International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 9, Issue 10, 2017

Original Article

SYNTHESIS, CHARACTERIZATION AND EVALUATION OF 4-HYDROXY-1-PHENYL/METHYL-3-(3-SUBSTITUTED-1-(SUBSTITUTEDIMINO) PROPYL) QUINOLINE-2(1*H*)-ONE DERIVATIVES AND 4-HYDROXY-1-PHENYL/METHYL-3-(1-(SUBSTITUEDIMINO) ETHYL) QUINOLINE-2(1*H*)-ONE DERIVATIVES AS POSSIBLE ANTICANCER AGENTS

S. N. MAMLE DESAI[a*], RUDRAX N. S. PRIOLKAR[a], HARSHANK A. NAIK KARMALI[a], PRABHAV D. AMBE[a], B. S. BIRADAR[b]

[a]Department of Pharmaceutical Chemistry, P. E. S.'s Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Ponda-Goa. 403401, [b]Department of Pharmacolgy, P. E. S.'s Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Ponda-Goa. 403401
Email: rpriolkar@gmail.com

Received: 23 May 2017 Revised and Accepted: 31 Aug 2017

ABSTRACT

Objective: Synthesis, characterization and evaluation of quinolin-2-one derivatives as possible anticancer agents.

Methods: A series of novel 4-hydroxy-1-phenyl/methyl-3-(3-substituted-1-(substitutedimino)propyl)quinolin-2(1*H*)-one derivatives IIa(1-5)/IIb(1-5) and 4-hydroxy-1-phenyl/methyl-3-(1-(substituedimino)ethyl)quinolin-2(1*H*)-one derivatives IIIa(1-3)/IIIb(1-3) were synthesised by nucleophilic addition of substituted anilines on 3-acetyl-4-hydroxy-1-phenyl/methylquinolin-2(1*H*)-one (a/b) and 4-hydroxy-3-(3-substitutedpropanoyl)-1-phenyl/methyl quinolin-2(1*H*)-one (Ia/Ib); respectively. The synthesised derivatives were characterised by spectral analysis and were tested for their *in vitro* anticancer activity against K562 and Hep 3b cell lines by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay method.

Results: The compounds were tested for their *in vitro* anticancer activity against K562 and Hep 3b cell lines at 10, 20, 25, 30 and 50 µg/ml concentration using MTT assay method. The compound 4-hydroxy-3-(3-morpholino-1-(phenylimino)propyl)-1-phenylquinolin-2(1*H*)-one (IIa-1) showed anticancer activity with IC_{50} value 20 µg as compared to the control against K562 cell lines. The compound 4-hydroxy-1-phenyl-3-(1-(phenylimino) ethyl) quinolin-2(1*H*)-one (IIIa-1) showed anticancer activity with IC_{50} value less than 10 µg.

Conclusion: The proposed method for the synthesis of novel derivatives is convenient and gives a good yield. Some of the synthesised compounds showed promising anticancer activity against K562 and Hep 3b cell lines. Compound IIa-1 (R=-C_6H_5; R_1= morpholine; R_2= C_6H_5-NH-) exhibited most potent activity against K562 cell lines. Compound IIIa-1 (R=-C_6H_5; R_3= C_6H_5-NH-) has been proved to be the most cytotoxic compound among the other derivatives against Hep 3b cell lines.

Keywords: Linomide, Quinolin-2-one, Anticancer, MTT assay

DOI: http://dx.doi.org/10.22159/ijpps.2017v9i10.20184

INTRODUCTION

The alarming rise of cancer cases has put strains on individuals, families and the society in which they live. The number of cancer cases and related deaths worldwide is related to double over the next 20-40 y. As per a report by world health organisation (WHO), it is estimated the number of new cancer cases will rise by about 70% over the next two decades [1]. There is a significant advancement in drug discovery and the modern chemotherapy has helped to lower the mortality rates. However, there is a need to develop novel bioactive molecules which would overcome the side effects and toxicity caused by the existing antineoplastic agents; without compromising for any therapeutic efficacy.

The quinolin-2-one moiety exhibits a versatile range of biological activity. The natural compounds containing the quinolin-2-one nucleus such as flindersine, dictamnine as well as their synthetic analogues are found to possess pharmacological activity and therapeutic utility [2-5]. Clinical significance of quinolin-2-one is well established and documented in the form of treatment of psychosis, as a β-blocker in an ophthalmic preparation, as an antacid and in congestive cardiac failure [6-9].

