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# QUINAZOLINONE: AN OVERVIEW

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**ABSTRACT**
Quinazolinone is a heterocyclic compound with a unique place in the field of medicnal chemistry. This quinazolinone has gain importance as antimicrobial, anti-inflammatory, anticonvulsant, analgesic, antihypertensive, antihyperlipidemic, diuretic, sedative, anticoccidial activity, antitubercular, antiviral, and anticancer agent. The chemistry of quinazolinone compounds has been the subject of considerable interest though there had been only scattered reports of the investigation of the medicinal properties of such compounds. This broad spectrum of biological and biochemical activities has been further facilitated by the synthetic versatility of quinazolinone which allows the generation of a large number of structurally diverse derivatives. This includes numerous analogues derived from substitution of the quinazolinone ring system, and derivatization of quinoline ring structure. Quinazolinone based drugs have broadened scope in remedying various dispositions in clinical medicines. Some quinazolinone derivatives have better activity than standard drugs and could become a new drugs for the market in future. Quinazolinone was proved to be useful in diuretic, anticancer, antihypertensive, NSAID, cardiovascular, hypnotic and antifolate drug discovery. This comprehensive study summarizes the different derivatives of substituted quinazolinone along with their chemistry, biological evaluation, and their major applications in the field of medicine and provide base for the future research work regarding modifications in quinazolinone moiety and its implementation in drug discovery and drug development.
**KEYWORDS:** Quinazolinone, Anticoccidial, Anticancer, Sedative, Antifolate.

## INTRODUCTION

Quinazolinone and their derivatives are building block for approximately 150 naturally occurring alkaloids isolated from a number of families of the plant kingdom, from microorganisms and animals. In light of the growing number of applications in recent years, there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazolinone derivatives. Compounds containing 4(3H)-quinazolinone ring system have showed antitumor, anticonvulsant, antitubercular activities, anti-inflammatory, analgesic, antimicrobial and anticoccidal activities[1-5]. Quinazolinones have been frequently used in medicine[6-8], such as quinethazone and metolazone and are used in medicine as diuretics while prazosin is a vasodilator, which is also used as an antihypertensive drug. Quinazolinones are also a class of drugs which function as hypnotic/sedatives that contain a 4-quiazolinone core. Their use has also been proposed in the treatment of cancer.[9] Examples include afloqualone, cloroqualone and diproqualone.

### Chemistry

Quinazolinone is a heterocyclic chemical compound with molecular formula $C_8H_6N_2O$. Quinazolinones are always high melting crystalline solids, insoluble in water and in most organic solvents but soluble in aqueous alkali. They are generally insoluble in dilute acids but are sometimes soluble in concentrated acids. Simple 4(3H)-quinazolinones, although insoluble in dilute acids, are soluble in 6N hydrochloric acid. 4(3H)-quinazolinones form stable monohydrochlorides, chloroplatinate, chloroaurates and picrates and their metal salts of silver, mercury, zinc, copper, sodium and potassium. There are two structural isomers, 2-quinazolinone and 4-quinazolinone (fig 1a,b), with the 4-isomer being the more common[10]. Recently quinozolone chemistry has got new direction due to some resemblance with folic acid[11]. Studies on chemistry has been increased because of its association in cancer chemotherapy. The analogs were slightly more potent than methotrexate as inhibitors of dihydrofolate reductase in human leukemia cells. The synthesis of quinazolines or quinazolones is mainly cyclisation from bifunctional intermediates[12].

### Biological Activities Of Quinazolinone Derivatives

### Antiviral

2,3-Disubstituted quinazolinones have been demonstrated to be associated with potent antiviral and antihypertensive acitivities. Quinazolin-4-(3H)-one is a versatile lead molecule for the design of potential bioactive agents. 2-Phenyl-3-Substituted Quinazolin-4-(3H)-ones and their derivatives have also shown significant anti-HIV activity[13-15]. Quinazolinones derivatives were screened for their wide spectrum anti-viral activity and they were found to be potential derivatives for further studies[16-18].

