Research Article

Microwave Assisted Synthesis, Characterization and Pharmacological Evaluation of Imidazolo Quinazoline-4-one Derivatives

Venakata Ramana Reddy*, Nadendla Rama Rao[1], R.Raja Reddy[2], R.Suthakaran[3]
*[2]Malla Reddy Pharmacy College, Dhulapally, Secunderabad, India.
[1]Acharya Nagarjuna University, Guntur, Andhra Pradesh, India.
[3]Teegala Ram Reddy College of Pharmacy, Meerpet, Hyderabad, India.
***Corresponding author's E-mail:**

Accepted on: 04-11-2013; **Finalized on:** 30-11-2014.

ABSTRACT

Novel series of imidazolo quinazoline-4-one derivatives analogs were synthesized and they were potentially screened for certain selective biological properties. All the synthesized compounds were characterized by IR, NMR, Mass spectroscopic analysis and physicochemical properties were analyzed. The compounds showed significant free radical scavenging activity compared with the standard drug ascorbic acid, antihistaminic action against histamine induced aerosolisation in guinea pig and its ileum in *in-vitro* method, anti-inflammatory action by carrageenan induced paw oedema, pylorus ligation induced gastric ulcer and *in-vitro* antitumor action in selective cancer cell lines.

Keywords: 4(3*H*)-Quinazolinone analogs, Antioxidant, Anti-inflammatory, Antihistaminic and anti-tumor activities, Spectral analysis, Ulcer index.

INTRODUCTION

Quinazolinones possesses a variety of interesting pharmacological activities including anti-oxidant, H_1-antihistaminic, anti-inflammatory and antitumor activities.[1] Quinazolinone has all the attributes necessary for a good pharmacophores.[2] A number of derivatives of this nucleus are in different stages of development as clinical agents for the treatment of different diseases. 3*H* (4) - Quinazolinone derivatives have evoked considerable attention in recent years as these are endowed with wide range of pharmacological activities.[3] It represents a useful nucleus for preparation of some new sedative / hypnotic and anticonvulsant agents since such a heterocyclic system possesses the pharmacophoric moiety.

MATERIALS AND METHODS

Synthesis

General scheme of 3-(2-((16Z)-4-subs.benzylidene-4,5-dihydro-5-oxo-2-phen-ylimidazol-1-yl) ethyl)-6,8-dibromo/unsubs.-2-methylquinazolin-4(3*H*)-one

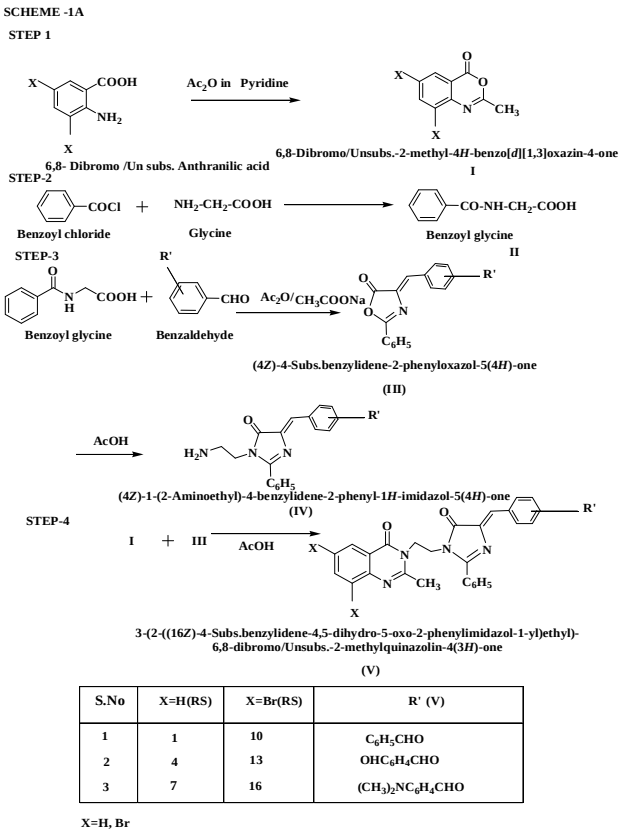
Spectral analysis

IR spectra will be done on a JASCO FT/IR-5300 spectrometer. Mass spectra will be taken with a Hewlwtt Packard model 5989B. NMR spectra will be taken on a Varian Gemini-2000 (500 MHz) spectrometer.

