Bioorganic & Medicinal Chemistry Letters 20 (2010) 3640–3644

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and molecular modeling studies of 3-chloro-4-substituted-1-(8-hydroxy-quinolin-5-yl)-azetidin-2-ones as novel anti-filarial agents

Santosh S. Chhajed [a,*], Puranik Manisha [b], Virupaksha A. Bastikar [c], Haldar Animeshchandra [d], V. N. Ingle [d], Chandrashekhar D. Upasani [e], Sachin S. Wazalwar [f]

[a] Department of Pharmaceutical Chemistry, S.M.B.T. College of Pharmacy, Dhamangaon, Dist – Nasik, MS, India
[b] Institute of Pharmaceutical Education and Research, Borgaon (Meghe), Wardha, MS, India
[c] Dr. D.Y. Patil Institute of Biotechnology and Bioinformatics, Belapur, Navi – Mumbai, India
[d] Department of Chemistry, R.T.M. Nagpur University, Nagpur, MS, India
[e] S.S.D.J. College of Pharmacy, Chandwad, Dist – Nashik, MS, India
[f] Rajiv Gandhi College of Engineering, Research & Technology, Chandrapur, MS, India

ARTICLE INFO

Article history:
Received 6 December 2009
Revised 22 April 2010
Accepted 23 April 2010
Available online 17 May 2010

Keywords:
Synthesis
Azetidin-2-ones
In vitro anti-filarial
Molecular docking, MDS

ABSTRACT

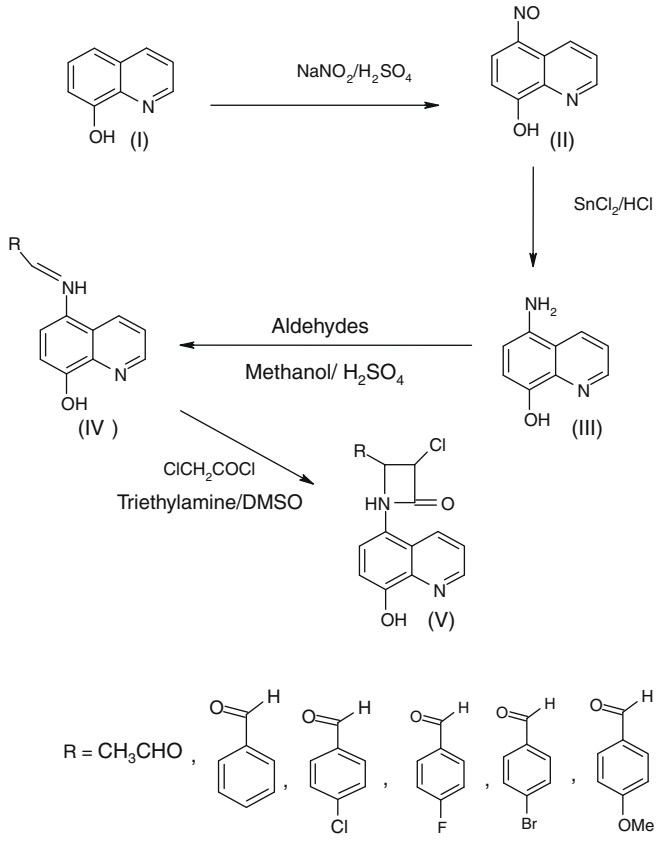
A series of 3-chloro-4-substituted-1-(8-hydroxy-quinolin-5-yl)-azetidin-2-ones were synthesized and evaluated for their in vitro anti-filarial activity. To pre-assess the anti-filarial behavior of synthesized compounds ($\mathbf{V_{a-f}}$) on a structural basis, automated docking studies were carried out with Molecular Design Suite (MDS v 3.5) into the active site of glutathione-*S*-transferase (GST) enzyme; scoring functions of these compounds at the active site of the GST enzyme were used for correlation with observed activity. Compounds $\mathbf{V_e}$ and $\mathbf{V_f}$ have shown good affinity for receptor GST, as well as in vitro anti-filarial potency.