Literature reviews have indicated linomide (fig. 1), a quinolin-2-one derivative as a lead molecule for the development of anticancer agents [10-12]. In continuation of our research works on linomide, we proposed the synthesis of novel linomide analogues by modifying substitutions on ring nitrogen, isosteric replacement of oxygen by substituted nitrogen and preparing mannich bases by exploiting the acidic hydrogen of the acetyl group. The present study aims at evaluating the anticancer activity of the synthesised novel compounds.

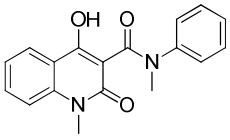
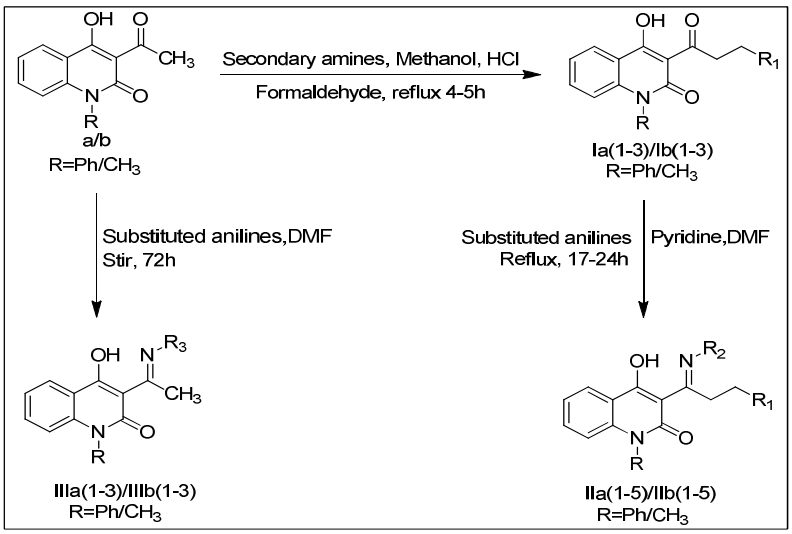


Fig. 1: Linomide [13]

MATERIALS AND METHODS

Materials

Chemicals used for the synthesis were purchased from Molychem-Mumbai and SD-Fine Chem Ltd; Mumbai. All the reagents and solvents were of laboratory grade. Fourier transform infrared (FTIR) spectra were recorded on Shimadzu IR affinity-1 spectrophotometer by using KBr pellets. The ^{1}H NMR and ^{13}C NMR was recorded on Bruker Avance II 400 NMR spectrometer using deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6) as solvents and tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed as delta (δ) values in parts per million (ppm). The mass spectra (MS) were recorded on Waters, Q-TOF Micromass.



Scheme 1: Synthesis of compounds IIa(1-5)/IIb(1-5) and IIIa(1-3)/IIIb(1-3)

Synthesis of 4-hydroxy-3-(3-substituted propanoyl)-1-phenyl/ methyl quinolin-2(1*H*)-one (Ia/Ib)

A solution of secondary amine (1 mmol) and formaldehyde (10 mmol) was stirred for five minutes. To this, a solution of compound 3-acetyl-4-hydroxy-1-phenyl/methyl quinolin-2(1*H*)-one (a/b, synthesized as per literature) (0.01 mol) in methanol was added with 0.05 ml of 1N HCl and refluxed for 4-5 h [14]. The progress of the reaction was monitored by thin layered chromatography (TLC). The solution was kept overnight for precipitation to take place. The compounds thus obtained were separated by filtration, washed with water and further recrystallized using a suitable solvent.

Synthesis of 4-hydroxy-3-(3-substituted-1-(substituted amino) propyl)-1-phenyl/methyl quinolin-2(1*H*)-one (II-a/II-b)

Compound I-a/I-b (1 mmol) was added to a solution of dimethylformamide (DMF) (0.2 mmol) and pyridine (0.2 mmol). To this mixture, substituted aniline (0.3 mmol) was added and refluxed for 17-24 h. The solution obtained was poured in ice cold water and kept overnight. The solid separated was filtered and recrystallized using a suitable solvent.

