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A simple and facile method for the synthesis of novel 5/7 trifluoromethyl-substituted 4(3H)-quinazolone regioisomers

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Abstract

The unsymmetrical 1,3-diketones **1** on reaction with malononitrile is resulted an interesting trifunctional intermediates **2** and **3**. The intermediate **2** is hydrolyzed to give 2,6-dicarboxamido aniline **4** which on cyclisation gave two regioisomers of 1,2-dihydro-4(3H)-quinazolinones **5** and **6**. The effect of substituents on compound **4** is characteristic for formation of regioisomers in different proportions. Each regioisomer on dehydrogenation under mild condition using active MnO_2 gave corresponding 4(3H)-quinazolones **7** and **8**, respectively.

Keywords: 2,6-Dicyanoanilines; Dicarboxamido anilines; 4(3H)-Quinazolones

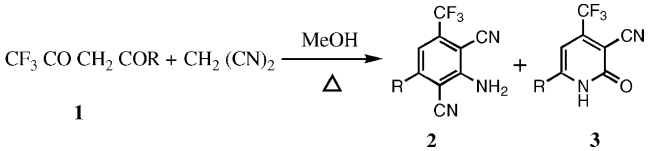
1. Introduction

In general, the quinazolones are considered to be important compounds in the fields of pharmacy and biology [1]. A number of these compounds have been found to have wide range of biological activities [2,3]. Some of these compounds are identified as drugs [4] such as quinethazone and metolazone and are used in medicine as diuretics while prazosin is a vasodilator, which is also used as an antihypertensive drug. The synthesis of quinazolines or quinazolones is mainly cyclisation from bifunctional intermediates. It is known in literature that the fluorine or trifluoromethyl group at a strategic position in a molecule enhances the activity of the molecule due to its lipophilic nature [5]. However, no report except [6] is available on the synthesis of fluorinated quinazolines or quinazolones. Our continued interest on fluorinated molecules of biological interest [7–9] prompted us to synthesize a number of new fluorinated molecules. In this process, we have developed a methodology for the synthesis of fluoroaromatics from fluoroaliphatics, affording two regioisomers. Here we are reporting these synthesis.

2. Results and discussion

The unsymmetrical 1,3-diketones **1** such as 1,1,1-trifluoro-2,4-pentanedione or benzoyl-1,1,1-trifluoro acetone on reaction with malononitrile gave an interesting trifunctional intermediate 2,6-dicyano-5-substituted-3-trifluoromethyl aniline **2** in addition to 3-cyano-4-trifluoromethyl-6-substituted 2(1H)-pyridone **3** in different proportions depending on R (Scheme 1).

The mode of reaction is initially condensation of two molecules of malononitrile with one molecule of 1,3-diketone and the resulted product undergoes intramolecular cyclisation to give an un-isolable intermediate **A**. The intermediate having two nitrile (CN) functions on same carbon and one of the nitrile is readily hydrolyzed to amide



1 2 3

Scheme 1.

