl)quinazoline-8-carbonitrile (**3d**)*

Yield: 130 mg (35%), a pale yellow solid, mp: 159 °C. IR (KBr) ($cm^{-1}$): 3449, 2987, 2236, 1570, 1460 and 1375. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.15 (t, 3H, $CH_3$), 2.65 (q, 2H, $CH_2$), 7.36–7.42 (m, 2H, aromatic), 7.55–7.62 (m, 3H, aromatic), 7.92 (s, 1H, aromatic-H). MS: *m/z* (%) 396 ($M^+$, 66). Anal. Calcd for $C_{19}H_{11}F_6N_3$: C, 57.73; H, 2.80; N, 10.63. Found: C, 57.98; H, 2.62; N, 10.48%.

### *4.2. General procedure for the preparation of compounds (**4** and **5**)*

A solution of *o*-aminonitrile **1** (1 mmol) in THF (3 mL) was added dropwise to a well-stirred solution of phenyl magnesium bromide (from bromobenzene, 2 mmol and magnesium, 2 mmol) in THF (3 mL) at 0 °C. The reaction mixture was further stirred at room temperature for 2 h, quenched with cold diluted HCl solution (5 mL) and extracted with $CHCl_3$. The combined extracts were washed with brine, dried on $Na_2SO_4$ and evaporated to obtain crude product mixture of two isomers. The isomers were separated by column chromatography on 100–200 silica gel (eluent:hexane/ethylacetate 93:7).

#### *4.2.1. 2-Amino-3-[imino(phenyl)methyl]-4-methyl-6-(trifluoromethyl)benzonitrile (**4a**)*

Yield: 180 mg (59%), a white solid, mp: 141 °C. IR (KBr) ($cm^{-1}$): 3407, 3260, 3162, 2216, 1649, 1609 and 1450. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta_{2.13}$ (s, 3H, $CH_3$), 4.82 (br., s, 2H, $NH_2$), 6.95 (s, 1H, aromatic-H), 7.4–7.52 (m, 3H, aromatic), 7.62–7.66 (m, 2H, aromatic). MS: *m/z* (%) 304 ($M^+$, 69). Anal. Calcd for $C_{16}H_{12}F_3N_3$: C, 63.36; H, 3.99; N, 13.86. Found: C, 63.20; H, 4.22; N, 14.03%.

#### *4.2.2. 2-Amino-3-[imino(phenyl)methyl]-6-methyl-4-(trifluoromethyl)benzonitrile (**5a**)*

Yield: 60 mg (20%), a white solid, mp: 135 °C. IR (KBr) ($cm^{-1}$): 3437, 3334, 3222, 2217, 1649 and 1447. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta_{2.6}$ (s, 3H, $CH_3$), 4.62 (br., s, 2H, $NH_2$), 6.97 (s, 1H, aromatic-H), 7.38–7.5 (m, 3H, aromatic), 7.62–7.7 (m, 2H, aromatic). MS: *m/z* (%) 304 ($M^+$, 41). Anal. Calcd for

$C_{16}H_{12}F_3N_3$: C, 63.36; H, 3.99; N, 13.86. Found: C, 63.57; H, 4.15; N, 13.67%.

#### 4.2.3. 3-Amino-2-[imino(phenyl)methyl]-5-(trifluoromethyl)biphenyl-4-carbonitrile (**4b**)

Yield: 50 mg (15%), a white solid, mp: 148 °C. IR (KBr) ($cm^{-1}$): 3404, 3248, 2215, 1608 and 1131. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 4.75 (br., s, 2H, $NH_2$), 7.12 (s, 1H, aromatic-H), 7.42–7.57 (m, 5H, aromatic), 7.6–7.62 (m, 3H, aromatic), 7.78–7.82 (m, 2H, aromatic). MS: *m/z* (%) 366 ($M^+$, 45). Anal. Calcd for $C_{21}H_{14}F_3N_3$: C, 69.04; H, 3.86; N, 11.50. Found: C, 68.80; H, 4.04; N, 11.70%.

