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Original article

Design, synthesis, structure–activity relationship and antibacterial activity series of novel imidazo fused quinolone carboxamides

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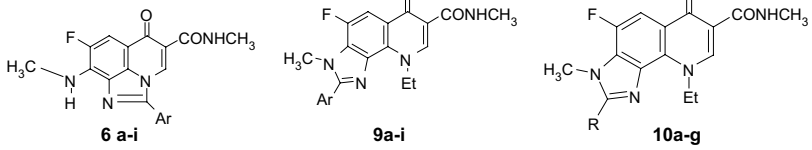
ABSTRACT

A series of novel 7,8 and 1,8 imidazo fused quinolone carboxamides are synthesized and evaluated against antibacterial activity. 1,8 Imidazo fused quinolones exhibit moderate antibacterial activity. Molecular modeling studies were carried out to optimize the pharmacophore.

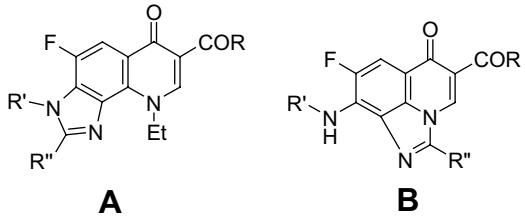


1. Introduction

Synthetic fluoroquinolones are widely accepted, useful and indispensable antibacterial agents. The structure–activity relationship of antibacterial quinolones has been extensively investigated, the optimum functionalities are found to be carboxyl group at C-3, carbonyl functionality at C-4, fluorine at C-6, a secondary amino group at C-7 position and an alkyl or aryl groups on N-1 position [1]. These include norfloxacin [2], perfloxacin [3], ofloxacin [4], ciprofloxacin [5] and enoxacin [6], etc. Though the fluoroquinolones captured the market as antibacterials, some of them are showing resistance to certain bacterial infections [7]. To overcome this problem, hetero-fused tricyclic quinolones are synthesized as a new class of compounds for their bio-evaluation and some of them are found to be as potent as ciprofloxacin. Among tricyclic compounds, imidazo [8–10], thiazolo [11], pyrazolo [12] pyrazino [13,14] and triazolo [10] fused non-fluorinated quinolones at 5,6 or 6,7 positions were reported by several research groups. Thiazolo fused quinolone at 2,3 positions has shown 10 times more activity than ciprofloxacin in vitro [15]. Seman et al. and Chang et al. [16] has reported the synthesis of imidazo [4,5,1-*ij*] quinolones as antiallergic agents. We have synthesized 1,8 and 7,8 hetero ring fused tricyclic quinolones retaining the well accepted functionalities in the system at appropriate positions.

2. Chemistry

We aimed to synthesize novel 7,8 and 1,8 hetero ring fused tricyclic fluoroquinolones of general structural formula A, B.



Retrosynthetic analysis of **A** and **B** shows the requirement of an important synthon 7,8-diamino-4-hydroxy quinoline. The latter is prepared from the condensation of 3-chloro-4-fluoroaniline **1** with

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EMME and followed by its cyclisation under thermal conditions produces 7-chloro-6-fluoro-4-hydroxy quinoline-3-carboxylic acid ethyl ester **2**. Nitration of the intermediate **2** with H_2SO_4/HNO_3 mixture to afford 7-chloro-6-fluoro-4-hydroxy-8-nitro-quinoline-3-carboxylic acid ethyl ester **3** as an exclusive product [17]. The nitrocompound **3** is subjected to ethylation using ethyl iodide in DMF in the presence of K_2CO_3 on heating at 80–90 °C for 15 h and found that the reaction was not proceed and recovered the starting material which is not been clearly understood. As an alternate strategy instead of alkylation, amination was attempted to get the amine/amide compound. Thus the compound **3** is reacted with excess of methyl amine solution at room temperature, undergone nucleophlic substitution at C-7 and carboxylic ester was transformed to *N*-carboxamide in a single step to give 6-fluoro-7-methylamino-8-nitro-4-hydroxy quinoline-3-*N*-methyl carboxamide **4** and reporting here for the first time. Reduction of C-8 nitro group of compound **4** using Pd and H_2 gave the desired 8-amino-6-fluoro-4-hydroxy-7-methylamino-quinoline-3-carboxylic acid methylamide **5** as the intermediate diamine (Scheme 1).

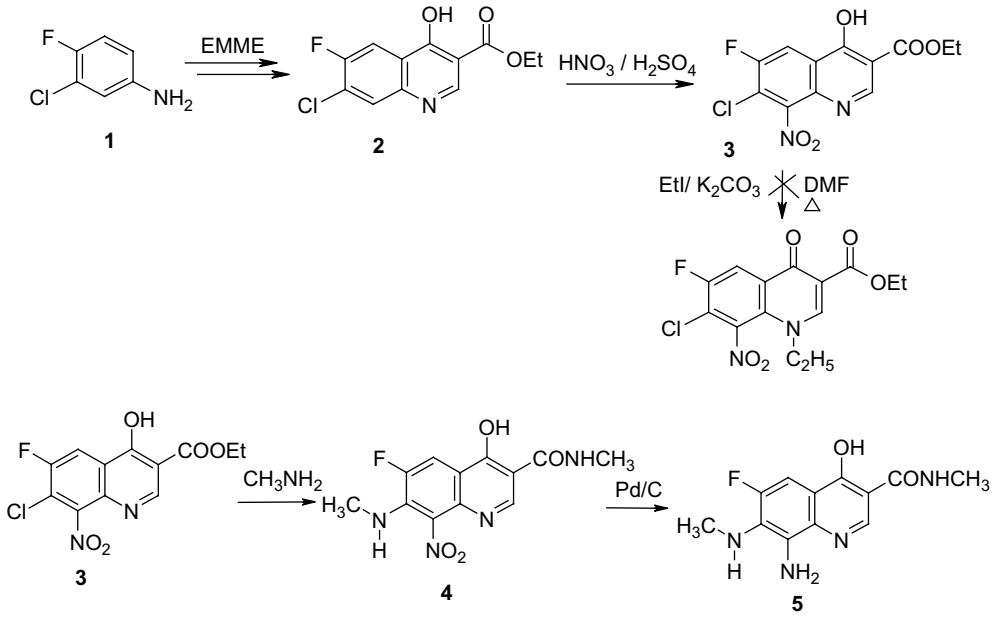
The 8-amino-6-fluoro-4-hydroxy-7-methylamino-quinoline-3-carboxylic acid methylamide **5** is further used as a synthon in preparing tricyclic quinolone derivatives. Quinoline diamine **5** is reacted with 4-fluorobenzaldehyde in equimolar proportions under acidic conditions to result a mixture of two compounds **6d**, **7d** in 1:6 ratio, respectively. The reaction is expected to go through the initial formation of Schiff's base and in situ cyclisation to give the tricyclic quinolone/quinoline. It may be more likely and well accepted observation that the ring fusion to a single ring is more facile than fusion with two rings, as a result 7,8 fused product was major in the product formation. This reaction has been extended to other aromatic aldehydes and obtained 1,8 fused quinolones **6a**–**i** and 7,8 fused quinolines **7a**–**i** in each case. This study confirms not only the versatility of the reaction but also opens for the condensation of various carbonyl compounds with active synthon (Scheme 2).

Further it has been observed that the aldehydes containing electron withdrawing group resulted 1,8 fused compound (**6h**) slightly higher yield than electron releasing substituents in aromatic aldehydes.

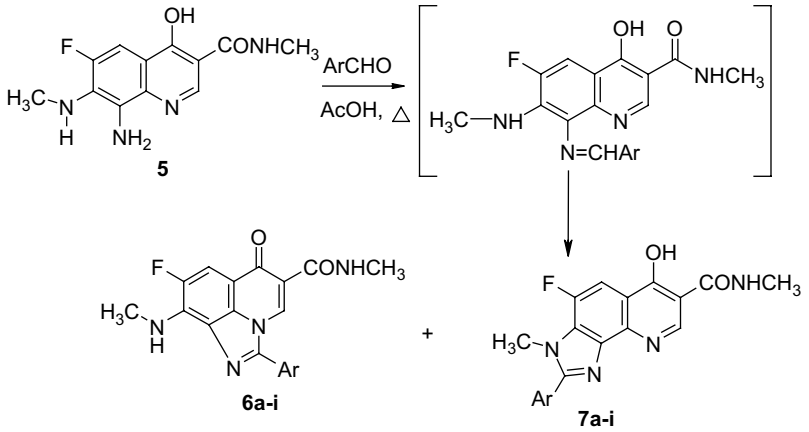
This reaction has been extended to quinoline diamine **5** with various aliphatic aldehydes in equimolar proportions under acidic conditions resulted exclusively a single compound. The formation of 1,8 fused product is not observed. The possible reason for the exclusive formation of 7,8 fused product could be the aromatic aldehydes are prone to more nucleophilic attack than aliphatic aldehydes. The 7,8 imidazo fused compounds 7,8 are further alkylated with ethyl iodide under basic conditions resulted 2-aryl-9-ethyl-4-fluoro-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide **9a**–**i** and 2-alkyl-9-ethyl-4-fluoro-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide **10a**–**g**, respectively (Scheme 3).