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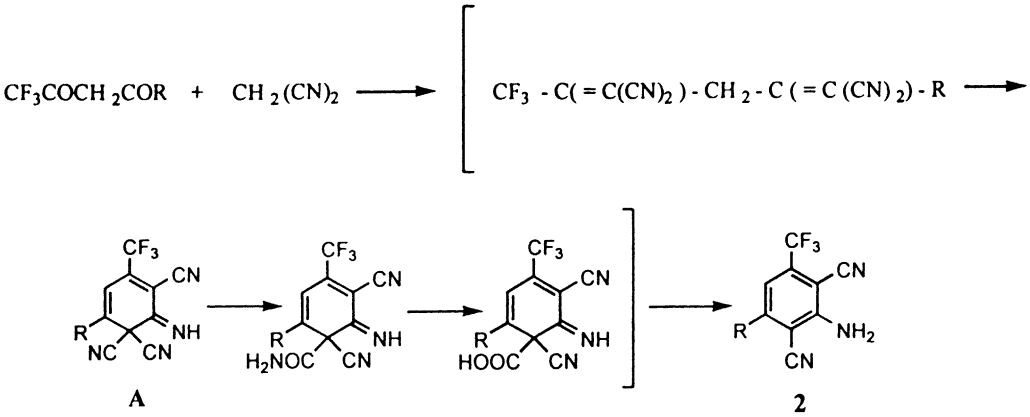
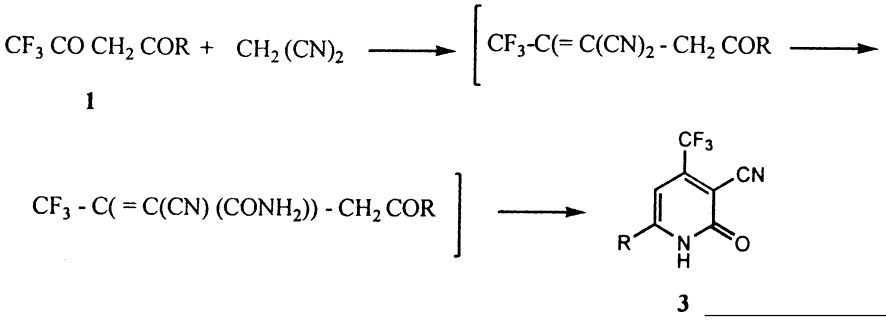
to give a carboxyl compound followed by decarboxylation to give compound **2**. The sequence of malononitrile reaction with 1,3-diketones is preferential attack at carbonyl carbon having CF_3 group, which is considered to be more electrophilic as reported earlier [10] in reaction of 1,3-diketones with cyanoacetamide.

The probable mechanism of formation of compound **2** has been detailed as follows.



In the same reaction, another compound **3** is also formed by parallel path where condensation of one molecule of malononitrile with one molecule of 1,3-diketone, the resulted product is hydrolyzed and intramolecularly cyclised to give product **3**.



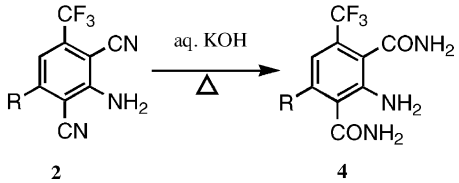
The distribution of products **2** and **3** in each reaction are mainly depending on the substituents present in 1,3-diketones. The presence of phenyl group in 1,3-diketones favors the formation of product **2** in major and product **3** as minor, whereas methyl group reverse the formation of products **2** and **3**. This is attributed to the electron deficiency arising at the carbonyl carbon due to phenyl group in 1,3-diketones which facilitates the reaction of second molecule of malononitrile to give product **2** in major, while methyl group reverses the product distribution due to its positive inductive effect. In an earlier report [11], where 1,3-diketones on reaction with malononitrile gave 3,6-dicyano-4-trifluoromethyl-2(1H)-pyridone in addition to compound **2** which is not in agreement with our results. The compounds **3a** and **3b** are alternately synthesized from 1,3-diketones and cyanoacetamide [12], comparing the mp, IR, ^{1}H NMR and mass spectrum with compound **3**, they were found to be similar. The number of compounds synthesized have been tabulated in Table 1.

Table 1
Trifluoromethyl-substituted benzene/2(1H)-pyridones

Compound number	R	Yield (%)	Fraction number	Melting point (°C)
2a	CH_3	25	I	200
3b	C_6H_5	22	II	300
3a	CH_3	70	II	234
2b	C_6H_5	64	I	168

The compound **2** is being an interesting trifunctional intermediate, it has been further utilized in the synthesis of 4(3H)-quinazolones. Thus, the compound **2** is hydrolyzed in aqueous potassium hydroxide under reflux conditions and obtained 2,6-dicarboxamido-3-trifluoromethyl-5-substituted anilines in quantitative yield **4** (Scheme 2).

