



SYNTHESIS, ANTI-VIRAL AND CYTOTOXICITY STUDIES OF SOME 2-PHENYL-3-SUBSTITUTED QUINAZOLIN-4-(3H)-ONES

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ABSTRACT

A Series of Novel 2-Phenyl-3-Substituted Quinazolin-4-(3H) one derivatives were synthesized and screened for anti-viral activity against panel of human pathogenic viruses. The structures of the synthesized compounds were characterized by means of their IR, ¹H-NMR data. The anti-HIV activities of the new compounds were screened *in vitro* anti-viral activity against replication of HIV-1 (IIB) and HIV-2 (ROD) in MT-4 cells using AZT-as standard. All the compounds displayed cytostatic properties in T-lymphocytes MT-4 cells. The compound 4-((4-oxo-2-phenylquinazolin-3(4H)-yl amino) methyl amino benzoic acid (QPAB) (CC₅₀=11.90 µg/ml) displayed significant toxic in this series. 2-amino-3-phenyl quinazolin-4(3H)-one (BN) exhibited anti-viral activity against Herpes Simplex virus-1,2 and Vaccinia virus in HEL cells at the concentration of 10 and 12 µg/ml, whereas cytotoxicity was found to be 100 µg/ml (SI = 10). Among these compounds, compounds (QIS and QMB) exhibited anti-viral activity against Vesicular Stomatitis virus in HeLa cells at the concentration of 12 µg/ml, whereas cytotoxicity was found to be 100 µg/ml (SI = 9).

Keywords: Antiviral, Quinazolin derivatives, cytotoxicity

INTRODUCTION

quinazolin-4-(3H)-one is a versatile lead molecule for the design of potential bioactive agents. alagarsamy *et al*¹, 2000; shah *et al*², 1995; and desai *et al*³, 1998 reported anti-hiv activity of 2-phenyl-3-substituted quinazolin-4-(3H)-ones. the literatures also reinforces that the 2-phenyl-3-substituted quinazolin-4-(3H)-ones also possess to have anti cancer^{4, 5, 6, 7} and marked antiviral^{8, 9, 10} activities against other viruses. a large number of quinazolines have been synthesized and studied for wide range of anti-viral activity but the anti-viral activities of quinazolines against viruses has not been well explored.

Anthranilic acid reacts with benzoyl chloride to form 2-phenyl-1, 3-benzoxazin-4-one by n-benzoylation followed by dehydrative cyclisation. 2-phenyl-3-amino quinazolin-4(3H)-one derivatives were synthesized by condensation of the compounds containing hydrazine hydrate with 2- phenyl-1, 3-benzoxazine-4-one. A series of 2-phenyl-3-substituted quinazolin-4(3H)-one derivatives were synthesized by condensation of the compounds containing primary aromatic amino group and formaldehyde with 2-phenyl-3-amino quinazolin-4(3H)-one by mannich reaction.

MATERIALS AND METHODS

Experimental section

Step-I

Anthranilic acid (0.1mol) was dissolved in 50 ml of pyridine. To this benzoyl chloride (0.2 mol.) was added drop wise with constant stirring at low temperature. When the addition of benzoyl chloride was completed, mixture was treated with 10% sodium bicarbonate solution (15 ml). After the effervescence ceased, mixture was filtered and washed repeatedly with water to remove inorganic materials. The crude drug thus obtained was recrystallised from ethanol.

Step-II

An equimolar (0.01 mol) mixture of benzoxazine and hydrazine hydrate was refluxed for 6hrs with 10ml of ethanol. The mixture was cooled to room temperature and poured into crushed ice, filter and then washed with water. The solid thus obtained was recrystallised from ethanol.

Step-III

An equimolar (0.01 mol) mixture of quinazolinone, aromatic primary amine and formaldehyde was refluxed for 6hrs with 10ml of ethanol

in acidic condition. The mixture was cooled to room temperature and poured into crushed ice, filter and then washed with water. The solid thus obtained was recrystallised from ethanol. The yield and melting point of synthesized compounds are shown in table no.2.

Melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded for KBr pellets on a (SHIMADZU-8400s) FT-IR spectrophotometer, ¹H-NMR spectra were determined BRUKER AMX 400 MHZ with tetramethylsilane as an internal standard. The sample is dissolved in DMSO-d₆ and the ¹H-NMR value is measured in δ ppm. The predicted IR and NMR values are tabulated in table no.3 and 4.