3. In vitro antibacterial activity

A number of imidazo fused tricyclic quinolones are prepared retaining the well accepted functionalities for their activity study and tested in vitro against representatives of Gram positive and Gram negative bacteria. The minimum inhibitory concentrations (MIC) are presented in Tables 1–3. In general 2-arylimidazo[4,5-l-*ij*]-6-oxo-8-fluoro-9-*N*-methylamino-3,6-dihydro quinolone-5-*N*-methyl carboxamide **6a**–**i** are fairly active than 2-aryl-3-methyl-imidazo[4,5-*h*]-4-fluoro-6-oxo-6,9-dihydro-9-ethylquinoline-7-*N*-methyl carboxamide **9a**–**i** and 2-alkyl-3-methylimidazo[4,5-*h*]-4-fluoro-6-oxo-6,9-dihydro-9-ethyl quinoline-7-methyl carboxamide **10a**–**g**. Among all the imidazo fused quinolones the compound containing furyl group as in **6a** showed moderate activity against Gram positive organisms (*Bacillus subtilis* and *Staphylococcus aureus*). When the aryl group is phenyl **6b** it was fairly active against *S. aureus* and the presence of electron releasing groups in the phenyl ring such as **6e**, **6f**, **6g** were also showed moderate activity against *Pseudomonas aeruginosa*, respectively. However, all the compounds **6a**–**i** and **9a**–**i** are inactive against *P. aeruginosa*. The compounds **9a**–**i** are inactive against *Klebsiella aerogenes*, **9b**, **9c**, **9e**, and **9g**–**i** are inactive against *Chromobacterium violaceum* and **9e**–**h** are inactive against *B. subtilis* and *Bacillus sphaericus*. The compound **10a** is inactive against all Gram positive and Gram negative microorganisms and **10d**, **10e** and **10g** are inactive against Gram positive microorganisms. The activity of the synthesis



Scheme 1.



Ar: **a** = furyl; **b**=Ph; **c** = 4-Cl-Ph; **d** = 4-F-Ph; **e** = 4-Me -Ph; **f** = 4-OMe -Ph; **g** = 4-N,N-dimethyl-Ph; **h** = 4-NO2 -Ph; **i** = 4-OH-Ph.

Scheme 2.

compounds was compared with standard drug ciprofloxacin under similar experimental conditions. The results are tabulated in Tables 1–3.

3.1. Molecular modeling studies

A series of quinolone derivatives tested for antibacterial activity were selected for the present study and the program of Windows ChemSW [18] was adopted for molecular modeling studies. The molecules were generated and energy minimization was carried out by using Molecular Modeling Pro. Numerous physicochemical properties and structural parameters have been devised earlier for QSAR studies [19–25]. Appropriate descriptors or parameters for the compounds, *Q*log *P* and MR were correlated to the observed antibacterial activity. The regression models are the QSAR molecular models that were used to predict and design a compound with best possible antibacterial property. The lipophilicity factor *P* is the most used property where *P* is defined by 1-octanol/water partition coefficient.

All the *Q*log *P* values used were calculated as per Bodor and Buchwald method in ChemSW. Steric Factor (MR): MR is the molar refractivity, the measure of steric factor, bulkiness of the molecule. It is molar volume corrected by the refractive index.

$$\mathrm{MR} = \left(n^2 - 1\right)\Big/\left(n^2 + 2\right) \times \mathrm{MW}/d$$

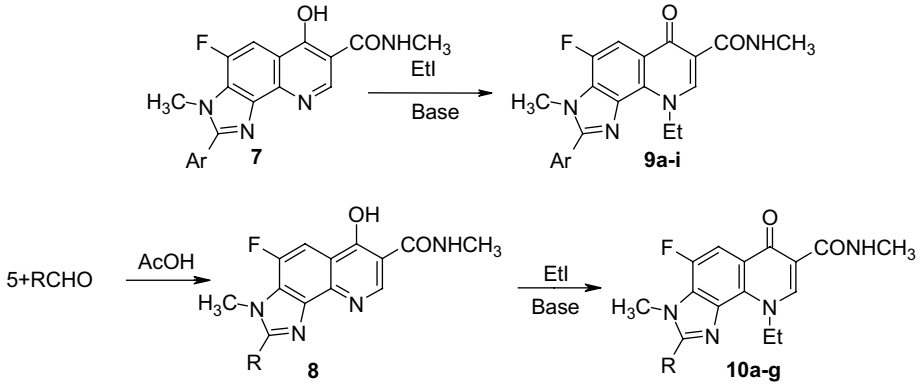
where MW/d is the volume, $(n^2-1)/(n^2+2)$ is the probability correction factor.

Relationship between antibacterial activity, expressed as log(1/IC_{50}) (from IC_{50} values) and the physicochemical parameters X_i (*Q*log *P* and MR) was analyzed statistically by fitting the data to correlation equations consisting of various combinations of these parameters.

$$\log(1/\mathrm{IC}_{50}) = \sum a_i X_i + \text{constant}.$$

The statistical optimization is used to propose the best correlation model. The constant and the correlation coefficient, a_i for each term were determined by the least squares method.

The antibacterial activities of quinolone derivatives against *S. aureus* (Table 1) were quantitatively analyzed in terms of physicochemical parameters by regression analysis. In the present study the quantitative structure–activity relationship (*QSAR*) technique was applied to arrive at a best possible pharmacophore. A model equation to correlate antibacterial activity with the physicochemical properties was generated and the structural features of a projected lead compound are discussed.



R: **a** = ethyl; **b** = propyl; **c** = isopropyl; **d** = n-butyl; **e** = isobutyl; **f** = pentyl; **g** = hexyl

Scheme 3.

Table 1
Antibacterial assay: minimum inhibitory concentration of compounds **6a–i**

Compounds	Microorganisms					
	Gram positive			Gram negative		
	Bacillus subtilis	*Bacillus sphaericus*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella aerogenes*	*Chromobacterium violaceum*
6a (R = furyl)	6.25	25	6.25	12.5	–	6.25
6b (R = phenyl)	12.5	25	6.25	12.5	–	12.5
6c (R = 4'-chlorophenyl)	25	25	25	25	–	6.25
6d (R = 4'-fluorophenyl)	25	25	25	25	–	6.25
6e (R = 4'-methoxy phenyl)	25	12.5	12.5	6.25	–	6.25
6f (R = 4'-methyl phenyl)	12.5	12.5	25	6.25	–	25
6g (R = 4'-hydroxy phenyl)	25	25	12.5	6.25	25	12.5
6h (R = 4'-nitro phenyl)	12.5	12.5	12.5	–	–	25
6i (R = 4'-$N(CH_3)_2$ phenyl)	12.5	25	25	–	–	25
Ciprofloxacin	0.78	0.78	0.39	0.78	0.78	0.39

Negative control (DMSO) – no activity.
Values are indicated in μg/ml.

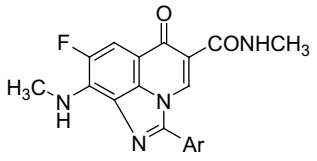
Table 2
Antibacterial assay: minimum inhibitory concentration of compounds **9a–i**

Compounds	Microorganisms					
	Gram positive			Gram negative		
	Bacillus subtilis	*Bacillus sphaericus*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella aerogenes*	*Chromobacterium violaceum*
9a (R = furyl)	25	25	12.5		–	25
9b (R = phenyl)	25	25	25	–	–	–
9c (R = 4'-chlorophenyl)	25	25	25	–	–	–
9d (R = 4'-fluorophenyl)	25	–	25	–	–	25
9e (R = 4'-methoxy phenyl)	–	–	–	–	–	–
9f (R = 4'-methyl phenyl)	–	–	–	–	–	25
9g (R = 4'-hydroxy phenyl)	–	–	25	–	–	–
9h (R = 4'-nitro phenyl)	–	–	25	–	–	–
9i (R = 4'-$N(CH_3)_2$ phenyl)	12.5	25	25	–		–
Ciprofloxacin	0.78	0.78	0.39	0.78	0.78	0.39

Negative control (DMSO) – no activity.
Values are indicated in μg/ml.

4. Results and discussion

The basic quinolone pharmacophore used in the present study is depicted below. Their structural details, activity data log ($1/IC_{50}$) and physicochemical parameter (*Q*log *P*, MR) are shown in Table 4.



