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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL SCREENING OF QUINAZOLINE-4-ONE ANALOGS

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ABSTRACT

In the present investigation, we have endeavoured to introduce phenyl at 2nd position of phenylquinazoline-4(3*H*)-one moiety and H/ *o*-OH/ *p*-$(CH_3)_2N$ in benzyl- lidene-4, 5-dihydro-5-oxo-2-phenylimidazol moiety with a view to evaluate them for possible antioxidant, anti-inflammatory, H_1-antihistaminic and antitumor activities. Hence, the synthesis of substituted 3-(2-((16Z)-4- H/ OH/ $(CH_3)_2N$- benzyl- idene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-2-phenylquinazolin-4(3*H*)-one. RS2, RS5, RS8) and 3-(2-((16Z)-4- H/ OH/ $(CH_3)_2N$-benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-phenyl-6,8-dibromoquinazolin-4(3*H*)-one (RS11,RS14, RS17) has been undertaken. All the compounds were characterised and biologically evaluated. Selective compounds shown significant biological actions.

Keywords: quinazoline-4-one analogs, spectral analysis, antioxidant, anti-inflammatory, H_1-antihistaminic and antitumor activities.

INTRODUCTION

Hetero cyclic chemistry research reached in all areas of drug discovery in recent days. More than three fourth of the bioactive drugs available in the market are all hetero cycles. Quinazolinone molecules were the superior lead molecules for the drugs from past immemorial. They involved in the skeleton of nearly 150 phytoconstituents.[1] Thus in the present investigation, imidazoloquinazolinone and quinoloquinazolinones are chosen as the heterocyclic systems and a known pharmacophore with antioxidant, H_1-antihistaminic activity, antiinflammatory and antitumor agents such as ethyl diamino imidazolines and ethyl diaminoquinoline group is built into position 3 of the quinazolinone nucleus.

MATERIALS AND METHODS

Synthesis

General scheme of 3-(2-((16Z)-4-subs.benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl) 6, 8-dibromo/unsubs.-2-phenylquinazolin-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 Hewett Packard model 5989B. NMR spectra will be taken on a Varian Gemini-2000 (500 MHz) spectrometer.

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Pharmacological evaluation

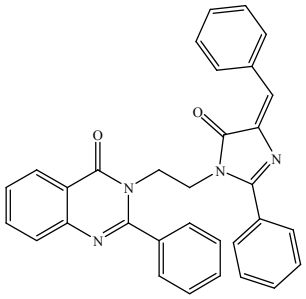
Literature survey revealed diverse biological and pharmacological significance of several nitrogen heterocyclic. This aspect has been drawing the attention of many scientists towards exploiting the biological importance of various heterocyclic compounds and to establish the relationship between their pharmacological potency and structural features. All the animals wherever used for pharmacological evaluations were procured from Malla Reddy Pharmacy College, Secunderabad, Andhra Pradesh, India and were obtained Institutional Animal Ethical Committee (IAEC) permission for all standard protocols Reg.No.1447/a/11/CPCSEA.

The compounds were screened for *In vitro* antioxidant assay by DPPH free radical scavenging method[2], antihistaminic activity by *In vitro* and *In vivo* method[3, 4, 5], carrageenan induced paw edema of antiinflammatory[6] activity and pylorus ligation induced gastric ulcers[7] and antitumor assay by MTT method in cancer cell lines of A-549[8], Vero[9] and HBL-500 cell[10]. All the animal experiments were done by the standard procedures and the results obtained were calculated and tabulated.

RESULTS AND DISCUSSION

Spectral data's

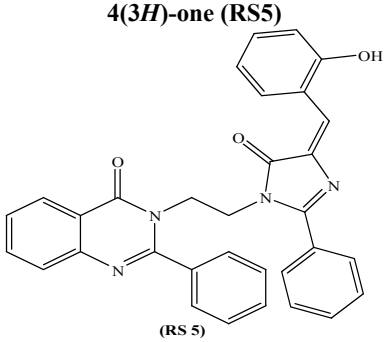
3-(2-((16E)-4-Benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl) -2-phenyl quinazolin-4(3*H*)-one (RS2)



(RS 2)

M.W. 496.56; M.F. $C_{32}H_{24}N_4O_2$; Yield 72%; M.P. 314^{o}C; R_f 0.49; IR (KBr) cm^{-1}:3120 (Ar-NH), 3014(Ar), 1658(C=O),1527 (CH); ^{1}H NMR ($CDCl_3$): 0.85 (s, 3H, CH_3), 3.6 , 3.8 (t, 2H, CH_2), 7.64(d, 1H, =CH-); EI-MS (70 eV) [m/z, %] : 77,79,144, 221, 247, 249, 419, 496, 495, 498. Elem. Anal. Calc'd for $C_{32}H_{24}N_4O_2$: C, 57.33; H, 3.31; Br, 23.84 N, 8.16; O, 7.36. Found: C, 57.53; H, 3.11; Br, 23.84; N, 8.16; O, 7.36.

