A Convenient One Pot Synthesis of 3-Cyano-9-methyl-2-methylthio-4-oxo-*4H*- pyrimido[2,1-*b*] pyrimido [4,5-*b*] Quinoline and its Reactions with Selected Nucleophiles

Sambhaji P. Vartale*, Vijay N. Bhosale, Sandeep V. Khansole and Ramdas N. Katapalle

Post-Graduate Research Center, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded-431602, India

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Abstract: 3-Amino-8-methyl pyrimido [4,5-*b*] quinoline (1) in N,N-dimethyl formamide (DMF) and anhydrous potassium carbonate reacted with ethyl-2-cyano-3,3-bismethyl thioacrylate **2** to afford novel heterocyclic compound 3-cyano-9-methyl-2-methylthio-4-oxo-*4H*-pyrimido [4,5-*b*] quinoline **3**. The latter were further reacted with selected N-, O- and C- nucleophiles such as arylamines, substituted phenols, heterylamines and compounds with an active methylene group.

Keywords: One pot synthesis, pyrimido quinoline, ketene dithioacetals, N,N-dimethyl formamide, ring anellation, pyrimidine ring.

INTRODUCTION

Quinoline and its derivatives are an interesting class of heterocyclic compounds with a wide range of applications as a drug. Most of the quinoline derivatives act as analgesics [1], antiamoebic [2-5], tryphocidal [6], antiseptic [7] and antiserotonin [8]. In addition to these, derivatives also exhibit good antimalarial [9, 10] antitubercular [11], antibacterial [12], antihistaminic [13], antineurodegerative [14], anticonvulsants [15], antitumor [16], anticancers [17, 18] and antiallergics [19] activities.

In the light of these valid observations, such fused quinoline with pyrimidine ring would exhibit some interesting pharmacological activities, further, the ring anellation to amino groups containing nitrogen heterocycles with ketene dithioacetals as reagent has been reported [20-22]. All this prompted our interest to continue the work directed to one pot synthesis of new heterocyclic compound 3-cyano-9-methyl-2-methylthio-4-oxo-*4H*-pyrimido [2,1-*b*] pyrimido [4,5-*b*] quinoline **3** and preparation of 2-substituted derivatives.

RESULT AND DISCUSSION

Compound **3** was prepared from the reaction of 3-amino-8-methyl pyrimido [4,5-*b*] quinoline **1** with ethyl -2-cyano-3,3-bismethyl thioacrylate **2** in the presence of N,N-dimethyl formamide and a catalytic amount of anhydrous potassium carbonate for 4 hours in 60% yield. The structure was established on the basis of elemental analysis, IR, PMR and mass spectral data. Spectral studies of compounds **3** showed that compound was stable as well as there was no linear anellated tetracyclic system formation, since, resulting linear anellated tetracyclic structure would be highly unstable and may not exhibit any tautomerism.

Scheme **1** represents a tentative mechanism pathway for the formation of compound **3**.

The compound **3** possesses a replaceable active methylthio group at the 2-position, which is activated by the ring 1-nitrogen atom, electron withdrawing 3-cyano group and activation of the methylthio group is also supported by the ring amide group of pyrimidine ring. Compound **3** was reacted with selected N-, O- and C- nucleophiles like aryl amines, substituted phenols, heteryl amines and compounds containing an active methylene group. These reactions resulted in the formation of 2-substituted derivatives of 3-cyano-9-methyl-2-methylthio-4-oxo-4*H*-pyrimido [2,1-*b*] pyrimido [4,5-*b*] quinoline **3**. According to this method, compound **3** independently, on reaction with p-chloro aniline, o-chloroaniline, o-methylaniline, p-methylaniline and p-methoxyaniline in N,N- dimethyl formamide and a catalytic amount of anhydrous potassium carbonate, afforded 3-cyano-2-(4'-chloroanilino/2'-chloroanilino/2'-methylanilino/4'-methylanilino/4'-methoxyanilino)-9-methyl-4-oxo-*4H*-pyrimido [2,1-*b*] pyrimido [4,5-*b*] quinoline **4a-4e** respectively (Scheme **2**). Under similar experimental conditions, compound **3** reacted independently with p-methylphenol, o-methylphenol, p-methoxyphenol, p-chloro phenol and o-chlorophenol, to yield 3-cyano-2-(4'-methyl phenoxy/2'-methyl phenoxy/4'-methoxyphenoxy/4'-chlorophenoxy/2'-chlorophenoxy)-9-methyl-4-oxo-*4H*-pyrimido [2,1-*b*] pyr-imido [4,5-*b*] quinoline **5a-5e** respectively (Scheme **2**).