Synthesis of 4-hydroxy-1-phenyl/methyl-3-(1-(substituted amino) ethyl) quinolin-2(1*H*)-one (IIIa/IIIb)

To a solution of the compound, a/b (3 mmol) in DMF, substituted anilines (3.6 mmol) were added and the reaction mixture was stirred at 20 ℃ for 72 h. The completion of the reaction was monitored by TLC. The solution thus obtained was poured in ice cold water and stirred till crystallization took place. The product was filtered and recrystallized using a suitable solvent.

Anticancer activity

The synthesized derivatives were screened for their *in vitro* anticancer activity against K562 and Hep 3b cell lines by MTT assay method. The cell lines for the anticancer activity were procured from the national centre for cell science (NCCS), Pune. The cell lines were maintained in 96 wells microtiter plate containing minimum essential medium (MEM) and were supplemented with 10% heat-inactivated foetal calf serum (FCS) containing 5% of a mixture of gentamicin (10 µg), penicillin (100 U/ml) and streptomycin (100 µg/ml); in presence of 5% CO_2 at 37 °C for 48-72 h.

The cell lines were treated with 10, 20, 25, 30 and 50 µg/ml solutions of the test compounds in dimethyl sulfoxide (DMSO). After incubation at 37 °C in a humidified atmosphere of 5% CO_2, 20 µl of a stock solution of MTT (5 mg in 1 ml of sterile phosphate buffered saline) was added to each well and plates were further incubated for 4 h. DMSO was used as a control. The supernatant was carefully aspirated, the precipitated crystals of formazan blue were solubilized by adding DMSO (100 µl) and optical density (OD) was measured at a wavelength of 570 nm by using LISA plus microplate reader. The percentage of surviving cells was calculated using the following formula:

$$\text{Percentage of surviving cells (\%)} = \frac{\text{Mean OD of test compound}}{\text{Mean OD of control}} \times 100$$

Table 1: List of derivatives IIa/IIb and IIIa/IIIb synthesized in scheme 1

Compound	R	R_1	R_2	R_3	% yield
IIa-1	-C_6H_5	Morpholine	C_6H_5-NH-	-	90.0
IIa-2	-C_6H_5	Morpholine	4-Cl-C_6H_4-NH-	-	88.35
IIa-3	-C_6H_5	*N*-Methylpiperazine	4-NO_2-C_6H_4-NH-	-	86.93
IIa-4	-C_6H_5	*N*-Methylpiperazine	4-Cl-C_6H_4-NH-	-	79.36
IIa-5	-C_6H_5	Piperidine	C_6H_5-NH-	-	81.12
IIb-1	-CH_3	Morpholine	C_6H_5-NH-	-	81.12
IIb-2	-CH_3	Morpholine	4-Cl-C_6H_4-NH-	-	93.0
IIb-3	-CH_3	*N*-Methylpiperazine	C_6H_5-NH-	-	84.09
IIb-4	-CH_3	*N*-Methylpiperazine	4-Cl-C_6H_4-NH-	-	88.65
IIb-5	-CH_3	Piperidine	C_6H_5-NH-	-	92.25
IIIa-1	-C_6H_5	-	-	C_6H_5-NH-	82.91
IIIa-2	-C_6H_5	-	-	4-Cl-C_6H_4-NH-	79.03
IIIa-3	-C_6H_5	-	-	4-Br-C_6H_4-NH-	84.26
IIIb-1	-CH_3	-	-	C_6H_5-NH-	85.25
IIIb-2	-CH_3	-	-	4-Cl-C_6H_4-NH-	89.12
IIIb-3	-CH_3	-	-	4-Br-C_6H_4-NH-	78.03

RESULTS

Spectral data of 4-hydroxy-3-(3-morpholinopropanoyl)-1-phenylquinolin-2(1*H*)-one (Ia-1)

IR (KBr, cm^{-1}): 3032.10 (aromatic C-H); 2927.94, 2854.65 (aliphatic C-H); 1629.85 (C=O acetyl); 1606.70 (C=O cyclic amide); 1267.23 (C-O-C).

Spectral data of 4-hydroxy-3-(3-(4-methylpiperazin-1-yl) propanoyl)-1-phenylquinolin-2(1*H*)-one (Ia-2)

IR (KBr, cm^{-1}): 3041.74 (aromatic C-H); 2891.30, 2762.06 (aliphatic C-H); 1629.85 (C=O acetyl); 1606.70 (C=O cyclic amide).