The identification of two amides ($CONH_2$) in a molecule with different environment is quite interesting in that, they appear at different chemical shifts in ^{1}H NMR and also crucial in identification of regioisomers in next step. In general, the amide protons appear as two broad singlets due to restricted rotation across the C=N bond because of double bond character. The difference in chemical shift of



Scheme 2.

protons in an amide depends upon the percentage of double bond character across C=N bond, which in turn depends on substituents. More the double bond character, more in chemical shift difference because of more non-equivalent nature of protons. Here, in compound **4b** one of the amides, which is *ortho* to CF_3 group and *para* to phenyl group, appeared as two broad singlets at δ 7.78 and 8.00. Whereas, another amide, which is *para* to CF_3 and *ortho* to phenyl group appeared as two broad singlets at δ 7.45 and 7.55. The chemical shift difference in one amide is δ 0.22 and in another it is δ 0.1. This is presumed to be the influence of CF_3 group in *ortho* position and phenyl group in *para* position and considered to enhance more double bond character due to electron withdrawing nature and observed the chemical shift difference of δ 0.22. It is consistent with our earlier report [13] in which the amide protons appeared as two broad singlets with chemical shift difference of δ 0.2. In addition, the amide protons, which are *ortho* to CF_3 and *para* to phenyl, appeared in down field when compared to other amide protons. Thus, the two amides have been identified based on the data. Similarly, in compound **4a** the amide protons *ortho* to CF_3 and *para* to CH_3 appeared in down field but the chemical shift difference is δ 0.05. This may be due to the CH_3 group, which enhances the electro-positive character in *para* position, as a result the chemical shift difference is observed as low. While other amide protons, which are *ortho* to CH_3 and *para* to CF_3, show the chemical shift difference δ 0.1 as in compound **4b**. The number of compounds synthesized have been tabulated in Table 2.

The compounds **4a** and **4b** were reacted with different aldehydes to give two regioisomers in each case in definite proportions. Each isomer has been separated through column of silicagel 100–200 mesh with hexane/ethyl acetate as eluents (Scheme 3).

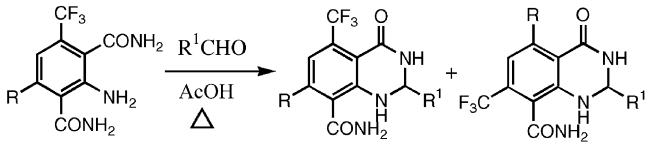
The substituents in compound **4** such as phenyl/methyl alter the formation of regioisomers. The phenyl substituent in compound **4** increases the formation of compound **5** relative to compound **6**. Whereas, CH_3 substituent in compound **4** reverses the regioisomers formation, i.e. formation of compound **6** is more than compound **5**. Each compound has been identified based on the particular amide present intact. The number of compounds synthesized have been tabulated in Table 3.

The compounds **5** and **6** independently dehydrogenated under mild conditions using active MnO_2 and obtained 4(3H)-quinazolones **7** and **8**, respectively (Scheme 4).

The number of compounds synthesized have been tabulated in Table 4.

Table 2
2,6-Dicarboxamido-substituted anilines

Compound number	R	Yield (%)	Melting point (°C)
4a	CH_3	82	240
4b	C_6H_5	87	269

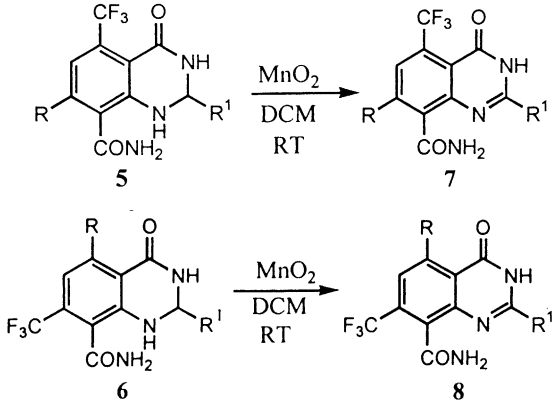


4 **5** **6**

Scheme 3.

Table 3
Trifluoromethyl-substituted quinazolines

Compound number	R	R^1	Yield (%)	Fraction number	Melting point (°C)
5a	CH_3	CH_3	35	I	290
6a	CH_3	CH_3	47	II	285
5b	CH_3	C_6H_5	37	I	282
6b	CH_3	C_6H_5	45	II	288
5c	C_6H_5	CH_3	49	I	266
6c	C_6H_5	CH_3	35	II	270
5d	C_6H_5	C_6H_5	49	I	255
6d	C_6H_5	C_6H_5	39	II	260



Scheme 4.

