G. Venkat Reddy, A. Chandra Shekhar, A. Ravi Kumar, G. Sathaiah,
B. Narsaiah, and P. Shanthan Rao*

Division of Fluoroorganics, Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500607, India
*E-mail: shanthanpp1954@gmail.com
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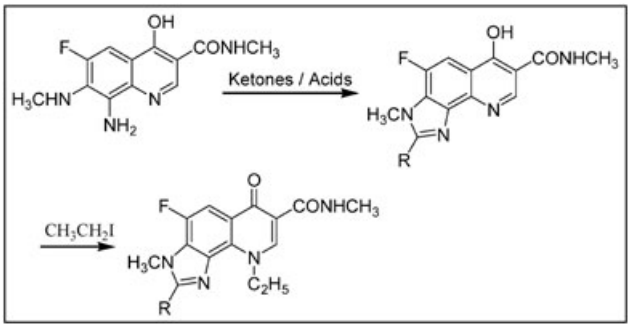

Studies on synthetic design of 7,8-imidazole fused fluoroquinolones from 8-amino-6-fluoro-4-hydroxy-*N*-methyl-7-(methyl amino)quinoline-3-carboxamide and ketones/carboxylic acids and their antibacterial activity.

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INTRODUCTION

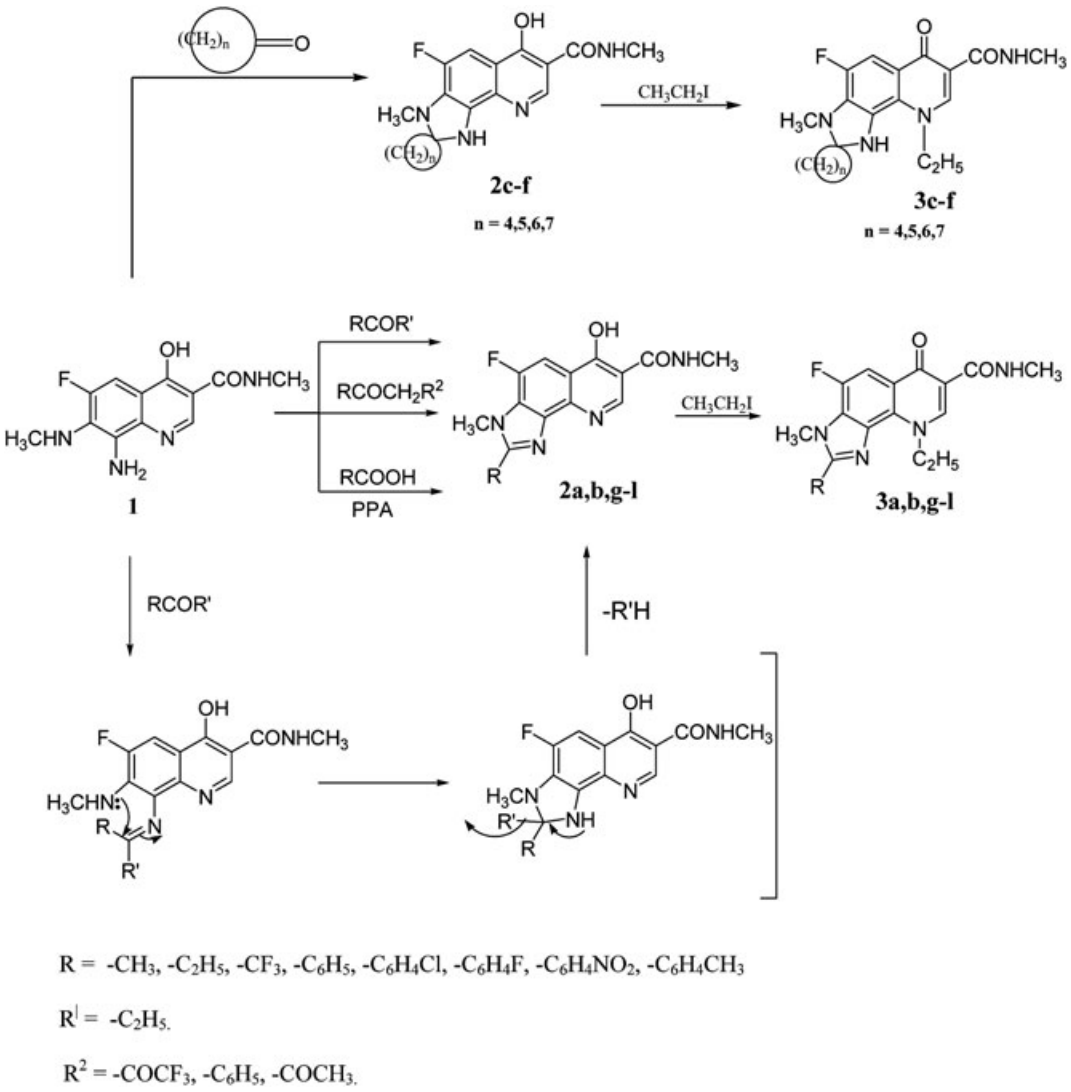
Fluoroquinolones have wide range of applications as anti-infectious reagents [1–3], though the fluoroquinolones dominating in the market as antibacterial agents in the last two decades, the concern is some of them are getting resistance to certain bacterial infections. Continuous search of new class of fluoroquinolone analogues is under progress world wide to get a promising molecule for future generation. Heteroring fused quinolones [4–6] are considered as potential molecules based on the findings of thiazole fused [7] at 2, 3 positions has shown 10 times more activity *in vitro* than ciprofloxacin. In continuation of our work on fluoroquinolones [8], we wish to report here, the synthesis of 7,8-imidazole fused fluoroquinolones retaining the active functionalities like carboxylic acid at C-3, carbonyl function at C-4, fluorine moiety at C-6, and smaller alkyl group on N-1 position.