- **thiazolyl quinazolinones derivative (fig 2a):** The pharmacological properties exhibited by thiazolyl quinazolinone derivatives have been of much significance in recent years. These compounds have been demonstrated to be associated with varying degree of antiviral activity *in vitro* and *in vivo* both . The antiviral activity has been attributed to a delay of penetration of virus into the cells. The extent of pharmacological effects of quinazolinone derivatives depends on the active group to which it is attached. Thiazolyl derivative show 75 % inhibition against *Japanese encephalitis virus* (JEV) *in vitro* studies[19].
- **novel 2-phenyl-3-disubstituted quinazolin-4(3h)-ones (fig 2b):** Among the new derivatives evaluated, specific antiviral activity was noted with compound QAA against *vaccinia virus*, *parainfluenza-3 virus* and *Punta Toro virus*, compound QOPD against *HSV-1*, *HSV-2* and *vaccinia virus*, and compounds QONA and PD-NFIN against *Coxsackie virus B4*[20].

### Antimicrobial Activity

Quanzolone are familiar group of heterocyclic compounds possessing a wide verity of antimicrobial activity. Quinazolinone derivatives show remarkable antimicrobial properties against microorganism associated with death in patients carrying immune compromised diseases.

- **N-1-3-(5-substituted-1, 3, 4-thiadiazol-2-yl)–(2-amino methyl)quinazolin-4(3h)-one (fig 3a)**: Quinazolin-4(3H)-one derivatives are considered as good antimicrobial agents. Most of the deivatives showing antimicrobial activities were synthesized for example derivatives of N1-3-(5-Substituted-1, 3, 4-thiadiazol-2-yl)–(2-amino methyl)quinazolin-4(3H)-one. Some derivatives possess antibacterial activity against *Escherichia*

*coli* (NCTC 10418), *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 29737). They were also screened for anti-fungal activity showing maximal activity against *Aspergillus niger* (NCIM 596), *Candida albicans* (NCIM 3102)[21].

- **2-(4-nitrophenoxy)-n-(4-oxo-2-phenylquinazolin-3(4h)-yl)acetamide (fig 3b)**: 2-(4-nitrophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (DK-2) showed maximum zone of inhibition (18 mm) against *S.aureus* as well as against *E. coli* (17 mm) which is higher than the standard drug ampicillin[22].
- **b-lactam-quinazolinone derivatives (fig 3c):** They show antibacterial activity against *Escherichia coli* and *Basillus subtilis* in vitro involving the two fold serial dilution technique as recommended by the National Committee for Clinical Laboratory Standards (NCCLS)[23].
- **4-oxo-thiazolidinyl quinazolin-4(3*H*)ones (fig 3d):** Antimicrobial evaluation of this compound was done. They showed antibacterial and antifungal activity when compared with the standard drugs drugs penicillin-G, ampicillin, and amoxicillin[24].

**Anticancer Activity**

Quinazolin-4-(3H)-One is a versatile lead molecule for the design of potential bioactive agents. Anti-cancer activity were studied for 2,3-disbstituted quinazolinones derivatives and they showed promising anticancer potential[25-27].

- **2-{[bis-(2-chloroethyl) amino| methyl}- 6, 8-dinitro-1- (4-substituted ethyl)-1h-quinazolin-4-one derivatives (fig 4a):** The 1, 6, 8- trisubstituted quinazolinones with a nitrogen mustard moiety connected through a methylene group at position 2 are effective in mice bearing Dalton's Lymphoma Ascites. Further, it is concluded that the quinazolinon-2-methyl nitrogen mustard with either a nitro or chloro group at para phenyl position is a most potent anticancer compound, which can be further developed. The synthesized compounds were screened for their anticancerous activity by short-term *in-vitro* antitumor activity and *in-vivo* anticancer activity by body weight analysis, mean survival time and percentage increase in life span methods in Swiss albino mice bearing DLA 1x106 cells/ml[28].
- **diphenyl quinazolinone (fig 4b)**: The related diphenyl quinazolinone is also a potent antimitotic agent, and is highly active *in vivo*[29]. The compound is highly insoluble, though incorporation of the compound into liposomes (several concentric layers of lipid bilayers) imparts water solubility to the drug, allowing transport into the cell. Once inside the cell, the liposome shell dissipates, leaving the drug free to exert its effects[30].