Table 4
4(3H)-Quinazolones

Compound number	R	R^1	Yield (%)	Melting point (°C)
7a	CH_3	CH_3	73	318
8a	CH_3	CH_3	75	327
7b	CH_3	C_6H_5	74	325
8b	CH_3	C_6H_5	76	337
7c	C_6H_5	CH_3	78	327
8c	C_6H_5	CH_3	76	331
7d	C_6H_5	C_6H_5	80	370
8d	C_6H_5	C_6H_5	80	310

3. Conclusion

The developed methodology from fluoroaliphatics to fluoroaromatics can be universally applicable to synthesize a variety of fluorinated heterocycles of biological interest. The identification of two amide groups in a molecule with different environment, which is crucial for identification of regioisomers, is a valuable addition.

4. Experimental

4.1. General

All the reagents were obtained from commercial sources and some of the starting materials were prepared by known methods. Melting points were determined in open glass capillaries using Fisher–Johns melting point instrument. IR spectra were recorded on FT-IR, Perkin-Elmer 1310 infrared spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini (200 and 50 MHz) in $CDCl_3$/DMSO-d_6 with tetramethylsilane as internal standard. The *J* values are given in Hertz. The mass spectra were measured on a VG micro mass 7070-H mass spectrometer. Elemental analysis were carried on Vario EL, Elementar instrument.

4.2. Typical procedure for the preparation of 2, 6-dicyano-3-trifluoromethyl-5-substituted anilines (**2a** and **2b**, and **3a** and **3b**)

A mixture of 1,1,1-trifluoro-2,4-pentanedione or benzoyl-1,1,1-trifluoroacetone (1 mmol) and malononitrile (2 mmol) was taken in methanol (15 ml) and heated to reflux for 6 h while stirring. During the reflux, the reaction was monitored by TLC using chloroform/hexane (75:25) as a solvent medium. After 6 h of reflux, the reaction mixture was brought to room temperature, as a result some solid was separated. The separated solid was filtered and washed with methanol. The solid is characterized as compound **3**. The filtrate was concentrated and the resulted residue was purified through column on silicagel using *n*-hexane/ethyl acetate (9:1) followed by ethyl acetate/*n*-hexane (5:1) as eluent. The two fractions were separated and found to be in different proportions depending on the substituent.

4.3. 2,6-Dicyano-3-trifluoromethyl-5-methyl aniline (**2a**)

IR (KBR) *v*: 3596, 3351, 3248, 2226, 1654, 1135 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.60 (s, 3H, CH_3); 5.44 (br., s, 2H, NH_2); 6.98 (s, 1H, H-4)). ^{13}C NMR (50MHz, $CDCl_3$) δ: 21.4, 101.1, 113, 114, 116.1, 149.2, 152.8. MS (*m*/*z*): 225 (M^+), 197,156, 69. Analysis. Calcd. for $C_{10}H_6F_3N_3$: C, 53.34%; H, 2.68%; N, 18.66%. Found: C, 53.45%; H, 2.79%; N, 19.22%.

4.4. 3-Cyano-4-trifluoromethyl-6-methyl-2(1H)-pyridone (**3a**)

Melting point: 234 °C, [11]: 234 °C.

4.5. 2,6-Dicyano-3-trifluoromethyl-5-phenyl aniline (**2b**)

IR (KBr) *v*: 3397, 3348, 3251, 2232, 1663, 1291, 1133 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 5.6 (br., s, 2H, NH_2); 7.15 (s, 1H, H-C (4)); 7.6 (s, 5H, aromatic H). ^{13}C NMR (50MHz, $CDCl_3$) δ: 114.1, 114.6, 119, 128.1, 128.5, 129.6, 134.8, 135.5, 136.2, 150.7, 154.1. MS (*m*/*z*): 287 (M^+), 260, 218, 164, 77. Analysis. Calcd. for $C_{15}H_8F_3N_3$: C, 62.72%; H, 2.8%; N, 14.62%. Found: C, 62.78%; H, 3.0%; N, 14.69%.

4.6. 3-Cyano-4-trifluoromethyl-6-phenyl-2(1H)-pyridone (**3b**)

Melting point: 300 °C, [11]: 301 °C.

