INFLAMMATION: SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF SOME NEW 4(3*H*) - QUINAZOLINONE ANALOGS AS ANTIOXIDANT, ANTIHISTAMINIC, ANTI-INFLAMMATORY AND ANTITUMOR AGENTS

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ABSTRACT

We have recently reported the discovery of numerous new compounds that are antioxidant, anti-histaminic, anti-inflammatory, and an anti-tumor agents. Title compounds were prepared from unsubstituted or dibromo substituted anthranilic acid and condensed with AC_2O / C_6H_5COCl / $ClCH_2COCl$ which donate methyl/phenyl/methylene chloride respedtively [(X= H, Ra, Rb, Rc) (X=Br, Rd, Re, Rf)] to get corresponding benzooxazine-one derivatives (2). The second heterocyclic moiety, coumarin derivatives have been prepared from condensation of resorcinol and ethylacetoacetate in presence of polyphosphoric acid (4). Compounds (4) were reacted with Unsubstituted, CH_3COCl, C_6H_5COCl, $C_6H_5CH_2Cl$, $Cl\text{-}CH_2\text{-}COCl$[R'$_{(1\text{-}5)}$], which donate H, CH_3CO, C_6H_5CO, $C_6H_5CH_2$, $Cl\text{-}CH_2\text{-}CO$ at position 7 (5). Later (5) was reacted with ethylene diamine to give corresponding substituted coumarin (6). Finally (6) was reacted with (2) in presence of Glacial CH_3COOH to get title compounds (7). The conversion of β-Lactone to β-Lactam is the principle mechanism. The compounds were characterized by spectral data and were subjected to antioxidant, antihistaminic activity, anti-inflammatory and anti-tumor activity.Some of the reported compounds have shown moderate to good activities.

Key words: *Quinazoline, Quinoline, Antioxidant, Antihistaminic activity, Anti-inflammatory, Anti-tumor.*

INTRODUCTION

Inflammation[1,2] is a response of a tissue to injury. Mast cells are found in the tissues in which contains mediators of inflammation and surface is coated with a variety of receptors which, when engaged by the appropriate ligand, trigger exocytosis of the granules. Mast cells releasing some of the mediators are Tumor Necrosis Factor-alpha (TNF∝), Chemokines, Relative Oxygen Species (ROS), Interleukin-1 (IL-1), Inflammasomes, Leucotrienes, and Prostaglandins. Inflammation have two faces, one which is good side to protects the body in the mode of isolating the damaged area, mobilizing effectors cells, molecules to the side , and in the later stages promoting healing. The second or another one is bad side, which have created numbers of disorders like all the many types of allergies and autoimmune diseases like asthma, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus and chronic obstructive pulmonary

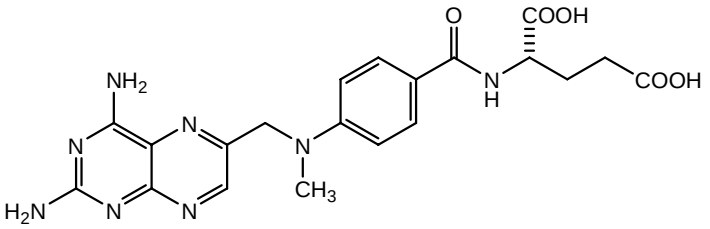
disease are primary one, disorders like in-appropriate inflammation by COX-1 and COX-2 (Cyclooxygenase) are secondary one and finally chronic inflammation is also a frequent cause of cancer , especially liver, lung, cervical, bladder, colon, pancreas, stomach etc. The reactive oxygen species (ROS) liberated during inflammation are powerful DNA-damaging agents, increasing mitosis in response to inflammation puts more cells at risk of mutations as they replicate their DNA during S phase and Apoptosis, the programmed death of damaged cells are suppressed in inflamed tissue. So cells with precancerous genetic mutations, which should have committed suicide, live on grow into a full-blown cancer.

Free radicals and oxygen derivatives are constantly generated in-vitro both by accident of chemistry and specific metabolic purposes[3]. The reactivity of free radicals varies with many causing inflammation or even severe damage to biological molecules, especially to DNA, lipids and proteins. The generation of free radicals during the metabolic process is now observed to be responsible wide range of human condition such as aging, cancer, atheroslerosis, arthritis, viral infection stroke, myocardial infraction, pulmonary condition, inflammatory bowel disease, neurogenerative disease and others may be produced by reactive oxygen species (e.g.) hydrogen peroxide scavenging (H_2O_2); hypochlorous acid scavenging (HOCl); hydroxyl radical scavenging (HO radical); peroxyl radical scavenging (ROO radical).The action of free radicals is counteracted by free radicals endogenous or exogenous or synthetic route. Our on goings literatures search reveals that substituted quinazoline and quinoline derivatives having high potent anti-oxidant property.

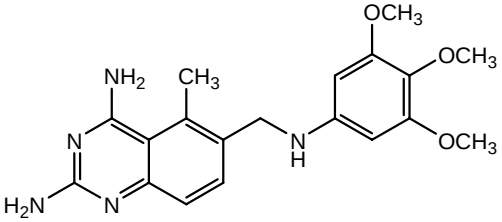
The prevalence of asthma and other allergic diseases is increasing providing a rapidly expanding marked for antiallergic drugs[4]. A common feature of first generation compounds includes two aryl or hetero aryl rings linked to an aliphatic tertiary amine via side chain (e.g., Diphen hydramine and Pheniramine) the second generation compounds (Terpenadine and Cetritizine) also contain many of the structural features of first generation compounds. The real breakthrough of non-sedative anti histamines came in the early 80s of 20^{th} century with the discovery of modern antihistamines like Loratadine, Azelastine, Flazelastine, Temelastine and magnostin, which were found to exhibit potent antihistaminic activity without a sleep – inducing effect. Asthma can no longer be viewed simply as reversible airway obstruction. It should be instead considered primarily as an inflammatory illness that has bronchial hyper activity and bronchospasm as its result. Asthma has been generally classified as either 'extrinsic' or 'intrinsic'. In many subjects, the asthmatic attack consists of two main phases, namely immediate phase and late phase. The literatures reveal excellent antihistaminic activity in quinazolines and substituted quinazolines.