**Antitubercular Activity**

It was also reported that 2 or 4-substituted thioquinazolinone derivatives were identified as a possible pharmacophore for antitubercular activity. In the quest for biologically potent anti-tubercular agents, as pharmaceutical chemists designed, synthesized and screened some 2-alkylthio-6-iodo-3- substituted-quinazolin-4-one derivatives to mimic those reported as potential antitubercular agents[31-34].

- **2-alkylthio-6-iodo-3-substituted-quinazolin-4-one (fig 5a)**: This derivative was screened for their *in vitro* antitubercular activity against *Mycobacterium tuberculosis* strain H Rv, using the 37 radiometric BACTEC 460-TB methodology and they showed good antitubercular activity[35].
- **N-3[4-(4-chlorophenyl thiazole-2-yl)-2-aminomethyl] quinazoline-4(3h)-one derivatives (fig 5b)**: A new series N-3[4-(4-chlorophenyl thiazole-2-yl)-2-aminomethyl] quinazoline-4(3H)-one derivatives are synthesized. The compounds are screened for their antitubercular activitiy using H37Rv stain. All the compounds have showed moderate to promising antitubercular activity[36].

**Anti-Inflammatory and Analgesic Activity**

Discovery of new safer anti-inflammatory drugs represents a challenging goal in research area[37-38]. Quinazolinone derivatives with 2,3-substitution are reported to possess significant analgesic and anti-inflammatory activity. Looking at the biological significance of quinazolinone nucleus, it was thought to synthesize new quinazolinone derivatives and screen them for their analgesic and anti-inflammatory activity[39-40].

- **2,3-disubstituted quinazolinone derivatives (fig 6a):** A series of some novel 2,3-disubstituted quinazolinone derivatives were synthesized by condensing 2-methyl/ 2-phenyl/6-bromo-2-methyl/6- bromo-2-phenyl/6, 8-dibromo-2-methyl/ 6, 8-dibromo-2-phenyl benzoxazines with compounds containing amino group. Derivatives showed good analgesic and anti-inflammatory activities[41].
- **novel 6,8-dibromo-4(3h)-quinazolinone derivatives (fig 6b):** Monobromoquinazolinone derivatives, that both mono and dibromoquinazolinone derivatives have significant anti-inflammatory and analgesic effect[42].
- **novel 3-(p-substituted phenyl)-6-bromo-4(3h)-quinazolinone derivatives (fig 6c):** Besides the diverse biological activity ascribed to quinazolinone derivatives and enzyme inhibitory effect of several 6-bromoquinazolinones and based on continuation of our drug research program on the development of safe quinazolinone anti-inflammatory agents, it was of interest to synthesize a novel series of 6-bromoquinazolin-4(3H)-ones incorporated into other heterocyclic moieties such as pyridine, pyran, pyrazoline, pyrimidone and/or pyrimidinethione ring systems to be evaluated for their antiinflammatory and analgesic activities. They showed promising anti-inflammatory and analgesic properties[43].

**Sedative – Hypnotic**

The 4(3H)-quinazolinone nucleus containing well known sedative-hypnotic activity. Methaqualone (2-methyl-3-o-tolyl-4(3H)-quinazolinone) is example of this case. The results and interpretations of past study on CNS activity of 2,3-disubstituted 4(3H)-quinazolinones reveal that it is more potent sedative – hypnotic[44].

- **1-(4-substituted-phenyl)-3-(4-oxo-2-propyl-4H-quinazolin-3-yl)-urea (H1-H12) derivatives (fig 7a)**: All the quinazolinone analogs showed potent sedative-hypnotic and CNS depressant activity. In the behavioral study using actophotometer scoring technique, the entire synthesized compounds showed decrease in locomotor activity where 37% was the lowest and 52% was the maximal decrease in locomotor activity when compared to phenytoin[45].

**Anticoccidial Activity**

The potent anticoccidial activity of febrifugine in poultry was discovered in the 1960's. Because of side effects, such as diarrhea, vomiting[46] and liver toxicity[47]. It has been precluded as an anticoccidial drug. Halofuginone is a broad-spectrum anticoccidial medicine with low toxicity and no cross-resistance[48]. The quinazoline ring might play a vital role in the anticoccidial activity; (1) the introduction of halogen groups might change the anticoccidial activity; (2) the anticoccidial activity of these compounds probably have a relationship with the 2′-carbonyl and 3″-hydroxyl or 2″-methoxy.