Filariasis comprises a group of diseases produced by the invasion of the lymphatic system or connective tissues by the nematodes *Filarioidea.* The most formidable pathogens of man include *Wuchereria bancrofti, Brugia* (*Wuchereria*) *malayi*, *Loa loa*, and *Onchocerca volvulus.* Current global estimates suggest that around 80 countries are endemic for lymphatic filariasis (LF).[1] An estimated population of 22 million is known to be the host for circulating microfilaria and 16 million people suffer from filarial manifestations like elephantiasis of limbs, genitals, and hydrocele.[2] Low priority was given to this disease, although it is responsible for significant morbidity and consequently the World Health Assembly has adopted a resolution on the global elimination of lymphatic filariasis as a public health problem.[3,4] The available control strategies have significant limitations as current drugs are principally macrofilaricidal and require annual repeated treatment for a number of years, thus there is still a need for the development of a macrofilaricidal agent or drug combination for the curative treatment or sustained suppression of the microfilariae.[5–8] Drug resistance to ivermectin appears to be another issue of concern, especially in areas where diethylcarbamazine (DEC) cannot be given. The candidate drug Diethylcarbamazine (DEC) which kills microfilaria has no effect on most of the adult filarial species and causes side effects.[9] Therefore, R&D activities are directed to the search of a new molecular structure as macrofilaricidal or at least a sterilizing agent.

A number of molecules from heterocycles are known as good anti-filarials agent.[10] Benzimidazoles[11] and triazines[12,13] have recently been shown to possess anti-filarial activity. Extensive work has been done on 4-aminoquinolines as anti-filarials. It is evident that bulky substituent at fourth position of quinolines are found to be good anti-filarial activity.[14] But no sincere efforts have been carried out in exploring 5th position of quinoline nucleus. In the present work, we have explored 8-hydroxyl-5-aminoquinoline derivatives as a new lead compounds in anti-filarial chemotherapy. Present work is an attempt to observe the combined effect of quinoline nucleus along with another equally potent β-lactam nucleus for the anti-filarial activity. Effect of a new series which incorporates the combination of two biologically active nuclei, that is, quinoline and β-lactam was studied for its anti-filarial properties. In the present work, we synthesized six new 3-chloro-4-substituted-1-(quinolin-5-yl) azetidin-2-ones, and tested for in vitro anti-filarial activity.

* Corresponding author. Tel.: +91 9850081911.
E-mail address: santosh_chhajed@rediffmail.com (S.S. Chhajed).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.04.106



Scheme 1. Synthetic protocol of compounds.

The synthesis of our target compounds $\mathbf{V_{a-f}}$ is outlined in Scheme 1. Structures of compounds ($\mathbf{IV_{a-f}}$) and ($\mathbf{V_{a-f}}$) are confirmed by spectral data and elemental analysis by CHN. Key intermediate 5-amino-8-hydroxyquinoline **(III)** was synthesized by nitrosation of 8-hydroxyquinoline (**I**),[15] followed by reduction of 5-nitroso-8-hydroxy quinoline (**II**) with tin metal in hydrochloric acid.[16] Compounds ($\mathbf{IV_{a-f}}$) were prepared by Schiff's base formation[17] between 5-amino-8-hydroxyquinoline (**III**) and 4-substituted/unsubstituted aliphatic/aromatic aldehydes. Target compounds ($\mathbf{V_{a-f}}$), ware prepared by cyclization of 5-(4-substituted/unsubstituted benzylideneamino)-quinoline-8-ol ($\mathbf{IV_{a-f}}$) with chloroacetyl chloride.[18] The synthesized scaffold was screened for in vitro anti-filarial activity against *B. malayi* by method of Chatterjee and co-workers.[19] Results are summarized in Table 1.