#### 4.2.4. 3-Amino-4-[imino(phenyl)methyl]-5-(trifluoromethyl)biphenyl-2-carbonitrile (**5b**)

Yield: 260 mg (73%), a white solid, mp: 167 °C. IR (KBr) ($cm^{-1}$): 3438, 3248, 2216, 1610, 1443 and 1132. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 5.52 (br., s, 2H, $NH_2$), 7.02 (s, 1H, aromatic-H), 7.12–7.15 (m, 10H, aromatic). MS: *m/z* (%) 366 ($M^+$, 46). Anal. Calcd for $C_{21}H_{14}F_3N_3$: C, 69.04; H, 3.86; N, 11.50. Found: C, 69.19; H, 3.66; N, 11.32%.

### 4.3. Preparation of 1,2-dihydroquinazolines (**6** and **8**)

In a sealed tube compound **4** or **5** (0.3 mmol) and benzaldehyde (0.45 mmol) was irradiated in the microwave oven at 300 W for 4–6 min. After completion of the reaction, the contents are cooled to room temperature and unsealed the tube for isolation of crude product. It is purified by column chromatography on 60–120 silica gel (eluent:hexane/ethylacetate 95:5).

#### 4.3.1. 5-Methyl-2, 4-diphenyl-7-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**6a**)

Yield: 70 mg (62%), a pale yellow solid, mp: 215 °C. IR (KBr) ($cm^{-1}$): 3376, 3061, 2214, 1612, 1509, 1444, 1358 and 1125. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.95 (s, 3H, $CH_3$), 5.32 (s, 1H, NH), 5.68 (s, 1H, C–H), 6.9 (s, 1H, aromatic-H), 7.38–7.45 (m, 8H, aromatic), 7.54–7.58 (m, 2H, aromatic). MS: *m/z* (%) 392 ($M^+$, 28). Anal. Calcd for $C_{23}H_{16}F_3N_3$: C, 70.58; H, 4.12; N, 10.74. Found: C, 70.42; H, 4.38; N, 10.95%.

#### 4.3.2. 2-(4-Chlorophenyl)-5-methyl-4-phenyl-7-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**6b**)

Yield: 80 mg (63%), a pale yellow solid, mp: 186 °C. IR (KBr) ($cm^{-1}$): 3302, 2919, 2217 and 1589. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.93 (s, 3H, $CH_3$), 5.28 (s, 1H, NH), 5.65 (s, 1H, C–H), 6.91 (s, 1H, aromatic-H), 7.36–7.4 (m, 5H, aromatic), 7.42–7.44 (m, 2H, aromatic), 7.51–7.54 (m, 2H, aromatic). MS: *m/z* (%) 426 ($M^+$, 32). Anal. Calcd for $C_{23}H_{15}ClF_3N_3$: C, 64.87; H, 3.55; N, 9.87. Found: C, 64.68; H, 3.38; N, 10.11%.

#### 4.3.3. 5-Methyl-2-(4-methylphenyl)-4-phenyl-7-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**6c**)

Yield: 70 mg (55%), a pale yellow solid, mp: 214 °C. IR (KBr) ($cm^{-1}$): 3312, 2921, 2222, 1529 and 1127. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta_{1.95}$ (s, 3H, $CH_3$), 2.41 (s, 3H, $CH_3$), 5.31 (s, 1H, N–H), 5.65 (s, 1H, C–H), 6.9 (s, 1H, aromatic-H), 7.2–7.23 (m, 2H, aromatic), 7.39–7.48 (m, 7H, aromatic). MS: *m/z* (%) 406 ($M^+$, 51). Anal. Calcd for $C_{24}H_{18}F_3N_3$: C, 71.10; H, 4.48; N, 10.36. Found: C, 71.27; H, 4.70; N, 10.17%.