Nonsteroidal anti-inflammatory drugs (NSAID) are commonly prescribed for the treatment of acute chronic inflammation, pain and fever. Most of NSAIDs that are available in market are known to inhibit isoforms, a constitutive form, COX-1 and an inducible form, COX-2, to offer therapeutic effect. However, long term clinical usage of NSAIDs is associated with significant side effects of gastrointestinal lesions, bleeding and nephrotoxicity[5]. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area. On our going medicinal chemistry research programme we have found that quinazoline and condensed quinazolines exhibit potent anti-inflammatory activity.

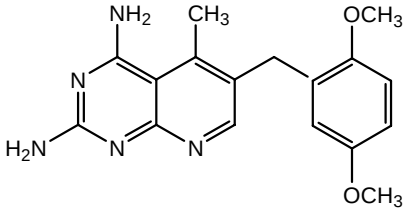
Dihydrofolate reductas (DHFR) is an enzyme of pivotal importance in biochemistry and medicinal chemistry. DHFR catalyzes the reduction of folate or 7,8 dihydro folate to tetra hydro folate and intimately couples with thymidylate synthase(TS).Inhibition of DHFR or TS activity in the absence of salvage leads to ‘ thymineless death.’ Compounds that inhibit DHFR exhibit an important role in clinical medicine as exemplified by the use of methotrexate (MTX, 1) in neoplastic diseases, inflammatory bowel diseases, and rheumatoid arthritis, as well as in psoriasis, and asthma. A new generation of potent lipophilic DHFR inhibitors such as trimetrexate (TMQ, 2), and piritrexim (PTX, 3) have shown antineoplastic and anti fungalm activities. A new seriesof quinazoline analogs is designed to posses a CH_3 /C_6H_5 /CH_2Cl at position 2 of quinazoline analogs, and H/ $COCH_3$/ COC_6H_5/ $CH_2C_6H_5$/ $COCH_2Cl$ at position 7 of quinoline moiety are known to contribute to the enhancement of the all the above mentioned activities.



METHOTREXATE (MTX, 1)



TRIMETREXATE (TMQ, 2)



PIRITREXIM (PTX, 3)

The key intermediate 6,8 - disubstituted -2- methyl/phenyl/chloromethyl benzooxasine - 4- one (2) was prepared by reacting 3,5- disubstituted anthranilic acid (1) with acetic anhydride in pyridine (a,d)/benzoyl chloride in dry benzene (c,f) yielded the desired 6,8 - disubstituted - 2- methyl/phenyl/chloromethyl benzooxasine - 4 - one (2) in good yield (82%)[6]. This was confirmed by presence of 0.9 in (CH_3), 3.4 (CH_2Cl) 7.14 to 7.4 (phenyl) and absence of 11 (COOH) and 4 (NH_2). The second key intermediate 7 – substituted oxy - 4 - methyl coumarin R’ $_{(1\text{-}5)}$ (4) from resorcinol (3) reacts with ethylacto acetate in presence of polyphosphoric acid to cyclise gave 7-hydroxy - 4 - methyl -*2H*-Chromen – 2 - one. The product obtained was treated with H/AC_2O in pyridine/C_6H_5 COCl in pyridine/ $C_6H_5CH_2Cl$ in C_2H_5OH / $ClCH_2COCl$ in

C_2H_5OH on 7^{th} – hydroxyl position of 7 – hydroxyl – 4 methyl -*2H* - chromen - 2- one. The compounds (4) was reacted with ethylene diamine (5) to give (2-aminoethyl) -7- substituted – oxy- 4- methyl quinolin - 2 (*1H*) - one (6).

The title compounds 6, 8 – dibromo - 3 (2-(7-substituted oxy - 4 - methyl - 2 - oxo – quinolin - 1 (*2H*) - yl) ethyl)- 2-methyl quinazoline - 4 (*3H*) - one (7) were obtained by the condensation of (2) lactone of substituted benzooxazine (2) with ethyl amine of quinoline (6)[7]. The changed proton value of 3.22 (CH_2) 2.91 (CH_2) and disappearance of 2.0 (NH_2) and appearance of 3.46 (CH_2) 3.26 (CH_2) 8.1- 7.8 (CH-quinazoline), 6.42, 7.11, 7.06, 6.35 (CH of quinoline) 1.71 (4-CH_3 of quinoline). The ^{13}C- NMR value for title compounds are 113.4 – 150.1 (Ar of quinazoline), 123.9 – 113.4 (dibromo), 161.5 (C= O) of quinazoline, 154.4(2C of quinazoline), 22.8 (CH_3), 46.9 (CH_2 Cl), 46.7, 46.5 (Ethylene bridge), 120.7, 148.8, 136 (CH for pyridine of quinolin), 121.9, 127.6, 104 (CH for Ar in quinoline).

EXPERIMENTAL

Synthesis of 2-methyl/phenyl/chloromethyl - 4*H* - benzo[*d*] [1, 3] oxazin - 4 - one (2) $R_{(a-f)}$

A mixture of disubstituted anthranilic acid (X=H,Br) (1) (0.12 mol) in acetic anhydride in few drops of pyridine (0.2 mol)/ benzoyl Chloride in dry pyridine (0.3 mol)/Chloro acetyl Chloride in drug benzene (0.12 mol) and followed by acetic anhydride (0.3 mol) in pyridine was reflux for 3 hours. The excess solvents were then distilled off under reduced pressure. The reaction mixture was filtered, washed, dried and re-crystallized with absolute ethanol for methyl and phenyl compounds, where as chloro methyl compounds used a mixture of Chloroform and ethyl acetate.