RESULTS AND DISCUSSION

Retro synthetic strategy of 7,8-fused imidazole quinolones requires an active synthon 6-fluoro-7-methylamino-8-amino-4-hydroxyquinoline-3-*N*-methyl carboxamide [8] **1** and carbonyl compounds. The reaction of 1 with ethyl methyl ketone as a representative case in acetic acid medium at 80°C temperature furnished a colorless solid and its IR spectrum showed broad absorption at 3400–3250 cm^{-1} due to the presence of —NH and —OH functions. The mass spectrum revealed molecular ion at *m/z* 289. The proton NMR spectrum showed signals for the presence of three methyl protons and aromatic protons. The spectral data is in favor of the structure 7,8-imidazole fused quinoline **2a** ($R=CH_3$) (Fig. 1). The reaction pathway is presumed that the initial formation of Schiff's base and its cyclization to form another intermediate cyclic imidazoline followed by the loss of ethane to afford stable five-membered imidazole **2a** (Fig. 1). The reaction has been extended to other aliphatic ketones and furnished the corresponding imidazole-fused quinolines. It was found that in case of unsymmetrical open chain monoketones the loss of bulky moiety in the form of ethane and benzene was observed, however, could not be isolated from the reaction mixture [9].

The condensation of diamine **1** with cyclic monoketones in presence of acetic acid at 80°C gave the corresponding Spiro cycloalkane imidazoline-fused quinolines **2c–f** (Table 1). Perhaps the compounds **2c–f** may be more stable at the reaction temperature, they did not get transformed in to the corresponding imidazoles. The IR and mass spectra are in agreement with the assigned structure **2**. The compounds **2a–f** are alkylated with ethyl iodide in presence of a base afforded the corresponding *N*-ethyl compounds **3a–f** in good yield (Fig. 1).

The reaction of quinoline diamine **1** with 1,3-diketones under refluxing conditions in acetic acid furnished



R = -CH_3, -C_2H_5, -CF_3, -C_6H_5, -C_6H_4Cl, -C_6H_4F, -$C_6H_4NO_2$, -$C_6H_4CH_3$

R^1 = -C_2H_5.