Pharmacological evaluation

A rapid progress in the work on 4(3*H*)-quinazolinones have been given rise to a number of compounds exhibiting a variety of potent pharmacological actions.[4] All the animals wherever used for pharmacological evaluations were procured from, Andhra Pradesh, India and were obtained Institutional Animal Ethical Committee (IAEC) permission for all standard protocols, the IAEC number is 1515/PO/A/11/CPCSEA.

SCHEME -1A



S.No	X=H(RS)	X=Br(RS)	R' (V)
1	1	10	C_6H_5CHO
2	4	13	OHC_6H_4CHO
3	7	16	$(CH_3)_2NC_6H_4CHO$

X=H, Br

Antioxidant activity

DPPH free radical scavenging assay

The free radical scavenging assay was conducted according to the procedure and method followed by Nesterova *et al.*[5]

Anti histaminic activity (*In-vitro and In-vivo*)

Histamine aerosol induced bronchoconstriction method was adopted for the in-vivo antihistaminic activity.[6] The *in vitro* antihistaminic activity was evaluated by measuring the inhibition of the isotonic contraction induced by histamine on isolated guinea pig ileum.[7]

Anti-inflammatory activity

Acute anti-inflammatory model (Carrageenan induced rat hind paw oedema). The method of Winter et al[8] was used with slight modification.

Ulcerogenicity index

Pyloric ligation was performed as described by behave et al.[9]

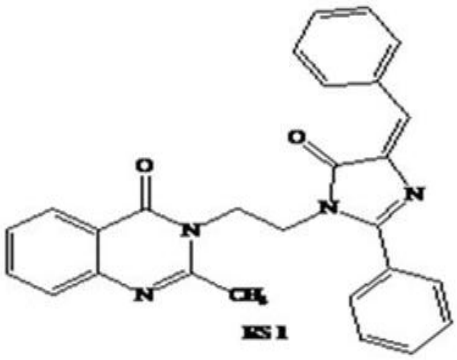
Antitumor activity (MTT assay)

The microculture tetrazolinium assay is based on metabolic reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide(MTT) to water insoluble blue fromazan crystal with mitochondrial dehydrogenase enzyme.[11,12] This will give direct correlation of viable cells.[10, 11]

RESULTS AND DISCUSSION

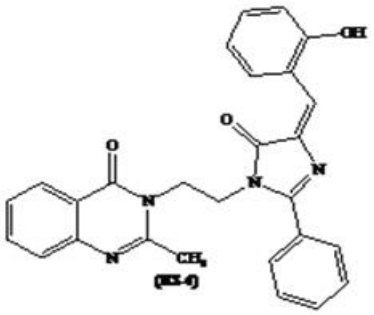
Physicochemical characters and spectral analysis data's were listed below: The compounds RS1, RS4, and RS7 have two active sites for substitutions namely methyl at position 2 of quinazoline and phenyl /OH-phenyl/ $(CH_3)_2N$-phenyl at 3(2(4- of imidazoline. There are three active sites for substitution in compounds **RS10, RS13**, and **RS16** namely dibromo at 6,8 and methyl at position 2 of quinazoline and ph. /OH-ph. / $(CH_3)_2N$-phenyl) at 3(2(4- of imidazoline moiety.