Synthesis of 1-(2-amino ethyl)-7-subs. Oxy-4-methyl quinoline-2-(1*H*)-one (6) $R'_{(1-5)}$

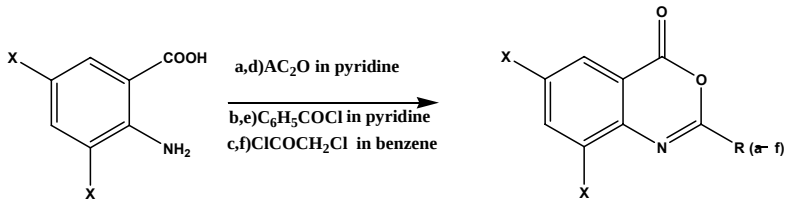
A mixture of polyphosphoric acid 160 g to a solution of (0.1 mol) of ethylacetoacetate.Stirr the mixture and head at 75-80^oC for 20 minutes, and then our into ice-water. Collect the pale yellow solid by suction filtration, wash with a little cold water and dry at 60^oC. The prepared compounds was recrystallised from dilute ethanol yields the pure, colorless compounds. Quinoline (0.1 mol) with various reactance like $H,(CH_3CO)_2O,C_6H_5COCl,C_6H_5CH_2Cl,ClCH_2COCl$ ($R'_{(1-5)}$) to give respective substituents **(4),** compound**(4)** (0.1 mol) with ethylene diamine (0.1 mol) react in presence of glacial acetic acid , filtered, dried, and recrystallised with absolute ethanol.

Synthesis of UN / 6, 8-dibromo-3-(2-(7-subs.oxy-4-methyl-2-oxoquinoine-1-(2*H*)-yl) ethyl)-2-subs. quinazoline-4-(3*H*)-one.

To a well stirred solution of (2) (0.1 mol) with (6) (0.1 mol) in Glacial acetic acid and reaction mixture was heated under reflux for 8 hr, add into crushed ice, filtered, dried and recrystallised with absolute ethanol. The Physical and Spectral data's shown in Table 1 & 2.

SCHEME

STEP-1



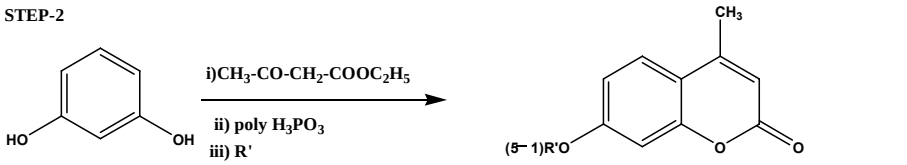
X=H,Br

1

6,8-dibromo-2-methyl/ phenyl / chloromethylene-4*H*-benzo[*d*][1,3]oxazin-4-one

2

STEP-2



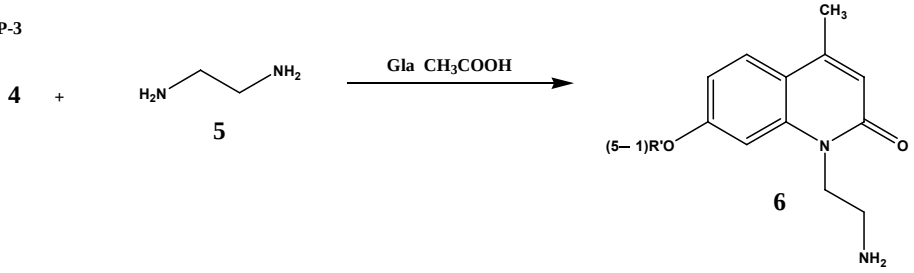
3

7-substituted oxy-4-methyl-2*H*-chromen-2-one

4

R' = H, $(CH_3CO)_2O$, C_6H_5COCl, $C_6H_5CH_2Cl$, $ClCH_2$-COCl

STEP-3

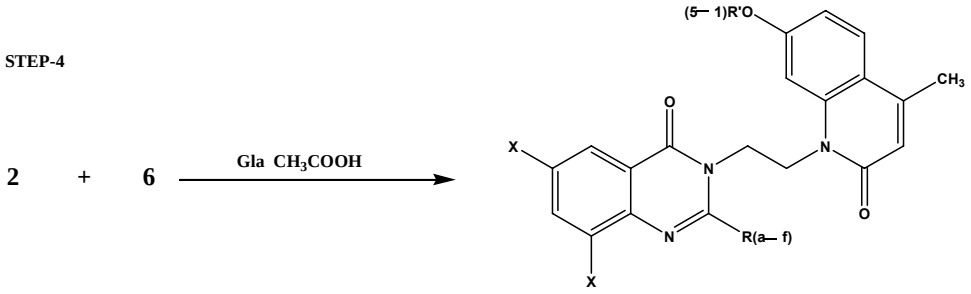


5

6

1-(2-aminoethyl)-7-substituted oxy-4-methylquinolin-2(1*H*)-one

STEP-4



6,8-dihalo subs -3-(2-(7-subs oxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2subs quinazolin-4(3*H*)-one

7

PHARMACOLOGICAL INVESTIGATION

Antioxidant activity[8, 9]

All the prepared compounds have been diluted in absolute ethanol to get 250, 100, 50, and 10 µg/ml concentrations. DPPH solution (2µ mol) has been prepared by absolute ethanol. Then 0.5 mL of DPPH solution (freshly prepared) were added.0.5 mL of DPPH solution and 0.5mL of absolute ethanol were used as control. Reaction mixture was allowed for 20 min. UV/Visible absorbance was at 517 nm. The % of scavenging has been calculated, Ascorbic acid was used as standard .The results are shown in Table 3.

Anti-histaminic activity[10]

***I) In vitro* studies (Guinea pig ileum method)**

The *in vitro* antihistaminic activity was evaluated by measuring the inhibition of the isotonic contraction induced by histamine on isolated guinea pig ileum. A healthy and adult guinea pig of either sex, weighing around 400 g was fasted for 24 hours, before taking up for experiment. It was killed by a blow on the head and exsanguinated. The abdomen was opened and ileo-ceacal junction was located. A portion of 10 cm nearer to the junction was rejected and ileum portion of the gut was taken and placed in a dish containing Tyrode's solution. The gut was cleared placing one end of it over the tip of a pipette (10 ml) containing warm (37^0C) Tyrode's solution and applying a very small head of pressure by filling the pipette. The mesentery was trimmed away and pieces of 2-3 cm length were cut. A thread was tied at each end taking care that the lumen of ileum remained open while mounting the tissue in the isolated organ bath. The piece was then mounted in an organ bath of 10 ml capacity containing Tyrode's solution maintained at 37 ± 1^{o}C. The tissue was allowed to equilibrate for 30 minutes and washed every 5 minutes. The tissue was aerated with air using an air bubbler. The response of the tissue to increasing doses of histamine was recorded on a smoked drum using a frontal writing lever with a magnification of 1:10 and a tension of 0.5 g. The sub maximal dose of the agonist was selected and the response of the tissue to this dose in the presence of increasing concentration (logarithmic doses) of the test compounds was recorded. The test compound was prepared in the form of suspension with 1% acacia solution. The dose corresponding to 50% inhibition (IC_{50}) was calculated by using suitable formula. The results are shown in Table 4 & Fig 1.