3-Cyano-2-pyrrolidino/piperidino/morpholino-9-methyl-4-oxo-*4H*-pyrimido[2,1-*b*] pyrimido [4,5-*b*] quinoline **6a-6c** were obtained by the condensation of compound **3** independently with pyrrolidine, piperidine and morpholine in N,N-dimethyl formamide and a catalytic amount of anhydrous potassium carbonate (Scheme **2**). Compound **3** on reaction independently with acetylacetone, ethyl acetoacetate, diethyl malonate and ethyl cyanoacetate in the

*Address correspondence to this author at the Post-Graduate Research Center, Department of Chemistry, Yeshwant Mahavidyalaya, Nanded-431602, India; Tel: +91 2462 269616; Fax: +91 2462 253726;
E-mail: spvartale@rediffmail.com

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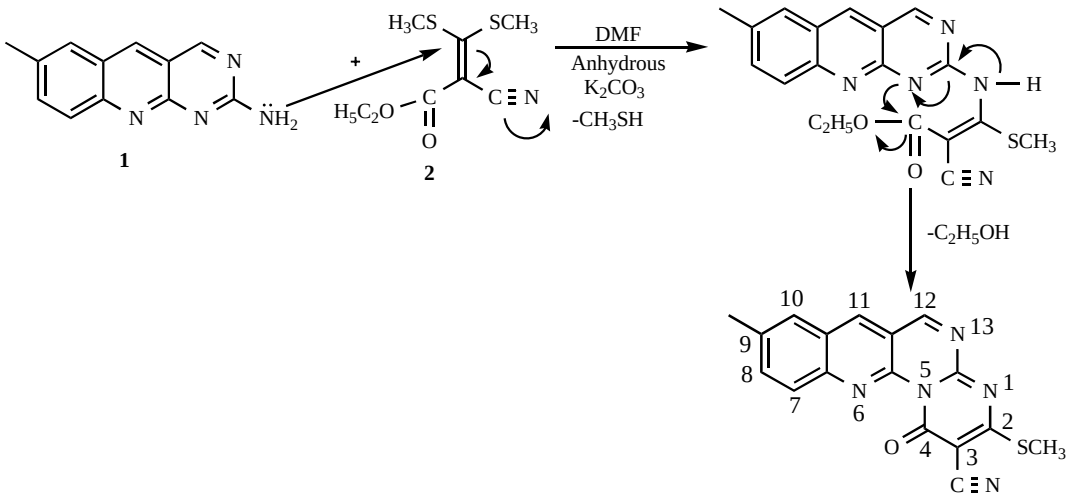
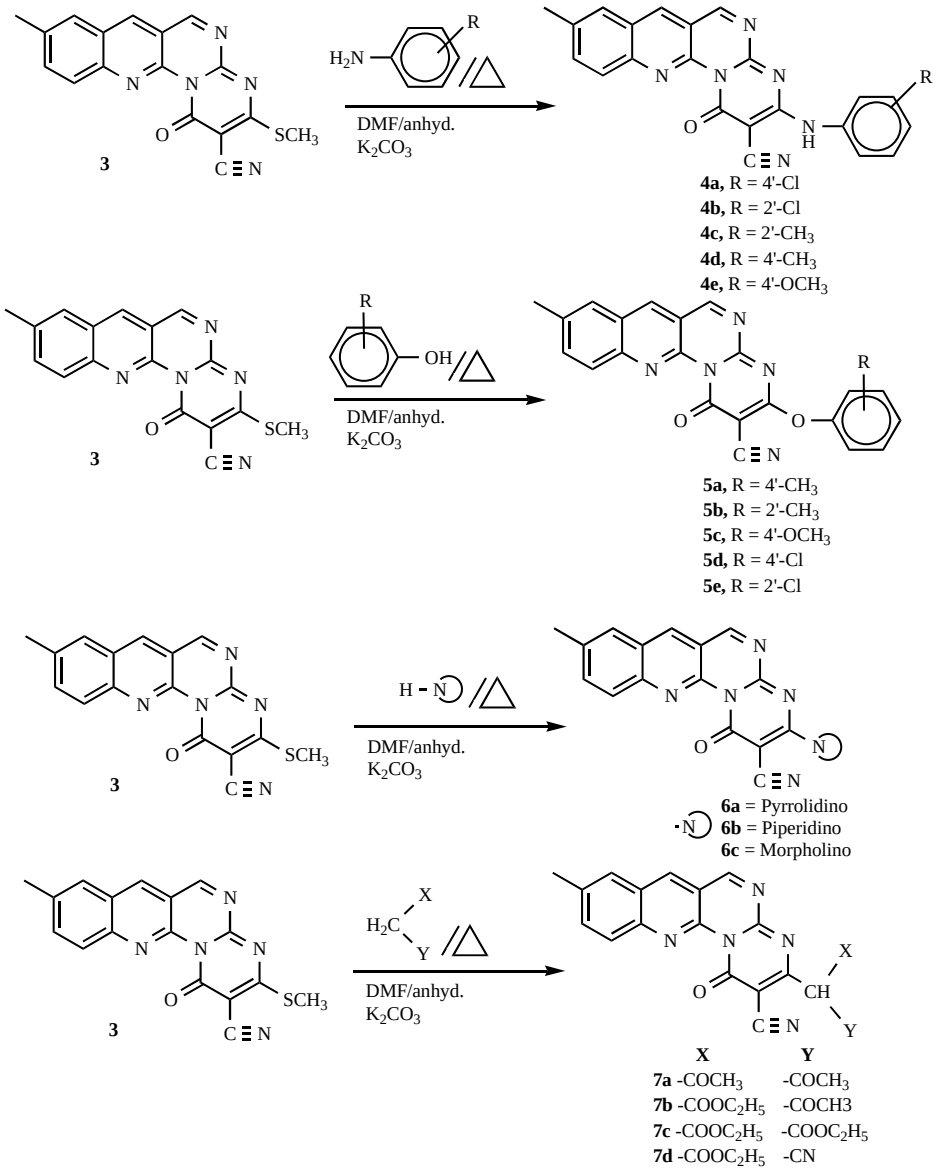


Scheme 1. Ring anellation to form compound **3**.



Scheme 2. Nucleophilic substitution reactions with selected nucleophiles.

presence of anhydrous potassium carbonate yielded compounds, characterized on the basis of their analytical and spectral data as 3-cyano-2-(α-acetylacetonyl/α-ethylacetoacetyl/α-diethylmalonyl/α-ethylcyanoacetyl)-9-methyl-4-oxo-*4H*- pyrimido [2-1-*b*] pyrimido [4,5-*b*] quinoline **7a-7d** respectively (Scheme **2**).

EXPERIMENTAL

All melting points were determined in open capillary tube and uncorrected. All the reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel-G plate using iodine vapour for detection. IR spectra were recorded in Nujol or as Potassium bromide pellets on a Shimadzu IR 8400S FT infrared spectrophotometer. The ^{1}H NMR were obtained on a FT Gemino 60 (60MHz) spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on a FT VG-7070H mass spectrophotometer using the EI technique at 70 eV. All reactions were carried out under ambient atmosphere. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