3-(2-((16E)-4-Benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-methylquinazolin-4(3*H*)-one (RS1)



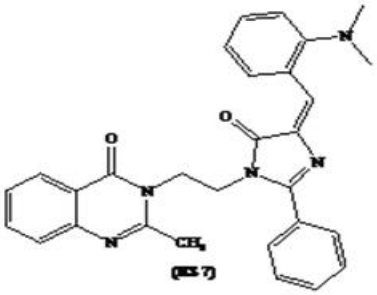
M.W. 434.49; M.F. $C_{27}H_{22}N_4O_2$;Yield 67%; M.P. 312^oC; R_f 0.48($CHCl_3$) ; IR(KBr) cm^{-1}:3120 (Ar-NH), 3014 (Ar), 1658(C=O),1527 (CH); ^1H NMR ($CDCl_3$): 0.9 (s, 3H, CH_3), 3.26 ,3.46 (t, 2H, CH_2), 7.64 (d, 1H, =CH-) 7.21-7.9 (m, 15H, heterocyc); EI-MS (70 eV) [m/z, %] :77, 90, 144, 159, 247, 434, 435, 436; Elem. Anal. Calc'd for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89; O, 7.36. Found: C, 74.54; H, 5.20; N, 12.79; O, 7.46.

3-(2-((16E)-4-(2-Hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenyl imidazol-1-yl)ethyl)-2-methylquinazolin-4(3*H*)-one (RS4)



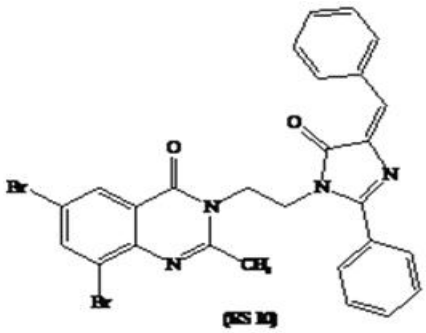
M.W 450.49; M.W. $C_{27}H_{22}N_4O_3$;Yield 94%; M.P. 331 ^0C ; R_f 0.51(CH_3Cl); IR (KBr cm^{-1}): 3122 (Ar-NH), 3010 (Ar-H), 1656 (C=O), 1510 (Lactone) ; Elem. Anal. Calc'd for $C_{27}H_{22}N_4O_3$: C, 71.99; H, 4.92; N, 12.44; O, 10.65. Found: C, 71.89; H, 5.02; N12.42; O, 10.67.

3-(2-((16E)-4-(2-(Dimethylamino) benzylidene)-4,5-dihydro-5-oxo- 2-phenylimidazol -1-yl) ethyl)-2-methylquinazolin-4(3*H*)-one (RS7)



M.W. 477.56; M.F. $C_{29}H_{27}N_5O_{2.}$; Yield 63%; M.P. 319 ^0C; R_f 0.46 (CH_3Cl) ; IR (KBr cm^{-1}): 3122(Ar-NH), 3010(Ar-H), 1656(C=O), 1510 (Lactone). Elem. Anal. Calc'd for $C_{29}H_{27}N_5O_2$: C, 72.94; H, 5.70; N, 14.66; O, 6.70. Found: C, 72.74; H, 5.90; N, 14.86; O, 6.50.

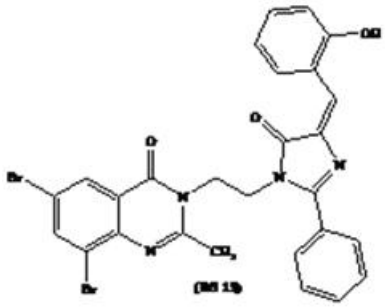
3-(2-((16E)-4-Benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (RS10)