4.7. Hydrolysis of compounds **2a** and **2b**

The compounds **2a** and **2b** (0.14 mmol) were dissolved in potassium hydroxide solution (25%, 20 ml) and heated to reflux for 7 h. Then the solution was cooled to 10–15 °C and neutralized with dilute HCl. The resulted solution was extracted with ethyl acetate, the extract was washed with water till washings are free from acid and dried over anhydrous sodium sulphate. The ethyl acetate was removed under reduced pressure. The residue was purified by passing through a column of silicagel using pure ethyl acetate as eluent to give compounds **4a** and **4b**.

4.8. 2,6-Dicarboxamido-3-trifluoromethyl-6-methyl aniline (**4a**)

IR (KBr) *v*: 3414, 3321, 3209, 1665, 1631 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.28 (s, 3H, CH_3); 4.82 (s, 2H, NH_2); 6.8 (s, 1H, H-C (4)); 7.65 (s, 1H, $CONH_2$); 7.75 (s, 1H, $CONH_2$); 7.85 (s, 1H, $CONH_2$); 7.9 (s, 1H, $CONH_2$). MS (*m*/*z*): 261 (M^+), 244, 216, 201, 69. Analysis. Calcd. for $C_{10}H_{10}F_3N_3O_2$: C, 45.98%; H, 3.85%; N, 16.08%. Found: C, 46.1%; H, 3.9%; N, 16.12%.

4.9. 2,6-Dicarboxamido-3-trifluoromethyl-6-phenyl aniline (**4b**)

IR (KBr) *v*: 3479, 3382, 3201, 1704, 1664,1370, 1294, 1127 cm^{-1}. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 5.05 (s, 2H, NH_2); 6.8 (s, 1H, H-C (4)); 7.39 (s, 5H, aromatic H); 7.45 (s, 1H, $CONH_2$); 7.55 (s, 1H, $CONH_2$); 7.78 (s, 1H, $CONH_2$); 8.0 (s, 1H, $CONH_2$). MS (*m*/*z*): 323, 305, 278, 242, 220, 194, 164, 85. Analysis. Calcd. for $C_{15}H_{12}F_3N_3O_2$: C, 55.73%; H, 3.74%; N, 12.99%. Found: C, 55.74%; H, 3.82%; N, 13.11%.

4.10. Reaction of compounds **4a** and **4b** with aldehydes

The compounds **4a** and **4b** (2 mmol) and aldehydes (2 mmol) were taken in acetic acid (5 ml). The homogenous reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC for 4 h. The reaction mixture was cooled and poured into crushed ice. The separated solid was filtered, washed with water till washings are neutral to litmus and dried. The dried product was found to contain two regioisomers **5** and **6**. Each isomer was separated by passing through column of silicagel in *n*-hexane/ethyl acetate in 3:1 ratio.

4.11. 1,2-Dihydro-2,7-dimethyl-5-trifluoromethyl-8-carboxamido-4(3H)-quinazolinone (**5a**)

IR (KBR) *v*: 3340, 3220, 2368, 1665, 1174, 616 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.45 (d, 3H, CH_3, $J = 20$ Hz); 2.69 (s, 3H, CH_3); 4.81 (m, 1H, methine H); 5.58 (s, 1H, NH); 6.81 (s, 1H, H-C (6)); 7.39 (s, 1H, $CONH_2$); 7.40 (s, 1H, $CONH_2$); 7.91 (s, 1H, CONH). MS (*m*/*z*): 287, 269. Analysis. Calcd. for $C_{12}H_{12}F_3N_3O_2$: C, 58.29%; H, 4.89%; N, 15.37%. Found: C, 58.25%; H, 4.95%; N, 15.92%.

4.12. 1,2-Dihydro-2,5-dimethyl-7-trifluoromethyl-8-carboxamido-4(3H)-quinazolinone (**6a**)

IR (KBr) *v*: 3314, 3225, 2365, 1665, 1524, 1172, 1137 cm^{-1}. ^1H NMR (200 Hz, DMSO -d_6) δ: 1.50 (d, 3H, CH_3, $J = 16$ Hz); 2.65 (s, CH_3, 3H); 4.80 (m, 1H, methine H); 5.5 (s, 1H, NH); 6.8 (s, 1H, H-C (6)); 7.35 (s, 1H, $CONH_2$); 7.37 (s, 1H, $CONH_2$); 7.82 (s, 1H, CONH). MS (*m*/*z*): 287 (M^+), 269, 272, 255, 154. Analysis. Calcd. for $C_{12}H_{12}F_3N_3O_2$: C, 58.29%; H, 4.89%; N, 15.37%. Found: C, 58.35%; H, 4.92%; N, 15.51%.