Glutathione-*S*-transferase (GST) (E.C. 2.5.1.18)[20] is one of the major detoxification system ubiquitous among eukaryotes and have been found in a wide range of parasitic helminthes. The inhibition of parasite GST(s) thus deprives the parasite of its major defense against oxidative stress and impairs its ability to survive. Filarial GST is therefore important target for anti-filarial drug design.[21] To pre-assess the anti-filarial behavior of synthesized compounds ($\mathbf{V_{a-f}}$) on a structural basis, automated docking studies were carried out and scoring functions, their binding affinities and orientation of these compounds at the active site of the GST enzyme were found out. Results are summarized in Table 2. The protein–ligand complex was constructed on the basis of the X-ray structure of GST (PDB deposition – 5GSS).[22] Docking was performed using Molecular Design Suite (MDS) v 3.5, into the 3D

Table 1
In vitro anti-filarial screening of compounds on *B. malayi*

Sr. No.	Compound	Percent loss of motility after 48 h Concentration (ng/mL)				
		20	40	60	80	100
1	$\mathbf{V_a}$	Nil	Nil	Nil	2	02
2	$\mathbf{V_b}$	Nil	10	19	36	59
3	$\mathbf{V_c}$	Nil	Nil	12	26	37
4	$\mathbf{V_d}$	Nil	Nil	3	16	23
5	$\mathbf{V_e}$	67	76	91	91	91
6	$\mathbf{V_f}$	53	61	67	76	81
7	DMSO	Nil	Nil	Nil	Nil	Nil

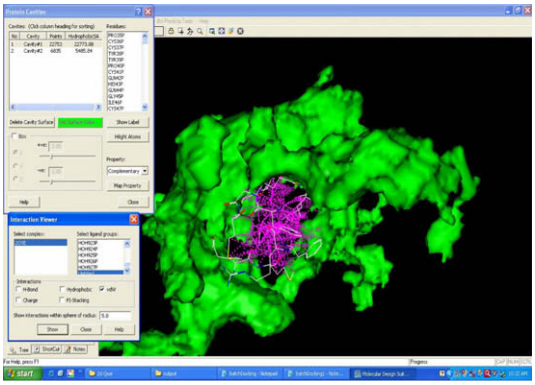
Note. Nil indicates no motility observed.

Table 2
Molecular docking showing binding score of synthesized compounds in the active site of GST

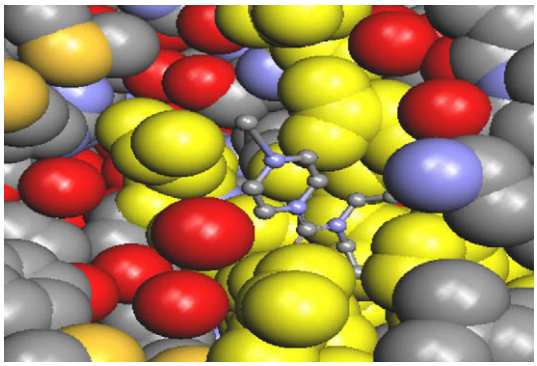
Sr. No.	Ligand	Binding score using GA dock
1	$\mathbf{V_a}$	17,623
2	$\mathbf{V_b}$	12,021
3	$\mathbf{V_c}$	14,092
4	$\mathbf{V_d}$	15,923
5	$\mathbf{V_e}$	10,112
6	$\mathbf{V_f}$	10,876
7	DEC	10,943

model of the catalytic site of GST enzyme, and to well correlate the obtained binding score with inhibitory activities of compounds. Obtained results were evaluated in terms of binding score into the catalytic site of GST, low binding scores represent high affinity for the receptor (Fig. 1).