6a-i

Table 5 presents a correlation matrix between the parameters *Q*log *P* and MR. The matrix shows a good correlation between *Q*log *P* and MR. The term close to unity indicates high colinearity while the value less than 0.5 indicates that non-colinearity exists between two parameters. The perusal of correlation matrix indicates either *Q*log *P* or MR is the indicative parameter. The regression technique was applied through the origin using these two explainable parameters. Monoparametric and biparametric QSAR equations were generated with *Q*log *P* and MR. The results of regression analysis were presented in Table 6. Eq. (1) (Table 6) shows that the correlation between activity and *Q*log *P* is moderate and percent explainable is 81.2%. The equation is found to be statistically fit. Eq. (2) represents the correlation

Table 3
Antibacterial assay: minimum inhibitory concentration of compounds **10a–g**

Compounds	Microorganisms					
	Gram positive			Gram negative		
	Bacillus subtilis	*Bacillus sphaericus*	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	*Klebsiella aerogenes*	*Chromobacterium violaceum*
10a (R = ethyl)	–	–	–	–	–	–
10b (R = propyl)	12.5	50	25	25	12.5	25
10c (R = isopropyl)	12.5	25	50	50	50	12.5
10d(R = butyl)	–	–	–	12.5	25	25
10e(R = isobutyl)	–	–	–	25	12.5	25
10f (R = pentyl)	25	50	25	25	12.5	25
10g (R = hexyl)	–	–	–	50	50	25
Ciprofloxacin	0.78	0.78	0.39	0.78	0.78	0.39

Negative control (DMSO) – no activity.
Values are indicated in μg/ml.

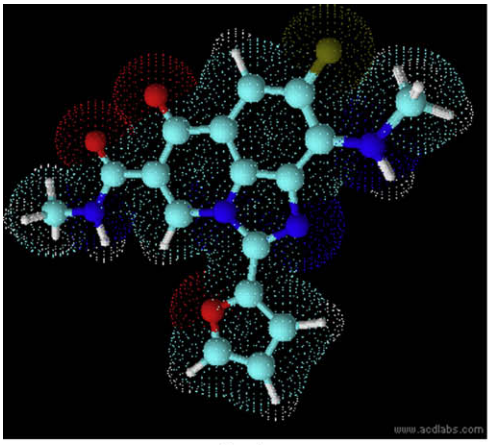
Table 4
Antibacterial activity and physicochemical parameters of quinolone derivatives

Compounds No.	Activity	Qlog *P*	MR
6a	1.2041	2.4427	96.0213
6b	0.6021	2.8852	100.826
6c	0.6021	2.6035	96.2377
6d	0.6021	2.9378	101.0625
6e	0.9031	2.4657	102.4845
6f	0.6021	2.3382	110.4499
6g	0.9031	2.4264	103.346
6h	0.9031	1.9621	97.7154
6i	0.6021	1.1434	88.262

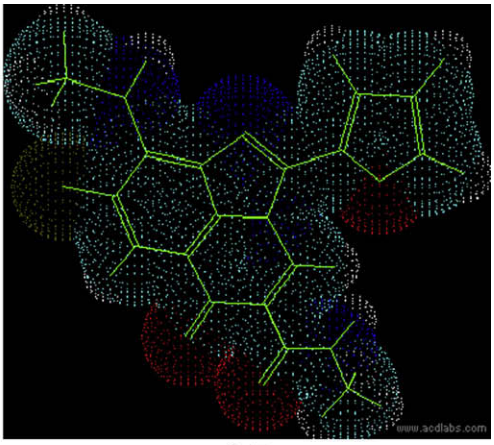
Table 5
Correlation matrix

	Activity	Qlog *P*	MR
Activity Pearson correlation	1.000	−0.685	−0.615
Sig (2-tailed)	–	0.042	0.078
Qlog *P* Pearson correlation	–	1.000	0.576
Sig (2-tailed)		–	0.104
MR Pearson correlation	–	–	1.000
Sig (2-tailed)			–

between activity and MR and its percent explainable in 90.4%. It is also found to be statistically fit. Eq. (3) is the biparametric analysis. It is statistically unfit because the probability factor of Qlog *P* is more than 50% of its coefficient. Both Eqs. (4) and (5) are found to be statistically valid. Eq. (5) is the most accepted equation. The predictive ability of the modeled equations was cross validated [19–25]. The quadratic form of this equation indicates the optimal value of MR decides the highest activity. In order to get optimal value, the activity was differentiated that respect to MR and equated to zero. The optimal value of MR is computed as 62.878 for its highest activity. Though molecules having this range of MR are not available in the data set, but **6a** is the furyl unsubstituted analogue found to be the highest activity and their MR values close to maximal value (62.878). Therefore, the size of the substitutent at position-2 is important in deciding the activity. As the size of the substituent increases, the activity decreases (Table 4). The ligands with smaller size of substituent of 2-aryl substituted tricyclic quinolones may suitably pit in the receptor site of the enzyme responsible for activity. The high antibacterial activity of the ligands, which efficiently inhibit the enzyme activity, may suitably bind to the receptor site.



6a A



6a B

5. Experimental

All the reagents were obtained from commercial sources. Melting points were determined in open glass capillaries using Fisher-Johns melting point instrument and was uncorrected. IR spectra were recorded on FT-IR, Perkin–Elmer 1310 infrared spectrometer. ^{1}H NMR spectra were recorded on Varian Gemini (200 MHz) in $CDCl_3$/DMSO-d_6/TFA as solvent. Chemical shifts are expressed in ppm down field from internal tetra methyl silane. The mass spectra were measured on a VG micro mass 7070-H mass spectrometer. Elemental analysis was carried on vario EL, Elemental instrument.

5.1. 6-Fluoro-4-hydroxy-7-methylamino-8-nitro-quinoline-3-carboxylic acid methylamide (**4**)

5.1.1. General procedure

Methyl amine (140 ml, 40%) was slowly added to 7-chloro-6-fluoro-4-hydroxy-8-nitroquinoline-3-carboxylic acid ethyl ester **3** (10 g, 31 mmol) and kept stirring for 24 h at 30 °C. The reaction mixture was neutralized with acetic acid while cooling and the separated solid was filtered, washed repeatedly with water till it is neutral to pH and dried to give the desired compound (8.7 g).

Mp: >300 °C, Yield: 92% IR (KBr) ν: 3490, 3272, 1669, 1511 cm^{-1}. ^{1}H NMR (TFA) δ: 3.12 (d, 3H, –CH_3, J = 9.1 Hz), 3.62 (d, 3H, –CH_3, J = 9.1 Hz), 8.32 (d, 1H, Ar–H, J_{H-F} = 6 Hz), 8.65 (d, 1H, –NH–), 9.25 (br s, 1H, –NH–), 9.3 (s, 1H, =CH–). Mass (EI *m*/*z*): 294 (M^+), 264, 237.

5.2. 8-Amino-6-fluoro-4-hydroxy-7-methylamino-quinoline-3-carboxylic acid methylamide (**5**)

5.2.1. General procedure

6-Fluoro-7-methyl amino-8-nitro-4-hydroxy-quinoline-3-*N*-methyl carboxamide **4** (5 g, 17 mmol) was dissolved in dimethyl formamide (250 ml) and added 10% Pd/C (300 mg) and hydrogen gas at atmospheric pressure for 20 h maintaining temperature at 30 °C. The catalyst was removed by filtration and filtrate was distilled to leave the residue. The residue was washed with water, filtered and dried to give 3.5 g of the title compound.

Mp: >300 °C, Yield: 78%. IR (KBr) ν: 3406, 3300–3210, 1648 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ: 2.94 (d, 3H, –CH_3, J = 9.3 Hz), 3.22 (d, 3H, –CH_3, J = 9 Hz); 5.74 (s, 2H, –NH_2); 7.32 (d, 1H, Ar–H, J_{H-}

Table 6
Model equations for the quinolone derivatives.

Eq. no.	Modeled eq.	R	R^2	R^2a	SEE	*F*
1	Activity = 0.325 (0.055) Qlog *P* PRESS = 1.2766, $q^2_{cv} = -1.5364$	0.901	0.812	0.789	0.399	34.583
2	Activity = 0.00828 (0.001) MR PRESS = 0.650, $q^2_{cv} = -0.291$	0.951	0.904	0.892	0.285	75.613
3	Activity = −0.355 (0.185) Qlog *P* + 0.0162 (0.004) MR PRESS = 0.4495, $q^2_{cv} = 0.106$	0.968	0.937	0.789	0.919	52.339
4	Activity = −0.377 (0.086) Qlog P^2 + 1.281 (0.219) Qlog *P* PRESS = 0.3383, $q^2_{cv} = 0.327$	0.975	0.950	0.936	0.219	66.794
5	Activity = −0.00033 (0.000) MR^2 + 0.0415 (0.013) MR PRESS = 0.3290, $q^2_{cv} = 0.346$	0.976	0.952	0.938	0.216	69.108

$_F$ = 62 Hz); 8.10 (d, 1H, –NH–); 8.32 (br s, 1H, –NH–); 8.53 (s, 1H, =CH–). Mass (EI *m*/*z*): 264 (M^+), 233.