***ii) In vivo* Studies (Histamine chamber method)**[11]

In this method thirty two healthy adult guinea pigs of either sex divided into group of 2 animals each weighing around 400 g, fasted overnight, were kept in histamine chamber, and exposed to histamine aerosol (0.5 % aqueous solution of histamine acid phosphate in a Nebulizer) until they collapse. Those that collapse within 2 minutes were revived with fresh air and used for this test. Twelve hours later, the animals were given an oral dose of test compound suspended in 1% acacia solution and after 1 hour for absorption; the guinea pigs were again exposed to the same concentration of histamine aerosol. Those that do not collapse within 6 minutes are deemed protected. Percentage protection has been measured by calculating the time of onset of convulsions. The results are shown in Table 4 & Fig 2.

Anti-inflammatory Studies [12, 13, 14]

Anti-inflammatory activity was evaluated by carrageenan-induced paw oedema test in rats. Male albino rats weighing between 100 – 200g were used for the experiment. The animals were provided with standard diet and water *ad libitum*, divided into six groups, each containing six animals, Toxicological test shown that 200mg/kg body weight was fixed as the safe dose for

acute anti-inflammatory screening. One group served as a standard (Ibuprofen) and another group served as control (1% CMC) and rest of the groups were used for the test drugs. Ibuprofen was given at 200 mg/kg body weight. Test compounds and Ibuprofen were suspended in 1%CMC, which was used as a vehicle for the control group. A solution of 1% Carrageenan was used as an inflammatory agent.Food was withdrawn overnight with adequate water before the experiment. The drugs were given orally. After 1 hour, a sub plantar injection of 0.05 ml of 1% Carrageenan was administered. The volume of the injected paw was measured with a plethysmograph immediately. The paw volume was again measured after 3 hours. The average paw volume in a group of drug treated rats was compared with that of a group with vehicle (control group) and the percentage inhibition of oedema was calculated using the formula. The results are shown in Table 5 & Fig 3.

% Inhibition = (1- Vt / Vc) x 100

Vt = Mean volume of the test drug Vc = Mean volume of the control

Antitumor Activity[15, 16]

Microculture tetrazolium (MTT) assay

0.1 ml of the cell suspension (containing 5 x 105 cells / 100 µl) and 0.1 ml of the compound solution (10, 20, 50, 100, 150 and 200 µg in DMSO such that the final concentration of DMSO in media is less than 1%) was added to the 96 well plates and kept in carbon dioxide incubator with 5% CO_2 at 37^oC for 72 hours. Blank contains only cell suspension and control wells contain 1% DMSO and cell suspension. After 72 hours, 20 µl of MTT was added and kept in carbon dioxide incubator for 2 hours followed by 80 µl of lysis buffer (15% SLS in 1:1 DMF and water). The plate was covered with aluminium foil to protect from light, and then the 96 well plates were kept on rotary shaker for 8 hours. After 8 hours the 96 well plates were processed on ELISA reader for absorption at 562 nm. The readings were averaged and viability of the test samples was compared with DMSO control.The results are shown in Table 6 & Fig 4.

RESULTS AND DISCUSSION

The title compounds were prepared from unsubtituted/6,8-dibromo-2-methyl/phenyl/chloromehylene-4H-benzo[d] [1,3] oxacin-4-one **2$_{a-f}$** react with 1-(2-amino ethyl)-7-substituted oxy-4-methyl quinoline-2(1*H*)-one **6$_{(1-5)}$** in presents of Glacial acetic acid to form 30 subtituents of unsubstituted/ 6,8-dibromo substituted-3-(2(7-subs. oxy-4-methyl-2-oxoquinoline-1-(2*H*)-yl)ethyl)-2-subs. quinazoline-4(3*H*)-one derivatives **7$_{(a-ziv)}$.** The intense bands around 3200, 1450,1650 cm^{-1} of IR Specta,5.03,0.9,3.46,7.4-7.9,6.3-7.1 δ of ^{1}H-NMR, 22.8,20.8,46.7,161.5,120.9-154.4,106.3-157.9 δ of ^{13}C-NMR and 361 was mass for 7a, similarly all the other compounds were confirmed by Spectral studies.All the prepared compounds 7(a-ziv) were evaluated for antioxidant, antihistamine, anti-inflammatory and antitumor activities. All of them were shown significant antioxidant activity,among 7 z,y,m,a,o,ziii were top most than others. The title compounds screened for antihistamine by In-

vitro and In-vivo standard methods,the compounds 7 r,ziv,g,h,l,zii,s,x,t are shown significant activity.

All the prepared compounds were screened for anti-inflammatory activity and shown considerable response from compounds like 7 r,ziv,g,h,l,zii,s. The titlt compounds tested for Antitumor against HBL-100 and He La cell lines, compounds 7 q,c,e,g,w,k,zi shown significant activity.

The new series of various quinazolines showed significant antioxidant, antihistamine, antiinflamatory and antitumor activities comparable to that of the standard drug used in the studies.