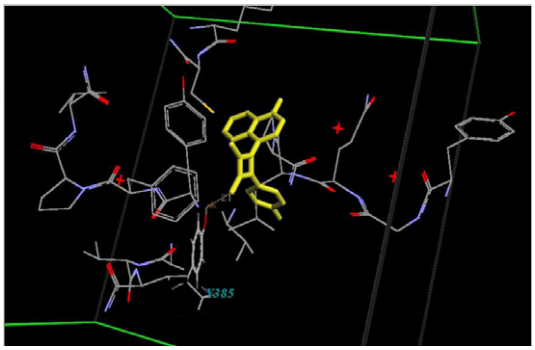
In summary, synthesis of 5-amino-8-hydroxyquinoline we selected a two step method consisting of nitrosation of 8-hydroxyquinoline, followed by reduction with tin and hydrochloric acid. When nitrosation is carried out at the 15–18 °C, the nitroso group was directed selectively to para position to the hydroxyl group. The target compounds $\mathbf{V_{a-f}}$ were prepared by cyclization of $\mathbf{IV_{a-f}}$ Schiff bases with chloroacetyl chloride. Triethylamine was used as base in this reaction to absorb released hydrochloric acid. Spectral data and elemental analysis by CHN of the target compounds ($\mathbf{V_{a-f}}$) are in accordance with their structures Tables 3 and 4. The synthesized scaffold was screened for in vitro anti-filarial activity against *B. malayi*. Results are summarized in Table 1. Compounds $\mathbf{V_e}$ and $\mathbf{V_f}$ showed promising activity against brugia. Compound $\mathbf{V_e}$ resulted in 91% loss of motility at concentration of 60 ng/mL and compound $\mathbf{V_f}$ shows 76% loss of motility at 80 ng/mL where as $\mathbf{V_b}$ shows moderate activity with 53% loss of motility at 100 ng/mL. Molecular docking analysis shows that compounds $\mathbf{V_b}$, $\mathbf{V_e}$, and $\mathbf{V_f}$ show minimum binding scores 10,112, 10,876, and 12,021, respectively, in the series. Results are summarized in Table 2. This shows that compounds $\mathbf{V_b}$, $\mathbf{V_e}$, and $\mathbf{V_f}$ possess more binding affinity for receptor glutathione-*S*-transferase than other compounds in the series. Further binding score of known anti-filarial agent, DEC is 10,943. It is evident from docking analysis that, binding affinity of compound $\mathbf{V_e}$ and $\mathbf{V_f}$, for enzyme GST is better than that of DEC. Good correlation was found in molecular docking analysis and in vitro anti-filarial screening for all the compounds. Compounds that showed good binding affinity for receptor were found to possess promising biological activity.



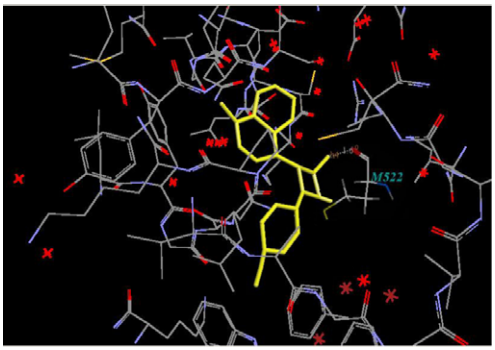
Molecule V_b in the active site of enzyme GST showing Van der Wals interactions



score 10943



Binding mode of compound V_e into the binding site of GST, it form hydrogen bond shown as white dotted lines showing one hydrogen bond between O of 2-oxo of azetidinone and Tyrosine -385 of distances of 2.1 A.U. it has binding score of 10112.



Binding mode of compound Vd into the binding site of GST, it has binding score 15923 and form hydrogen bond shown as white dotted line, showing one hydrogen bond between O of 2-oxo of azetidinone and Methionine -522 of distances of 1.1 A.U.

Fig. 1. Best poses, orientations, hydrogen bond formed, and Van der Waals interactions of synthesized compounds with GST.