5.3. Procedure for the preparation of imidazo [4,5-h]/imidazo [4,5,1-ij], aryl substituted quinolines (**6** and **7**)

A mixture of diamine **5** (10 mmol) and aromatic aldehyde (10 mmol) was taken in acetic acid (10 ml) and refluxed for 4 h. The reaction mixture was cooled and poured on to crushed ice. The resulted solid was filtered, washed with water and dried. The filtrate was neutralized with ammonia solution but additional solid was not obtained. The separated solid was passed through column on silica gel using chloroform to get the 1,8 fused compound and methanol as eluent to isolate the 7,8 fused compound.

5.3.1. 8-Fluoro-2-furan-2-yl-9-methylamino-6-oxo-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6a**)

Mp: 285–287 °C, Yield: 8.1%. IR (KBr) *ν*: 3197, 1672 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 3.02 (d, 3H, $-CH_3$, *J* = 9.4 Hz); 3.45 (d, 3H, $-CH_3$, *J* = 9.2 Hz); 6.78 (d, 1H, furyl, *J* = 6.5 Hz); 7.24 (m, 1H, furyl, *J* = 6.7 Hz); 7.74 (d, 1H, Ar–H, J_{H-F} = 6.2 Hz); 7.89 (d, 1H, furyl, *J* = 6.8 Hz); 8.92 (br s, 1H, –NH–); 9.48 (s, 1H, Ar–H); 9.68 (br s, 1H, –NH–). Mass (EI *m*/*z*): 340 (M^+), 281, 253. Analysis Calcd. for $C_{17}H_{13}FN_4O_3$: C, 60.01%; H, 3.85%; N, 16.46%. Found: C, 60.20%; H, 3.80%; N, 16.34%.

5.3.2. 8-Fluoro-9-methylamino-6-oxo-2-phenyl-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6b**)

Mp: 289–290 °C, Yield: 9.1%. IR (KBr) *ν*: 3212, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 3.08 (d, 3H, $-CH_3$, *J* = 9.4 Hz); 3.45 (d, 3H, $-CH_3$, *J* = 9.1 Hz); 7.67 (m, 3H, phenyl); 7.79 (d, 1H, Ar–H, J_{H-F} = 6.3 Hz); 7.93 (m, 2H, phenyl); 8.92 (m, 1H, –NH–); 9.48 (s, 1H, Ar–H); 9.65 (m, 1H, –NH–). Mass (EI *m*/*z*): 350 (M^+), 320, 293, 265. Analysis Calcd. for $C_{19}H_{15}FN_4O_2$: C, 65.13%; H, 4.31%; N, 15.99%. Found: C, 65.20%; H, 4.30%; N, 15.94%.

5.3.3. 2-(4-Chloro-phenyl)-8-fluoro-9-methylamino-6-oxo-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6c**)

Mp: >300 °C, Yield: 9.2%. IR (KBr) *ν*: 3216, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 3.05 (d, 3H, $-CH_3$, *J* = 9.3 Hz); 3.44 (d, 3H, $-CH_3$, *J* = 9.1 Hz); 7.62 (d, 2H, phenyl, *J* = 6.5 Hz); 7.74 (d, 1H, Ar–H, J_{H-F} = 6.2 Hz); 7.93 (d, 2H, phenyl, *J* = 6.4 Hz); 8.90 (br s, 1H, –NH–); 9.41 (s, 1H, Ar–H); 9.64 (br s, 1H, –NH–). Mass (EI *m*/*z*): 384 (M^+), 325, 297. Analysis Calcd. for $C_{19}H_{14}ClFN_4O_2$: C, 59.37%; H, 3.6%; N, 14.56%. Found: C, 59.20%; H, 3.50%; N, 14.64%.

5.3.4. 8-Fluoro-2-(4-fluoro-phenyl)-9-methylamino-6-oxo-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6d**)

Mp: 287–288 °C, Yield: 8.9%. IR (KBr) *ν*: 3221, 1681 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 3.04 (d, 3H, $-CH_3$, *J* = 9.3 Hz); 3.44 (d, 3H, $-CH_3$, *J* = 9.1 Hz); 7.32 (m, 2H, phenyl); 7.74 (d, 1H, Ar–H, J_{H-F} = 6.1 Hz); 7.95 (m, 2H, phenyl); 8.92 (br s, 1H, –NH–); 9.42 (s, 1H, Ar–H); 9.67 (br s, 1H, –NH–). Mass (EI *m*/*z*): 368 (M^+), 309, 281. Analysis Calcd. for $C_{19}H_{14}F_2N_4O_2$: C, 61.95%; H, 3.83%; N, 15.21%. Found: C, 61.90%; H, 3.73%; N, 15.24%.

5.3.5. 8-Fluoro-9-methylamino-6-oxo-2-p-tolyl-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6e**)

Mp: 291–292 °C, Yield: 5.1%. IR (KBr) *ν*: 3190, 1670 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 2.22 (s, 3H, $-CH_3$); 3.04 (d, 3H, $-CH_3$, *J* = 9.4 Hz); 3.41 (d, 3H, $-CH_3$, *J* = 9.2 Hz); 7.62 (d, 2H, phenyl, *J* = 6.3 Hz); 7.84 (d, 1H, Ar–H, J_{H-F} = 6.1 Hz); 7.94 (d, 2H, phenyl, *J* = 6.3 Hz); 8.93 (br s, 1H, –NH–); 9.47 (s, 1H, Ar–H); 9.63 (br s, 1H, –NH–). Mass (EI *m*/*z*): 364 (M^+), 305, 277. Analysis Calcd. for $C_{20}H_{17}FN_4O_2$: C, 65.92%; H, 4.70%; N, 15.37%. Found: C, 65.91%; H, 4.75%; N, 15.40%.

5.3.6. 8-Fluoro-2-(4-methoxy-phenyl)-9-methylamino-6-oxo-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6f**)

Mp: 295–297 °C, Yield: 7.5%. IR (KBr) *ν*: 3212, 1675 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 3.17 (d, 3H, $-CH_3$, *J* = 9.2 Hz); 3.47 (d, 3H, $-CH_3$, *J* = 9.3 Hz); 4.07 (s, 3H, $-OCH_3$); 7.2 (d, 2H, phenyl, *J* = 6.2 Hz); 7.73 (d, 1H, Ar–H, J_{H-F} = 6.5 Hz); 7.96 (d, 2H, phenyl, *J* = 6.4 Hz); 8.92 (br s, 1H, –NH–); 9.44 (s, 1H, Ar–H); 9.60 (br s, 1H, –NH–). Mass (EI *m*/*z*): 380 (M^+), 323, 295. Analysis Calcd. for $C_{20}H_{17}FN_4O_3$: C, 63.15%; H, 4.50%; N, 14.72%. Found: C, 63.20%; H, 4.45%; N, 14.84%.

5.3.7. 2-(4-Dimethylamino-phenyl)-8-fluoro-9-methylamino-6-oxo-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6g**)

Mp: >300 °C, Yield: 10%. IR (KBr) *ν*: 3202, 1680 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 3.02 (d, 3H, $-CH_3$, *J* = 9.4 Hz); 3.17 (s, 6H, $-N(CH_3)_2$); 3.42 (d, 3H, $-CH_3$, *J* = 9.2 Hz); 6.70 (d, 2H, phenyl, *J* = 6.1 Hz); 6.91 (d, 1H, Ar–H, J_{H-F} = 6.4 Hz); 7.80 (d, 2H, phenyl, *J* = 6.3 Hz); 8.81 (br s, 1H, –NH–); 9.54 (s, 1H, Ar–H); 9.72 (br s, 1H, –NH–). Mass (EI *m*/*z*): 393 (M^+), 334, 306. Analysis Calcd. for $C_{21}H_{20}FN_5O_2$: C, 64.11%; H, 5.12%; N, 17.80%. Found: C, 64.20%; H, 5.20%; N, 17.91%.