- **4-(2-methoxyphenyl)-2-oxo-butyl-quinazolinones (fig 8a)**: A series of 4-(2-methoxyphenyl)-2-oxo-butyl-quinazolinones were designed and synthesized based on the structure of febrifugine. The biological activity test results indicated that they exhibited

anticoccidial activities against *Eimeria tenella* in the chicken diet with a dose of 9 mg/kg. Compared with halofuginone, these compounds have the advantages of shorter synthetic routes and lower cost[49].

**Antihyperlipidemic Activity**

The 4(3H)-quinazolinone derivatives (a derivative of the parent compound quinazoline) have been shown as a group of compounds of broad medical interest. The antihyperlipidemic and antihypercholesterolemic activities of quinazolinone derivatives are reported and the activities of the tested compounds were almost equal to that of β-sitosterol (a plant sterol of hypolipidemic activity)[50].

- **6, 8-dibromo-2-methy-4 (3H) quinazolinone (fig 9a)**: The effects of subchronic treatments (4 weeks) of hypercholesterolemic (single) and diabetic-hypercholesterolemic (combined) rats with 4 (3H) quinazolinone and 2 halogenated derivatives (6,8-dibromo-2-methy-4(3H) quinazolinone and 6-iodo-2-methyl-4(3H) quinazolinone) at a sublethal dose level (2 mg/Kg) on cholesterol metabolism were investigated. Bezafibrate, a hypolipidemic drug was used as a reference compound for data comparison[51].

**Antihypertensive**

Novel substituted quinazolinones possessing angiotensin II (AII) antagonistic activity and useful as antihypertensive agents are disclosed. The compounds are also useful for treating congestive heart failure and in the treatment of elevated intraocular pressure.

- **2-butyl-6-methyl-3-[(2′-(tetrazol-5-yl)biphenyl-4-yl)methyl]quinazolin-4(3H)-one** (**fig 10a)**: It is one of the quinazolinone having antihypertensive activity and show cardiovascular activity also.

**Application of Quinazolinone in Drug Discovery (fig 11)**

Quinazolinone are considered as a privileged scaffold in drug discovery and drug development. Among the two isomers of quinazolinone, 4-(3H)-Quinazolinone being more common show various biological activities and prove its major application in the field of medicine. Quinazolinone derivatives were proved to be useful in diuretic, anticancer, antihypertensive, NSAID, cardiovascular, hypnotic and antifolate drug discovery.(fig 11) (table 1)

**CONCLUSION**

This review give an outlook on the research developments regarding quinazolinone moiety. This heterocyclic moiety has great biological and medicinal significance. A large array of quniazolinone derivatives possess a variety of medicinal properties. These properties include antimicrobial, anti-inflammatory, anticonvulsant, analgesic, antihypertensive, antihyperlipidemic, diuretic, sedative, anticoccidial activity, antitubercular, antiviral, and anticancer activity. Quinazolinone is considered as an important lead compound in drug discovery and drug development. Quinazolinone occupy a distinct and unique place in the field of medicine. This article also provide a base for the future research work regarding possible modifications in quinazolinone moiety and its implementation in drug discovery.

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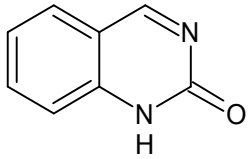
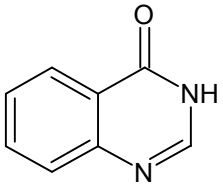
**Table 1: Quinazolinone Derivatives As Medicines**

