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SYNTHESIS, ANTI-HIV ACTIVITY AND CYTOTOXICITY STUDIES OF NOVEL 2-PHENYL, 3-SUBSTITUTED QUINAZOLIN-4(3*H*)-ONE DERIVATIVES

P. SELVAM[*], P. BABU, PADAM RAJ RATHORE and MYRIAM WITVROUW[a]

Arulmigu Kalasalingam College of Pharmacy, Anand Nagar, KRISHNANKOIL – 626190 (T.N.) INDIA
[a]Molecular Medicine, Katholieke Universiteit-Leuven and IRC KULAK, Kapucijnenvoer 33, B-3000 Leuven, FLANDERS (Belgium)

ABSTRACT

A series of novel 2, 3-disubstituted quinazolin-4(3H)-one derivatives have been synthesized by condensation of 2-substituted benzo[1, 3]oxazine-4-ones and primary amines. Their chemical structures were assigned by means of spectral analysis (FT-IR, ^{1}H-NMR, MS). Synthesized compounds were screened for *in vitro* antiviral activity against HIV-1(IIIB) in MT-4 cells. All the compounds displayed cytostatic properties in T lymphocytes cells and compounds QPABA and MSQN exhibited 19 and 16 percent maximum protection, respectively against HIV-1 at sub toxic concentration.

Key ward: Quinazolin-4(3H)-one, Anti-HIV activity, MT-4 cells, MTT method.

INTRODUCTION

Quinazolin-4(3*H*)-one is a versatile lead molecule for the design of potential bioactive agents and 2, 3-disubstituted quinazolin-4(3*H*)-ones were reported to possess anti-HIV[1-3], and antiviral[4-7]activities. We have previously synthesized novel heterocyclic compounds and screened for antiviral activity and some of the derivatives exhibited some activity against HIV and vaccinia virus[8-11]. A large number of quinazolines have been synthesized and studied for wide range of antiviral activity, but the antiviral activity against HIV virus of quinazolines is relatively less explored. Based on these findings, some new 6-bromo/6, 8-dibromo-2, 3-disubstituted quinazolinones were synthesized (**Scheme 1**) and screened for anti-HIV activity.

[*]Author for correspondence; E-mail: periyasamy_selvam@yahoo.co.in

EXPERIMENTAL

Melting points were determined using an open ended capillary tube method and are uncorrected. FT-IR spectra were recorded on Perkin Elmer–1605 series FT-IR in KBr disc. ^{1}H NMR spectra were recorded at 400 MHz on a Bruker FT-NMR spectrophotometer using TMS as internal standard.

General synthetic method for preparation of compounds

An equimolar mixture (0.01 mol) of 2-substituted benzo[1, 3]oxazine-4-one[12] and compounds with primary aromatic amino group were prepared and the mixture was refluxed for 6 h in 10 mL of pyridine. Upon cooling, the mixture was poured onto crushed ice. The precipitated solid was collected and recrystallized from ethanol to give the desired title compounds. The yields and the melting points of the compounds are given in Table 1.

Table 1: Characterization data of synthesized compounds

Compound code	Mol. Formula	Yield (%)	M.P(°C)	R_f Value
QSM	$C_{24}H_{18}N_4O_4S$	57.6	78-82	0.648
MSM	$C_{24}H_{17}N_4O_4SBr$	66.3	165-172	0.51
QSN	$C_{27}H_{18}N_4O_6S$	92.6	70-73	0.512
QAA	$C_{21}H_{14}N_2O_3$	72.7	148-154	0.118
QPABA	$C_{21}H_{14}N_2O_3$	51.6	135-139	0.384
QPP	$C_{22}H_{18}N_2O_2$	62.8	134-140	0.213
QOPD	$C_{20}H_{15}N_3O$	55.1	150-156	0.407
QAP	$C_{19}H_{13}N_3O$	68.1	72-75	0.424
DSM	$C_{24}H_{16}N_4O_6SBr$	59.5	154-158	0.361
MSN	$C_{27}H_{17}N_4O_6SBr$	80.2	106-112	0.661
DSN	$C_{27}H_{16}N_4O_6SBr_2$	55.3	80-85	0.574
QSB	$C_{27}H_{20}N_3O_3S$	63.5	107-110	0.176
QONA	$C_{20}H_{13}N_3O_3$	48.7	86-89	0.385
QPNA	$C_{20}H_{13}N_3O_3$	85.8	70-74	0.417