Spectral data of 4-hydroxy-1-methyl-3-(3-morpholino-propanoyl) quinolin-2(1*H*)-one (Ib-1)

IR (KBr, cm^{-1}): 3076.46 (aromatic C-H); 2887.44, 2777.50 (aliphatic C-H); 1631.78 (C=O acetyl); 1606.70 (C=O cyclic amide); 1269.16 (C-O-C).

Spectral data of 4-hydroxy-1-methyl-3-(3-(4-methylpiperazin-1-yl)propanoyl) quinolin-2(1*H*)-one (Ib-2)

IR (KBr, cm^{-1}): 2912.51**,** 2762.06 (aliphatic C-H); 1631.78 (-C=O acetyl); 1606.70 (-C=O cyclic amide).

Spectral data of 4-hydroxy-3-(3-morpholino-1-(phenylimino) propyl)-1-phenylquinolin-2(1*H*)-one (IIa-1)

IR (KBr, cm^{-1}): 3442.94 (O-H stretch); 3099.16 (aromatic C-H); 2922.16 2852.72 (aliphatic C-H); 1643.35 (-C=N); 1610.56 (-C=O cyclic amide); 1271.09 (C-O-C); ^{1}H NMR ($CDCl_3$, δ ppm): 12.50 (s, 1H, OH); 8.27-6.64 (m, 14H, Ar-H); 4.03 (t, 4H, 2,6-CH_2 of morpholine); 3.79 (t, 2H,-CH_2 of 3-propyl); 2.43 (t, 4H, 3,5-CH_2 of morpholine); 1.20 (t, 2H,-CH_2 of 2-propyl); ^{13}C NMR ($CDCl_3$, δ ppm): 166.17(1C, C=N); 160.63 (1C, C=O amide); 158.28 (1C, C-OH); 132.17-116.02 (19C, aromatic carbon); 75.92 (1C,-CH_2 of 3-propyl); 66.02 (2C, 2,6-CH_2 of morpholine); 54.85 (2C, 3,5-CH_2 of morpholine); 21.03 (1C,-CH_2 of 2-propyl); Mass (m/z) = 453 [M^+].

Spectral data of 3-(1-((4-chlorophenyl) imino)-3-morpholinopropyl)-4-hydroxy-1-phenylquinolin-2(1H)-one (IIa-2)

IR (KBr, cm^{-1}): 3089.96 (aromatic C-H); 2983.88, 2875.86 (aliphatic C-H); 1645.33 (C=N); 1612.49 (C=O cyclic amide); 744.52 (C-Cl).

Spectral data of 4-hydroxy-1-methyl-3-(3-morpholino-1(-phenylimino)propyl) quinolin-2(1*H*)-one (IIb-1)

IR (KBr, cm^{-1}): 3012.81 (aromatic C-H); 2887.44, 2752.42 (aliphatic C-H); 1644.15 (C=N); 1610.56 (-C=O cyclic amide); 1273.02 (C-O-C); ^{1}H NMR ($CDCl_3$, δ ppm): 12.61 (s, 1H, OH); 8.13-6.53 (m, 9H, Ar-H); 4.13 (t, 4H, 2,6-CH_2 of morpholine); 3.72 (t, 2H,-CH_2 of 3-propyl); 2.61(s, 3H, N-CH_3); 2.29 (t, 4H, 3,5-CH_2 of morpholine); 1.20 (t, 2H, CH_2 of 2-propyl).

Spectral data of 4-hydroxy-1-methyl-3-(3-(4-methylpiperazin-1-yl)-1-(phenylimino)propyl) quinolin-2(1*H*)-one (IIb-3)

IR (KBr, cm^{-1}): 3039.81 (aromatic C-H)**;** 2891.30 2779.42 (aliphatic C-H); 1646.27 (C=N); 1612.49 (-C=O cyclic amide); ^{1}H NMR ($CDCl_3$, δ ppm): 12.41 (s, 1H, OH); 8.26-7.21 (m, 9H, Ar-H); 3.72 (s, 3H, N-CH_3); 3.21 (t, 2H, CH_2 of 3-propyl); 2.51 (t, 8H, 2,3,5,6-CH_2 of *N*-Methyl piperazine); 2.01 (s, 3H, N-CH_3); 1.63 (t, 2H, CH_2 of 2-propyl).