Table 1. Physical data

Compd (7)	X	R_{a-f}	R'_{1-5}	Mol. Formula	M.W.	M.P.(^{0}k)	Yield (%)
a	H	CH_3	H	$C_{21}H_{19}N_3O_3$	361	987	69
b	H	CH_3	$COCH_3$	$C_{23}H_{21}N_3O_4$	403	997	69
c	H	CH_3	C_6H_4CO	$C_{28}H_{23}N_3O_4$	465	1023	67
d	H	CH_3	$C_6H_4CH_2$	$C_{28}H_{25}N_3O_3$	451	1010	65
e	H	CH_3	$COCH_2Cl$	$C_{23}H_{20}ClN_3O_4$	437	989	74
f	H	C_6H_5	H	$C_{26}H_{21}N_3O_3$	423	999	73
g	H	C_6H_5	$COCH_3$	$C_{28}H_{23}N_3O_4$	465	1012	71
h	H	C_6H_5	C_6H_4CO	$C_{33}H_{25}N_3O_4$	527	1022	72
i	H	C_6H_5	$C_6H_4CH_2$	$C_{33}H_{27}N_3O_3$	513	1102	74
j	H	C_6H_5	$COCH_2Cl$	$C_{28}H_{22}ClN_3O_4$	513	1011	68
k	H	CH_2Cl	H	$C_{21}H_{18}ClN_3O_3$	395	1011	78
l	H	CH_2Cl	$COCH_3$	$C_{23}H_{20}ClN_3O_4$	437	1007	67
m	H	CH_2Cl	C_6H_4CO	$C_{28}H_{27}ClN_3O_4$	499	1001	77
n	H	CH_2Cl	$C_6H_4CH_2$	$C_{28}H_{24}ClN_3O_3$	485	1006	75
o	H	CH_2Cl	$COCH_2Cl$	$C_{24}H_{22}ClN_3O_4$	451	1012	77
p	Br	CH_3	H	$C_{21}H_{17}Br_2N_3O_3$	519	1004	71
q	Br	CH_3	$COCH_3$	$C_{23}H_{19}Br_2N_3O_4$	561	969	72
r	Br	CH_3	C_6H_4CO	$C_{28}H_{21}Br_2N_3O_4$	623	1233	68
s	Br	CH_3	$C_6H_4CH_2$	$C_{28}H_{23}Br_2N_3O_3$	609	1032	78
t	Br	CH_3	$COCH_2Cl$	$C_{23}H_{18}Br_2ClN_3O_4$	595	1102	79
u	Br	C_6H_5	H	$C_{26}H_{19}Br_2N_3O_3$	581	1086	68
v	Br	C_6H_5	$COCH_3$	$C_{28}H_{21}Br_2N_3O_4$	623	1052	76
w	Br	C_6H_5	C_6H_4CO	$C_{33}H_{23}Br_2N_3O_4$	685	1135	74
x	Br	C_6H_5	$C_6H_4CH_2$	$C_{33}H_{25}Br_2N_3O_3$	671	1115	75
y	Br	C_6H_5	$COCH_2Cl$	$C_{28}H_{20}Br_2ClN_3O_4$	657	1082	79
z	Br	CH_2Cl	H	$C_{21}H_{19}Br_2N_5O_3$	553	1033	68
zi	Br	CH_2Cl	$COCH_3$	$C_{23}H_{18}Br_2ClN_3O_4$	595	999	69
zii	Br	CH_2Cl	C_6H_4CO	$C_{28}H_{20}Br_2ClN_3O_4$	657	1082	66
ziii	Br	CH_2Cl	$C_6H_4CH_2$	$C_{28}H_{22}Br_2ClN_3O_3$	643	1062	78
ziv	Br	CH_2Cl	$COCH_2Cl$	$C_{23}H_{17}Br_2Cl_2N_3O_4$	630	1029	66