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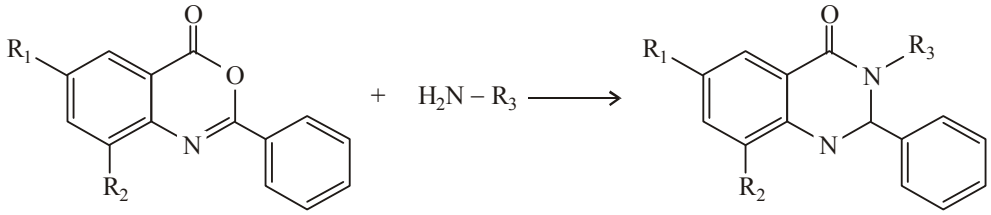
Compound code	Mol. Formula	Yield (%)	M.P(˚C)	R_f Value
QPH	$C_{20}H_{15}N_3O$	55.1	110-118	0.381
DSB	$C_{27}H_{19}N_3O_3SBr$	66.1	124-130	0.385
QPAP	$C_{20}H_{14}N_2O_2$	80.7	156-162	0.271

Scheme 1: Synthetic protocol of studied compounds



Compound Code	R_1	R_2	R_3
QSM	H	H	-Sulphamethoxazole
MSM	Br	H	-Sulphamethoxazole
DSM	Br	Br	-Sulphamethoxazole
QAP	H	H	-2-Aminopyridine
QSN	H	H	-(p-Nitrobenzoyl)-sulphonamide
MSN	Br	H	-(p-Nitrobenzoyl)-sulphonamide
DSN	Br	Br	-(p-Nitrobenzoyl)-sulphonamide
QAA	H	H	o-Aminobenzoic acid
Q-PABA	H	H	p-Aminobenzoic acid
QPP	H	H	p-Ethoxy-aniline
Q-OPD	H	H	-Anthanilic acid
QPH	H	H	-Aniline
Q-PAP	H	H	p-Aminophenol
Q-ONA	H	H	o-Nitrophenol
Q-PNA	H	H	p-Nitrophenol
QSB	H	H	-(p-Benzoyl)-sulphonamide
DSB	Br	Br	-(p-Benzoyl)-sulphonamide

QAA: IR (KBr) cm^{-1}: 1697 (C=O), 1661 (C=N), 1537 (C=C), 3128 (OH): ^1H NMR (DMSO-d_6): 8.1-7.1 (m, 13H, Ar-H), 11.6 (s, 1H, COOH); EI-MS (m/e): 342.

QPP: IR (KBr) cm^{-1}: 1603(C=O), 1511(C=N), 1325(C=C), 1046 (C-O-C), 3277 (Alkyl); ^1H NMR (DMSO-d_6): 8.1-6.9 (m, 13H, Ar-H), 1.4 (t, 2H, CH_2), 4.0(q, 3H, CH_3).EI-MS (m/e) : 342.

QOPD: IR (KBr) cm^{-1}: 1303 (NH), 1654 (C=O), 1590 (C=N), 1514 (C=C), ^1H NMR (DMSO-d_6): 8.2-7.2 (m, 13H, Ar-H), 4.0(s, 1H, Ar-C-NH). EI-MS (m/e): 313.

QPABA: IR (KBr) cm^{-1}: 3279 (OH), 3063(Ar-H), 1700 (C=O), 1652 (C=N), 1593 (C=C); ^1H NMR (DMSO-d_6): 7.2-8.1 (m, 13H, Ar-H), 10.5 (s, 1H, CO<u>OH</u>) EI-MS (m/e): 342.