Spectral data of compound 3-(1-((4-chlorophenyl)imino)ethyl)-4-hydroxy-1-phenylquinolin-2(1*H*)-one (IIIa-2)

IR (KBr, cm^{-1}): 3055.24 (aromatic-C-H); 2924.09, 2850.35 (aliphatic C-H); 1656.85 (-C=N); 1612.49 (-C=O cyclic amide); 759.95 (C-Cl); ^{1}H NMR ($CDCl_3$, δ ppm):16.35 (s, 1H, OH); 8.20-6.51 (m, 13H, Ar-H); 2.24 (s, 3H,-CH_3); ^{13}C NMR ($CDCl_3$, δ ppm):175.40 (1C, C=N); 167.36 (1C, C=O amide); 161.30 (1C, C-OH); 149.64-110.37 (19C, aromatic carbon); 31.43 (1C, aliphatic carbon); Mass (m/z) = 389 [M+1].

Spectral data of compound 3-(1-((4-bromophenyl)imino)ethyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one. (IIIa-3)

IR (KBr, cm^{-1}): 3057.17 (aromatic-C-H); 2902.87 (aliphatic C-H); 1654.92 (-C=N), 1600.92 (-C=O cyclic amide); 704 (C-Br); ^{1}H NMR ($CDCl_3$, δ ppm):16.23(s, 1H, OH), 8.17-6.68 (m, 13H, Ar-H); 2.09 (s, 3H,-CH_3).

Table 2: Results for anticancer activity on K562 cell line

S. No.	Sample	Concentration (µg)	Absorbance	Results as observed	IC_{50} (µg)
1.	IIa-1	10	0.350	<50% lysis	20 µg
2.		20	0.347	50% lysis	
3.		25	0.336	50% lysis	
4.		30	0.327	50% lysis	
5.		50	0.323	>50% lysis	
6	IIa-2	10	1.766	No lysis	-
7		20	1.699	No lysis	
8		25	0.801	No lysis	
9		30	0.742	No lysis	
10		50	0.457	<50% lysis	
11	IIa-3	10	0.816	No lysis	50 µg
12		20	0.718	No lysis	
13		25	0.544	No lysis	
14		30	0.453	<50% lysis	
15		50	0.352	50% lysis	
16	IIb-1	10	0.634	No lysis	50 µg
17		20	0.443	<50% lysis	
18		25	0.418	<50% lysis	
19		30	0.403	<50% lysis	
20		50	0.399	50% lysis	
21	IIb-3	10	0.266	>50% lysis	-
22		20	0.252	>50% lysis	
23		25	0.252	>50% lysis	
24		30	0.248	>50% lysis	
25		50	0.191	>50% lysis	
26	IIb-5	10	1.521	No lysis	-
27		20	0.825	No lysis	
28		25	0.694	No lysis	
29		30	0.468	No lysis	
30		50	0.411	<50% lysis	
96	Control	00	0.688	No lysis	-

Table 3: Results for anticancer activity on Hep 3b cell line

S. No.	Sample	Concentration (µg)	Absorbance	Results as observed	IC_{50} (µg)
1.	IIIa-1	10	0.397	>50% lysis	<10 µg
2.		20	0.388	>50% lysis	
3.		25	0.325	>50% lysis	
4.		30	0.287	>50% lysis	
5.		50	0.281	>50% lysis	
6	IIIb-1	10	0.721	<50% lysis	20 µg
7		20	0.570	50% lysis	
8		25	0.488	>50% lysis	
9		30	0.423	>50% lysis	
10		50	0.359	>50% lysis	
11	IIIa-2	10	0.606	<50% lysis	20 µg
12		20	0.527	50% lysis	
13		25	0.303	>50% lysis	
14		30	0.299	>50% lysis	
15		50	0.260	>50% lysis	
16	IIIb-2	10	0.822	<50% lysis	25 µg
17		20	0.672	<50% lysis	
18		25	0.585	50% lysis	
19		30	0.571	50% lysis	
20		50	0.486	>50% lysis	
21	IIIa-3	10	0.698	<50% lysis	20 µg
22		20	0.558	50% lysis	
23		25	0.425	>50% lysis	
24		30	0.360	>50% lysis	
25		50	0.335	>50% lysis	
26	IIIb-3	10	0.995	No lysis	25 µg
27		20	0.613	<50% lysis	
28		25	0.591	50% lysis	
29		30	0.477	>50% lysis	
30		50	0.472	>50% lysis	
96	Control	00	1.079	No lysis	-

Spectral data of 4-hydroxy-1-methyl-3-(1-(phenylimino) ethyl) quinolin-2(1*H*)-one. (IIIb-1)

IR (KBr, cm^{-1}): 3078.39, (aromatic C-H); 2983.88, 2852.93 (aliphatic C-H); 1655.29(-C=N); 1612.49 (-C=O cyclic amide).