Biological investigation

Anti-HIV assay

Anti HIV assay compounds were tested for their inhibitory effects against replication of HIV-1 (IIB) and HIV-2 (ROD) in MT-4 cells. The MT-4 cells were grown and maintained in RPMI-1640 DM Medium supplemented with 10% (v/v) heat-inactivated Fetal

Calf Serum (FCS), 2 mM-glutamine, 0.1% sodium bicarbonate and 20 mcg/ml gentamicin (culture medium). Inhibitory effect of test compounds on HIV-1 and HIV-2 replications were monitored by inhibition of virus-induced cytopathic effect in MT-4 cells and were estimated by MTT assay. Briefly, 50 ml of HIV-1 and HIV-2 (100-300 CCID₅₀) were added to a flat-bottomed micro titer tray with 50 ml of medium containing various concentrations of compounds. MT-4 cells were added at a final concentration of 6 x 10⁵ cells/mL. After 5 days of incubation at 37°C, the number of viable cells were determined by the 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) method. Cytotoxicity of test compounds against mock infected MT-4 cells was also assessed by the MTT method. Compounds were evaluated for their inhibitory effect on the replication of HIV-1 & HIV-2 in human MT-4 cells. The anti-HIV and cytotoxicity data are presented in Table 5.

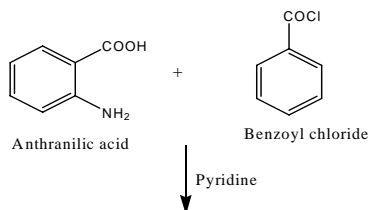
Anti-viral assay

Anti-viral activity and cytotoxicity of the synthesized compounds were determined by an *in vitro* cell culture technique. The anti-viral assays were based on inhibition of virus-induced cytopathicity in HeLa cells (VSV and RSV), HEL cells (HSV-1 and HSV-2), Vero cells (Parainfluenza-3, Reovirus-1, Sindbis virus, Coxsackie virus B4 and Punta Toro virus). Briefly, confluent cell culture in 96-wells micro titer plates were inoculated with 100 CCID₅₀ of virus, 1 CCID₅₀ being the virus dose required to infect 50% of the cell cultures. After 1 hr.

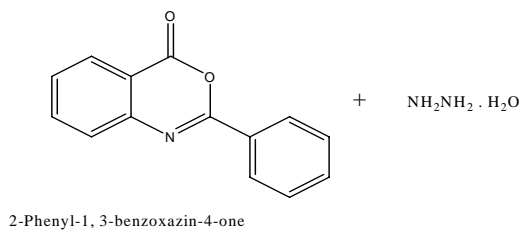
virus adsorption period, residual virus was removed, and the cell cultures were incubated in the presence of varying concentrations (400,200 and 100µg/ml) of the test compounds. Viral cytopathicity

was recorded as soon as it reached completion in the control virus-infected cell cultures that were treated with the test compounds. The anti-viral and cytotoxicity data are presented in Tables 6-8.

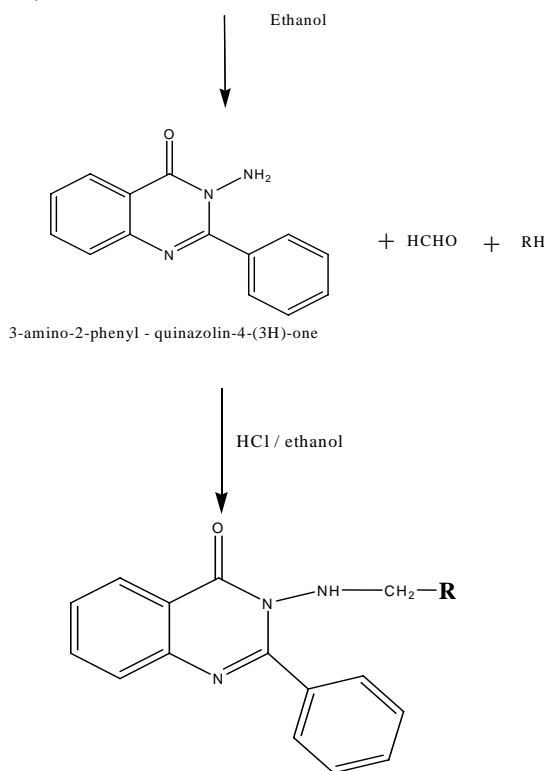
Step-I



Step-II



Step-III



Scheme

RESULTS AND DISCUSSION

A Series of 2-Phenyl-3-substituted Quinazolin-4(3H)-one derivatives were synthesized and screened for antiviral activities against pathogenic human viruses.