Table 3
Physicochemical and spectral data for compounds $\mathbf{IV_{a-f}}$

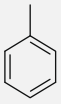
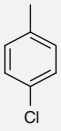
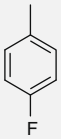
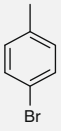
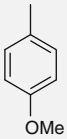
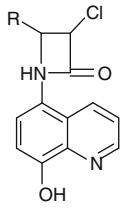
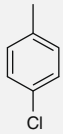
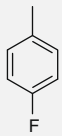
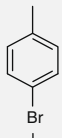
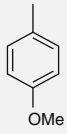
Sr. No.	Compound	–R	Mp (°C)	^{1}H NMR (dppm), IR (cm^{-1}, KBr), mass (*m*/*e*)
1	$\mathbf{IV_a}$		122–124	^{1}H NMR: δ 9.52 (s, 1H, Ar–OH), δ 7.02 (s, N=CH–), δ 6.8–8.9 (m, Ar–H). IR (cm^{-1}): 3382.75 (O–H str), 1642.19 (C=N str of imines), 1250 (phenolic C–O str), *m*/*z* = 249
2	$\mathbf{IV_b}$	 Cl	187–189	^{1}H NMR: δ 7.44 (s, 1H, N=CH–), 6.96–9.45 (m, Ar–H), 10.41 (s, 1H, Ar–OH). IR (cm^{-1}): 2931.78 (C–H str), 1647.69 (C=N str of imines), 1261.13 (aromatic C=C str), 1238.12 (C–O str of phenols), *m*/*z* = 282
3	$\mathbf{IV_c}$	 F	244–246	^{1}H NMR: δ 7.24 (s, 1H, N=CH–), 6.96–8.9 (m, Ar–H), 9.74 (s, 1H, Ar–OH). IR (cm^{-1}): 2939.04 (C–H str), 1648.62 (C=N str of imines), 1267.35 (aromatic C=C str), 1249.54 (C–O str of phenols), *m*/*z* = 269
4	$\mathbf{IV_d}$	 Br	68–70	^{1}H NMR: δ 7.21 (s, 1H, N=CH–), 6.61–8.6 (m, Ar–H), 9.53 (s, 1H, Ar–OH). IR (cm^{-1}): 2932.24 (C–H str), 1647.62 (C=N str of imines), 1277.28 (aromatic C=C str), 1249.87 (C–O str of phenols), *m*/*z* = 326
5	$\mathbf{IV_e}$	 OMe	134–136	^{1}H NMR: δ 3.8 (s, 3H, Ar–OCH_3), δ 6.96 (s, 1H, N=CH–), 6.9–8.9 (m, Ar–H), 9.75 (s, 1H, Ar–OH). IR (cm^{-1}): 3310.35 (O–H str), 3134.37 (aromatic C–H str), 1653.07 (C=N str of imines), 1255 and 1043.54 (C–O str of phenyl alkyl ether), *m*/*z* = 278
6	$\mathbf{IV_f}$	$-CH_3$	112–114	^{1}H NMR: δ 8.1 (s, 1H, N=CH–), 9.74 (s, 1H, Ar–OH). IR (cm^{-1}): 2939.04 (C–H str), 1648.62 (C=N str of imines), 1267.35 (aromatic C=C str), 1249.54 (C–O str of phenols), *m*/*z* = 186

Table 4
Spectral and analytical data for target compounds (**V_{a-f}**)