| S.NO | DRUG | IUPAC NAME | ACTIVITY | Ref. |
|---|---|---|---|---|
| 1 | Methaqualone | 2-methyl-3-o-tolyl-4(3H)-quinazolinone | Hypnotic | 52 |
| 2 | Etaqualone | 3-(2-ethylphenyl)-2-methyl-quinazolin-4-one | Sedative, Hypnotic | 53 |
| 3 | Afloqualone | 6-amino- 2-(fluoromethyl)- 3-(2-methylphenyl) quinazolin- 4-one | Sedative, Hypnotic, Anticancer | 54, 9 |
| 4 | Cloroqualone | 3-(2,6-Dichlorophenyl)-2-ethyl-4-quinazolinone | Sedative, Antitussive | 54, 9 |
| 5 | Diproqualone | 3-(2,3-dihydroxypropyl)-2-methyl-quinazolin-4-one | Anxiolytic, Analgesic, Antihistamine, Rheumatoid Arthritis | 55, 9 |
| 6 | Quinethazone | 7-chloro-2-ethyl-4-oxo-1,2,3,4-tetrahydroquinazoline-6-sulfonamide | Antihypertensive | 56 |
| 7 | Fluproquazone | 4-(4-fluorophenyl)-7-methyl-1-propan-2-ylquinazolin-2-one | NSAID | 57, 58 |
| 8 | Tiacrilast | (E)-3-[6-(Methylthio)-4-oxoquinazolin-3(4H)-yl]propenoic acid | Antiallergic | 59 |
| 9 | Halofuginone | 7-Bromo-6-chloro-3-[3-[(2S,3R)-3-hydroxy-2-piperidinyl]-2-oxopropyl]-4-quinazolinone | Coccidiostat, Antitumor, Autoimmune disorders | 60 |
| 10 | Raltitrexed | *N*-[(5-{methyl[(2-methyl-4-oxo-1,4-dihydroquinazolin-6-yl)methyl]amino}-2-thienyl)carbonyl]-L-glutamic acid | Anticancer | 61 |



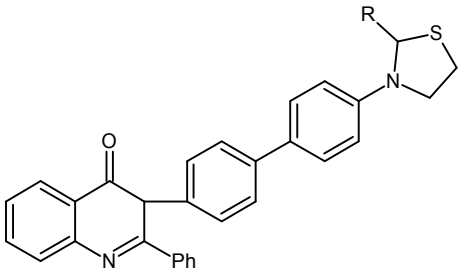
2-Quinazolinone



4-Quinazolinone

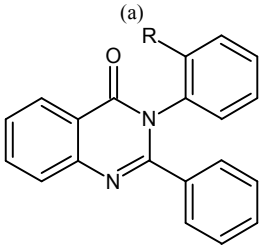
(a) (b)

**fig 1: two isomers of quinazolinone (a, b)**



R = p-chlorophenyl

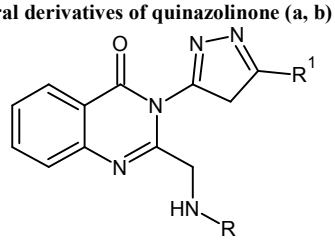
(a)



R = $NO_2$ (QONA), $NH_2$ (QOPD), COOH (QAA)

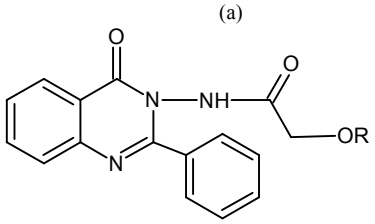
(b)

**fig 2: antiviral derivatives of quinazolinone (a, b)**



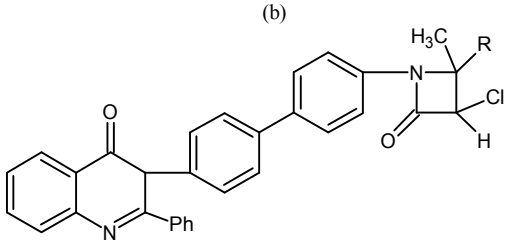
where R and R1 = various aromatic substituents

(a)



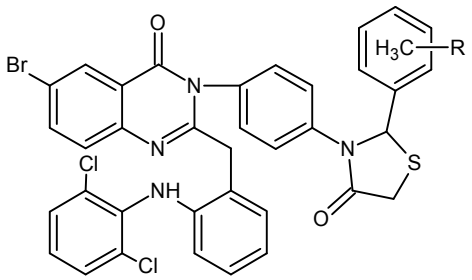
R = 4-$NO_2$.$C_6H_4$ = DK-2

(b)



R = p-chlorophenyl, o-hydroxyphenyl, p-hydroxyphenyl, (4-OH,3-$OCH_3$-phenyl), (3-OH, 4-$OCH_3$-phenyl)