MSM: IR (KBr) cm^{-1}: 3094 (NH), 1701 (C=O), 1601 (C=N), 1520 (NO_2), 1097 (SO_2), 510(Br); ^1H NMR (DMSO-d_6): 8.4-7.3 (m, 17H, Ar-H), 8.6 (s, 1H, NH) EI-MS (m/e): 536.

QSN: IR (KBr) cm^{-1}: 3067 (Ar-H), 1765 (C=O), 1313 (C=N), 1610 (C=C), 1473(NO_2); ^1H NMR (DMSO-d_6): 8.2-7.4 (m, 17H, Ar-H), 8.4 (d, 1H,NH). EI-MS (m/e):526.

QSM: IR (KBr) cm^{-1}: 1615 (C=O), 1311 (C=N), 1519 (C=C), 1019 (C-O-C); ^1H NMR (DMSO-d_6): 8.3-7.4 (m, 14H, Ar-H), 3.4 (s, 1H, NH), 2.5(s, 3H, methyl); EI-MS (m/e) : 458.

QAP: IR (KBr) cm^{-1}: 1671 (C=O), 1374 (C=N), 1537 (C=C), 3266(Ar H); ^1H NMR (DMSO-d_6): 8.5-7.1 (m, 13H, Ar-H). EI-MS (m/e):299.

Anti-HIV activity

The compounds were tested for anti-HIV activity against the replication of HIV-1(III_B) in MT-4 cells[11]. Anti-HIV activity and cytotoxicity of AZT were also determined by a similar method in MT-4 cells. The anti-HIV activity and cytotoxicity data are presented in Table 2.

Table 2: Anti-HIV activity of quinazolin-4(3*H*)-one derivative in MT-4 cells

Code	EC_{50} [a] (µM)	CC_{50} [b] (µM)	Max. Protection (%)
QAA	>17.19	17.19	5
QONA	>35.06	35.06	13

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Code	EC_{50} [a] (µM)	CC_{50} [b] (µM)	Max. Protection (%)
QOPD	>48.48	48.48	8
QPABA	>154.34	154.34	19
QPAP	>23.39	23.39	1
QPH	>92.48	92.48	1
QPNA	>97.16	97.16	7
QPP	>250	250	3
DQSB	>34.58	34.58	1
DQSN	>70.72	70.72	4
DSM	>57.20	57.20	3
MQSM	>59.20	59.20	1
MQSN	>102.08	102.08	16
QAP	>141.71	141.71	1
QSB	>70.57	70.57	6
QSM	>53.95	53.95	3
QSN	>47.05	47.05	1
AZT	0.0064	65.90	106

[a]50% Effective concentration of compound, achieving 50% protection of MT-4 cells against the cytopathic effect of HIV. [b]50% Cytotoxic concentration of compound, required to reduce the viability of mock- infected MT-4 cells by 50%

RESULTS AND DISCUSSION

Anthranilic acid reaction with benzoyl chloride yielded 2-phenyl-1, 3-benzoxazin-4-one by N-acylation via dehydrative cyclization[12]. A series of novel 2, 3-disubstituted quinazolin-4(3*H*)-one derivatives were synthesized by condensation of the compounds containing primary aromatic amino group with 2-substituted-1, 3-benzoxazine-4-one to afford 2, 3-disubstituted quinazolin-4(3*H*)-one derivatives.

All the compounds displayed cytostatic properties in T lymphocytes cells and the compound **QAA** (CC_{50}=17.19 µM) was found to be more toxic in this series. Compounds

QPABA and **MSQN** exhibited 19 and 16 percent maximum protections, respectively, against replication of HIV-1 in acutely infected MT-4 cells at sub toxic concentrations. Further molecular modification in this series may help in optimizing antiviral activity.

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