3-Cyano-9-methylthio-4-oxo-4H-pyrimido[2,1-b]pyrimido [4,5-b] quinoline 3

A mixture of 3-amino-8-methyl pyrimido [4,5-*b*] quinoline **1** (2.10g, 0.01 mol) and ethyl-2-cyano-3,3-bismethyl thioacrylate 2 (2.21 g, 0.01 mol) was refluxed in the presence of N,N- dimethyl formamide (15 mL) and anhydrous potassium carbonate for (10 mg) 4 h. The reaction mixture was cooled to room temperature and poured in to ice cold water. The separated solid was filtered, washed with water and recrystallized from N,N- dimethyl formamide-ethanol mixture to afford compound **3.** (1.99g, 60% yield), Mp: 118-120^{o}C; EI-MS (m/z-RA%) : 333 (M+, 15) 332 (10), 232 (20), 157 (45), 154 (20), 138 (15), 137 (35), 79 (100); IR (cm^{-1}, KBr) : 2208 (CN), 1680 (CO); ^{1}H NMR (DMSO-d_6, ppm) : 2.4 (s, 3H, SCH_3), 2.6 (s, 3H, Ar-CH_3), 7.2-8.0 (m, 3H, Ar-H), 8.2 (s, 1H, CH=N) 8.5 (s, 1H-C=CH quin.); ^{13}C NMR (300 MHz, $CDCl_3$, ppm) 21.3, 110, 114.8, 118.3, 121, 124.9, 125.9, 130.2, 130.8, 136.2, 148.8, 162, 163.7, 165, 166.2, 176.5, 177.4.Found: C,60.96; H, 3.08; N,20.88.$C_{17}H_{11}N_5OS$. Calcd: C, 61.26;H,3.30.N,21.02.

General procedure for 3-Cyano-2-(4'-chloroanilino/2'-chloroanilino/2'-methyl/aniline/4'-methylanilino/4'-methoxyanilino)-9-methyl-4-oxo-4H-pyrimido[2,1-b]pyrimido [4,5-b]quinoline 4a-e

A mixture of compound 3(3.33 g, 0.01 mol), N,N-dimethyl formamide (15 mL), anhydrous potassium carbonate (10 mg) and appropriate substituted anilines (0.01 mol) was refluxed for 6 h. the reaction mixture was cooled to room temperature and poured into ice cold water. The products **4a-e** thus obtained were crystallized from DMF-ethanol solvent.

4a: (2.68g, 65% yield), Mp: 170-172^{o}C; IR (cm^{-1}, KBr): 3315 (NH), 2210 (CN), 1678 (CO); ^{1}H NMR (DMSO-d_6,ppm) : 2.6 (s, 3H, Ar-CH_3), 4.1 (s, 1H,-NH), 6.5-8.0 (m, 7H,Ar-H), 8.3 (s, 1H, CH=N-), 8.5 (s, 1H,-C=CH), ^{13}C NMR (300 MHz, $CDCl_3$, ppm): 21.3, 74.3, 114.2, 116.5, 117.2, 121.0, 123.6, 124.3, 124.8, 130.3, 130.9, 135.4, 144.8, 148.3, 163.0, 163.7, 166.1, 174.4. Found: C, 63.72; H, 2.85; N, 20.10. $C_{22}H_{13}N_6OCl$. Calcd: C, 64.00; H, 3.12; N, 20.36.

4b: (2.55g, 62% yield), Mp: 175-176 ^{o}C; IR (cm^{-1}, KBr): 3321 (NH), 2211 (CN), 1680 (CO); ^{1}H NMR (DMSO-d_6,ppm) : 2.6 (s,3H,Ar-CH_3), 4.0(s,1H,-NH), 6.5-8.0 (m,7H,Ar-H), 8.2 (s,1H,CH=N-),8.5(s,1H,-C=CH). Found : C, 63.72; H, 2.85; N, 20.11. $C_{22}H_{13}N_6OCl$. Calcd: C, 64.00; H, 3.12; N, 20.36.