M.W. 592.28; M.F. $C_{27}H_{20}Br_2N_4O_2$;.Yield 79%; M.P. 315^oC; R_f 0.48(CH_3Cl); IR (KBr) cm^{-1}:3322 (Ar-NH), 3013(Ar), 1650(C=O),1520 (CH); ^1H NMR ($CDCl_3$): 0.85 (s, 3H, CH_3), 3.6 , 3.8 (t, 2H, CH_2), 7.1(d, 1H, =CH-) 7.21-7.9 (m, 15H, heterocyc) ; EI-MS (70 eV) [m/z, %] : 77, 79, 125, 275, 300, 314, 342, 573, 590, 594, 595; Elem.Anal. Calc'd for

$C_{27}H_{20}Br_2N_4O_2$: C, 54.75; H, 3.40; Br, 26.98; N, 9.46; O, 5.40. Found: C, 54.45; H, 3.70; Br, 26.98; N, 9.26; O, 5.60.

3-(2-((16E)-4-(2-Hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-6,8-dibromo-2-methylquinazolin-4(3*H*)-one(RS 13)



M.W. 608.28; M.F. $C_{27}H_{20}Br_2N_4O_3$; Yield 84%; M.P. 301 ^{0}C; R_f 0.46; IR (KBr cm^{-1}): 3323 (Ar-NH), 3350 (Ar-H), 3013 (Ar)1650(C=O), 1520 (Lactone); Elem. Anal. Calc'd for $C_{27}H_{20}Br_2N_4O_3$: C, 53.31; H, 3.31; Br, 26.57; N, 9.21; O, 7.89. Found: C, 53.11; H, 3.51; Br, 26.47, N, 9.01; O, 7.89.

3-(2-((16E)-4-(2-(Dimethylamino)benzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (RS 16)

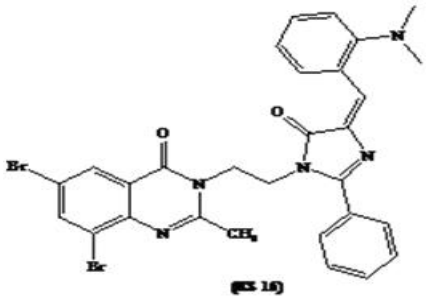


Table 1: DPPH radical scavenging activity of 3-(2-((19Z)-4-subs.-benzylidene- 4, 5-dihydro- 5- oxo-2-phenylimidazol-1-yl) ethyl)-6, 8-dibromo-2-subs Quinazolin -4(3*H*)-one

COM	% Scavenging					
	10µg/mL	25µg/mL	50µg/mL	100µg/mL	250µg/mL	500µg/mL
RS1	30.054±0.78	39.876±07	49.702±0.7	59.524±0.7	69.354±0.75	79.174±0.7
RS4	12.842±0.95	25.572±09	32.604±0.9	42.484±0.8	52.374±0.87	82.016±0.8
RS7	11.15±4.476	28.46±2.7	35.472±2.4	43.418±2.1	51.374±1.77	75.218±0.9
RS10	20.308±1.04	30.11±1.2	40.032±0.9	49.894±0.9	59.764±0.92	79.486±0.8
RS13	25.442±1.32	31.75±0.9	45.362±3.7	49.898±7.7	55.826±2.79	75.55±2.84
RS16	13.406±1.07	23.266±10	33.13±1.00	42.99±0.97	52.854±0.94	82.444±0.8
STD	49.908±2.71	59.726±23	67.636±2.33	77.454±1.50	87.272±1.58	94.8±0.187

* % Inhibition= (C-T) / C x 100, C- Control absorbance, T- Test absorbance ; Significant levels p <0.01 as compared with the respective control; [a]Each value represents the means ± SD (n=6)

Table 2: H_1-Antihistaminic activity of 3-(2-((16Z)-4-subs.-benzylidene-4, 5-dihydro-oxo-2-phenylimidazol-1-yl) ethyl)-6, 8-H/dibromo-2-methyl quinazolin -4(3*H*)-ones