The inhibitory effect of anti-viral drugs on the HIV-induced cytopathic effect (CPE) in human lymphocyte MT-4 cell culture was determined by the MT-4/MTT-assay. Cytotoxicity of test compounds against mock-infected MT-4 cells was also assessed by the MTT method. All the compounds displayed cytostatic properties in T-lymphocytes MT-4 cells. The compound 4-((4-oxo-2-

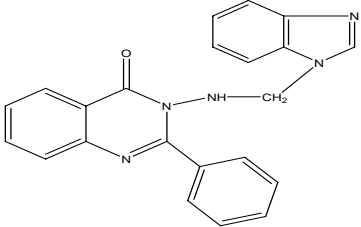
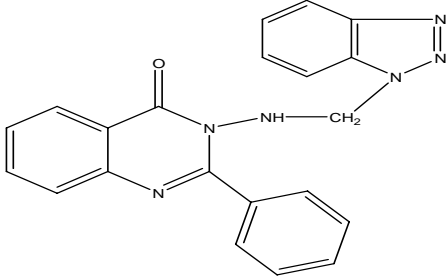
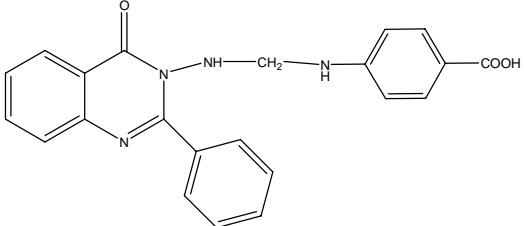
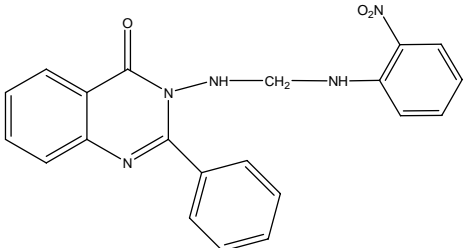
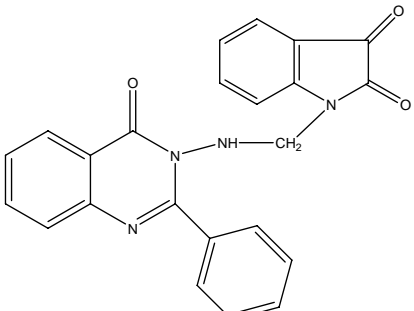
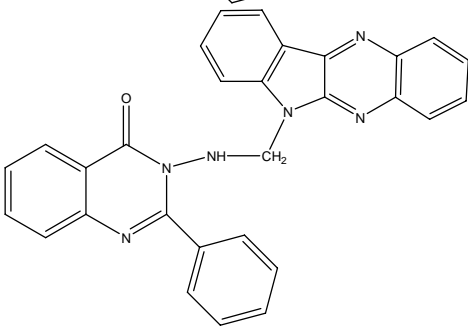
phenylquinazolin-3(4H)-yl amino) methyl amino benzoic acid (QPAB) (CC_{50} =11.90 µM) was found to be more toxic in this series.

The synthesized compounds were tested for anti-viral against HeLa Cells (VSV and RSV) HEL cells (HSV-1 and HSV-2) and Vero cells (Parainfluenza-3, Reovirus-1, Sindbis virus, Coxsackie virus B4 and Punta Toro virus. 2-amino-3-phenyl quinazolin-4(3H)-one (BN) exhibited anti-viral activity against Herpes Simplex virus-1,2 and Vaccinia virus in HEL cells at the concentration of 10 and 12 µg/ml, whereas cytotoxicity was found to be 100 µg/ml ($\text{SI} = 10$). Among these compounds, compounds (QIS and QMB) exhibited anti-viral activity against Vesicular Stomatitis virus in HeLa cells at the

concentration of 12 µg/ml, whereas cytotoxicity was found to be 100 µg/ml (SI = 9).