5.3.8. 8-Fluoro-9-methylamino-2-(4-nitro-phenyl)-6-oxo-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6h**)

Mp: >300 °C, Yield: 13%. IR (KBr) *ν*: 3252, 1690 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 3.1 1 (d, 3H, $-CH_3$, *J* = 9.1 Hz); 3.53 (d, 3H, $-CH_3$, *J* = 9.5 Hz); 7.83 (d, 1H, Ar–H, J_{H-F} = 6.2 Hz); 8.2 (d, 2H, phenyl, *J* = 6.2 Hz); 8.60 (d, 2H, phenyl, *J* = 6.3 Hz); 9.27 (br s, 1H, –NH–); 9.53 (s, 1H, Ar–H); 9.72 (br s, 1H, –NH–). Mass (EI *m*/*z*): 395 (M^+), 336, 308. Analysis Calcd. for $C_{19}H_{14}FN_5O_4$: C, 57.72%; H, 3.56%; N, 17.71%. Found: C, 57.65%; H, 3.40%; N, 17.84%.

5.3.9. 8-Fluoro-2-(4-hydroxy-phenyl)-9-methylamino-6-oxo-6H-imidazo[4,5,1-ij]quinoline-5-carboxylic acid methylamide (**6i**)

Mp: >300 °C, Yield: 5.6%. IR (KBr) *ν*: 3400–3252, 1681 cm^{-1}. ^1H NMR ($CDCl_3$) *δ*: 3.02 (d, 3H, $-CH_3$, *J* = 9.4 Hz); 3.42 (d, 3H, $-CH_3$, *J* = 9.5 Hz); 7.65 (d, 2H, phenyl, *J* = 6.1 Hz); 7.75 (d, 1H, Ar–H, J_{H-F} = 6.5 Hz); 7.94 (d, 2H, phenyl, *J* = 6.7 Hz); 8.95 (br s, 1H, –NH–);

9.43 (s, 1H, Ar–H); 9.61 (b, 1H, –NH–); 10.12 (br s, 1H, –OH). Mass (EI *m*/*z*): 366 (M^+), 307, 279. Analysis Calcd. for $C_{19}H_{15}FN_4O_3$: C, 62.29%; H, 4.12%; N, 15.29%. Found: C, 62.20%; H, 4.20%; N, 15.40%.

*5.3.10. 4-Fluoro-2-furan-2-yl-6-hydroxy-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7a**)*

Mp: >300 °C, Yield: 60%. IR (KBr) *ν*: 3350–3250, 1660 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 3.04 (d, 3H, $–CH_3$, $J = 9.5$ Hz); 4.16 (s, 3H, $–CH_3$); 6.71 (d, 1H, furyl, $J = 6.4$ Hz); 7.25 (m, 1H, furyl); 7.62 (d, 1H, furyl, $J = 6.7$ Hz); 8.08 (d, 1H, Ar–H, $J_{H–F} = 6.1$ Hz); 8.76 (s, 1H, Ar–H); 10.04 (br s, 1H, –NH–); 13.03 (br s, 1H, –OH). Mass (FAB): 341 ($M^+ + 1$), 310, 282.

*5.3.11. 4-Fluoro-6-hydroxy-3-methyl-2-phenyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7b**)*

Mp: >300 °C, Yield: 60.4%. IR (KBr) *ν*: 3350–3250, 1680 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 3.05 (d, 3H, $–CH_3$, $J = 9$ Hz); 4.14 (s, 3H, $–CH_3$); 7.43 (m, 3H, phenyl); 7.74 (m, 2H, phenyl); 7.90 (d, 1H, Ar–H, $J_{H–F} = 6.1$ Hz); 8.81 (s, 1H, Ar–H); 10.03 (m, 1H, –NH–); 13.02 (br s, 1H, –OH). Mass (FAB): 351 ($M^+ + 1$), 320, 292.

*5.3.12. 2-(4-Chloro-phenyl)-4-fluoro-6-hydroxy-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7c**)*

Mp: >300 °C, Yield: 61%. IR (KBr) *ν*: 3350–3250, 1685 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 3.04 (d, 3H, $–CH_3$, $J = 9.5$ Hz); 4.13 (s, 3H, $–CH_3$); 7.41 (d, 2H, phenyl, $J = 6.5$ Hz); 7.73 (d, 2H, phenyl, $J = 6.4$ Hz); 7.91 (d, 1H, Ar–H, $J_{H–F} = 6.2$ Hz), 8.75 (s, 1H, Ar–H); 10.08 (br s, m, 1H, –NH–); 13.01 (br s, 1H, –OH). Mass (FAB): 385 ($M^+ + 1$), 354, 326.

*5.3.13. 4-Fluoro-2-(4-fluoro-phenyl)-6-hydroxy-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7d**)*

Mp: >300 °C, Yield: 59%. IR (KBr) *ν*: 3350–3250, 1687 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 3.02 (d, 3H, $–CH_3$, $J = 9.2$ Hz); 4.16 (s, 3H, $–CH_3$); 7.44 (m, 2H, phenyl); 7.73 (m, 2H, phenyl); 7.92 (d, 1H, Ar–H, $J_{H–F} = 6.4$ Hz); 8.82 (s, 1H, Ar–H); 10.03 (br s, 1H, –NH–); 13.01 (br s, 1H, –OH). Mass (FAB): 369 ($M^+ + 1$), 338, 310.

*5.3.14. 4-Fluoro-6-hydroxy-3-methyl-2-*p*-tolyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7e**)*

Mp: >300 °C, Yield: 63%. IR (KBr) *ν*: 3350–3250, 1663 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 2.24 (s, 3H, $–CH_3$); 3.06 (d, 3H, $–CH_3$, $J = 9.2$ Hz); 4.13 (s, 3H, $–CH_3$); 7.48 (d, 2H, phenyl, $J = 6.5$ Hz); 7.72 (d, 2H, phenyl, $J = 6.5$ Hz); 7.91 (d, 1H, Ar–H, $J_{H–F} = 6.2$ Hz); 8.85 (s, 1H, Ar–H); 10.03 (br s, 1H, –NH–); 13.04 (br s, 1H, –OH). Mass (FAB): 365 ($M^+ + 1$), 334, 306.

*5.3.15. 4-Fluoro-6-hydroxy-2-(4-methoxy-phenyl)-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7f**)*

Mp: >300 °C, Yield: 61%. IR (KBr) *ν*: 3350–3250, 1680 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 3.02 (d, 3H, $–CH_3$, $J = 9.2$ Hz); 3.93 (s, 3H, $–OCH_3$); 4.14 (s, 3H, $–CH_3$); 7.43 (d, 2H, phenyl, $J = 6.5$ Hz); 7.75 (d, 2H, phenyl, $J = 6.6$ Hz); 7.91 (d, 1H, Ar–H); 8.86 (s, 1H, Ar–H); 10.01 (br s, 1H, –NH–); 13.01 (br s, 1H, –OH). Mass (FAB): 381 ($M^+ + 1$), 350, 322.

*5.3.16. 2-(4-Dimethylamino-phenyl)-4-fluoro-6-hydroxy-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7g**)*

Mp: >300 °C, Yield: 58%. IR (KBr) *ν*: 3350–3250, 1675 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 2.95 (s, 6H, $–CH_3$); 3.05 (d, 3H, $–CH_3$, $J = 9.4$ Hz); 4.17 (s, 3H, $–CH_3$); 7.43 (d, 2H, phenyl, $J = 6.6$ Hz); 7.72 (d, 2H, phenyl, $J = 6.5$ Hz); 7.96 (d, 1H, Ar–H, $J_{H–F} = 6.4$ Hz); 8.84 (s, 1H, Ar–H); 10.08 (br s, 1H, –NH–); 13.02 (br s, 1H, –OH). Mass (FAB): 394 ($M^+ + 1$), 363, 335.

*5.3.17. 4-Fluoro-6-hydroxy-3-methyl-2-(4-nitro-phenyl)-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7h**)*

Mp: >300 °C, Yield: 50%. IR (KBr) *ν*: 3350–3250, 1690 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 3.05 (d, 3H, $–CH_3$, $J = 9.5$ Hz); 4.15 (s, 3H, $–CH_3$); 7.62 (d, 2H, phenyl, $J = 6.5$ Hz); 7.78 (d, 1H, Ar–H, $J_{H–F} = 6.1$ Hz); 8.74 (d, 2H, phenyl, $J = 6.2$ Hz); 9.33 (s, 1H, Ar–H); 10.01 (br s, 1H, –NH–); 13.06 (br s, 1H, –OH). Mass (FAB): 396 ($M^+ + 1$), 365, 337.

*5.3.18. 4-Fluoro-6-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**7i**)*

Mp: >300 °C, Yield: 59%. IR (KBr) *ν*: 3370–3250, 1680 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 3.01 (d, 3H, $–CH_3$, $J = 9.4$ Hz); 4.16 (s, 3H, $–CH_3$); 7.42 (d, 2H, phenyl, $J = 6.6$ Hz); 7.78 (d, 2H, phenyl, $J = 6.4$ Hz); 7.92 (d, 1H, Ar–H, $J_{H–F} = 6.2$ Hz); 8.84 (s, 1H, Ar–H); 10.07 (br s, 1H, –NH–); 12.51 (br s, 1H, –OH); 13.06 (br s, 1H, –OH). Mass (FAB): 367 ($M^+ + 1$), 336, 308.