#### 4.3.4. 2-(4-Fluorophenyl)-5-methyl-4-phenyl-7-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**6d**)

Yield: 70 mg (61%), a pale yellow solid, mp: 250 °C. IR (KBr) ($cm^{-1}$): 3370, 2925, 2218 and 1578. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.95 (s, 3H, $CH_3$), 5.27 (s, 1H, N–H), 5.64 (s, 1H, C–H), 6.92 (s, 1H, aromatic-H), 7.1–7.14 (m, 2H, aromatic), 7.38–7.42 (m, 5H, aromatic), 7.54–7.58 (m, 2H, aromatic). MS: *m/z* (%) 410 ($M^+$, 63). Anal. Calcd for $C_{23}H_{15}F_4N_3$: C, 67.48; H, 3.69; N, 10.26. Found: C, 67.25; H, 3.85; N, 10.45%.

#### 4.3.5. 7-(Trifluoromethyl)-2,4,5-triphenyl-1,2-dihydroquinazoline-8-carbonitrile (**6e**)

Yield: 80 mg (60%), a pale yellow solid, mp: 172 °C. IR (KBr) ($cm^{-1}$): 3071, 2834, 2221, 1683 and 1291. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 5.46 (s, 1H, N–H), 5.48 (s, 1H, C–H), 7.19 (s, 1H, aromatic-H), 7.62–7.67 (m, 13H, aromatic), 8.1–8.15 (m, 2H, aromatic). MS: *m/z* (%) 454 ($M^+$, 44). Anal. Calcd for $C_{28}H_{18}F_3N_3$: C, 74.16; H, 4.01; N, 9.27. Found: C, 74.34; H, 4.22; N, 9.11%.

#### 4.3.6. 7-Methyl-2,4-diphenyl-5-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**8a**)

Yield: 80 mg (65%), a pale yellow solid, mp: 167 °C. IR (KBr) ($cm^{-1}$): 3310, 2223, 1594, 1276 and 1122. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.63 (s, 3H, $CH_3$), 5.25 (s, 1H, NH), 5.4 (s, 1H, C–H), 6.95 (s, 1H, aromatic-H), 7.32–7.35 (m, 5H, aromatic), 7.42–7.45 (m, 3H, aromatic), 7.6–7.63 (m, 2H, aromatic). MS: *m/z* (%) 392 ($M^+$, 38). Anal. Calcd for $C_{23}H_{16}F_3N_3$: C, 70.58; H, 4.12; N, 10.74. Found: C, 70.79; H, 3.93; N, 10.92%.

#### 4.3.7. 2-(4-Chlorophenyl)-7-methyl-4-phenyl-5-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**8b**)

Yield: 80 mg (64%), a pale yellow solid, mp: 162 °C. IR (KBr) ($cm^{-1}$): 3304, 2922, 2219 and 1592. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.62 (s, 3H, $CH_3$), 5.31 (s, 1H, NH), 5.41 (s, 1H, C–H), 6.98 (s, 1H, aromatic-H), 7.32–7.36 (m, 4H, aromatic), 7.38–7.42 (m, 3H, aromatic). MS: *m/z* (%) 426 ($M^+$, 52). Anal. Calcd for $C_{23}H_{15}ClF_3N_3$: C, 64.87; H, 3.55; N, 9.87. Found: C, 65.12; H, 3.38; N, 9.68%.

#### 4.3.8. 7-Methyl-2-(4-methylphenyl)-4-phenyl-5-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**8c**)

Yield: 70 mg (59%), a pale yellow solid, mp: 158 °C. IR (KBr) ($cm^{-1}$): 3310, 2922, 2224, 1531 and 1129. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.38 (s, 3H, $CH_3$), 2.61 (s, 3H, $CH_3$), 5.32 (s, 1H, N–H), 5.41 (s, 1H, C–H), 6.98 (s, 1H, aromatic-H), 7.32–7.36 (m, 4H, aromatic), 7.48–7.52 (m, 3H, aromatic), 7.6–7.62

(m, 2H, aromatic). MS: *m/z* (%) 406 ($M^+$, 55). Anal. Calcd for $C_{24}H_{18}F_3N_3$: C, 71.10; H, 4.48; N, 10.36. Found: C, 71.25; H, 4.70; N, 10.18%.