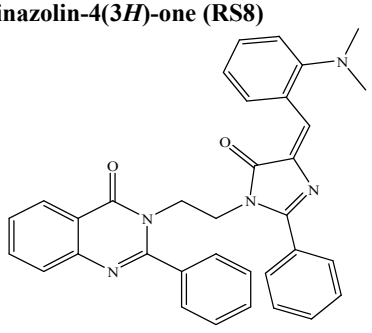
3-(2-((16E)-4-(2-Hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-phenylquinazolin-4(3*H*)-one (RS5)



(RS 5)

M.W. 512.56; M.F. $C_{32}H_{24}N_4O_3$; Yield 79%; M.P. 317 ^{0}C; R_f 0.48; IR (KBr cm^{-1}):3380 (Ar-OH), 3010(Ar-H), 3013(Ar)1657(C=O), 1521 (Lactone). Elem. Anal. Calc'd for $C_{32}H_{24}N_4O_3$: C, 74.99; H, 4.72; N, 10.93; O, 9.36. Found: C, 74.79; H, 4.92; N, 10.63; O, 9.66.

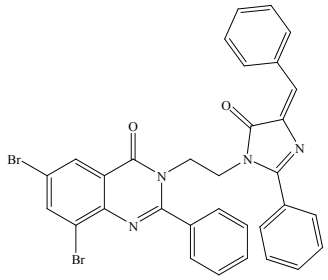
3-(2-((16E)-4-(2-(Dimethylamino)benzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-2-phenylquinazolin-4(3*H*)-one (RS8)



(RS 8)

M.W. 539.63; M.F. $C_{34}H_{29}N_5O_2$; Yield 79%; M.P. 314^{0}C; R_f 0.51; IR (KBr cm^{-1}): 3322(Ar-NH), 3013(Ar), 1656(C=O), 1523 (Lactone); Elem. Anal. Calc'd for $C_{34}H_{29}N_5O_2$: C, 75.68; H, 5.42; N, 12.98; O, 5.93. Found: C, 75.48; H, 5.63; N, 12.78; O, 6.13.

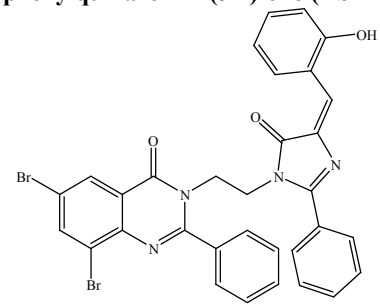
3-(2-((16E)-4-Benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-6,8-dibromo-2-phenylquinazolin-4(3*H*)-one (RS11)



(RS11)

M.W.654; M.F. $C_{32}H_{22}Br_2N_4O_2$; Yield 94%; M.P. 297 ^{0}C; R_f 0.44; IR (KBr cm^{-1}): 3332 (Ar-NH), 3012(Ar), 1652(C=O), 1522(Lactone); Elem. Anal. Calc'd for $C_{32}H_{22}Br_2N_4O_2$: C, 58.74; H, 3.39; Br, 24.42; N, 8.56; O, 4.89. Found: C, 58.54; H, 3.59; Br, 24.22;N, 8.36; O, 5.09.

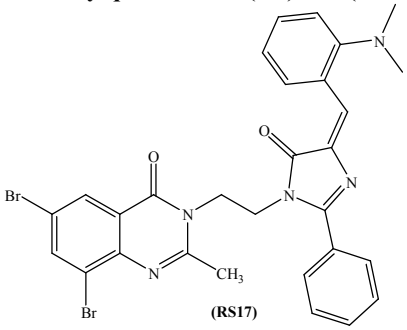
3-(2-((16E)-4-(2-Hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-6,8-dibromo-2-phenylquinazolin-4(3*H*)-one (RS 14)



(RS 14)

M.W. 670.35; M.F. $C_{32}H_{22}Br_2N_4O_3$; Yield 94%; M.P. 302^{0}C ; R_f 0.49; IR (KBr cm^{-1}): 3332 (Ar-NH), 3012(Ar), 1652(C=O), 1522(Lactone). Elem. Anal. Calc'd for $C_{32}H_{22}Br_2N_4O_3$: C, 57.33; H, 3.31; Br, 23.84; N, 8.36; O, 7.16. Found: C, 5753; H, 3.11; Br, 23.84; N, 8.16; O, 7.36.