Table 1: List of compounds synthesized

S. no	Compound code	Structure	Name of the compound
1.	QSM		N[4-((4-oxo-2-Phenyl Quinazolin-3(4H)methyl) sulphanilamido-isoxazole
2.	QSS		N[4-((4-oxo-2-Phenyl Quinazolin-3(4H)methyl amino)Phenylsulfonyl] acetamide
3.	QSD		N[4-((4-oxo-2-Phenyl Quinazolin-3(4H)methyl)Phenylsulfonyl] acetamide
4.	QPH		2-[[4-oxo-2-phenyl quinazolin-3(4H)-yl amino)-N-(4,6 dimethyl-2-pyrimidinyl) benzene sulphonamide.
5.	QBA		N-[[4-oxo-2-phenyl quinazolin-3(4H)-yl amino] methyl] benzamide.
6.	QCF		1-cyclopropyl-6-fluoro-4-oxo-7-[4-((4-oxo-2-phenyl quinazolin-3(4H)-yl amino) methyl) piperazin-1-yl]-1, 4-dihydroquinolin-3-carboxylic acid.
7.	QNF		1-Ethyl-6-fluoro-4-oxo-7-[4-((4-oxo-2-phenyl quinazolin-3-(4H)-yl amino) methyl) piperazin-1-yl] 1, 4-dihydroquinolin-3-carboxylic acid.

8.	QBI		3-[[1H-benzo[d]imidazol-1-yl] methyl amino]-2-phenylquinazolin-4(3H)-one.
9.	QBT		3-[[1H-benzo[d][1,2,3] triazol-1-yl] methyl amino]-2-phenylquinazolin-4(3H)-one.
10.	QPAB		4-[[4-oxo-2-phenylquinazolin-3(4H)-yl amino] methyl amino] benzoic acid.
11.	QNA		3-[[2-nitrophenyl amino] methyl amino]-2-phenyl quinazolin-4(3H)-one.
12.	QIS		1-[[4-oxo-2-phenyl quinazolin-3-(4H)-yl amino] methyl] indoline-2, 3-dione.
13.	QIP		3-[[6H-indolo [3,2-b] quinazolin-6-yl]methyl amino]-2-phenyl quinazolin-4(3H)-one.

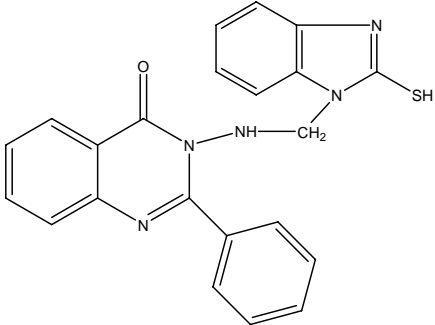
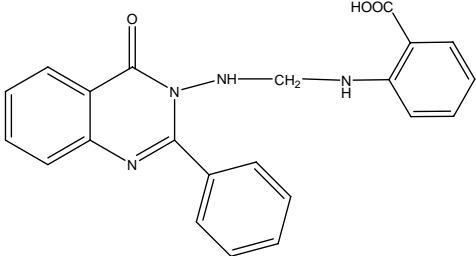
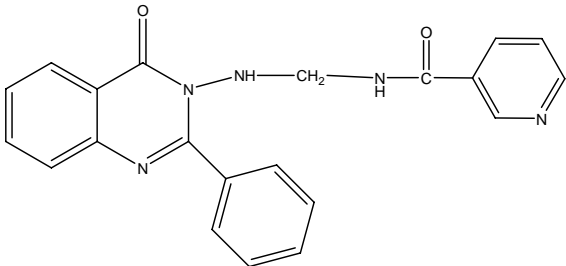
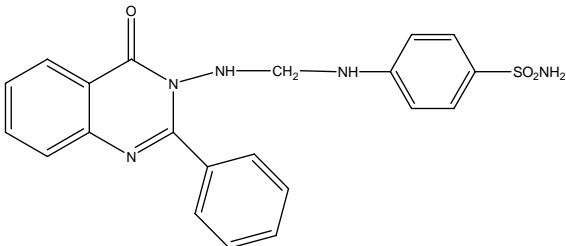
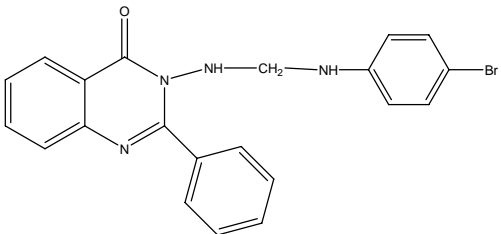
14.	QMB		3-[(2-mercapto-1H)-benzo[d]imidazol-1-yl)methyl amino]-2-phenyl quinazolin-4(3H)-one.
15.	QAA		2-[(4-oxo-2-phenyl quinazolin-3(4H)-yl)amino]methyl amino] benzoic acid.
16.	QNI		N-[(4-oxo-2-phenyl quinazolin-3(4H)-yl)amino]methyl] nicotinamide.
17.	QSA		4-[(4-oxo-2-phenyl quinazolin-3(4H)-yl)amino]methyl amino] benzene sulfonamide.
18.	QBR		3-[(4-bromo phenyl amino) methyl amino] - 2-phenyl quinazolin-4(3H)-one.