Spectral data of 3-(1-((4-chlorophenyl) imino) ethyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one. (IIIb-2)

IR (KBr, cm^{-1}): 3078.39 **(**aromatic C-H); 2941.44, 2924.09 (aliphatic C-H); 1651.07 (-C=N); 1563.60 (C=O cyclic amide).

Anticancer activity

The 4-hydroxy-3-(3-substituted-1-(substituted amino)propyl-1-phenyl/ methyl quinolin-2(1*H*)-one derivatives and 4-hydroxy-1-phenyl/ methyl-3-(1-substituted imino) methyl quinolin-2(1*H*)-one derivatives were tested for their *in vitro* anticancer activity against K562 and Hep 3b cell lines by MTT assay method and the results are presented in table 2 and table 3.

DISCUSSION

The synthetic routes of the compounds are outlined in scheme-1. The compounds were satisfactorily characterized by IR and NMR spectral data. The presence of–C=N stretch between 1660-1640 cm^{-1} in the IR spectra of compounds from series IIa/IIb and IIIa/IIIb and also the presence of signals such as two triplets at δ 4.13 and 2.29 respectively for eight protons of morpholine substituent in ^1H NMR spectrum of compound IIb-1; and singlet at 16.35 for one proton of–OH, multiplet at 8.20-6.51 for thirteen aromatic protons and singlet at 2.2 for three protons of methyl group in ^1H NMR spectrum of compound IIIa-2 confirmed the synthesis of the derivatives. Similarly, results from the ^{13}C NMR spectra and mass spectra of the compounds also proved the completion of reactions.

Selected compounds from the IIa/IIb series were tested for their *in vitro* anticancer activity against K562 cell line and those from the IIIa/IIIb series were evaluated for their *in vitro* anticancer activity against Hep 3b cell line. Compound IIa-1 (R=-C_6H_5 and R_1= morpholine; R_2= C_6H_5-NH-) showed the least IC_{50} value of 20 µg and thus was the most potent compound against K562 cell line. Compounds IIa-3 and IIb-1 had moderate potencies with an IC_{50} value of 50 µg. The compounds IIa-2, IIb-3 and IIb-5 showed no cell lysis and were inactive. When evaluated for *in vitro* anticancer activity against Hep 3b cell line, all of the tested derivatives from IIIa/IIIb series exhibited cell lysis. The compound IIIa-1 (R=-C_6H_5 and R_3= C_6H_5-NH-) was found to be most cytotoxic with an IC_{50} of less than 10 µg. The compounds IIIb-2, IIIb-3 (IC_{50} value of 25 µg) and IIIb-1, IIIa-2, IIIa-3 (IC_{50} value of 20 µg) were found to be moderately potent.

CONCLUSION

The proposed method for the synthesis of novel quinolin-2-one derivatives is convenient and gives a good yield. Some of the synthesised compounds showed significant *in vitro* anticancer activity against K562 and Hep 3b cell lines. Compound IIa-1 (R=-C_6H_5; R_1= morpholine; R_2= C_6H_5-NH-) exhibited most potent activity against K562 cell lines. Compound IIIa-1 (R=-C_6H_5; R_3= C_6H_5-NH-) was proved to be the most cytotoxic compound among the other derivatives against Hep 3b cell lines.

ACKNOWLEDGEMENT

We are thankful to the authorities of Sophisticated Analytical Instrumentation Facility, Panjab University, Chandigarh, for providing the facilities of spectral analysis such as ^1H NMR, ^{13}C NMR and mass. Our sincere gratitude is directed to Dr. Kishore Bhat, Professor and Head, Department of Microbiology, Maratha Mandal's NGH Institute of Dental Sciences and Research Centre, Belgaum, Karnataka for providing the biological activity facility to carry out the anticancer activity.