Compound	–R	Mp (°C)	CHN calculated % found %			^{1}H NMR (ppm), IR (cm^{-1}, KBr), mass (*m*/*e*)
			C	H	N	
V_a		166–168	66.57 66.49	4.03 3.92	8.63 8.55	δ 9.6 (s, 1H, Ar–OH), 5.0 (s, 1H, C_4–H), δ 5.4 (s, 1H, C_3–H), 6.9–8.9 (m, Ar–H), 3294.66 (O–H str), 1747.34 (C=O str), 3119.37, (C–H str) 2889.02 (asym. and sym. C–H str). *m*/*e* – 325
V_b		134–136	60.19 60.09	3.37 3.28	7.80 7.70	δ 9.5 (s, 1H, Ar–OH), δ 5.1 (s, 1H, C_4–H), δ 5.6 (s, 1H, C_3–H), δ 6.8–8.9 (m, Ar–H), 3305.12 (O–H str), 3157 (aromatic C–H str), 2937.43, 2900.65 (asym. and sym. C–H str) 1749.32 (C=O str). *m*/*e* – 345
V_c		220–222	63.08 63.01	3.53 3.43	8.17 8.11	δ 9.5 (s, 1H, Ar–OH), δ 5.2 (s, 1H, C_4–H), δ 5.4 (s, 1H, C_3–H), δ 6.7–8.6 (m, Ar–H), 3315.12 (O–H str), 3152 (aromatic C–H str), 2929.87, 2904.65 (asym. and sym. C–H str) 1747.43 (C=O str). *m*/*e* – 342
V_d		182–184	56.67 56.56	3.25 3.18	3.48 3.41	δ 9.4 (s, 1H, Ar–OH), δ 5.2 (s, 1H, C_4–H), δ 5.8 (s, 1H, C_3–H), δ 6.8–9.3 (m, Ar–H), 3305.12 (O–H str), 3157 (C–H str), 2937.33, 2896.00 (asym. and sym. C–H str) 1749.46 (C=O str). *m*/*e* – 402
V_e		117–119	64.32 64.21	4.26 4.19	7.90 7.80	δ 3.8 (s, 3H, Ar–OCH_3), 6.96 (s, 1H, N=CH–), 6.9–8.8 (m, Ar–H), 9.75 (s, 1H, Ar–OH), 3353.98 (O–H str), 3151 (C–H str), 2956.82 and 2937.35 (asym. and sym. C–H str), 1747.32 (C=O str), 1248.67 and 1035.56 (C–O str). *m*/*e* – 342
V_f	–CH_3	92–94	59.44 59.49	4.22 4.16	10.66 10.57	δ 10.1 (s, 1H, Ar–OH), δ 5.4 (s, 1H, C_4–H), δ 6.1 (s, 1H, C_3–H), δ 2.3 (s, 3H –CH_3), 3335.01 (O–H str), 2928.12, 2909.18 (asym. and sym. C–H str) 1739.09 (C=O str). *m*/*e* – 262

Acknowledgments

Our sincere thanks go to Dr. M.V.R. Reddy and Dr. Kalyan Gosami, Department of Biochemistry, J.B. Tropical Disease Research Centre, MGIMS, Sevagram, MS, India, for in vitro anti-filarial screening. Professor Dr. Anjali Rahatgaonkar, Department of Chemistry, Institute of Science, Nagpur, SAIF Chandigarh, Punjab University for spectral studies.