R^2 = -$COCF_3$, -C_6H_5, -$COCH_3$.

Figure 1. Synthesis of imidazole-fused fluoroquinolines/fluoroquinolones.

crystalline compounds characterized as imidazole-fused quinolines **2a**, **g**, **h** but not diazepine fused quinolines based on their mass spectra. The formation of the products revealed that the initial attack of the amine functionality of diamine on methyl attached carbonyl carbon of unsymmetrical 1,3-diketones but not on the CF_3 attached carbonyl functions. During cyclization, it is presumed that by the loss of acetone, trifluoroacetone, or acetophenone moieties resulted more stable alkyl/aryl imidazole-fused quinoline compounds (Table 1). This observation is in agreement with our earlier publication [10]. The compounds **2g**, **h** are alkylated with ethyl iodide to furnish ethyl derivatives **3g**, **h** (Fig. 1).

The reaction of diamine **1** with aromatic carboxylic acids in presence of PPA at 100–110°C gave exclusively 2-aryl substituted imidazole-fused quinolines **2h–l** (Table 1) but not 1,8-fused quinolones even in traces (Fig. 1). They are comparable in all respects with the compounds obtained from diamine **1** and aromatic aldehydes [8] reported in our earlier publication.

CONCLUSIONS

Reaction of quinoline diamine with different ketones/carboxylic acids furnished imidazole-fused fluoroquinolines and further on ethylation afforded fluoroquinolones and evaluated antibacterial activity.

Antibacterial activity. The fluorinated imidazole-fused quinolones tested for their antibacterial activity against *Bacillus subtilis*, *Bacillus sphaerius*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsielle aerogenes*, and *Chromobacterium violaceum* species. None of the compounds showed promising activity compared with the standard drug ciprofloxacin. The minimum inhibitory concentration (MIC) was determined by broth dilution method.

Table 1

Synthesis of imidazole-fused fluoroquinolines/fluoroquinolones.

Ketone/acid	Product	
	Compound no.	R
Acetone	**2a,3a**	CH_3
Methylethylketone	**2a**	CH_3
Methylisobutylketone	**2a**	CH_3
Acetophenone	**2a**	CH_3
3-Pentanone	**2b,3b**	C_2H_5
Cyclopentanone	**2c,3c**	*n*1
Cyclohexanone	**2d,3d**	*n*2
Cycloheptanone	**2e,3e**	*n*3
Cyclooctanone	**2f,3f**	*n*4
2,4-Pentanedione	**2a**	CH_3
1,1,1-Trifluoro-2,4-pentanedione	**2a**	CH_3
1-Phenyl-1,3-butanedione	**2a**	CH_3
1,1,1,5,5,5-Hexafluoro-2, 4-pentanedione	**2g,3g**	CF_3
1,1,1-Trifluoro-4-phenyl-2, 4-butanedione	**2h**	Ph
Benzoicacid	**2h**	Ph
4-Chlorobenzoicacid	**2i**	C_6H_4Cl
4-Fluorobenzoicacid	**2j**	C_6H_4F
4-Nitrobenzoicacid	**2k**	$C_6H_4NO_2$
4-Methylbenzoicacid	**2l**	$C_6H_4CH_3$

R = alkyl group in the product; *n* = no. of carbons in cyclic ring. For cyclopentanone [*n*1 = 4], cyclohexanone [*n*2 = 5], cycloheptanone [*n*3 = 6], and cyclooctanone [*n*4 = 7].

EXPERIMENTAL

General. Melting points were determined in open glass capillaries on a Fisher Johnes melting point apparatus and are uncorrected. IR spectra were recorded on FTIR Schimadzu Perkin-Elmer 1310 infrared spectrophotometer. ^{1}H-NMR (200MHz) spectra were recorded on varian Gemini spectrometer in $CDCl_3$/DMSO-d_6 solvent using TMS as internal standard. Mass spectra were recorded on a VG-micro mass 7070H instrument at 70 eV. Elemental analyses were carried out an EI Elemental vario EL (Germany) apparatus.