Compound	Substituent's			*In vivo* studies		*In vitro* studies	% CNS
	X	R a-c	R' 1-3	T.O.C (Sec)	% Prot'n	(IC_{50}) (ng/mL) 1x10^{-3}	Depr't
RS1	H	CH_3	C_6H_5	1079±13.730	91.84	4.2	4.44
RS4	H	CH_3	C_6H_4OH	783±5.718	88.76	4.32	3.52
RS7	H	CH_3	$C_6H_4N(CH_3)_2$	672±10.756	86.9	4.22	4.13
RS8	H	C_6H_5	$C_6H_4N(CH_3)_2$	1130±7.211	92.21	1.9	4.92
RS9	H	CH_2Cl	$C_6H_4N(CH_3)_2$	817±6.229	89.23	3.9	3.68
RS10	Br	CH_3	C_6H_5	722±5.701	87.82	2.1	2.96
RS13	Br	CH_3	C_6H_4OH	784±8.746	88.78	4.21	2.82
RS16	Br	CH_3	$C_6H_4N(CH_3)_2$	853±5.805	89.68	2.11	3.67
Control				88±0.8367			
CPM				1232±11.454	92.86	1	19.4
CTZ							7.46

*T.O.C = Time of onset of convulsant, % Prot'n = % Protection, % CNS Depr't = % CNS depressant, CPM= Chlorpheneramine maleate, CTZ= Cetrizine

M.W. 635.35; M.F. $C_{29}H_{25}Br_2N_5O_2$; Yield 78%; M.P. 307 ^{0}C; R_f 0.48 (CH_3Cl); IR (KBr cm^{-1}): 3333 (Ar-NH), 3013 (Ar-H), 3013 (Ar), 1638(C=O), 1520 (Lactone); Elem.Anal. Calc'd for $C_{29}H_{25}Br_2N_5O_2$:C, 54.82; H, 3.97; Br, 25.15; N, 11.02; O, 5.04. Found: C, 54.62; H, 4.17; Br, 25.05; N, 11.10; O, 5.06.

Pharmacological screening

The newly synthesized compounds scavenged the free radicals produced by the DPPH and they were compared with the standard ascorbic acid. All the compounds were shown significant antioxidant property. Antihistaminic

actions were mediated by blocking Histamine receptors and the animals shown better recoverment after the histamine aerosolisation. The time spent for being for normal reaction after aerosolisation was more when compared with the control animals. The synthesized compounds were compared with the standard drug chlorpheniramine maleate.

Table 3: Percent protection anti inflammatory activity of quinazoline-4(3*H*)-one analogs

Comp'd	% Protection			
	30 min	1 h	2 h	3 h
RS1	36±1.789	41±1.414	44± 1.871	34±1.414
RS10	37±2.098	49± 1.414	50± 1.789	30± 2.366

*Comp'd = Compound, Significant levels p <0.01 as compared with the respective control, [a] Each value represents the means ± SD (n=6)

Table 4: Ulcerogenicity index of quinazoline-4(3*H*)-one analog

Comp'd	Substituent's			Ulcer index
	X	R a-c	R' 1-3	
RS1	H	CH_3	C_6H_5	0.54± 0.02483
RS10	Br	CH_3	C_6H_5	0.69±0.01472
Control				0.14± 0.01414
Std				1.7± 0.0216

*Significant levels p <0.01 as compared with the respective control; [a] Each value represents the means ± SD (n=6)

Table 5: Antitumor activity of 3-(2-((19Z)-4-subs.-benzylidene-4,5-dihydro-5- oxo-2-phenylimidazol-1-yl) ethyl)-6,8-H/dibromo-2-subs.quinazolin- (3*H*)-ones

Comp'd	Substituent's			IC_{50} µg/ML		
	X	R a-c	R' 1-3	Vero	A-549	HBL-100
RS1	H	CH_3	C_6H_5	40.11	22.97	51.87
RS4	H	CH_3	C_6H_4OH	39.9	23.12	48.31
RS7	H	CH_3	$C_6H_4N(CH_3)_2$	71.9	35.33	152
RS10	Br	CH_3	C_6H_5	28.87	12.22	53.19
RS13	Br	CH_3	C_6H_4OH	32.78	14.95	52.54
RS16	Br	CH_3	$C_6H_4N(CH_3)_2$	27.19	13.75	46.76
STD				4.7	3.2	25