#### 4.3.9. 2-(4-Fluorophenyl)-7-methyl-4-phenyl-5-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**8d**)

Yield: 70 mg (61%), a pale yellow solid, mp: 169 °C. IR (KBr) ($cm^{-1}$): 3372, 2923, 2221 and 1599. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.6 (s, 3H, $CH_3$), 5.25 (s, 1H, N–H), 5.4 (s, 1H, C–H), 6.97 (s, 1H, aromatic-H), 7.47–7.5 (m, 4H, aromatic), 7.57–7.62 (m, 3H, aromatic), 7.76–7.8 (m, 2H, aromatic). MS: *m/z* (%) 410 ($M^+$, 36). Anal. Calcd for $C_{23}H_{15}F_4N_3$: C, 67.48; H, 3.69; N, 10.26. Found: C, 67.69; H, 3.52; N, 10.45%.

#### 4.3.10. 2,4,7-Triphenyl-5-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**8e**)

Yield: 80 mg (63%), a pale yellow solid, mp: 160 °. IR (KBr) ($cm^{-1}$): 3069, 2829, 2224, 1681 and 1291. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 5.64 (s, 1H, N–H), 5.85 (s, 1H, C–H), 6.95–6.99 (m, 2H, aromatic), 7.03–7.12 (m, 5H, aromatic), 7.14–7.18 (m, 3H, aromatic), 7.2 (s, 1H, aromatic-H), 7.44–7.49 (m, 2H, aromatic), 7.57–7.59 (m, 2H, aromatic). MS: *m/z* (%) 454 ($M^+$, 28). Anal. Calcd for $C_{28}H_{18}F_3N_3$: C, 74.16; H, 4.01; N, 9.27. Found: C, 74.34; H, 4.25; N, 9.07%.

#### 4.3.11. 2-(4-Chloro-phenyl)-4,7-diphenyl-5-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**8f**)

Yield: 90 mg (65%), a pale yellow solid, mp: 195 °C. IR (KBr) ($cm^{-1}$): 3304, 2815, 2222, 1683, 1597, 1293 and 1136. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 5.6 (s, 1H, N–H), 5.81 (s, 1H, C–H), 6.9–6.98 (m, 2H, aromatic), 7.02–7.1 (m, 8H, aromatic), 7.19 (s, 1H, aromatic-H), 7.41–7.45 (m, 2H, aromatic), 7.57–7.62 (m, 2H, aromatic). MS: *m/z* (%) 488 ($M^+$, 40). Anal. Calcd for $C_{28}H_{17}ClF_3N_3$: C, 68.93; H, 3.51; N, 8.61. Found: C, 68.70; H, 3.70; N, 8.78%.

#### 4.3.12. 4,7-Diphenyl-2-p-tolyl-5-(trifluoromethyl)-1,2-dihydroquinazoline-8-carbonitrile (**8g**)

Yield: 80 mg (58%), a pale yellow solid, mp: 152 °C. IR (KBr) ($cm^{-1}$): 2919, 2851, 2545, 2227, 1679, 1531 and 1142. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.47 (s, 3H, $CH_3$), 5.54 (s, 1H, N–H), 5.8 (s, 1H, C–H), 6.92–6.97 (m, 2H, aromatic), 7.18 (s, 1H, aromatic-H), 7.21–7.28 (m, 5H, aromatic), 7.36–7.4 (m, 3H, aromatic), 7.52–7.59 (m, 4H, aromatic). MS: *m/z* (%) 468 ($M^+$, 43). Anal. Calcd for $C_{29}H_{20}F_3N_3$: C, 74.51; H, 4.31; N, 8.99. Found: C, 74.70; H, 4.10; N, 8.75%.

### 4.4. Preparation of quinazolines (**7** and **9**)

A mixture of compound **4** or **5** (0.3 mmol) and benzaldehyde (0.45 mmol) was taken in a sealed tube and irradiated in the microwave oven at 450 W for 4–9 min. Reaction mixture was cooled and purified by column chromatography (eluent:hexane/ethylacetate 97:3).