4.13. 1,2-Dihydro-2-phenyl-5-trifluoromethyl-7-methyl-8-carboxamido-4(3H)-quinazolinone (**5b**)

IR (KBr) *v*: 3510, 3450, 3160, 1690, 1120 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.69 (s, 3H, CH_3); 5.75 (s, 1H, methine H); 6.08 (s, 1H, NH); 6.81 (s, 1H, H-C (6)); 7.35 (m, 3H, aromatic H, 1H $CONH_2$); 7.40 (s, 1H, $CONH_2$); 7.55 (m, 2H, aromatic H); 8.09 (s, 1H, CONH). MS (*m*/*z*): 349 (M^+), 331, 272, 255, 77. Analysis. Calcd. for $C_{17}H_{14}F_3N_3O_2$: C, 58.45%; H, 4.03%; N, 12.02%. Found: C, 58.52%; H, 4.32%; N, 12.13%.

4.14. 1,2-Dihydro-2-phenyl-5-methyl-7-trifluoromethyl-8-carboxamido-4(3H)-quinazolinone (**6b**)

IR (KBr) *v*: 3439, 3294, 3184, 2925, 1668, 1132 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.39 (s, 3H, CH_3); 5.69 (s, 1H, methine H); 6.52 (s, 1H, NH); 6.93 (s, 1H, H-C (6)); 7.39 (m, 3H, aromatic H); 7.54 (m, 2H, aromatic H); 7.79 (s, 1H, $CONH_2$); 7.87 (s, 1H $CONH_2$); 8.30 (s, 1H, CONH). MS (*m*/*z*): 349 (M^+), 331, 305, 272, 256, 104, 77. Analysis. Calcd. for $C_{17}H_{14}F_3N_3O_2$: C, 58.45%; H, 4.03%; N, 12.02%. Found: C, 58.52%; H, 4.32%; N, 12.13%.

4.15. 1,2-Dihydro-2-methyl-5-trifluoromethyl-7-phenyl-8-carboxamido-4(3H)-quinazolinone (**5c**)

IR (KBr) *v*: 3440, 3350, 3100, 1652, 1162 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.48 (d, 3H, CH_3 $J = 16$ Hz); 4.8 (m, 1H, methine H); 6.19 (s, 1H, NH); 6.98 (s, 1H, H-C (6)); 7.09 (s, 1H, $CONH_2$); 7.19 (s, 1H, $CONH_2$); 7.42 (s, 5H, aromatic H); 8.15 (s, 1H, CONH). MS (*m*/*z*): 349 (M^+) 333, 316. Analysis. Calcd. for $C_{17}H_{14}F_3N_3O_2$: C, 58.45%; H, 4.03%; N, 12.02%. Found: C, 58.50%; H, 4.15%; N, 12.14%.

4.16. 1,2-Dihydro-2-methyl-5-phenyl-7-trifluoromethyl-8-carboxamido-4(3H)-quinazolinone (**6c**)

IR (KBr) *v*: 3350, 3290, 3090, 1690, 1120 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.45 (d, 3H, CH_3, $J = 18$ Hz); 4.85 (m, 1H, methine H); 5.80 (s, 1H, NH); 6.83 (s, 1H, H-C (6),); 7.29 (s, 5H, aromatic H); 7.42 (s, 1H, $CONH_2$); 7.61 (s, 1H, $CONH_2$); 7.95 (s, 1H, CONH). MS (*m*/*z*): 349 (M^+), 334, 317, 158, 69. Analysis. Calcd. for $C_{17}H_{14}F_3N_3O_2$: C, 58.45%; H, 4.03%; N, 12.02%. Found: C, 58.51%; H, 4.22%; N, 12.08%.