Table 2: Characterization data of compounds

Compound Code	Molecular formula	% Yield	M.P. (°C)	R _f value	Molecular weight
QSM	C ₂₅ H ₂₂ N ₆ O ₄ S	67.6	180 – 182	0.64	302
QSS	C ₂₃ H ₂₁ N ₅ O ₄ SNa	70.7	160 – 164	0.60	486
QSD	C ₂₇ H ₂₅ N ₇ O ₃ S	89.5	206 – 210	0.56	527
QPH	C ₂₃ H ₁₆ N ₄ O ₃	57.3	155 – 158	0.44	396
QBA	C ₂₂ H ₁₈ N ₄ O ₂	61.3	120 – 122	0.38	370
QCF	C ₃₁ H ₂₉ N ₆ O ₄ F	58.1	221 – 226	0.62	581
QNF	C ₃₁ H ₂₇ N ₆ O ₄ F	73.6	210 – 215	0.53	579
QBI	C ₂₂ H ₁₇ N ₅ O	80.4	100 – 104	0.47	367
QBT	C ₂₁ H ₁₆ N ₆ O	53.4	166 – 170	0.40	368
QPAB	C ₂₂ H ₁₈ N ₄ O ₃	58.2	180 – 184	0.47	366

QNA	C ₂₁ H ₁₇ N ₅ O ₃	53.4	110 – 115	0.84	367
QIS	C ₂₃ H ₁₆ N ₄ O ₃	48.7	140 – 146	0.47	376
QIP	C ₂₉ H ₂₀ N ₆ O	55.7	100 – 104	0.76	468
QMB	C ₂₂ H ₁₇ N ₅ OS	85.8	170 – 176	0.55	379
QAA	C ₂₂ H ₁₈ N ₄ O ₃	61.3	231 – 235	0.60	366
QNI	C ₂₁ H ₁₇ N ₅ O ₂	62.8	132 – 136	0.49	371
QSA	C ₂₁ H ₁₉ N ₅ O ₃ S	53.4	223 – 227	0.63	391
QBR	C ₂₁ H ₁₇ N ₄ OBr	55.3	106 – 110	0.86	401

Table 3: Characteristic IR absorption bands

S. no	Compound	-NH stretching (Cm ⁻¹)	-C=N stretching (Cm ⁻¹)	-C=C stretching (Cm ⁻¹)	-C=O stretching (Cm ⁻¹)	-SO ₂ stretching (Cm ⁻¹)	-CF stretching (Cm ⁻¹)
1.	BN	3212	1598	1606	1664	-	-
2.	QSD	3397	1508	1612	1603	1432	-
3.	QPH	3206	1528	1603	1729	-	-
4.	QBA	3305	1573	1633	1723	-	-
5.	QNF	3296	1481	1630	1718	-	1092
6.	QBI	3249	1591	1594	1676	-	-
7.	QBT	3143	1370	1521	1655	-	-
8.	QNA	3377	1509	1445	1672	-	-