#### 4.4.1. 5-Methyl-2,4-diphenyl-7-(trifluoromethyl)quinazoline-8-carbonitrile (**7a**)

Yield: 80 mg (73%), a pale yellow solid, mp: 193 °C. IR (KBr) ($cm^{-1}$): 3074, 2229, 1568 and 1141. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.28 (s, 3H, $CH_3$), 7.5–7.59 (m, 8H, aromatic), 7.61 (s, 1H, aromatic-H), 8.73–8.79 (m, 2H, aromatic). MS: *m/z* (%) 390 ($M^+$, 35). Anal. Calcd for $C_{23}H_{14}F_3N_3$: C, 70.95; H, 3.62; N, 10.79. Found: C, 70.77; H, 3.87; N, 10.58%.

*4.4.1.1. X-ray crystallography.* Compound **7a**. $C_{23}H_{14}F_3N_3$: $M_w = 389.37$, pale yellow block crystal 0.35 mm × 0.25 mm × 0.12 mm, $a = 6.2910(4)$ Å, $b = 24.2900(15)$ Å, $c = 12.6105(8)$ Å, $\beta = 103.313(1)^\circ$, $V = 1875.2(2)$ Å$^3$, monoclinic, space group $P2_1/c$, $\rho_{calc} = 1.379$ mg m$^{-3}$, $\lambda = 0.71073$ Å, $\mu$(Mo K$\alpha$) = 0.104 mm$^{-1}$, $F_{0\,0\,0} = 800$, $T = 273(2)$ K. Data collection yielded 15,902 reflections resulting in 4376 unique, averaged reflections, 3561 with $I > 2\sigma(I)$, $\theta$ range: 1.68–25.00°. Full-matrix least-squares refinement led to a final $R = 0.0470$, $wR = 0.1249$ and GOF = 1.061. Intensity data were measured on Bruker Smart Apex with CCD area detector. CCDC 273388 contains supplementary crystallographic data for the structure **7a**.

#### 4.4.2. 2-(4-Chlorophenyl)-5-methyl-4-phenyl-7-(trifluoromethyl)quinazoline-8-carbonitrile (**7b**)

Yield: 90 mg (75%), a pale yellow solid, mp: 260 °C. IR (KBr) ($cm^{-1}$): 3479, 2912, 2225, 1522 and 1126. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.25 (s, 3H, $CH_3$), 7.45–7.49 (m, 2H, aromatic), 7.52–7.59 (m, 5H, aromatic), 7.62 (s, 1H, aromatic-H), 8.68–8.72 (m, 2H, aromatic). MS: *m/z* (%) 424 ($M^+$, 48). Anal. Calcd for $C_{23}H_{13}ClF_3N_3$: C, 65.18; H, 3.09; N, 9.91. Found: C, 64.99; H, 2.88; N, 10.06%.

#### 4.4.3. 5-Methyl-2-(4-methylphenyl)-4-phenyl-7-(trifluoromethyl)quinazoline-8-carbonitrile (**7c**)

Yield: 80 mg (69%), a pale yellow solid, mp: 236 °C. IR (KBr) ($cm^{-1}$): 3480, 2915, 2222, 1528 and 1130. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.25 (s, 3H, $CH_3$), 2.5 (s, 3H, $CH_3$), 7.29–7.32 (m, 2H, aromatic), 7.52–7.59 (m, 5H, aromatic), 7.6 (s, 1H, aromatic-H), 8.6–8.65 (m, 2H, aromatic). MS: *m/z* (%) 404 ($M^+$, 54). Anal. Calcd for $C_{24}H_{16}F_3N_3$: C, 71.46; H, 4.00; N, 10.42. Found: C, 71.63; H, 4.23; N, 10.19%.