4.17. 1,2-Dihydro-2,7-diphenyl-5-trifluoromethyl-8-carboxamido-4(3H)-quinazolinone (**5d**)

IR (KBr) *v*: 3468, 3186, 1688, 1513, 1288, 1175 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 5.5 (s, 1H, methine H); 6.38 (s, 1H, NH); 6.42 (s, 1H, $CONH_2$); 6.58 (s, 1H, $CONH_2$); 6.92 (s, 1H, H-C (6)); 7.15 (s, 5H, aromatic H); 7.8 (s, 1H, CONH). MS (*m*/*z*): 412 (M^+), 393, 375, 317, 185, 93. Analysis. Calcd. for $C_{22}H_{16}F_3N_3O_2$: C, 64.23%; H, 3.92%; N, 10.21%. Found: C, 64.28%; H, 3.98%; N, 10.29%.

4.18. 1,2-Dihydro-2,5-diphenyl-7-trifluoromethyl-8-carboxamido-4(3H)-quinazolinone (**6d**)

IR (KBr) *v*: 3437, 3296, 3175, 1670, 1456, 1118 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 5.82 (s, 1H, methine H); 6.50 (s, 1H, NH); 6.92 (s, 1H, H-C (6)); 7.3 (s, 5H, aromatic H); 7.38 (m, 3H, aromatic H); 7.42 (s, 1H, $CONH_2$); 7.58 (s, 1H, $CONH_2$); 7.63 (m, 2H, aromatic H); 8.23 (s, 1H, CONH). MS (*m*/*z*): 411 (M^+) 393, 307, 185, 93. Analysis. Calcd. for $C_{22}H_{16}F_3N_3O_2$: C, 64.23%; H, 3.92%; N, 10.21%. Found: C, 64.28%; H, 3.98%; N, 10.3%.

4.19. Dehydrogenation of quinazolinones (**5** and **6**)

The compound **5** or **6** (0.16 mmol) was dissolved in dry dichloromethane (10 ml), active MnO_2 (650 mg) was added

and stirred for 2 h at room temperature. The reaction mixture was filtered and washed with dichloromethane. The filtrate is concentrated and the resulted residue is purified through column of silicagel using ethyl acetate/hexane (60:40) as eluents to give compounds **7** and **8** respectively.

*4.20. 2,7-Dimethyl-5-trifluoromethyl-8-carboxamido-4(3H)-quinazolone (**7a**)*

IR (KBr) *v*: 3311, 3162, 2938, 1687, 1620, 1383 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.39 (s, 3H, CH_3); 2.8 (s, 3H, CH_3); 6.98 (s, 1H, H-C (6)); 7.28 (s, 1H, $CONH_2$); 7.3 (s, 1H, $CONH_2$); 12.1 (s, 1H, CONH). MS (*m*/*z*): 285, 269, 242, 194, 42. Analysis. Calcd. for $C_{12}H_{10}F_3N_3O_2$: C, 58.77%; H, 4.11%; N, 17.13%. Found: C, 58.86%; H, 4.19%; N, 17.21%.

*4.21. 2,5-Dimethyl-7-trifluoromethyl-8-carboxamido-4(3H)-quinazolone (**8a**)*

IR (KBr) *v*: 3448, 3368, 1686, 1623, 1383, 1140 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.4 (s, 3H, CH_3); 2.6 (s, 3H, CH_3); 7.32 (s, 1H, H-C (6)); 7.34 (s, 1H, $CONH_2$); 7.39 (s, 1H, $CONH_2$); 12.1 (s, 1H, CONH). MS (*m*/*z*): 285, 269, 242, 194, 141, 117, 69. Analysis. Calcd. for $C_{12}H_{10}F_3N_3O_2$: C, 58.77%; H, 4.11%; N, 17.13%. Found: C, 58.82%; H, 4.13%; N, 17.17%.

*4.22. 2-Phenyl-5-trifluoromethyl-7-methyl-8-carboxamido-4(3H)-quinazolone (**7b**)*

IR (KBr) *v*: 3372, 3165, 1680 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.73 (s, 3H, CH_3); 7.29 (s, 1H, H-C (6)); 7.37 (m, 3H, aromatic H); 7.39 (s, 1H, $CONH_2$); 7.5 (s, 1H, $CONH_2$); 7.5 (m, 2H, aromatic H); 12.3 (s, 1H, CONH). MS (*m*/*z*): 347 (M^+), 331, 304, 255, 104. Analysis. Calcd. for $C_{17}H_{12}F_3N_3O_2$: C, 58.79%; H, 3.48%; N, 12.09%. Found: C, 58.82%; H, 3.52%; N, 12.15%.