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 (RS17)

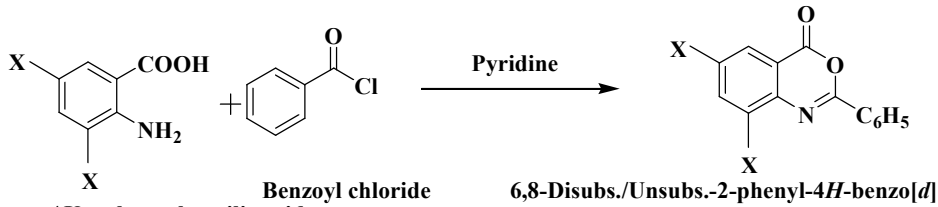


(RS17)

M.W. 635.35; M.F. $C_{29}H_{25}Br_2N_5O_2$; Yield 94%; M.P. 307^{0}C; R_f 0.48; IR (KBr cm^{-1}): 3321 (Ar-NH), 3011(Ar), 1658(C=O), 1522(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, 11.12; O, 5.04.

SCHEME -1B

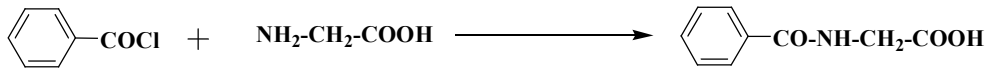
STEP 1



6,8-Dibromo/ Unsubs.anthranilic acid — Benzoyl chloride — 6,8-Disubs./Unsubs.-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one

I

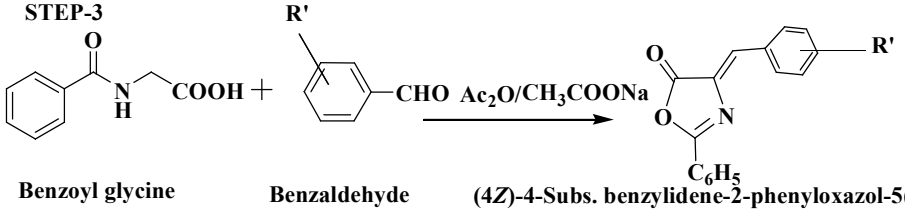
STEP-2



Benzoyl chloride — Glycine — Benzoyl glycine

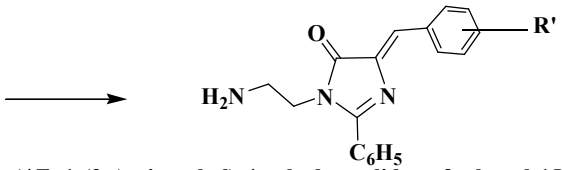
II

STEP-3



Benzoyl glycine — Benzaldehyde — (4*Z*)-4-Subs. benzylidene-2-phenyloxazol-5(4*H*)-one

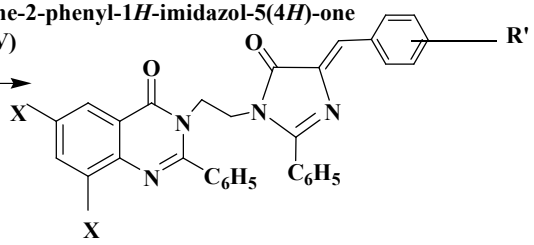
(III)



(4*Z*)-1-(2-Aminoethyl)-4-subs.benzylidene-2-phenyl-1*H*-imidazol-5(4*H*)-one

(IV)

STEP-4 I + III — AcOH



3-(2-((16*Z*)-4-Subs.benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl) 6,8-dibromo/Unsubs.-2-phenylquinazolin-4(3*H*)-one

(V)

S.No	X=H(RS)	X=Br(RS)	R (V)
1	2	11	C_6H_5CHO
2	5	14	OHC_6H_4CHO
3	8	17	$(CH_3)_2NC_6H_4CHO$

X=H, Br

Pharmacological screening

The antioxidant activities of the compounds were determined by the DPPH free radical scavenging assay. All the compounds shown significant antioxidant activity against the DPPH. The test compounds were compared with the standard drug ascorbic acid.