Table 2. Spectral data

Comd (7)	M+1	^{13}C-NMR	^{1}H-NMR	IR CM^{-1}
a	361	22.8, 20.8, 46.7, 161.5, 120.9-154.4,106.3-157.9	5.03.0.9, 3.46,7.4 –7.9,6.3-7.1	3200, 1450, 1650
b	403	22.8, 20.3, 46.7, 169.0, 120.9-154.4,106.3-157.9	2.08,0.9, 3.26, 7.4 –7.9, 6.3-7.1	3200, 3400, 1680
c	465	128.7-134, 46.7,46.5, 165.2, 120.9-154.4	7.41-8.14,0.9, 3.26, 7.3 - 7.6	3250, 1480, 1650
d	451	70.9, 127.2-141.2, 109-160.1, 120.9-154.4	5.2,7.19, 3.46, 7.6, 0.9, 1.71	3400, 2900, 1700
e	437	40.1, 163.4, 46.5,46.7, 120.9-154.4, 106.3-157.9	4.32, 3.26, 3.46, 7.6, 0.9,1.70	3000, 1510, 1680
f	423	22.8, 20.8, 46.7, 161.5, 120.9-154.4,106.3-157.9	5.03, 7.29-7.62, 3.46, 6.3-7.1	3200, 2900, 1680
g	465	22.8, 20.3, 46.7, 169.0, 120.9-154.4,106.3-157.9	2.08, 7.29-7.62,3.26, 6.3-7.1	3200, 3420, 1650
h	527	128.7-134, 46.7,46.5, 165.2, 120.9-154.4	7.41-8.14, 3.26, 7.29 - 7.62, 1.72	3000, 1450, 1650
i	513	70.9, 127.2-141.2, 109-160.1, 120.9-154.4	5.2, 7.41-8.14,7.19, 3.46,1.71	3400, 2900, 1670
j	513	40.1, 163.4, 46.5,46.7, 120.9-154.4, 106.3-157.9	4.32, 7.41-8.14,3.26, 7.6, 0.9	3100, 1470, 1640
k	395	22.8, 20.8, 46.7, 161.5, 120.9-154.4,106.3-157.9	5.03, 3.4, 3.46,7.4 –7.9, 6.3-7.1	3150, 1500, 1650
l	437	22.8, 20.3, 46.7, 169.0, 120.9-154.4,106.3-157.9	2.09, 3.4, 3.26, 7.4 –7.9, 6.3-7.1	3420, 1520, 1680
m	499	128.7-134, 46.7,46.5, 165.2, 120.9-154.4	7.41-8.14, 3.26, 7.3 - 7.6,1.72	2900, 3000, 1680
n	485	70.9, 127.2-141.2, 109-160.1, 120.9-154.4	5.19,7.20, 3.46, 7.6, 1.71	3400, 2920, 1650
o	451	40.1, 163.4, 46.5,46.7, 120.9-154.4, 106.3-157.9	4.30, 3.41, 3.26, 3.46, 7.61	3200, 1300, 1680
p	519	22.8, 20.8, 46.7, 161.5, 120.9-154.4,106.3-157.9	5.06, 0.9, 3.46,7.4 –7.8, 6.3-7.2	3100, 2920, 1650
q	561	22.8, 20.3, 46.7, 169.0, 120.9-154.4,106.3-157.9	2.07, 0.9, 3.26, 7.4 –7.7, 6.3-7.2	3200, 1400, 3400
r	623	128.7-134, 46.7,46.5, 165.2, 120.9-154.4	7.41-8.14, 0.9, 3.26, 7.29- 7.6	2900, 1470, 1680
s	609	70.9, 127.2-141.2, 109-160.1, 120.9-154.4	5.2, 7.41-8.14, 3.46, 0.9,1.71	2920, 1450, 1700
t	595	40.1, 163.4, 46.5,46.7, 120.9-154.4, 106.3-157.9	4.30, 3.26, 3.46, 7.6, 0.9,1.71	2100, 1500, 1680
u	581	22.8, 20.8, 46.7, 161.5, 120.9-154.4,106.3-157.9	5.0,7.29-7.62,3.46,7.4 –7. 9	3200, 1600, 1700
v	623	22.8, 20.3, 46.7, 169.0, 120.9-154.4,106.3-157.9	2.07, 3.26, 7.4 –7.9, 6.3-7.1	3380, 1450, 1650
w	685	128.7-134, 46.7,46.5, 165.2, 120.9-154.4	7.41-8.14, 3.26, 7.3 - 7.6, 1.70	3200, 1400, 1700
x	671	70.9, 127.2-141.2, 109-160.1, 120.9-154.4	5.21,7.19, 3.46, 7.6, 6.37-7.17	3500, 1450, 1720
y	657	40.1, 163.4, 46.5,46.7, 120.9-154.4, 106.3-157.9	4.32, 7.27-7.63, 3.46, 7.6	2900, 1470, 1650
z	553	22.8, 20.8, 46.7, 161.5, 120.9-154.4,106.3-157.9	5.03, 3.4, 3.46,7.4 –7.9, 6.3-7.2	2900, 1450, 1700
zi	595	22.8, 20.3, 46.7, 169.0, 120.9-154.4,106.3-157.9	2.03, 3.26, 7.4 –7.8, 6.3-7.0	3400, 1500, 1650
zii	657	128.7-134, 46.7,46.5, 165.2, 120.9-154.4	7.41-8.14, 3.26, 7.29 - 7.6, 1.71	3200, 1450, 1650
ziii	643	70.9, 127.2-141.2, 109-160.1, 120.9-154.4	5.2,7.19, 3.46, 7.6, 0.9, 5.0	3450, 1450, 1700
ziv	630	40.1, 163.4, 46.5,46.7, 120.9-154.4, 106.3-157.9	4.32, 7.29-7.62, 3.46, 1.71	2900, 1470, 1650

Table 3. Antioxidant activity

Compound 7		10µg/ml	50µg/ml	100µg/ml	250µg/ml	Control
1	**a**	0.07±0.09018(30.69)	0.09±0.079(60.39)	0.031±0.070(70.29)	0.010±0.005727(90.09)	0.101±0.019011
2	**b**	0.08±0.070(20.00)	0.03±0.00952(70.00)	0.0171±0.0148(82.82)	0.17±0.019018(30.69)	0.100±0.019018
3	**c**	0.09±0.0576(18.18)	0.06±0.0148(45.45)	0.054±0.0142(50.90)	0.052±0.0112(52.72)	0.011±0.019018
4	**d**	0.089±0.071(11.88)	0.069±0.031(31.68)	0.06±0.033(40.59)	0.064±0.031(40.54)	0.0101±0.0198
5	**e**	0.08±0.072(20.00)	0.03±0.0009(70.00)	0.025±0.0057(75.00)	0.022±0.051(78.00)	0.1±0.01818
6	**f**	0.093±0.181(15.45)	0.02±0.066(72.72)	0.021±0.0061(81.18)	0.0158±0.054(85.63)	0.11±0.01888