*4.23. 2-Phenyl-5-methyl-7-trifluoromethyl-8-carboxamido-4(3H)-quinazolone (**8b**)*

IR (KBr) *v*: 3370, 3166, 1675 cm^{-1}. ^1H NMR (200 MHz. DMSO-d_6) δ: 2.54 (s, 3H, CH_3); 7.3 (s, 1H, H-C (6)); 7.5 (m, 5H, aromatic H); 8.21 (s, 1H, $CONH_2$); 8.28 (s, 1H, $CONH_2$); 12.1 (s, 1H, CONH). MS (*m*/*z*): 347 (M^+), 330, 304, 104, 69. Analysis. Calcd. for $C_{17}H_{12}F_3N_3O_2$: C, 58.79%; H, 3.48%; N, 12.09%. Found: C, 58.76%; H, 3.40%; N, 12.05%.

*4.24. 2-Methyl-5-trifluoromethyl-7-phenyl-8-carboxamido-4(3H)-quinazolone (**7c**)*

IR (KBr) *v*: 3376, 3182, 3057, 1687, 1383 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.39 (s, 3H,CH_3); 7.23 (s, 1H, H-C (6)); 7.25 (s, 5H, aromatic H); 7.35 (s, 1H, $CONH_2$); 7.4 (s, 1H, $CONH_2$); 12.4 (s, 1H, CONH). MS (*m*/*z*): 347 (M^+), 304, 164, 42. Analysis. Calcd. for $C_{17}H_{12}F_3N_3O_2$: C, 58.79%; H, 3.48%; N, 12.09%. Found: C, 58.81%; H, 3.52%; N, 12.16%.

*4.25. 2-Methyl-5-phenyl-7-trifluoromethyl-8-carboxamido-4(3H)-quinazolone (**8c**)*

IR (KBr) *v*: 3375, 3182, 1685, 1380 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.4 (s, 3H, CH_3); 7.22 (s, 1H, H-C (6)); 7.5 (s, 5H, aromatic H); 7.85 (s, 1H, $CONH_2$); 7.9 (s, 1H, $CONH_2$); 12.1 (s, 1H, CONH). MS (*m*/*z*): 347 (M^+), 332, 304, 154, 91, 69. Analysis. Calcd. for $C_{17}H_{12}F_3N_3O_2$: C, 58.79%; H, 3.48%; N, 12.09%. Found: C, 58.80%; H, 3.52%; N, 12.12%.

*4.26. 2,7-Diphenyl-5-trifluoromethyl-8-carboxamido-4(3H)-quinazolone (**7d**)*

IR (KBr) *v*: 3370, 3175, 1685 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 7.25 (s, 1H, H-C (6)); 7.58 (s, 5H, aromatic H); 7.6 (m, 3H, aromatic H); 7.63 (m, 2H, aromatic H); 7.88 (s, 1H, $CONH_2$); 7.90 (s, 1H, $CONH_2$); 12.37 (s, 1H, CONH). MS (*m*/*z*): 409 (M^+), 307, 154. Analysis. Calcd. for $C_{22}H_{14}F_3N_3O_2$: C, 64.54%; H, 3.44%; N, 10.26%. Found: C, 64.63%; H, 3.51%; N, 10.31%.

*4.27. 2,5-Diphenyl-7-trifluoromethyl-8-carboxamido-4(3H)-quinazolone (**8d**)*

IR (KBr) *v*: 3469, 3226, 1672, 1359, 1135, 698 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6) δ: 7.35 (s, 1H, H-C (6)); 7.38 (s, 5H, aromatic H); 7.42 (m, 5H, aromatic H); 8.1 (s, 1H, $CONH_2$); 8.2 (s, 1H, $CONH_2$); 12.32 (s, 1H, CONH). MS (*m*/*z*): 409 (M^+), 393, 307, 176, 154, 136, 107. Analysis. Calcd. for $C_{22}H_{14}F_3N_3O_2$: C, 64.54%; H, 3.44%; N, 10.26%. Found: C, 64.71%; H, 3.54%; N, 10.50%.

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