AUTHORS CONTRIBUTION

Ms. Saili S. Desai (Department of Pharmaceutical Chemistry, P. E. S.'s Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Ponda-Goa) was in charge of the synthetic bench work. Mr. Rudrax N. S. Priolkar (Department of Pharmaceutical Chemistry, P. E. S.'s Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Ponda-Goa) and Mr. Harshank A. Naik Karmali (Department of

Pharmaceutical Chemistry, P. E. S.'s Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Ponda-Goa) were responsible for interpretation of the spectra. Mr. Prabhav D. Ambe (Department of Pharmaceutical Chemistry, P. E. S.'s Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Ponda-Goa) and Mr. B. S. Biradar (Department of Pharmacology, P. E. S.'s Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Ponda-Goa) assisted in the anticancer activity studies. Dr. S. N. Mamle Desai (Department of Pharmaceutical Chemistry, P. E. S.'s Rajaram and Tarabai Bandekar College of Pharmacy, Farmagudi, Ponda-Goa) is the research guide and supervised the overall research work.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. www.who.int/media centre/factsheets/fs297/en. [Last accessed on 15 Mar 2017]
2. Thomas K. The pyrano route to 4-hydroxy-2-quinolones and 4-hydroxy-2-pyridones. IL Farmacol 1999;54:309-15.
3. Afzal O, Kumar S, Haidar R, Ali R, Kumar R, Jaggi M, *et al.* A review on anticancer potential of bioactive heterocycle quinoline. Eur J Med Chem 2015;97:871-910.
4. Ohashi T, Oguro Y, Tanaka T, Shiokawa Z, Shibata S, Sato Y, *et al.* Discovery of pyrrolo[3,2-*c*]quinolin-4-one derivatives as novel hedgehog signalling inhibitors. Bioorg Med Chem 2012;20:5496.
5. Zhang Q, Chen Y, Zheng YQ, Xia P, Xia Y, Yang ZY, *et al.* Synthesis and bioactivity of 4,10-dimethylpyridino[2,3-*h*]quinolin-2(1H)-one-9-carboxylic acid and its esters. Bioorg Med Chem 2003;11:1031.
6. Maria GR, Shivlingrao MD, Soniya N, Jairus F, Prasad T, *et al.* Synthesis and evaluation of 2-(4-methoxy-2-oxo-1-phenyl/ methyl-1,2-dihydroquinolin-3-yl)-2-methyl-3-(phenyl/ substitutedphenylamino)thiazolidin-4-one as antibacterial and anticancer agents. Indian J Chem 2016; 55B:1254-8.
7. Trianquand C, Romanet JP, Nordmann JP, Allaire C. Efficacy and safety of long-acting carteolol 1% once daily. A double-masked, randomised study. J Fr Opthalmol 2003;26:131-6.
8. Ogino K, Hobara T, Ishiyama H, Yamasaki K, Kobayashi H, Izumi Y, *et al.* Antiulcer mechanism of action of rebamipide, a novel antiulcer compound, on diethyldithiocarbamate-induced antral gastric ulcers in rats. Eur J Pharmacol 1992;212:9-13.
9. De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, *et al.* Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis. J Psychopharmacol 2012;26:603-17.
10. Qun L, Keith WW, Weibo W, Nan-Horng L, Akiyo C, Wen-zhen G, *et al.* Design, synthesis and activity of achiral analogues of 2-quinolones and indoles as non-thiol farnesyltransferase inhibitors. Bioorg Med Chem Lett 2005;15:2033-9.
11. Jiangdong S, Zili X, Michael AI, Chandrashekhar K, Bulbul P, Zhigen H, *et al.* Structure-activity relationships studies of the anti-angiogenic activities of linomide. Bioorg Med Chem Lett 2003;13:1187-9.
12. Jochmans D. Novel HIV-1 reverse transcriptase inhibitors. Virus Res 2008;134:171-85.
13. Khan SR, Mhaka A, Pili R, Issacs JT. Synthesis and antiangiogenic activity of linomide. Bioorg Med Chem Lett 2001;11:451-2.
14. Roschger P, Fiala W, Stadlbaurer W. Nucleophilic substitution and ring closure reactions of 4-chloro-3-nitro-2-quinolones. J Heterocyclic Chem 1992;29:225.

How to cite this article

- SN Mamle Desai, Rudrax NS Priolkar, Harshank A Naik Karmali, Prabhav D Ambe, BS Biradar. Synthesis, characterization and evaluation of 4-hydroxy-1-phenyl/methyl-3-(3-substituted-1-(substituted amino)propyl) quinoline-2(1*H*)-one derivatives and 4-hydroxy-1-phenyl/methyl-3-(1-(substituted imino)ethyl) quinoline-2(1*H*)-one derivatives as possible anticancer agents. Int J Pharm Pharm Sci 2017;9(10):240-244.