The *in-vitro* antihistaminic assay was potent and the contractions were reduced after the addition of compounds dilution. Histamine was one of the inflammatory mediators. The compounds were screened for anti-inflammatory action against carrageenan induced paw volume and the percentage inhibition and reduction in paw volume were significant as they compared with Indomethacin. The severity of the ulcer score and the ulcer index was reduced by the novel compounds compared with ranitidine in pylorus ligation induced ulcer in rats. This show the compounds possess cytoprotective activity. MTT assay confirms the anticancer nature of the compounds tested against A-549, Vero and HBL-500 cell lines.

CONCLUSION

The conventional and microwave methods were adopted for synthesizing the title compounds. The physical, spectral and an analytical data of the title compounds were discussed. The possible potent antioxidant, H_1-antihistaminic agents without sedation, anti-inflammatory with less ulcerative effect and antitumor activities with fewer side effects for the new condensed quinazolines were studied.

REFERENCES

1. Y.S. Sadanandam, K. Ram Mohan Reddy, A. Bhaskar Rao, Eur. J. Med. Chem., 22, 1987, 169-173.
2. Armarego WLF, In : Katritzky A.R., Boulton A.J., Lagowski J.M. (Eds.), Advances in Heterocyclic Chemistry, Academic Press, NewYork, 1963, 1 – 62.
3. S. Johne, Progress in Drug Research, 26, 1982, 259-341.
4. Moghadam KR, Mohammad S, One pot synthesis of substituted quinazolin- 4(3*H*) ones under microwave irradiation by cyclocondensation of anthranilic acid, formic acid (or an ortho ester), and an amine, J Chem Res, 11, 1998, 702.
5. Nesterova NA, Kovalenko SI, Belenichev IF, Formation of combinatorial library of quinazoline-4-yl-hydrazones with antioxidant activity, Medichna Khimiya, 6(3), 2004, 14-21.
6. Francis JE, Cash WD, Psychoyos S, Bernard PS, Lowell RA, Some triazolo [1, 5-c] quinazolines as benzodiazepine antagonists, anxiety modulators, adenosine antagonists, antihistaminics and CNS stimulants, J Med Chem., 34, 1991, 281.
7. Mizutani Takashi, Nagase Tsuyoshi, Sato Nagaaki, Kanatani Akio, Tokita Shigeru, Preparation of quinazoline derivatives as histamine H3 receptor antagonists, PCT Int Appl., WO 2005115993 A1, 8 Dec 2005, 233.
8. Zabeer A, Bhagat A, Gupta OP, Synthesis and bronchodilator activity of new quinazoline derivatives, Eur J Med Chem., 41(3), 2006, 429-434.
9. DiMauro Erin F, Newcomb John, and Nunes Joseph J, Discovery of amino quina- zolines as potent, orally bioavailable inhibitors of Ick: synthesis, SAR, and *in vivo* anti-inflammatory activity, J Med Chem., 49(19), 2006, 5671-86.
10. Kumar Ashok, Tyagi Mridula, Srivastava VK, Synthesis and anticancer and hypotensive activities of some new 3-(substituted arylidiene) hydrazinoacetyl amino-2-methyl-6-bromo-quinazolin-4(3*H*)-ones, Indian J Chem., 42B(9), 2003, 2142.
11. Murugan V, Thomas Caroline C, Sharma GVS, Synthesis of 6, 8-dibromo-2-substituted quinazolin-4(3*H*)-ones as a new class of anticancer agents, Indian J Pharm Sci., 65(4), 2003, 386.

Source of Support: Nil, **Conflict of Interest:** None.