References and notes

1. Fischer, P.; Manoempil, T.; Supali, G. S.; Rucker, P. *Trans. R. Soc. Trop. Med. Hyg.* **2006**, *11*, 464.
2. Thomas, P. A. *Parasitology* **2001**, *122*, S65.
3. Ottesen, E. A. *Trop. Med. Int. Health* **2000**, *5*, 591.
4. Ottesen, E. A. *Am. J. Trop. Med. Hyg.* **1989**, *41*, S9.
5. Michael, E. D.; Bundy, A. P. *Parasitol. Today* **1997**, *13*, 472.
6. Khan, A. M.; Mahanta, J. *Curr. Sci.* **2005**, *88*, 1718.
7. Das, P. K.; Pani, S. P. *Int. Med. Sci. Acad.* **2000**, *13*, 18.
8. Hoerauf, A.; Volkmann, L.; Hamelmann, C.; Adjei, O.; Buttner, D. W. *Lancet* **2000**, *35*, 1242.
9. Chauhan, P. M. S.; Singh, S. N.; Chatterjee, R. K. *Indian J. Chem., Sect B* **1993**, *32*, 858.
10. Tripathi, R. P.; Katiyar, D.; Dwivedi, N.; Singh, B. K.; Pandey, J. *Curr. Med. Chem.* **2006**, *13*, 3319.
11. Collier, L.; Balows, A.; Sussman, M. *Parasitology* **1998**, *5*, 349.
12. Bose, C.; Agarwal, S. K.; Chatterjee, R. K.; Srivastava, V. M. *Indian J. Chem., Sect B* **1994**, *33*, 32.
13. Srivastava, S.; Chauhan, P. M.; Bhaduri, A. P.; Murthy, P. K.; Chatterjee, R. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 313.
14. Tewari, S.; Chauhan, P. M. S.; Bhaduri, A. P.; Chatterjee, R. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1409.
15. *Synthesis of 5-nitroso-8-hydroxyquinoline (**I**):* 8-Hydroxyquinoline (7.34 g, 0.05 mol) was dissolved in a continuously stirred solution of 66.7 mL of distilled water and 3 mL of concentrated sulfuric acid at 15–18 °C. Sodium nitrite (3.67 g) in distilled water (6.78 mL), was added drop wise to the reaction mixture over a period of 30–40 min at 15–18 °C, mixture was maintained at this temperature for 3 h. The reaction mixture was neutralized with 40% sodium hydroxide solution. It was then acidified with glacial acetic acid to pH 3.0–4.0. Yellow precipitate obtained was filtered, washed with distilled water, and dried. Yield: 6.7 g (89.5%) mp: 234–236 °C.
16. *Synthesis of 5-amino-8-hydroxyquinoline (**III**).* 0.174 g (0.01 mol) of 5-nitroso-8-hydroxyquinoline in 25 mL of concentrated hydrochloric acid was allowed to warm. To this was added slowly, in small portions tin (Sn) metal (0.236 g, 0.02 mol). The reaction mixture was heated at reflux for 6 h in boiling water bath. The reaction mixture was allowed to cool to room temperature. To the reaction mixture was slowly added 20% solution of sodium hydroxide to get the precipitate. 5-Amino-8-hydroxyquinoline was extracted with ether. Yield: 0.154 g (79.87%), mp: 137–140 °C, IR (cm^{-1}): 3360.41–3270.26 (asymmetric and symmetric N–H str, respectively), 1609.02 (N–H def) 1250 (C–N str), ^{1}H NMR: δ 9.9 (s, 1H, Ar–OH), δ 6.6–8.9 (M, Ar–H) δ 3.97 (s, =N–H, Ar–NH_2).
17. *General procedure for synthesis of Schiff bases (**IV_{a-f}**):* Equimolar quantities of substituted aromatic/aliphatic aldehydes and 5-amino-8-hydroxy quinoline were dissolved in 20 mL of warm dry ethanol. To it 1–2 drops of concentrated sulfuric acid were added and heated at reflux for 2–3 h. After standing for approximately 24 h at room temperature, the crystalline product was separated by filtration and dried. Physicochemical and spectral data is summarized in Table 3.
18. *General procedure for synthesis of 3-chloro-1-(8-hydroxyquinolin-5-yl)-4-substituted-azetidin-2-one(**V_{a-f}**):* To 0.01 M substituted 5-(benzylideneamino)-

quinoline-8-ols (**IV$_{a-f}$**), 20 mL of 1,4 dioxane was added. The mixture was warmed to dissolve. The resultant solution was allowed to cool, and to it was added 0.01 M triethylamine and 0.01 M chloroacetyl chloride with stirring. Mixture was refluxed on the boiling water bath for 3–4 h. It was allowed to cool and filtered at pump, air dried. Physicochemical and spectral data for synthesized scaffold (**V$_{a-f}$**) is summarized in the Table 4.

19. Mukherjee, M.; Misra, S.; Chatterjee, R. K. *Acta Trop.* **1998**, *70*, 251.
20. Gupta, S.; Srivastava, A. K. *Acta Parasitol.* **2005**, *50*, 1230.
21. Ahmad, R.; Srivastava, A. K. *Helminthologia* **2008**, *45*, 114.
22. Oakley, A. J.; Bello, M. L.; Battistoni, A.; Ricci, G.; Rossjohn, J.; Villar, H. O.; Parker, M. W. *J. Mol. Biol.* **1997**, *274*, 84.