#### 4.4.4. 2-(4-Fluorophenyl)-5-methyl-4-phenyl-7-(trifluoromethyl)quinazoline-8-carbonitrile (**7d**)

Yield: 80 mg (70%), a pale yellow solid, mp: 140 °C. IR (KBr) ($cm^{-1}$): 2930, 2230, 1535, 1473 and 1126. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 2.25 (s, 3H, $CH_3$), 7.21–7.26 (m, 2H, aromatic), 7.55–7.62 (m, 5H, aromatic), 7.62 (s, 1H, aromatic-H), 8.78–8.82 (m, 2H, aromatic). MS: *m/z* (%) 408 ($M^+$, 67). Anal. Calcd for $C_{23}H_{13}F_4N_3$: C, 67.81; H, 3.22; N, 10.32. Found: C, 67.63; H, 3.42; N, 10.51%.

#### 4.4.5. 7-(Trifluoromethyl)-2,4,5-triphenyl-quinazoline-8-carbonitrile (**7e**)

Yield: 90 mg (70%), a pale yellow solid, mp: 245 °C. IR (KBr) ($cm^{-1}$): 3069, 2832, 2222, 1682 and 1289. $^1H$ NMR

(200 MHz, $CDCl_3$): δ 7.43 (s, 1H, aromatic-H), 7.45–7.52 (m, 7H, aromatic), 7.59–7.63 (m, 3H, aromatic), 8.11–8.17 (m, 5H, aromatic). MS: *m/z* (%) 452 ($M^+$, 41). Anal. Calcd for $C_{28}H_{16}F_3N_3$: C, 74.49; H, 3.57; N, 9.31. Found: C, 74.67; H, 3.35; N, 9.11%.

#### *4.4.6. 7-Methyl-2,4-diphenyl-5-(trifluoromethyl)quinazoline-8-carbonitrile (**9a**)*

Yield: 100 mg (83%), a pale yellow solid, mp: 287 °C. IR (KBr) ($cm^{-1}$): 3461, 2922, 2220, 1737 and 1126. $^1H$ NMR (200 MHz, $CDCl_3$): δ 2.92 (s, 3H, $CH_3$), 7.5–7.55 (m, 5H, aromatic), 7.57–7.6 (m, 3H, aromatic), 7.8 (s, 1H, aromatic-H), 8.71–8.75 (m, 2H, aromatic). MS: *m/z* (%) 390 ($M^+$, 42). Anal. Calcd for $C_{23}H_{14}F_3N_3$: C, 70.95; H, 3.62; N, 10.79. Found: C, 70.76; H, 3.79; N, 10.56%.

#### *4.4.7. 2-(4-Chlorophenyl)-7-methyl-4-phenyl-5-(trifluoromethyl)quinazoline-8-carbonitrile (**9b**)*

Yield: 100 mg (82%), a pale yellow solid, mp: 282 °C. IR (KBr) ($cm^{-1}$): 3478, 2915, 2220, 1528 and 1128. $^1H$ NMR (200 MHz, $CDCl_3$): δ 2.92 (s, 3H, $CH_3$), 7.45–7.52 (m, 5H, aromatic), 7.54–7.6 (m, 2H, aromatic), 7.84 (s, 1H, aromatic-H), 8.65–8.71 (m, 2H, aromatic). MS: *m/z* (%) 424 ($M^+$, 60). Anal. Calcd for $C_{23}H_{13}ClF_3N_3$: C, 65.18; H, 3.09; N, 9.9. Found: C, 64.97; H, 2.94; N, 10.09%.

#### *4.4.8. 7-Methyl-2-(4-methylphenyl)-4-phenyl-5-(trifluoromethyl)quinazoline-8-carbonitrile (**9c**)*

Yield: 90 mg (78%), a pale yellow solid, mp: 278 °C. IR (KBr) ($cm^{-1}$): 3480, 2918, 2221, 1530 and 1132. $^1H$ NMR (200 MHz, $CDCl_3$): δ 2.45 (s, 3H, $CH_3$), 2.9 (s, 3H, $CH_3$), 7.29–7.31 (m, 2H, aromatic), 7.45–7.51 (m, 3H, aromatic), 7.53–7.59 (m, 2H, aromatic), 7.78 (s, 1H, aromatic-H), 8.59–8.62 (m, 2H, aromatic). MS: *m/z* (%) *404* ($M^+$, 29). Anal. Calcd for $C_{24}H_{16}F_3N_3$: C, 71.46; H, 4.00; N, 10.42. Found: C, 71.70; H, 3.82; N, 10.56%.