4c: (2.66g, 68% yield), Mp: 172-174 ^{o}C; IR (cm^{-1}, KBr): 3330 (NH),2210 (CN), 1679 (CO); ^{1}H NMR (DMSO-d_6,ppm) : 2.6 (s,6H, two Ar-CH_3), 4.0 (s,1H,-NH), 6.4-8.0 (m,7H,Ar-H), 8.1 (s,1H,CH=N-),8.5 (s,1H,-C=CH). Found: C, 70.00; H, 3.91; N,21.20. $C_{23}H_{16}N_6O$. Calcd: C,70.05; H,4.06; N,21.31.

4d: (2.6 g, 66% yield), Mp: 180-181 ^{o}C; IR (cm^{-1},KBr): 3331 (NH), 2208 (CN), 1680 (CO); ^{1}H NMR (DMSO-d_6,ppm) : 2.6 (s,6H, two Ar-CH_3), 4.0 (s,1H,-NH), 6.4-8.0 (m,7H,Ar-H), 8.1 (s,1H,CH=N-),8.5 (s,1H,-C=CH). Found: C, 69.90; H, 4.00; N, 21.09. $C_{23}H_{16}N_6O$. Calcd: C, 70.05; H, 4.06; N, 21.31.

4e: (2.54 g, 62% yield), Mp: 176-177 ^{o}C; IR (cm^{-1}, KBr): 3318 (NH), 2210 (CN), 1676 (CO); ^{1}H NMR (DMSO-d_6,ppm) : 2.6 (s,3H, Ar-CH_3), 3.8 (s,3H,-OCH_3),4.0 (s,1H,-NH), 6.4-8.0 (m,7H,Ar-H), 8.0 (s,1H,CH=N-),8.5 (s,1H,-C=CH). Found: C, 67.10; H, 3.65; N, 20.18. $C_{23}H_{16}N_6O_2$. Calcd: C, 67.31; H, 3.90; N, 20.48.

General procedure for 3-cyano-2-(4'-methylphenoxy/2'-methylphenoxy/4'-methoxy phonoxy/4'-chlorophenoxy)-9-methylthio-4-oxo-4H-pyrimido[2,1-b]pyrimido[4,5-b] quinoline 5a-e

A mixture of compound 3(3.33 g, 0.01 mol), N,N-dimethyl formamide (15 mL), anhydrous potassium carbonate (10 mg) and appropriate substituted phenols (0.01 mol) was refluxed for 6 h. The reaction mixture was cooled to room temperature and poured into ice cold water. The products **4a-e** thus obtained were crystallized from DMF-ethanol solvent.

5a: (2.75g, 70% yield), Mp: 275-277^{o}C, IR (cm^{-1}, KBr) : 2209 (CN), 1677 (CO); ^{1}H NMR (DMSO-d_6, ppm) :2.4 (s, 6H, two Ar-CH_3),6.6-8.0(m,8H,Ar-H), 8.5(s,1H,CH=C quin.); ^{13}C NMR (300 MHz, $CDCl_3$, ppm): 20.9, 21.3, 76.2, 114.4, 116.8, 117.2, 121.0, 124.7, 124.9, 129.8, 130.3, 130.8, 131.9, 135.4, 148.3, 153.6 , 163.0,163.2,164.0,166.1,164.0. Found: C; 70.10; H, 3.51; N, 17.50. $C_{23}H_{15}N_5O_2$. Calcd: C, 70.22; H, 3.81; N, 17.81.

5b: (2.82g, 72% yield), Mp: 279-280^{o}C; IR (cm^{-1},KBr) : 2211(CN), 1679 (CO); ^{1}H NMR (DMSO-d_6, ppm) : 2.5 (s, 6H, two Ar-CH_3), 6.6-8.0 (m,8H, Ar-H), 8.5 (s,1H,CH=C quin.); Found: C, 70.10; H, 3.61; N, 17.65.$C_{23}H_{15}N_5O_2$. Calcd: C, 70.22; H, 3.81; N, 17.81.