General procedure for the preparation of imidazo [4,5-*h*] quinolines (2a–h). A mixture of quinoline diamine (10 mmol) and acyclic monoketones/cyclic ketones/1,3-diketones (10 mmol) was dissolved in acetic acid (10 mL) and refluxed (for ethyl methyl ketone the reaction temperature was 80°C) for 3.5 h. The reaction mixture was cooled and poured on to crushed ice. The resulted solid was filtered, washed with water, and dried. The solid was purified through column on silica gel using chloroform and methanol as eluent gave the title compounds.

4-Fluoro-6-hydroxy-N, 2,3-trimethyl-3H-imidazo [4,5-h] quinoline-7-carboxamide (2a). Yield 70%; mp > 300°C; IR (KBr): 3175 (NH), 1654 (CO) cm^{-1}; ^{1}H-NMR (200 MHz, dimethylsulfoxide-d_6): δ 2.8 (3H, s, CH_3), 3.0 (3H, d, CH_3), 4.0 (3H, s, CH_3), 8.0 (1H, d, ArH), 8.7 (1H, s, ArH), 10.0 (1H, br, NH), 13.0 (1H, br, OH); Mass (FAB): 289 (M + 1, 42%), 258 (M-$NHCH_3$, 100%), 230 (M-$CONHCH_3$, 60%); Anal. Calcd. for $C_{14}H_{13}FN_4O_2$: C, 58.32; H, 4.55; N, 19.44. Found: C, 58.44; H, 4.40; N, 19.42.

2-Ethyl-4-fluoro-6-hydroxy-N, 3-dimethyl-3H-imidazo [4,5-h] quinolinecarboxamide (2b). Yield 71%; mp: > 300°C; IR (KBr): 3169 (NH), 1650 (CO) cm^{-1}; ^{1}H-NMR (200 MHz, dimthylsulfoxide-d_6): δ 1.5 (3H, t,CH_3), 2.9 (2H, q, CH_2), 3.0 (3H, d, CH_3), 4.0 (3H, s, CH_3), 8.0 (1H, d, ArH), 8.7 (1H, s, ArH), 10.0 (1H, br, NH), 13.0 (1H, br, OH); Mass (FAB) 303 (M + 1, 42%), 272 (M-$NHCH_3$, 100%), 244 (M-$CONHCH_3$, 62%); Anal. Calcd. for $C_{15}H_{15}FN_4O_2$: C, 59.59; H, 5.0; N, 18.53. Found: C, 59.54; H, 5.20; N, 18.62.

3-Methyl-4-fluoro-6-hydroxy-1H-spiro [imidazoline [4,5-h] quinoline-2, 1′-cyclopentane]-7-N-methyl carboxamide (2c). Yield 71%; mp: > 300°C; IR (KBr): 3190 (NH), 1655 (CO), 1610 (SPIRO C) cm^{-1}; Mass (FAB): 331 (M + 1, 45%), 300 (M-$NHCH_3$, 100%), 272 (M-$CONHCH_3$, 62%); Anal. Calcd. for $C_{17}H_{19}FN_4O_2$: C, 61.80; H, 5.75; N, 16.95. Found: C, 61.70; H, 5.72; N, 16.82.

3-Methyl-4-fluoro-6-hydroxy-1H-spiro [imidazoline (4,5-h) quinoline-2, 1′-cyclohexane]-7-N-methyl carboxamide (2d). Yield 69%; mp: > 300°C; IR (KBr): 3190 (NH), 1650 (CO), 1610 (SPIRO C) cm^{-1}; Mass (FAB): 345 (M + 1, 45%), 314 (M-$NHCH_3$, 100%), 286 (M-$CONHCCH_3$, 62%); Anal. Calcd. for $C_{18}H_{21}FN_4O_2$: C, 62.77; H, 6.14; N, 16.26. Found: C, 62.70; H, 6.12; N, 16.12.