#### *4.4.9. 2-(4-Fluorophenyl)-7-methyl-4-phenyl-5-(trifluoromethyl)quinazoline-8-carbonitrile (**9d**)*

Yield: 100 mg (80%), a pale yellow solid, mp: 276 °C. IR (KBr) ($cm^{-1}$): 3074, 2925, 2359, 2214, 1536, 1472 and 1126. $^1H$ NMR (200 MHz, $CDCl_3$): δ 2.92 (s, 3H, $CH_3$), 7.18–7.22 (m, 2H, aromatic), 7.49–7.58 (m, 5H, aromatic), 7.8 (s, 1H, aromatic-H), 8.72–8.78 (m, 2H, aromatic). MS: *m/z* (%) 408 ($M^+$, 43). Anal. Calcd for $C_{23}H_{13}F_4N_3$: C, 67.81; H, 3.22; N, 10.32. Found: C, 67.62; H, 3.42; N, 10.54%.

#### *4.4.10. 2,4,7-Triphenyl-5-(trifluoromethyl)quinazoline-8-carbonitrile (**9e**)*

Yield: 110 mg (85%), a pale yellow solid, mp: 255 °C. IR (KBr) ($cm^{-1}$): 3068, 2832, 2223, 1681 and 1288. $^1H$ NMR (200 MHz, $CDCl_3$): δ 7.05–7.11 (m, 8H, aromatic), 7.33–7.38 (m, 2H, aromatic), 7.55–7.59 (m, 3H, aromatic), 7.84 (s, 1H, aromatic-H), 8.81–8.85 (m, 2H, aromatic). MS: *m/z* (%) 452 ($M^+$, 39). Anal. Calcd for $C_{28}H_{16}F_3N_3$: C, 74.49; H, 3.57; N, 9.31. Found: C, 74.72; H, 3.72; N, 9.50%.

#### *4.4.11. 2-(4-Chlorophenyl)-4,7-diphenyl-5-(trifluoromethyl)quinazoline-8-carbonitrile (**9f**)*

Yield: 130 mg (88%), a pale yellow solid, mp: 214 °C. IR (KBr) ($cm^{-1}$): 3303, 2825, 2221, 1682, 1293 and 1132. $^1H$ NMR (200 MHz, $CDCl_3$): δ 7.08–7.13 (m, 8H, aromatic), 7.32–7.37 (m, 2H, aromatic), 7.53–7.57 (m, 2H, aromatic), 7.86 (s, 1H, aromatic-H), 8.73–8.78 (m, 2H, aromatic). MS: *m/z* (%) 486 ($M^+$, 42). Anal. Calcd for $C_{28}H_{15}ClF_3N_3$: C, 69.21; H, 3.11; N, 8.65. Found: C, 69.37; H, 2.92; N, 8.86%.

#### *4.4.12. 4,7-Diphenyl-2-p-tolyl-5-(trifluoromethyl)quinazoline-8-carbonitrile (**9g**)*

Yield: 110 mg (82%), a pale yellow solid, mp: 193 °C. IR (KBr) ($cm^{-1}$): 3304, 2819, 2219, 1680, 1290 and 1136. $^1H$ NMR (200 MHz, $CDCl_3$): δ 2.49 (s, 3H, $CH_3$), 7.05–7.16 (m, 8H, aromatic), 7.32–7.39 (m, 4H, aromatic), 7.8 (s, 1H, aromatic-H), 8.67–8.72 (m, 2H, aromatic). MS: *m/z* (%) 466 ($M^+$, 45). Anal. Calcd for $C_{29}H_{18}F_3N_3$: C, 74.83; H, 3.90; N, 9.03. Found: C, 74.65; H, 4.14; N, 8.86%.

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