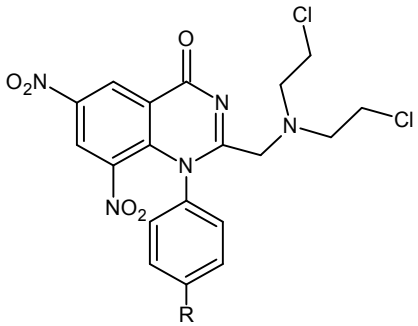
(c)



R = 2-Cl, 4-Cl, 2-OH, 4-OH, 4-$OCH_3$, 2-$NO_2$, 3-$NO_2$, 4-$N(CH_3)_2$, 3,4,5-$OCH_3$, 2-OH, 4-$N(C_2H_5)_2$

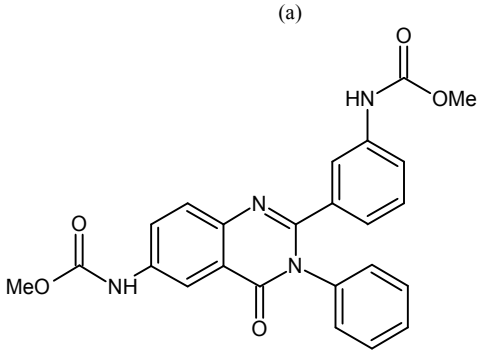
(d)

**fig 3: antimicrobial derivatives of quinazolinone (a, b, c, d)**



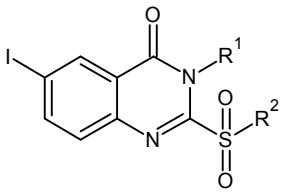
R = H, Cl, $NO_2$, $OCH_3$, $OC_2H_5$, $CH_3$

(a)



(b)

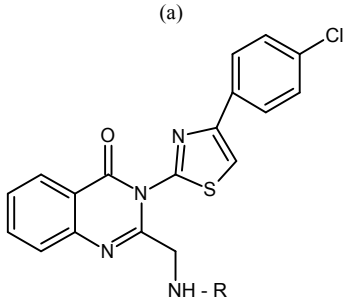
**fig 4: anticancer derivatives of quinazolinone (a, b)**



$R^1 = R^2$ = benzyl

$R^1 = R^2$ = phenyl

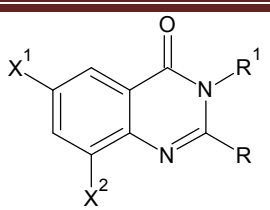
(a)



R = $C_6H_4Cl$, $C_6H_4F$, $C_6H_4NO_2$, $C_6H_4CH_3$, $C_6H_4OCH_3$, $C_6H_4COOH$ and other heterocyclic derivatives

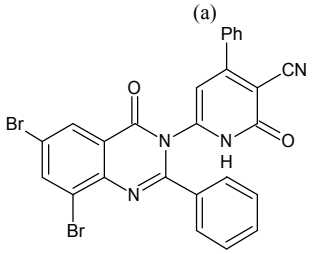
(b)

**fig 5: antitubercular activity of quinazolinone derivatives (a, b)**

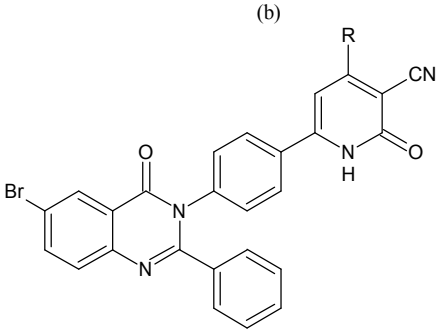


X1, $X^2$ = H, Br; R = $CH_3$, $C_6H_5$; $R^1$ = -$NHCOC_6H_5$, -$N(COC_6H_5)_2$

(a)



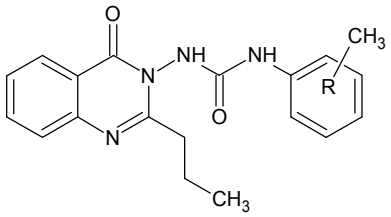
(b)



R = various aromatic substituents

(c)

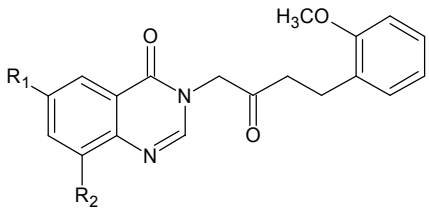
**fig 6: anti-inflammatory and analgesic derivatives of quinazolinone (a, b, c)**