*5.3.19. 2-Ethyl-4-fluoro-6-hydroxy-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**8a**)*

Mp: >300 °C, Yield: 65%. IR (KBr) *ν*: 3175, 1654 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 1.54 (m, 3H, $–CH_3$); 2.93 (t, 2H, $–CH_2$, $J = 9.2$ Hz); 3.04 (d, 3H, $–CH_3$, $J = 9.6$ Hz); 4.03 (s, 3H, $–CH_3$); 8.02 (d, 1H, Ar–H, $J_{H–F} = 6.2$ Hz); 8.78 (s, 1H, Ar–H); 10.01 (br s, 1H, –NH–); 13.03 (br s, 1H, –OH). Mass (FAB): 303 ($M^+ + 1$), 272, 244.

*5.3.20. 4-Fluoro-6-hydroxy-3-methyl-2-propyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**8b**)*

Mp: >300 °C, Yield: 62%. IR (KBr) *ν*: 3169, 1652.5 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 1.22 (t, 3H, CH_3, $J = 9.6$ Hz); 2.04 (m, 2H, $–CH_2$); 2.86 (t, 2H, $–CH_2$, $J = 9.7$ Hz); 3.02 (d, 3H, $–CH_3$, $J = 9.6$ Hz); 4.07 (s, 3H, $–CH_3$); 8.03 (d, 1H, Ar–H, $J_{H–F} = 6.1$ Hz); 8.77 (s, 1H, Ar–H); 10.06 (br s, 1H, –NH–); 13.07 (br s, 1H, –OH). Mass (FAB): 327 ($M^+ + 1$), 296, 268.

*5.3.21. 4-Fluoro-6-hydroxy-2-isopropyl-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**8c**)*

Mp: >300 °C, Yield: 63%. IR (KBr) *ν*: 3165, 1652 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 1.26 (m, 6H, CH_3); 1.92 (m, 2H, $–CH_2$); 2.88 (m, 1H, –CH–); 3.03 (d, 3H, $–CH_3$, $J = 9.5$ Hz); 4.04 (s, 3H, $–CH_3$); 8.05 (d, 1H, Ar–H, $J_{H–F} = 6.1$ Hz); 8.72 (s, 1H, Ar–H); 10.07 (br s, 1H, –NH–); 13.05 (br s, 1H, –OH). Mass (FAB): 327 ($M^+ + 1$), 296, 268.

*5.3.22. 2-Butyl-4-fluoro-6-hydroxy-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**8d**)*

Mp: >300 °C, Yield: 61%. IR (KBr) *ν*: 3164, 1654 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 1.2–1.14 (m, 5H, CH_3); 1.93 (m, 2H, $–CH_2$); 2.88 (t, 2H, $–CH_2$, $J = 9.5$ Hz); 3.04 (d, 3H, $–CH_3$, $J = 9.3$ Hz); 4.08 (s, 3H, $–CH_3$); 8.03 (d, 1H, Ar–H, $J_{H–F} = 6.4$ Hz); 8.77 (s, 1H, Ar–H); 10.03 (br s, 1H, –NH–); 13.09 (br s, 1H, –OH). Mass (FAB): 341 ($M^+ + 1$), 310, 282.

*5.3.23. 4-Fluoro-6-hydroxy-2-isobutyl-3-methyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**8e**)*

Mp: >300 °C, Yield: 61%. IR (KBr) *ν*: 3163, 1651 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 1.24–1.13 (m, 6H, CH_3); 1.98 (m, 1H, –CH–); 2.73 (d, 2H, $–CH_2$, $J = 9.5$ Hz); 3.05 (d, 3H, $–CH_3$, $J = 9.4$ Hz); 4.04 (s, 3H, $–CH_3$); 8.07 (d, 1H, Ar–H, $J_{H–F} = 6.2$ Hz); 8.72 (s, 1H, Ar–H); 10.09 (br s, 1H, –NH–); 13.03 (br s, 1H, –OH). Mass (FAB): 341 ($M^+ + 1$), 310, 282.

*5.3.24. 4-Fluoro-6-hydroxy-3-methyl-2-pentyl-3*H-*imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**8f**)*

Mp: >300 °C, Yield: 60%. IR (KBr) *ν*: 3300–3145, 1644 cm^{-1}. ^1H NMR (DMSO-d_6) *δ*: 1.26–1.33 (m, 7H, $–CH_2CH_2CH_3$); 1.97 (m, 2H, $–CH_2$); 2.85 (t, 2H, $–CH_2$, $J = 9.4$ Hz); 3.03 (d, 3H, $–CH_3$, $J = 9.3$ Hz); 4.04 (s, 3H, $–CH_3$); 8.08 (d, 1H, Ar–H, $J_{H–F} = 6.4$ Hz); 8.75 (s, 1H, Ar–H); 10.02 (br s, 1H, –NH–); 13.07 (br s, 1H, –OH). Mass (FAB): 355 ($M^+ + 1$), 324, 297.

*5.3.25. 4-Fluoro-2-hexyl-6-hydroxy-3-methyl-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**8g**)*

Mp: >300 °C, Yield: 60%. IR (KBr) ν: 3300–3145, 1643 cm^{-1}. ^1H NMR (DMSO-d_6) δ: 1.25–1.35 (m, 9H, $-CH_2CH_2CH_2CH_3$); 1.96 (m, 2H, $-CH_2$); 2.82 (t, 2H, $-CH_2$, $J = 9.2$ Hz); 3.01 (d, 3H, $-CH_3$, $J = 9.3$ Hz); 4.05 (s, 3H, $-CH_3$); 8.02 (d, 1H, Ar–H, $J_{H-F} = 6.4$ Hz); 8.78 (s, 1H, Ar–H); 10.03 (br s, m, 1H, –NH–); 13.06 (br s, 1H, –OH). Mass (FAB): 369 ($M^+ + 1$), 338, 311.

*5.4. Procedure for the ethylation of aryl/alkyl substituted imidazo [4,5-*h*]hydroxy quinolines (**9a–i** and **10a–i**)*

A mixture of aryl/alkyl substituted imidazo [4,5-h]hydroxy quinolines **7**/**8** (0.6 mmol) potassium carbonate (1.5 mmol), ethyl iodide (3 mmol) in DMF (5 ml) was heated at 80–90 °C with stirring for 15 h. The mixture was evaporated to dryness by distilling DMF and extracted the residue with chloroform. The $CHCl_3$ layer was washed with water, dried over sodium sulphate, concentrated to half the volume and purified by passing through column chromatography using silica gel to give the *N*-ethylated products **9** & **10**, respectively.

*5.4.1. 9-Ethyl-4-fluoro-2-furan-2-yl-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9a**)*

Mp: 287–288 °C, Yield: 78%. IR (KBr) ν: 3193, 1659, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.69 (t, 3H, $-CH_3$, $J = 9.1$ Hz); 3.01 (d, 3H, $-CH_3$, $J = 9.3$ Hz); 4.34 (s, 3H, $-CH_3$); 5.27 (q, 2H, $-CH_2-$, $J = 9.3$ Hz); 6.72 (d, 1H, furyl, $J = 6.3$ Hz); 7.25 (m, 1H, furyl); 7.76 (d, 1H, furyl, $J = 6.3$ Hz); 8.17 (d, 1H, Ar–H, $J_{H-F} = 6$ Hz); 8.73 (s, 1H, Ar–H); 10.08 (br s, 1H, –NH–). Mass (FAB): 369 ($M^+ + 1$), 338, 310. Analysis Calcd. for $C_{22}H_{21}FN_4O_3$: C, 64.69%; H, 5.18%; N, 13.71%. Found: C, 64.54%; H, 5.30%; N, 13.62%.

*5.4.2. 9-Ethyl-4-fluoro-3-methyl-6-oxo-2-phenyl-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9b**)*

Mp: 293–294 °C, Yield: 85%. IR (KBr) ν: 3297, 1672 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.65 (t, 3H, $-CH_3$, $J = 9.5$ Hz); 3.03 (d, 3H, $-CH_3$, $J = 9.3$ Hz); 4.27 (s, 3H, $-CH_3$); 5.21 (q, 2H, $-CH_2-$, $J = 9.7$ Hz); 7.69 (m, 3H, phenyl); 7.82 (m, 2H, phenyl, $J = 6.5$ Hz); 8.17 (d, 1H, Ar–H, $J_{H-F} = 6.3$ Hz); 8.73 (s, 1H, Ar–H); 10.04 (br s, m, 1H, –NH–). Mass (FAB): 379 ($M^+ + 1$), 348, 326. Analysis Calcd. for $C_{21}H_{19}FN_4O_2$: C, 66.65%; H, 5.06%; N, 14.80%. Found: C, 66.60%; H, 5.0%; N, 14.84%.