7	**g**	0.12±0.100(07.69)	0.1±0.091(23.00)	0.09±0.0072(30.00)	0.88±0.070(32.00)	0.130±0.011018
8	**h**	0.12±0.081(14.28)	0.101±0.062(27.85)	0.099±0.0054(29.28)	0.09±0.044(35.71)	0.14±0.0192
9	**i**	0.098±0.012(19.00)	0.075±0.008(38.01)	0.052±0.0007(58.67)	0.041±0.0071(66.94)	0.121±0.0186
10	**j**	0.08±0.031(20.79)	0.04±0.009(60.39)	0.03±0.008(70.29)	0.021±0.0081(80.19)	0.101±0.0188
11	**k**	0.10±0.023(16.6)	0.07±0.08(41.66)	0.06±0.005(50.00)	0.04±0.03(66.00)	0.12±0.0177
12	**l**	0.122±0.018(6.15)	0.1±0.0101(23.07)	0.9±0.009(30.76)	0.88±0.009(32.30)	0.13±0.0199
13	**m**	0.06±0.02(37.62)	0.04±0.09(60.39)	0.03±0.0042(70.29)	0.0162±0.041(83.96)	0.101±0.0188
14	**n**	0.08±0.072(20.79)	0.04±0.009(60.39)	0.028±0.008(66.39)	0.017±0.0083(83.19)	0.101±0.0188
15	**o**	0.072±0.081(28.2)	0.071±0.018(30.69)	0.0571±0.0016(43.46)	0.0571±0.011(43.46)	0.011±0.0199
16	**p**	0.089±0.081(11.88)	0.069±0.072(31.68)	0.06±0.0015(40.59)	0.061±0.019(40.59)	0.101±0.0199
17	**q**	0.081±0.09(20.79)	0.04±0.009(60.39)	0.0317±0.008(70.29)	0.021±0.009(80.19)	0.102±0.0202
18	**r**	0.142±0.08(6.15)	0.09±0.092(30.76)	0.088±0.0092(32.30)	0.8±0.08(38.46)	0.131±0.0198
19	**s**	0.112±0.032(7.43)	0.1±0.098(17.35)	0.09±0.0092(25.6)	0.088±0.0083(27.27)	0.121±0.0182
20	**t**	0.109±0.003(9.91)	0.08±0.009(38.88)	0.07±0.00816(42.14)	0.06±0.0052(50.41)	0.121±0.0167
21	**u**	0.10±0.072(9.09)	0.06±0.099(45.45)	0.04±0.0082(63.63)	0.015±0.006(86.36)	0.11±0.0188
22	**v**	0.10±0.001(16.6)	0.07±0.0092(41.66)	0.06±0.0083(50.02)	0.04±0.094(60.01)	0.12±0.0176
23	**w**	0.09±0.0011(18.18)	0.07±0.0083(36.36)	0.05±0.0081(54.54)	0.042±0.0063(61.81)	0.11±0.01652
24	**x**	0.11±0.0012(1.78)	0.093±0.0109(16.96)	0.092±0.0083(17.85)	0.088±0.0072(21.42)	0.112±0.01982
25	**y**	0.05±0.080(58.67)	0.02±0.0099(83.47)	0.01±0.0090(91.73)	0.008±0.0080(93.38)	0.101±0.019011
26	**z**	0.05±0.023(58.67)	0.03±0.0083(83.47)	0.02±0.0073(91.73)	0.01±0.0062(93.38)	0.101±0.01882
27	**zi**	0.09±0.01(10.00)	0.07±0.0083(30.00)	0.05±0.0063(50.00)	0.04±0.0052(60.00)	0.1±0.0182
28	**zii**	0.12±0.023(14.28)	0.09±0.0098(35.71)	0.08±0.0088(42.85)	0.06±0.0078(52.14)	0.14±0.0172
29	**ziii**	0.08±0.001(27.27)	0.06±0.0090(45.45)	0.042±0.008(61.81)	0.032±0.0073(70.90)	0.11±0.0172
30	**ziv**	0.13±0.061(7.80)	0.10±0.0092(29.07)	0.09±0.0083(36.17)	0.089±0.062(36.87)	0.141±0.0187

Table 4. Antihistamine activity

	In vivo		**In vitro**
Compound 7	**Onset of convulsions (s) Mean ± SD**	**% Protection**	**IC_{50} g/ml 1 x 10^{-5}**
r	960 ±24	80.50	1.88
ziv	920 ±22	71.25	1.86
g	970 ±20	79.23	1.78
h	940 ±16	79.24	3.48
l	920 ±18	76.00	2.35
zii	980 ±22	78.10	2.28
s	950 ±18	72.80	1.94
x	960 ±22	78.16	2.28
t	958 ±18	76.80	2.14
std	1225 ±26		0.55
Control	108 ±12		