Where, R = H, F, Cl, Br, I, $NO_2$, o-$CH_3$, m-$CH_3$, p-$CH_3$, $C_2H_5$, $OCH_3$, $OC_2H_5$

(a)

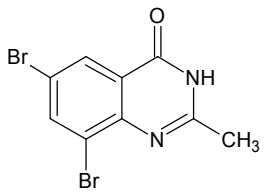
**fig 7: sedative – hypnotic derivatives of quinazolinone**



$R_1$=H,$R_2$=H; $R_1$=Br,$R_2$=H; $R_1$=Br,$R_2$=Br; $R_1$=I,$R_2$=H; $R_1$=I,$R_2$=Br; $R_1$=Cl,$R_2$=H; $R_1$=H,$R_2$=Cl; $R_1$=Cl,$R_2$=Br

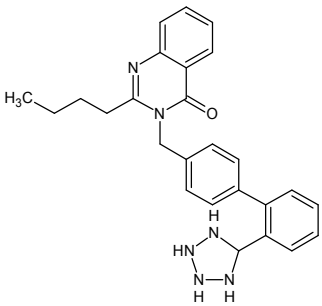
(a)

**fig 8: anticoccidial derivatives of quinazolinone (a)**



(a)

**fig 9: antihyperlipidemic derivatives of quinazolinone (a)**



(a)

**fig 10: antihypertensive derivatives of quinazolinone (a)**

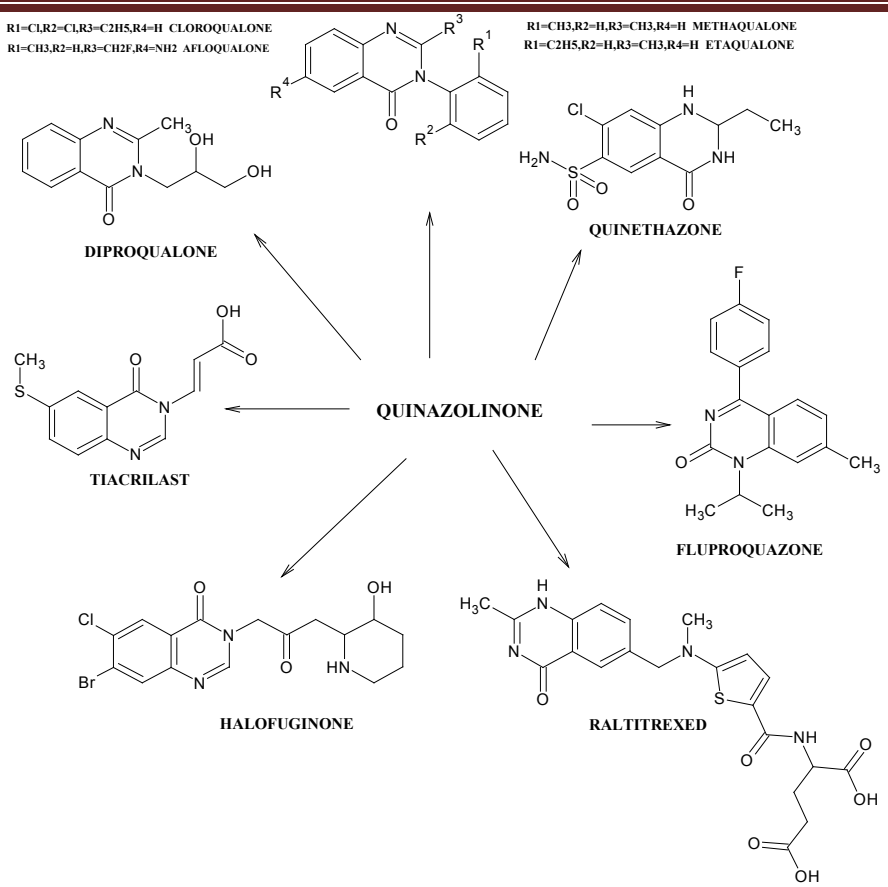



**fig 11: application of quinazolinone in drug discovery**