3-Methyl-4-fluoro-6-hydroxy-1H-spiro [imidazoline (4,5-h) quinoline-2, 1′-cycloheptane]-7-N-methyl carboxamide (2e). Yield 65%; mp: > 300°C; IR (KBr): 3195 (NH), 1644 (CO), 1600 (SPIRO C) cm^{-1}; Mass (FAB): 359 (M + 1, 42%), 328 (M-$NHCH_3$, 100%), 300 (M-$CONHCH_3$, 59%); Anal. Calcd. for $C_{19}H_{23}FN_4O_2$: C, 63.67; H, 6.46; N, 15.63. Found: C, 63.70; H, 6.42; N, 15.72.

3-Methyl-4-fluoro-6-hydroxy-1H-spiro [imidazoline [4,5-h] quinoline-2, 1′-cyclooctane]-7-N-methyl carboxamide (2f). Yield 70%; mp: > 300°C; IR (KBr): 3190 (NH), 1660 (CO) cm^{-1}; Mass (FAB): 373 (M + 1, 42%), 342 (M-$NHCH_3$, 100%), 314 (M-$CONHCH_3$, 62%); Anal. Calcd. for $C_{20}H_{25}FN_4O_2$: C, 64.49; H, 6.76; N, 15.04. Found: C, 64.40; H, 6.72; N, 15.0.

4-Fluoro-6-hydroxy-N,3-dimethyl-2-(trifluoromethyl)-3H-imidazo [4,5-h] quinoline-7-carboxamide (2g). Yield 74%; mp > 300°C; IR (KBr): 3197 (NH), 1663 (CO) cm^{-1}; ^{1}H-NMR (dimethylsulfoxide-d_6): δ 3.0 (3H, d, CH_3), 4.2 (3H, s, CH_3), 8.0 (1H, d, ArH), 8.9 (1H, s, ArH), 10.0 (1H, br, NH), 13.0 (1H, br, OH); Mass (FAB): 343 (M + 1, 48%), 312 (M-$NHCH_3$, 100%), 284 (M-$CONHCH_3$, 60%); Anal. Calcd. for $C_{14}H_{10}F_4N_4O_2$: C, 49.13; H, 2.94; N, 16.37. Found: C, 49.14; H, 2.95; N, 16.42.

4-Fluoro-6-hydroxy-N, 3-dimethyl-2-phenyl-3H-imidazo [4,5-h] quinoline-7-carboxamide (2h). Yield 70.4%; mp > 300°C; IR (KBr): 3350–3250 (NH), 1680 (CO) cm^{-1}; ^{1}H-NMR (dimethylsulfoxide-d_6): δ 3.0 (3H, d, CH_3), 4.1 (3H, s, CH_3), 7.4 (3H, m, Ph), 7.7 (2H, d, Ph), 7.9 (1H, d, ArH), 8.8 (1H, s, ArH), 10.0 (1H, br, NH), 13.0 (1H, br, OH); Mass (FAB): 351 (M + 1, 40%), 320 (M-$NHCH_3$, 100%), 292 (M-$CONHCH_3$, 62%); Anal. Calcd. for $C_{19}H_{15}FN_4O_2$: C, 65.13; H, 4.32; N, 15.99. Found: C, 65.20; H, 4.30; N, 15.94.

General method for the ethylation of imidzo [4,5-*h*] 2-alkyl substituted quinolines (3a–g). A mixture of imidazole-fused quinolines (1 mmol), potassium carbonate (3 mmol), ethyl iodide (5 mmol), and DMF (5 mL) was heated at 80–90°C with constant stirring for 15 h. The solvent was removed under vacuum and the residue was extracted with $CHCl_3$. The organic solvent was washed with water, dried over sodium sulfate, and

distilled. The final residue was purified by passing through a column of silica gel to give the corresponding ethylated products, respectively.