Table 4: ¹H NMR SPECTRAL DATA

S. no	Compound	Hydrogen	δ Value in ppm	Multiplicity	Solvent
1.	BN	-Ar-H (9H) -NH ₂ (2H)	6-8.7 5.9	Multiplet Singlet	DMSO-D ₆
2.	QSD	-Ar-H (13H) -NH (1H)	6.3-8.7 4.7	Multiplet Singlet	DMSO-D ₆
3.	QPH	-Ar-H (13H) -NH (1H) -CH ₂ (2H)	6.9-8.1 11.2 4.4	Multiplet Singlet Singlet	DMSO-D ₆
4.	QBA	-Ar-H (14H) -NH (1H) -CH ₂ (2H)	6.9-8.1 4.9 3.2	Multiplet Singlet Singlet	DMSO-D ₆
5.	QNF	-Ar-H (11H) -NH (1H) -CH ₂ (2H) -COOH (1H)	6.9-8 9.4 4.3 9	Multiplet Singlet Singlet Singlet	DMSO-D ₆
6.	QBI	-Ar-H (13H) -NH (1H) -CH ₂ (2H)	6.6-8.7 4.8 4.2	Multiplet Singlet Singlet	DMSO-D ₆
7.	QBT	-Ar-H (9H) -NH (1H) -CH ₂ (2H)	6-8.8 4.7 3.4	Multiplet Singlet Singlet	DMSO-D ₆
8.	QNA	-Ar-H (9H) -NH (1H) -CH ₂ (2H)	6.5-8.8 4.8 4.2	Multiplet Singlet Singlet	DMSO-D ₆

Table 5: Anti-hiv activity and cytotoxicity of synthesized compounds in mt-4 cells

S. no.	Compound code	Strain	EC50 ^a (µg/ml)	CC50 ^b (µg/ml)	Maximum protection
1.	QAA	IIIB	>57.18	57.18 ± 6.32	5
		ROD	>57.18	57.18 ± 6.32	10
2.	QBA	IIIB	>106.10	106.10 ± 11.18	4
		ROD	>106.10	106.10 ± 11.18	3
3.	QBI	IIIB	>71.85	71.85 ± 1.16	6
		ROD	>71.85	71.85 ± 1.16	3
4.	QBR	IIIB	>60.63	60.63 ± 5.59	8
		ROD	>60.63	60.63 ± 5.59	5
5.	QBT	IIIB	>61.33	61.33 ± 4.48	3
		ROD	>61.33	61.33 ± 4.48	6
6.	QCF	IIIB	>52.48	52.48 ± 6.75	13
		ROD	>52.48	52.48 ± 6.75	12
7.	QIP	IIIB	>74.20	74.20 ± 2.43	1

8.	QIS	ROD	>74.20	74.20 ± 2.43	2
		IIIB	>27.93	27.93 ± 25.87	5
9.	QNA	ROD	>27.93	27.93 ± 25.87	5
		IIIB	>68.70	68.70 ± 7.95	2
10.	QMB	ROD	>68.70	68.70 ± 7.95	5
		IIIB	>66.65	66.65 ± 7.16	4
11.	QNF	ROD	>66.65	66.65 ± 7.16	5
		IIIB	>61.80	61.80 ± 3.40	1
12.	QNI	ROD	>61.80	61.80 ± 3.40	10
		IIIB	>125	>125	3
13.	QPAB	ROD	>125	>125	1
		IIIB	>11.90	11.90 ± 0.42	5
14.	QPH	ROD	>11.90	11.90 ± 0.42	17
		IIIB	>125	>125	2
15.	AZT	ROD	>125	>125	13
		IIIB	0.0012	65.9 ± 6.1	126
		ROD	0.00062	65.9 ± 6.1	148

^a Concentrations required to inhibit the cytopathic effect of HIV-1(III_B) in MT-4 cells by 50%.

^b Concentrations required to cause cytotoxicity to 50% of the MT-4 cells

All the Values are SD of two independent experiments. IIIB – HIV-1, ROD – HIV-2

Table 6: Cytotoxicity and anti-viral activity of compounds in HEL cell cultures

Compound code	Minimum cytotoxic concentration ^a (µg/ml)	EC ₅₀ ^b (µg/ml)			
		Herpes simplex virus-1 (KOS)	Herpes simplex virus-2 (G)	Vaccinia virus	Herpes simplex virus-1 TK-KOS ACV ^r
BN	>100	10	10	12	10
QAA	100	>20	>20	>20	>20
QBA	>100	>100	>100	>100	>100
QBI	100	>20	>20	>20	>20
QBR	100	>20	>20	>20	>20
QBT	>100	>100	>100	>100	>100
QCF	100	>20	>20	>20	>20
GIP	100	>20	>20	>20	>20
QIS	20	>4	>4	>4	>4
QNA	>100	>100	>100	>100	>100
QMB	>100	>100	>100	>100	>100
QNF	100	>20	>20	>20	>20
QNI	100	>20	>20	>20	>20
QPAB	100	>20	>20	>20	>20
QPH	100	>20	>20	>20	>20
QSA	100	>20	>20	>20	>20
QSD	100	>20	>20	>20	>20
QSM	100	>20	>20	>20	>20
QSS	100	>20	>20	>20	>20
Brivudin (µM)	>250	0.04	50	10	>250
Ribavirin (µM)	>250	>250	>250	>250	>250
Acyclovir (µM)	>250	2	2	7	2
Ganciclovir (µM)	>100	0.06	0.1	>100	12