5c: (3.02g, 74% yield). Mp:282-283^{o}C; IR(cm^{-1},KBr):2209(CN),1681 (CO); ^{1}H NMR (DMSO-d_6, ppm) : 2.5 (s, 3H, Ar-CH_3), 3.8 (s,3H,-OCH_3), 6.6-7.9 (m,8H, Ar-H), 8.5 (s,1H,CH=C quin.). Found: C, 67.13; H, 3.30; N, 17.00. $C_{23}H_{15}N_5O_3$ Calcd: C, 67.48; H, 3.66; N, 17.11.

5d: (3.24 g, 78% yield), Mp: 268-270^{o} C; IR (cm^{-1}, KBr) : 2213 (CN), 1686 (CO); ^{1}H NMR (DMSO-d_6, ppm) : 2.6 (s, 3H, Ar-CH_3), 6.6-7.9 (m,8H, Ar-H), 8.5 (s,1H,CH=C quin.) Found: C, 63.61; H, 2.60; N, 16.58. $C_{22}H_{12}N_5O_2Cl$. Calcd: C, 63.92; H, 2.90; N, 16.94.

5e: (3.0g, 73% yield), Mp: 272-273^{o}C; IR(cm^{-1},KBr) : 2209 (CN), 1678 (CO); ^{1}H NMR (DMSO-d_6, ppm) : 2.6 (s, 3H, Ar-CH_3), 6.7-8.0 (m,8H, Ar-H), 8.5 (s,1H,CH=C quin.) Found: C, 63.69; H, 2.61; N,16.59.$C_{22}H_{12}N_5O_2Cl$. Calcd: C, 63.92; H, 2.90; N, 16.94.

General procedure for 3-cyano-2-pyrrolidino/piperidino/ morpholino-9-methyl-4-oxo-4H-pyrimido [2,1-b] pyrimido[4,5-b] quinoline 6a-c

A mixture of compound 3 (3.33 g, 0.01 mol), N,N-dimethyl formamide (15 mL), anhydrous potassium carbonate (10 mg) and appropriate cyclic secondary amines (0.01 mol) was refluxed for 5 h and the mixture was poured into ice cold water. The products **6a-c** thus obtained were crystallized from DMF-ethanol solvent.

6a: (2.84g, 80% yield), Mp:241-242^{o}C; IR (cm^{-1},KBr) : 2208 (CN), 1675 (CO); ^{1}H NMR (DMSO-d_6, ppm): 1.5 (t,4H, two -CH_2–), 2.8 (t,4H, two-NCH_2–), 2.4 (s, 3H, Ar-CH_3), 7.0-7.9 (m, 4H,Ar-H), 8.4 (s,1H,CH=C quin.); ^{13}C NMR (300 MHz, $CDCl_3$, ppm): 21.3, 23.4, 46.0, 72.2, 114.0, 117.1, 121.3, 124.7, 124.9, 130.3, 130.9, 135.4, 148.2, 163.0, 163.7, 164.0, 166.1, 182.0 Found: C,67.15; H, 4.20; N, 23.32. $C_{20}H_{16}N_6O$. Calcd: C, 67.41; H, 4.49; N, 23.59.

6b: (2.96g, 80% yield), Mp: 252-254^{o}C; IR (cm^{-1},KBr):2210(CN),1679(CO); ^{1}H NMR (DMSO-d_6, ppm): 1.6 (t,6H, three CH_2), 2.4 (s, 3H, Ar-CH_3), 2.7 (t,4H, two-NCH_2),7.3-7.9 (m, 4H,Ar-H), 8.5 (s,1H,CH=C quin.). Found: C, 68.01; H, 4.54; N, 22.52. $C_{21}H_{18}N_6O$. Calcd: C, 68.10; H, 4.86; N, 22.70.

6c: (3.12g, 84% yield), Mp: 221-222^{o}C; IR (cm^{-1}, KBr) : 2211 (CN), 1680 (CO). ^{1}H NMR (DMSO-d_6, ppm) : 2.4 (s, 3H, Ar-CH_3), 2.6 (t,4H, -NCH_2–), 3.8 (t,4H, OCH_2), 7.3-7.9 (m, 4H, Ar-H), 8.5 (s, 1H, Ar-CH=N). Found: C, 64.20; H, 4.10; N, 22.22. $C_{20}H_{16}N_6O_2$. Calcd: C, 64.51; H, 4.30; N, 22.58.