9-Ethyl-4-fluoro-N, 2,3-trimethyl-6-oxo-6, 9-dihydro-3H-imidazo [4,5-h] quinoline-7-carboxamide (3a). Yield 70%; mp: > 300°C; IR (KBr): 3185 (NH), 1644 (CO), 1608 (amide CO) cm^{-1}; ^{1}H-NMR (dueterated chloroform): δ 1.5 (3H, t, CH_3), 2.9 (3H, s, CH_3), 3.0 (3H, d, CH_3), 4.0 (3H, s, CH_3), 4.8 (2H, q, CH_2), 8.0 (1H, d, ArH), 8.7 (1H, s, ArH), 10.0 (1H, br, NH); Mass (FAB): 317 (M + 1, 45%), 286 (M-$NHCH_3$, 100%), 258 (M-$CONHCH_3$, 58%); Anal. Calcd. for $C_{16}H_{17}FN_4O_2$.: C, 60.75; H, 5.42; N, 17.71. Found: C, 60.70; H, 5.20; N, 17.62.

2,9-Diethyl-4-fluoro-N,3-dimethyl-6-oxo-6,9-dihydro-3H-imidazo[4,5-h]quinoline-7-carboxamide (3b). Yield 81%; mp: > 281°C; IR (KBr): 3193 (NH), 1650 (CO), 1596 (amide CO) cm^{-1}; ^{1}H-NMR (dueterated chloroform): δ 1.5 (6H, m, $2CH_3$), 2.9 (2H, t, CH_2), 3.0 (3H, d, CH_3), 4.0 (3H, s, CH_3), 5.0 (2H, q, CH_2), 8.0 (1H, d, ArH), 8.7 (1H, s, ArH), 10.0 (1H, br, NH); Mass (FAB): 331 (M + 1, 44%), 300 (M-$NHCH_3$, 100%), 272 (M-$CONHCH_3$, 62%); Anal. Calcd. for $C_{17}H_{19}FN_4O_2$: C, 61.81; H, 5.80; N, 16.96. Found: C, 61.70; H, 5.72; N, 16.82.

3-Methyl-4-fluoro-6-oxo-6, 9-dihydro-9-ethyl-1H-spiro [imidazoline (4,5-h) quinoline-2, 1′-cyclopentane]-7-N-methyl carboxamide (3c). Yield 70%; mp > 300°C; IR (KBr): 3269 (NH), 1709 (CO), 1630 (amide CO) cm^{-1}; ^{1}H-NMR (dueteratedcholoroform): δ 1.5 (6H, m, $2CH_3$), 1.9–2.4 (8H, m, CH_2), 3.0 (3H, d, CH_3), 4.1 (3H, s, CH_3), 5.1 (2H, q, CH_2), 5.7 (1H, s, NH), 8.1 (1H, d, ArH), 8.7 (1H, s, ArH), 10.0 (1H, br, NH); Mass (FAB): 359 (M + 1, 41%), 328 (M-$NHCH_3$, 100%), 300 (M-$CONHCH_3$, 62%); Anal. Calcd. for $C_{19}H_{23}FN_4O_2$: C, 63.67; H, 6.47; N, 15.63. Found: C, 63.60; H, 6.44; N, 15.62.

3-Methyl-4-fluoro-6-oxo-6, 9-dihydro-9-ethyl-1H-spiro [imidazoline (4,5-h) quinoline-2, 1′-cyclohexane]-7-N-methyl carboxamide (3d). Yield 80%; mp: > 300°C; IR (KBr): 3283 (NH), 1659 (CO), 1620 (amide CO) cm^{-1}; ^{1}H-NMR (dueterated chloroform): δ 1.5 (6H, m, CH_3), 2.8–2.2 (10H, m, CH_2), 3.0 (3H, d, CH_3), 4.0 (3H, s, CH_3), 5.0 (2H, q, CH_2), 5.7 (1H, s, NH), 8.0 (1H, d, ArH), 8.7 (1H, s, ArH), 10.1 (1H, br, NH); Mass (FAB): 373 (M + 1, 40%), 342 (M-$NHCH_3$, 100%), 314 (M-$CONHCH_3$, 60%); Anal. Calcd. for $C_{20}H_{25}FN_4O_2$: C, 64.49; H, 6.76; N, 15.04, Found: C, 64.44; H, 6.73; N, 15.10.