*5.4.3. 2-(4-Chloro-phenyl)-9-ethyl-4-fluoro-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9c**)*

Mp: >300 °C, Yield: 87%. IR (KBr) ν: 3216, 1661, 1623 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.63 (t, 3H, $-CH_3$, $J = 9.4$ Hz); 3.04 (d, 3H, $-CH_3$, $J = 9.2$ Hz); 4.26 (s, 3H, $-CH_3$); 5.27 (q, 2H, $-CH_2-$, $J = 9.4$ Hz); 7.62 (d, 2H, phenyl, $J = 6.3$ Hz); 7.86 (d, 2H, phenyl, $J = 6.6$ Hz); 8.24 (d, 1H, Ar–H, $J_{H-F} = 6.1$ Hz); 8.86 (s, 1H, Ar–H); 10.07 (br s, m, 1H, –NH–). Mass (FAB): 413 ($M^+ + 1$), 383, 355. Analysis Calcd. for $C_{21}H_{18}ClFN_4O_2$: C, 61.09%; H, 3.41%; N, 13.57%. Found: C, 61.06%; H, 3.30%; N, 13.54%.

*5.4.4. 9-Ethyl-4-fluoro-2-(4-chloro-phenyl)-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9d**)*

Mp: 290–292 °C, Yield: 85%. IR (KBr) ν: 3206, 1663, 1624 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.65 (t, 3H, $-CH_3$, $J = 9.3$ Hz); 3.02 (d, 3H, $-CH_3$, $J = 9.4$ Hz); 4.23 (s, 3H, $-CH_3$); 5.27 (q, 2H, $-CH_2-$, $J = 9.4$ Hz); 7.35 (m, 2H, phenyl, $J = 6.5$ Hz); 7.86 (m, 2H, phenyl, $J = 6.6$ Hz); 8.14 (d, 1H, Ar–H, $J_{H-F} = 6.3$ Hz); 8.82 (s, 1H, Ar–H); 10.07 (br s, m, 1H, –NH–). Mass (EI m/z): 396 (M^+), 339, 311, 296. Analysis Calcd. for $C_{21}H_{18}F_2N_4O_2$: C, 63.63%; H, 4.57%; N, 14.13%. Found: C, 63.60%; H, 4.50%; N, 14.2%.

*5.4.5. 9-Ethyl-4-fluoro-3-methyl-6-oxo-2-*p*-tolyl-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9e**)*

Mp: >300 °C, Yield: 83%. IR (KBr) ν: 3196, 1651, 1619 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.63 (t, 3H, $-CH_3$, $J = 9.4$ Hz); 2.42 (s, 3H, $-CH_3$); 3.07 (d, 3H, $-CH_3$, $J = 9.3$ Hz); 4.24 (s, 3H, $-CH_3$); 5.21 (q, 2H, $-CH_2-$, $J = 9.5$ Hz); 7.45 (d, 2H, phenyl, $J = 6.5$ Hz); 7.66 (d, 2H, phenyl, $J = 6.2$ Hz); 8.14 (d, 1H, Ar–H, $J_{H-F} = 6.1$ Hz); 8.73 (s, 1H, Ar–H); 10.08 (br s, 1H, –NH–). Mass (EI m/z): 392 (M^+), 361, 335, 307. Analysis Calcd. for $C_{22}H_{21}FN_4O_2$: C, 67.33%; H, 5.39%; N, 14.27%. Found: C, 67.40%; H, 5.50%; N, 14.2%.

*5.4.6. 9-Ethyl-4-fluoro-2-(4-methoxy-phenyl)-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9f**)*

Mp: >300 °C, Yield: 81%. IR (KBr) ν: 3226, 1660, 1622 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.64 (t, 3H, $-CH_3$, $J = 9.2$ Hz); 3.03 (d, 3H, $-CH_3$, $J = 9.4$ Hz); 3.97 (s, 3H, $-CH_3$); 4.21 (s, 3H, $-CH_3$); 5.26 (q, 2H, $-CH_2-$, $J = 9.5$ Hz); 7.14 (d, 2H, phenyl, $J = 6.4$ Hz); 7.78 (d, 2H, phenyl, $J = 6.5$ Hz); 8.15 (d, 1H, Ar–H, $J_{H-F} = 6.4$ Hz); 8.79 (s, 1H, Ar–H); 10.08 (br s, 1H, –NH–). Mass (FAB): 409 ($M^+ + 1$), 377, 349. Analysis Calcd. for $C_{22}H_{21}FN_4O_3$: C, 64.69%; H, 5.18%; N, 13.71%. Found: C, 64.54%; H, 5.30%; N, 13.62%.

*5.4.7. 2-(4-Dimethylamino-phenyl)-9-ethyl-4-fluoro-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9g**)*

Mp: >300 °C, Yield: 81%. IR (KBr) ν: 3206, 1659, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.66 (t, 3H, $-CH_3$, $J = 9$ Hz); 2.94 (s, 6H, $-N(CH_3)_2$); 3.03 (d, 3H, $-CH_3$, $J = 9$ Hz); 4.21 (s, 3H, $-CH_3$); 5.26 (q, 2H, $-CH_2-$, $J = 9$ Hz); 6.84 (d, 2H, phenyl, $J = 6.5$ Hz); 7.63 (d, 2H, phenyl, $J = 6.5$ Hz); 8.07 (d, 1H, Ar–H, $J_{H-F} = 6$ Hz); 8.72 (s, 1H, Ar–H); 10.05 (br s, 1H, –NH–). Mass (FAB): 422 ($M^+ + 1$), 391, 363. Analysis Calcd. for $C_{23}H_{24}FN_5O_2$: C, 65.54%; H, 5.73%; N, 16.61%. Found: C, 65.44%; H, 5.70%; N, 16.62%.

*5.4.8. 9-Ethyl-4-fluoro-3-methyl-2-(4-nitro-phenyl)-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9h**)*

Mp: >300 °C, Yield: 80%. IR (KBr) ν: 3336, 1672, 1627 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.66 (t, 3H, $-CH_3$, $J = 9.4$ Hz); 3.01 (d, 3H, $-CH_3$, $J = 9.3$ Hz); 4.24 (s, 3H, $-CH_3$); 5.27 (q, 2H, $-CH_2-$, $J = 9.7$ Hz); 7.66 (d, 2H, phenyl, $J = 6.3$ Hz); 7.83 (d, 2H, phenyl, $J = 6.5$ Hz); 8.27 (d, 1H, Ar–H, $J_{H-F} = 6.2$ Hz); 8.85 (s, 1H, Ar–H); 10.09 (br s, 1H, –NH–). Mass (EI m/z): 423 (M^+), 366, 338. Analysis Calcd. for $C_{21}H_{18}FN_5O_4$: C, 59.57%; H, 4.28%; N, 16.54%. Found: C, 59.54%; H, 4.30%; N, 16.62%.

*5.4.9. 2-(4-Ethox-phenyl)-9-ethyl-4-fluoro-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**9i**)*

Mp: >300 °C, Yield: 80%. IR (KBr) ν: 3213, 1658, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.64 (m, 6H, $-CH_3$); 3.05 (d, 3H, $-CH_3$, $J = 9.4$ Hz); 4.25 (m, 5H, $-CH_3$, $-CH_2-$); 5.21 (q, 2H, $-CH_2-$, $J = 9.2$ Hz); 7.01 (d, 2H, phenyl, $J = 6.2$ Hz); 7.71 (d, 2H, phenyl, $J = 7.4$ Hz); 8.11 (d, 1H, Ar–H, $J_{H-F} = 6.3$ Hz); 8.71 (s, 1H, Ar–H); 10.02 (br s, 1H, –NH–). Mass (FAB): 423 ($M^+ + 1$), 392, 364. Analysis Calcd. for $C_{23}H_{23}FN_4O_3$: C, 63.95%; H, 5.87%; N, 14.20%. Found: C, 63.84%; H, 5.8 0%; N, 14.32%.