^aRequired to cause a microscopically detectable alteration of normal cell morphology.

^bRequired to reduce virus-induced

Table 7: Cytotoxicity and anti-viral activity of compounds in Vero cell cultures

Compound Code	Minimum cytotoxic concentration ^a (µg/ml)	EC ₅₀ ^b (µg/ml)				
		Para influenza-3 virus	Reovirus-1	Sindbis virus	Coxsackie virus B4	Punta Toro virus
BN	>100	>100	>100	>100	>100	>100
QAA	100	>20	>20	>20	>20	>20
QBA	≥100	>100	>100	>100	>100	>100
QBI	>100	>100	>100	>100	>100	>100
QBR	100	20	>20	>20	>20	>20
QBT	>100	>100	>100	>100	>100	>100
QCF	100	>20	>20	>20	>20	>20
QIP	100	>20	>20	>20	>20	>20
QIS	100	>20	>20	>20	>20	>20

QNA	100	>20	>20	>20	>20	>20
QMB	100	>20	>20	>20	>20	>20
QNF	100	>20	>20	>20	>20	>20
QNI	100	>20	>20	>20	>20	>20
QPAB	100	>20	>20	>20	>20	>20
QPH	100	>20	>20	>20	>20	>20
QSA	100	>20	>20	>20	>20	>20
QSD	100	>20	>20	>20	>20	>20
QSM	>100	>100	>100	>100	>100	>100
QSS	100	>20	>20	>20	>20	>20
DS-5000	>100	>100	>100	>100	>100	>100
(S)-DHPA (μM)	>250	>250	250	>250	>250	>250
Ribavirin (μM)	>250	112	146	>250	>250	50

^aRequired to cause a microscopically detectable alteration of normal cell morphology.

^bRequired to reduce virus-induced cytopathogenicity by 50 %.

Table 8: Cytotoxicity and anti-viral activity of compounds in HeLa cell cultures

Compound code	Minimum cytotoxic concentration ^a ($\mu\text{g/ml}$)	EC ₅₀ ^b ($\mu\text{g/ml}$)		
		Vesicular stomatitis virus	Coxsackie virus B4	Respiratory syncytial virus
BN	100	>20	>20	>20
QAA	100	>20	>20	>20
QBA	≥ 100	>100	>100	>100
QBI	≥ 20	>20	>20	>20
QBR	100	>20	>20	>20
QBT	>100	>100	>100	>100
QCF	100	>20	>20	>20
QIP	≥ 20	>20	>20	>20
QIS	100	12	>20	>20
QNA	100	>20	>20	>20
QMB	100	12	>20	>20
QNF	100	>20	>20	>20
QNI	100	>20	>20	>20
QPAB	≥ 20	>20	>20	>20
QPH	100	>20	>20	>20
QSA	100	>20	>20	>20
QSD	100	>20	>20	>20
QSM	100	>20	>20	>20
QSS	>100	>100	>100	>100
DS-5000	>100	4	>100	4
(S)-DHPA (μM)	>250	112	>250	>250
Ribavirin (μM)	>250	12	146	10

^aRequired to cause a microscopically detectable alteration of normal cell

morphology, ^bRequired to reduce virus-induced cytopathogenicity by 50 %.

CONCLUSION

Result of present study evacuate that the series of 2-phenyl-3-substituted -4(3H)-one compounds elucidate promising antiviral activities against a series of pathogenic viruses including HIV.

The Anti-HIV studies of synthesized compounds showed significant cytotoxic effects against both HIV-I and HIV-II types of viruses compared to standard.

From the results obtained, we also concluded that the compounds exhibit good degree of cytotoxic effect against other viruses like HSV-I, HSV-II, Para influenza-3, Coxsackie virus B₄ and Punta Toro virus.

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