3-Methyl-4-fluoro-6-oxo-6, 9-dihydro-9-ethyl-1H-spiro [imidazoline (4,5-h) quinoline-2, 1′-cycloheptane]-7-N-methyl carboxamide (3e). Yield 75%; mp: > 300°C; IR (KBr): 3263 (NH), 1660 (CO), 1620 (amide CO) cm^{-1}; ^{1}H-NMR (dueterated chloroform): δ 1.5 (6H, m, CH_3), 2.8 (4H, m, CH_2), 2.2–1.9 (8H, m, CH_2), 3.0 (1H, d, CH_3), 4.1 (3H, s, CH_3), 5.0 (2H, q, CH_2), 5.6 (1H, s, NH), 8.0 (1H, d, ArH), 8.6 (1H, s, ArH), 10.0 (1H, br, NH); Mass (FAB): 387 (M + 1, 42%), 356 (M-$NHCH_3$, 100%), 328 (M-$CONHCH_3$, 62%); Anal. Calcd. for $C_{21}H_{27}FN_4O_2$: C, 65.26; H, 7.04; N, 14.49. Found: C, 65.20; H, 7.12; N, 14.62.

3-Methyl-4-fluoro-6-oxo-6, 9-dihydro-9-ethyl-1H-spiro [imidazoline (4,5-h) quinoline-2, 1′-cyclooctane]-7-N-methyl carboxamide (3f). Yield 70%; mp: > 300°C; IR (KBr): 3193 (NH), 1659 (CO), 1620 (amide CO) cm^{-1}; ^{1}H-NMR (dueterated chloroform): δ 1.3–1.5 (6H, m, CH_3), 2.8 (4H, m, CH_2), 2.2–1.8 (10H, m, CH_2), 3.0 (3H, d, CH_3) 3.8 (3H, s, CH_3), 5.1 (2H, q, CH_2), 5.7 (1H, s, NH), 8.0 (1H, d, ArH), 8.7 (1H, s, ArH), 10.0 (1H, br, NH); Mass (FAB): 401 (M + 1, 46%), 370 (M-$NHCH_3$, 100%), 342 (M-$CONHCH_3$, 64%); Anal. Calcd. for $C_{22}H_{29}FN_4O_2$: C, 65.97; H, 7.29; N, 13.98. Found: C, 65.90; H, 7.24; N, 13.92.

9-Diethyl-4-fluoro-N, 3-dimethyl-6-oxo-2-(trifluoromethyl)-6, 9-dihydro-3H-imidazo [4,5-h] quinoline-7-carboxamide (3g). Yield 81%; mp: 275°C; IR (KBr): 3240 (NH), 1656 (CO), 1612 (amide CO) cm^{-1}; ^{1}H-NMR (dueterated chloroform): δ 1.6 (3H, t, CH_3), 3.1 (3H, d, CH_3), 4.3 (3H, s, CH_3), 5.1 (2H, q, CH_2), 8.2 (1H, d, ArH), 8.7 (1H, s, ArH), 9.9 (1H, br, NH); Mass (FAB) 371 (M + 1, 48%), 340 (M-$NHCH_3$, 100%), 312 (M-$CONHCH_3$, 60%); Anal. Calcd. for $C_{16}H_{14}F_4N_4O_2$: C, 51.89; H, 3.81; N, 15.13. Found: C, 51.80; H, 3.72; N, 15.12.

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