*5.4.10. 2,9-Diethyl-4-fluoro-3-methyl-6-oxo-6,9-dihydro-3*H*-imidazo[4,5-*h*]quinoline-7-carboxylic acid methylamide (**10a**)*

Mp: 281–283 °C, Yield: 81%. IR (KBr) ν: 3193, 1659, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.52 (m, 6H, CH_3); 2.95 (t, 2H, $-CH_2$, $J = 9.2$ Hz); 3.04 (d, 3H, $-CH_3$, $J = 9.4$ Hz); 4.04 (s, 3H, $-CH_3$); 5.01 (q, 2H, $-CH_2-$, $J = 9.7$ Hz); 8.04 (d, 1H, Ar–H, $J_{H-F} = 6.2$ Hz); 8.73 (s, 1H, Ar–H); 10.04 (br s, 1H, –NH–). Mass (EI m/z): 330 (M^+), 273, 245. Analysis Calcd. for $C_{17}H_{19}FN_4O_2$: C, 61.80%; H, 5.79%; N, 16.95%. Found: C, 61.70%; H, 5.72%; N, 16.82%.

*5.4.11. 9-Ethyl-4-fluoro-3-methyl-6-oxo-2-propyl-6,9-dihydro-3H-imidazo[4,5-h]quinoline-7-carboxylic acid methylamide (**10b**)*

Mp: 287–288 °C, Yield: 80%. IR (KBr) ν: 3183, 1659, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.23 (t, 3H, CH_3, $J = 9.2$ Hz); 1.57 (t, 3H, $-CH_3$, $J = 9.5$ Hz); 2.07 (m, 2H, $-CH_2$); 2.80 (t, 2H, $-CH_2$, $J = 9.7$ Hz); 3.07 (d, 3H, $-CH_3$, $J = 9.5$ Hz); 4.06 (s, 3H, $-CH_3$); 5.02 (q, 2H, $-CH_2-$, $J = 9.4$ Hz); 8.04 (d, 1H, Ar–H, $J_{H-F} = 6.1$ Hz); 8.74 (s, 1H, Ar–H); 10.02 (br s, 1H, –NH–). Mass (EI m/z): 344 (M^+), 287, 259. Analysis Calcd. for $C_{18}H_{21}FN_4O_2$: C, 62.77%; H, 6.14%; N, 16.26%. Found: C, 62.70%; H, 6.20%; N, 16.32%.

*5.4.12. 9-Ethyl-4-fluoro-2-isopropyl-3-methyl-6-oxo-6,9-dihydro-3H-imidazo[4,5-h]quinoline-7-carboxylic acid methylamide (**10c**)*

Mp: 285–286 °C, Yield: 84%. IR (KBr) ν: 3179, 1659, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.20 (m, 6H, CH_3); 1.54 (t, 3H, $-CH_3$, $J = 9.2$ Hz); 1.92 (m, 2H, $-CH_2$); 2.87 (m, 1H, –CH–); 3.02 (d, 3H, $-CH_3$, $J = 9.3$ Hz); 4.06 (s, 3H, $-CH_3$); 5.04 (q, 2H, $-CH_2-$, $J = 9.4$ Hz); 8.04 (d, 1H, Ar–H, $J_{H-F} = 6.2$ Hz); 8.73 (s, 1H, Ar–H); 10.08 (br s, 1H, –NH–). Mass (EI m/z): 344 (M^+), 287, 259. Analysis Calcd. for $C_{18}H_{21}FN_4O_2$: C, 62.77%; H, 6.14%; N, 16.26%. Found: C, 62.69%; H, 6.10%; N, 16.12%.

*5.4.13. 2-Butyl-9-ethyl-4-fluoro-3-methyl-6-oxo-6,9-dihydro-3H-imidazo[4,5-h]quinoline-7-carboxylic acid methylamide (**10d**)*

Mp: 291–293 °C, Yield: 76%. IR (KBr) ν: 3178, 1659, 1620 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.2–1.1 (m, 5H, $-CH_2CH_3$); 1.5 (t, 2H, $-CH_3$, $J = 9.2$ Hz); 1.9 (m, 2H, $-CH_2$); 2.8 (t, 2H, $-CH_2$, $J = 9.4$ Hz); 3 (d, 3H, $-CH_3$, $J = 9.7$ Hz); 4.0 (s, 3H, $-CH_3$); 5.04 (q, 2H, $-CH_2-$, $J = 9.3$ Hz); 8.05 (d, 1H, Ar–H, $J_{H-F} = 6.4$ Hz); 8.73 (s, 1H, Ar–H); 10.05 (br s, 1H, –NH–). Mass (EI m/z): 358 (M^+), 327, 301, 273, 43. Analysis Calcd. for $C_{19}H_{23}FN_4O_2$: C, 63.67%; H, 6.46%; N, 15.63%. Found C, 63.50%; H, 6.40%; N, 15.42%.

*5.4.14. 9-Ethyl-4-fluoro-2-isobutyl-3-methyl-6-oxo-6,9-dihydro-3H-imidazo[4,5-h]quinoline-7-carboxylic acid methylamide (**10e**)*

Mp: 282–284 °C, Yield: 77%. IR (KBr) ν: 3159, 1649, 1610 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.26–1.13 (m, 6H, CH_3); 1.52 (t, 3H, $-CH_3$, $J = 9.2$ Hz); 1.92 (d, 2H, $-CH_2$, $J = 9.7$ Hz); 2.75 (m, 1H, –CH–); 3.04 (d, 3H, $-CH_3$, $J = 9.6$ Hz); 4.06 (s, 3H, $-CH_3$); 5.02 (q, 2H, $-CH_2-$, $J = 9.5$ Hz); 8.01 (d, 1H, Ar–H, $J_{H-F} = 6.2$ Hz); 8.71 (s, 1H, Ar–H); 10.02 (br s, 1H, –NH–). Mass (EI m/z): 358 (M^+), 301, 273, 43. Analysis Calcd. for $C_{19}H_{23}FN_4O_2$: C, 63.67%; H, 6.46%; N, 15.63%. Found: C, 63.60%; H, 6.40%; N, 15.52%.

*5.4.15. 9-Ethyl-4-fluoro-3-methyl-6-oxo-2-pentyl-6,9-dihydro-3H-imidazo[4,5-h]quinoline-7-carboxylic acid methylamide (**10f**)*

Mp: 287–289 °C, Yield: 74%. IR (KBr) ν: 3149, 1619, 1590 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.22–0.91 (m, 7H, $-CH_2CH_2CH_3$); 1.52 (t, 3H, $-CH_3$, $J = 9.4$ Hz); 1.95 (m, 2H, $-CH_2$); 2.82 (t, 2H, $-CH_2$, $J = 9.3$ Hz); 3.04 (d, 3H, $-CH_3$, $J = 9.2$ Hz); 4.05 (s, 3H, $-CH_3$); 5.06 (q, 2H, $-CH_2-$, $J = 9.7$ Hz); 8.03 (d, 1H, Ar–H, $J_{H-F} = 6.1$ Hz); 8.71 (s, 1H, Ar–H); 10.02 (br s, 1H, –NH–). Mass (EI m/z): 372 (M^+), 315, 287, 43. Analysis Calcd. for $C_{20}H_{25}FN_4O_2$: C, 64.49%; H, 6.76%; N, 15.04%. Found: C, 64.40%; H, 6.50%; N, 15.32%.

*5.4.16. 9-Ethyl-4-fluoro-2-hexyl-3-methyl-6-oxo-6,9-dihydro-3H-imidazo[4,5-h]quinoline-7-carboxylic acid methylamide (**10g**)*

Mp: 286–287 °C, Yield: 73%. IR (KBr) ν: 3145, 1630, 1592 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.2–0.9 (m, 9H, $-CH_2CH_2CH_2$ CH_3); 1.5 (t, 3H, $-CH_3$, $J = 9.5$ Hz); 1.9 (m, 2H, $-CH_2$); 2.8 (t, 2H, $-CH_2$, $J = 9.5$ Hz); 3.0 (d, 3H, $-CH_3$, $J = 9.6$ Hz); 4.0 (s, 3H, $-CH_3$); 5.0 (q, 2H, $-CH_2-$, $J = 9.4$ Hz); 8.0 (d, 1H, Ar–H, $J_{H-F} = 6.2$ Hz); 8.7 (s, 1H, Ar–H); 10.0 (br s, m, 1H, –NH–). Mass (FAB): 387 ($M^+ + 1$), 356, 328. Analysis Calcd. for $C_{21}H_{27}FN_4O_2$: C, 65.26%; H, 7.04%; N, 14.49%. Found: C, 65.40%; H, 7.20%; N, 14.32%.

5.5. Antibacterial activity procedure

The minimum inhibitory concentration was done by broth dilution method (NCCLS1982). A set of sterilized test tubes with nutrient broth medium capped with cotton plugs 1–9. The test compound is dissolved in suitable solvent and concentration of 100 μg/ml of the test compound is added in the first test tube, which is serially diluted from 1 to 9. A fixed volume of 0.5 ml overnight culture is added in all the test tubes and are incubated at 37 °C for 24 h. After 24 h, these tubes were measured for turbidity.

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