General procedure for 3-Cyano-2(α-acetyl acetonyl/α-ethylacetoacetyl/α-ethylacetoacetyl/α-diethyl malonyl/α-ethyl cyanoacetyl)-9-methyl-4-oxo-4H-pyrimido[2,1-b] pyrimido[4,5-b] quinoline 7a-d

A mixture of compound 3 (3.33 g, 0.01 mol), N,N-dimethyl formamide (15 mL), anhydrous potassium carbonate (10 mg) and appropriate compounds containing an active methylene group (0.01 mol) was refluxed for 4 to 6 h. The reaction mixture was cooled at room temperature and poured into ice cold water. The products **7a-d** thus obtained were crystallized from DMF-ethanol solvent.

7a: (2.88g, 75% yield), Mp: 241-243^{o}C; IR (cm^{-1},KBr) : 2210 (CN), 16.78 (cyclic CO), 1685 (CO), 1248 (C-O); ^{1}H NMR (DMSO-d_6, ppm): 2.1 (s,6H,two $COCH_3$), 2.4 (s, 3H, Ar-CH_3), 3.9 (s,1H,-CH), 7.4-8.0 (m, 4H,Ar-H), 8.5 (s,1H,CH=C quin.); ^{13}C NMR (300 MHz, $CDCl_3$, ppm): 21.3, 22.2, 66.7, 97.0, 114.3, 117.2, 121.0, 124.7, 124.9, 130.3, 130.8, 135.4, 163.0, 163.5, 163.7, 166.1, 166.3, 167.4, 206. Found : C, 65.10; H, 3.64; N, 1.51.$C_{21}H_{15}N_5O_3$. Calcd: C, 65.45; H, 3.89; N, 1.81.

7b: (3.11g, 75% yield), Mp: 285-286^{o}C; IR (cm^{-1},KBr) : 2209 (CN), 1735 (CO of ester), 1684 (CO), 1678 (cyclic CO), 1245 (C-O); ^{1}H NMR (DMSO-d_6, ppm): 1.4 (t,3H,-CH_3), 2.2 (s,3H,$COCH_3$), 2.4 (s, 3H, Ar-CH_3), 3.9 (s,1H,-CH), 4.2(q,2H,-OCH_2-), 7.4-8.0 (m, 4H,Ar-H), 8.5 (s,1H,CH=C quin.); Found : C, 63.30; H, 3.92; N, 16.50. $C_{22}H_{17}N_5O_4$. Calcd: C, 63.61; H, 4.09; N, 16.86.

7c: (3.47g, 78% yield), m.p.251-253^{o}C; IR (cm^{-1},KBr): 2211(CN), 1740 (CO of ester), 1678 (cyclic CO), 1258 (C-O); ^{1}H NMR (DMSO-d_6, ppm): 1.4 (t,6H,two-CH_3), 2.4 (s,3H,ArCH_3), 3.9 (s,1H,-CH), 4.2(q, 4H,two-OCH_2-), 7.4-8.0 (m, 4H,Ar-H), 8.5 (s,1H,CH=C quin.); Found: C, 61.90; H, 4.05; N, 15.48. $C_{23}H_{19}N_5O_5$ requires C, 62.02; H, 4.26; N, 15.73.

7d: (2.9g, 73% yield), Mp**:** 262-263^{o}C; IR (cm^{-1}, KBr) : 2211 (CN), 1739 (CO of ester), 1675 (cyclic CO); ^{1}H NMR (DMSO-d_6, ppm): 1.4 (t,3H,CH_3), 2.4 (s,3H,ArCH_3), 4.0 (s,1H,-CH), 4.2 (q, 2H,-OCH_2-), 7.4-8.0 (m, 4H,Ar-H), 8.5 (s,1H,CH=C quin.); Found: C, 63.10; H, 3.28; N, 20.90. $C_{21}H_{14}N_6O_3$. Calcd: C, 63.31; H, 3.51; N, 21.10.

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