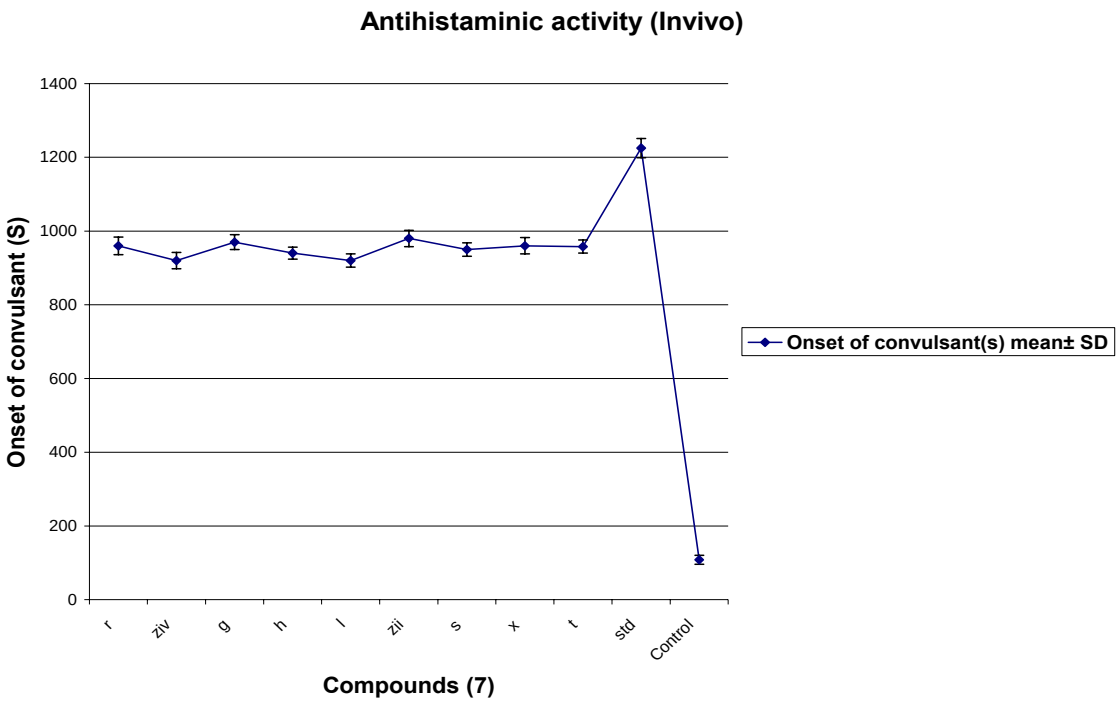


Fig 1. Onset of convulsions in antihistamine activity

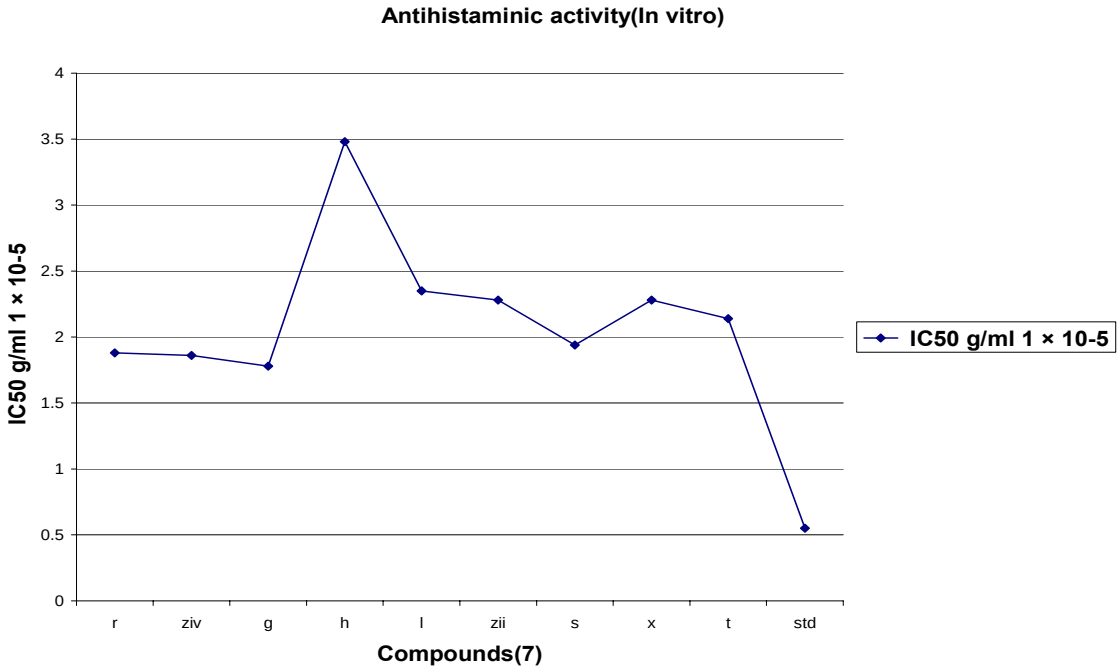


Fig 2. % Protection

Table 5. Anti-inflammatory activity

Comp (7)	Mean oedema vol (0-3 hrs)	Reduction in oedema vol (%)
Control	0.42±0.197	-------
Std	0.16±0.017	91.13
r	0.27±0.17	40.39
ziv	0.26±0.19	32.89
g	0.28±0.171	40.14
h	0.75±0.03	83.89
l	0.12±0.049	72.79
zii	0.19±0.077	59.57
s	0.09±0.037	80.49

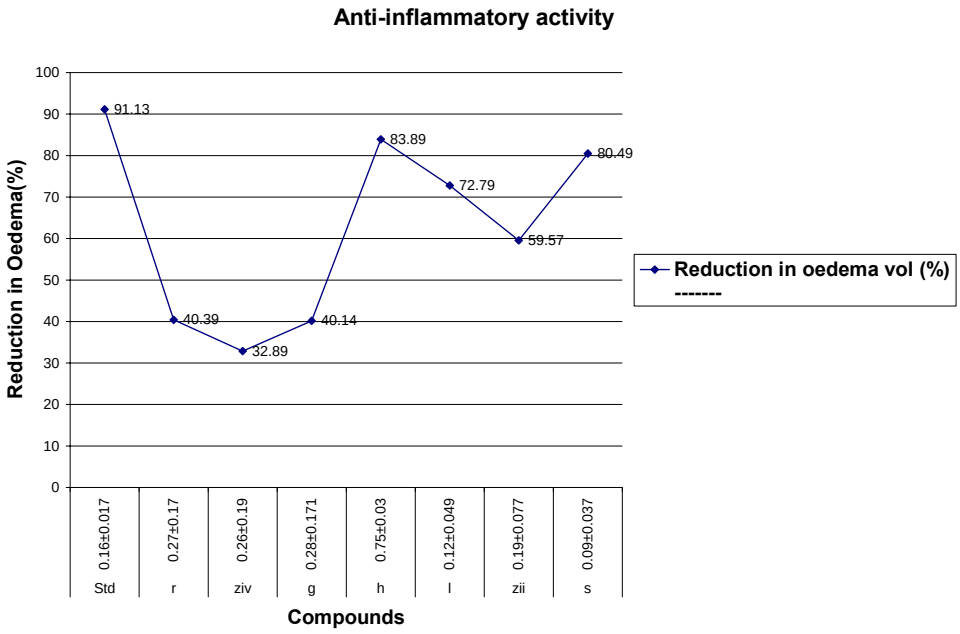


Fig 3. % Reduction in paw oedema volume

Table 6. Anti-tumor activity

Comp (7)	HBL-100 cell lines IC_{50} (μM)	HeLa cell lines IC_{50} (μM)
Cisplatin(STD)	25	25
7q	180	167
7c	197	187
7e	240	211
7g	234	201

7w	214	198
7k	201	197
7zi	241	225

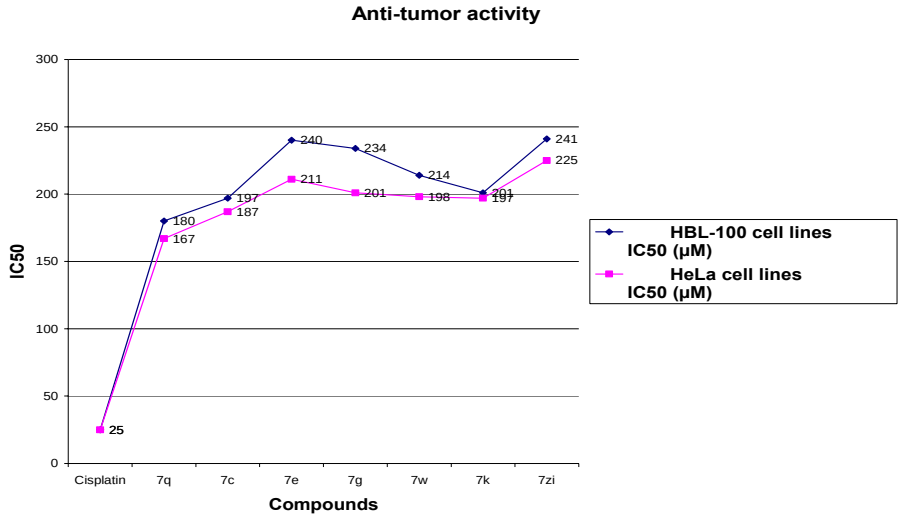


Fig 4. IC50 of HBL-100 and HeLa cell lines

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