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

C0M	% Scavenging					
	10µg/mL	25µg/mL	50µg/mL	100µg/mL	250µg/mL	500µg/mL
RS2	26.098±5.198	35.534±0.8255	44.92±3.275	53.86±2.756	62.804±2.162	81.046±1.109
RS5	23.27±4.836	34.652±1.553	42.506±3.299	51.934±2.799	61.426±2.356	80.328±1.452
RS8	15.818±5.778	32.316±2.044	37.92±3.71	45.282±3.59	52.558±3.387	74.298±2.841
RS11	16.688±5.551	25.418±1.744	33.96±2.277	40.626±0.2793	50.118±1.694	74.348±1.112
RS14	20.154±0.8547	28.17±0.1012	39.916±0.835	49.798±0.8286	59.686±0.8266	79.448±0.8211
RS17	19.954±0.8483	29.742±0.8355	39.524±0.8271	49.31±0.8247	59.096±0.8155	78.668±0.8127
STD	49.908±2.719	59.726±2.335	67.636±2.335	77.454±1.504	87.272±1.584	94.8±0.1871

* % 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)

In vivo antihistaminic action was evaluated by histamine aerosolisation induced bronchoconstriction in guinea pigs. The animals showed better protection time after the test compounds administration. The time elapsed for breathing normal was more when compared with standard drug Cetrizine. *In vitro* bioassay for histaminic action was performed in guinea pig ileum was shown reduction in the contraction of the smooth muscle. Hence, the blocking of the histaminic receptors

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-methylquinazolin -4(3*H*)-ones

Comp'd	Substituents			***In vivo* studies**		***In vitro* studies (IC_{50}) (ng/mL) $1x10^{-3}$**	**% CNS Depr't**
	X	**R a-c**	**R' 1-3**	**T.O.C (Sec)**	**% Prot'n**		
RS2	H	C_6H_5	C_6H_5	1058±7.021	91.68	4.24	5.14
RS5	H	C_6H_5	C_6H_4OH	1079±5.657	91.84	4.2	3.78
RS8	H	C_6H_5	$C_6H_4N(CH_3)_2$	1130±7.211	92.21	1.9	4.92
RS11	Br	C_6H_5	C_6H_5	1062±5.050	91.72	1.7	4.38
RS14	Br	C_6H_5	C_6H_4OH	1089±6.221	91.92	1.8	3.65
RS17	Br	C_6H_5	$C_6H_4N(CH_3)_2$	1120±6.943	92.14	1.75	2.96
Control				88±0.8367			
CPM				1232±11.454	92.86	1	19.4
CTZ							7.46

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

The compounds shown anti inflammatory activity against carrageenan induced paw oedema compared with the standard drug Indomethacin.

Table 3: Percent protection antiinflammatory activity of quinazoline-4(3*H*)-one analog

Comp'd	% Protection			
	30 min	**1 h**	**2 h**	**3 h**
RS2	34±1.871	47± 1.633	52± 1.472	34± 1.414
RS11	34±1.472	45± 2.074	47±1.722	30± 1.871
STD	46±2.429	53± 2.16	65± 1.871	43±1.871

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

Also the synthesized compounds shown reduction in the ulcer index and gastric acid secretion in the pylorus ligation induced ulcer in experimental animals. All the compounds were acting against the tumour cells A-549, Vero and HBL-500 cell lines.

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

Comp'd	Substituent's			Ulcer index
	X	**R a-c**	**R' 1-3**	
RS2	H	C_6H_5	C_6H_5	0.5± 0.01871
RS11	Br	C_6H_5	C_6H_5	0.6±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 4: 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	Substituents			$IC_{50\ \mu g/ML}$		
	X	R a-c	R' 1-3	Vero	A-549	HBL-100
RS2	H	C_6H_5	C_6H_5	60.23	23.23	83.19
RS5	H	C_6H_5	C_6H_4OH	62.11	42.73	212
RS8	H	C_6H_5	$C_6H_4N(CH_3)_2$	68	41.23	51.87
RS11	Br	C_6H_5	C_6H_5	29.86	33	51.98
RS14	Br	C_6H_5	C_6H_4OH	32.43	12.21	61.11
RS17	Br	C_6H_5	$C_6H_4N(CH_3)_2$	23.7	12.32	53.22
STD				4.7	3.2	25

CONCLUSION

Microwave heating is a very efficient energy source and can be used significantly to reduce reaction time of numerous organic reactions. It allows preparation of many numb-ers of compounds at the same time in the microwave cavity. Therefore, it is very useful in parallel synthesis and combinatorial synthesis. All the tested compounds exhibited remarkable biological activities.

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