BIOLOGICAL IMPORTANCE OF QUINAZOLINE DERIVATIVES A REVIEW

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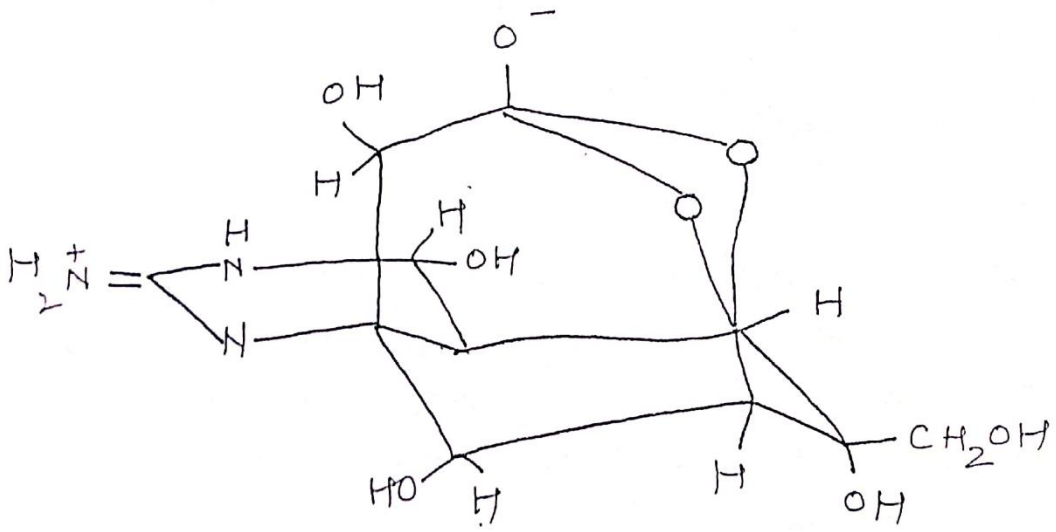
Abstract:

Quinazoline and quinazolinone have drawn a huge consideration owing to their expanded applications in the field of pharmaceutical chemistry. Quinazoline and quinazolinone are reported for their diversified biological activities and compounds with different substitutions bring together to knowledge of a target with understanding of the molecule types that might interact with the target receptors. Several quinazoline derivatives both natural and synthetic have been found to possess significant physiological activity. Being considered as advantaged scaffold, the alteration is made with different substituent.

Several quinazoline derivatives both natural and synthetic have been found to possess significant physiological activity.[1-3] Apart from this, several quinazoline derivatives have been found as plant growth regulators having application in agriculture.[4-6] In addition, certain quinazoline derivative have found application in industry also.[7-12]

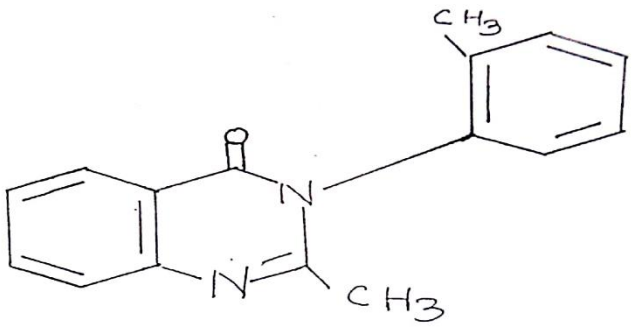
The most active quinazoline derivative is Tetradotoxin (I) which is a powerful neurotoxin.



Tetradotoxin (I)

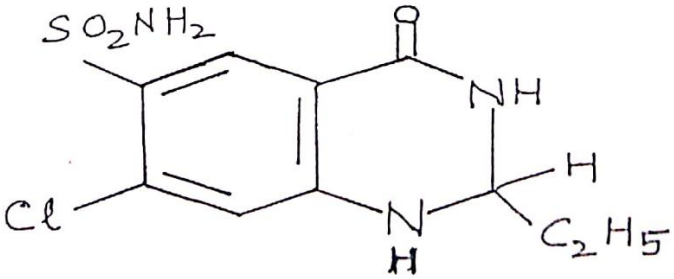
Among the synthetic quinazolines; the hypnotics 3,4-dihydro-2-methyl 4-oxo-o-tolylyl quinazoline was examined extensively and is now used clinically and is marketed in several countries under a number of brand names e.g. methaqualone[13-15], Revonal[14-15,] Metolquin[16], Zolone, Dilunal[17], QZ-2[18], Tnazolone[19] and Melsedin1[13-14].

Its hypnotic activity is comprable to that of barbiturates. Its biological activity has been the subject of extensive research[20-21]. Methaqualone (II) was found superior to sodium phenobarbitone as an anti-convulsant against metrazole induced seizures[18].



Methaqualone (II)

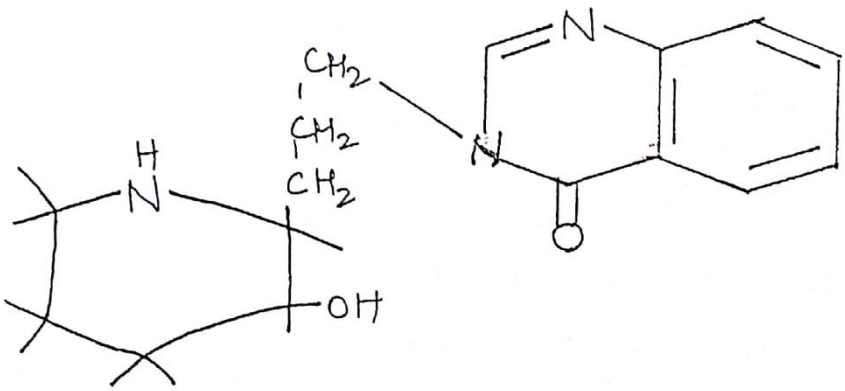
Structure-activity relationship studies suggested that oxo-quinazoline structure is apparently responsible for the effect of these drugs on the nervous system. Also it has been reported that 3,4-dihydro. 4-oxo[22-24],1,2,3,4 -tetrahydro-2,4-di oxo[22-30], 1,2,3,4 -tetrahydro-4-oxo-2-thio[25] and 1,2,3,4 -tetrahydro-4-oxo-quinazoline[25] have hypnotic and hypotensive activity.



Quinethazone (III)

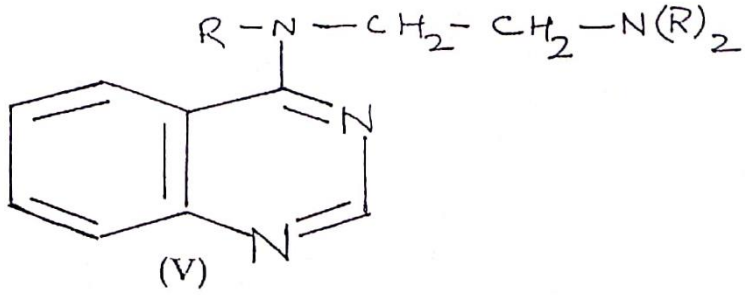
7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-6-sulphamoylquinazoline (III) is very effective non-mercural diuretic which is now administered clinically. It is marketed under the names quinethazone, Aquamox and Hydramox. Clinical studies showed that it caused rapid excretion of water and sodium ions. The duration of the activity was 24 hours and an optimal weekly dose of 100-150mg generally sufficed. Its diuretic potency was similar to cholorthiazide.

Febrifungie (IV) and many of its derivatives show anti-malarial activity.



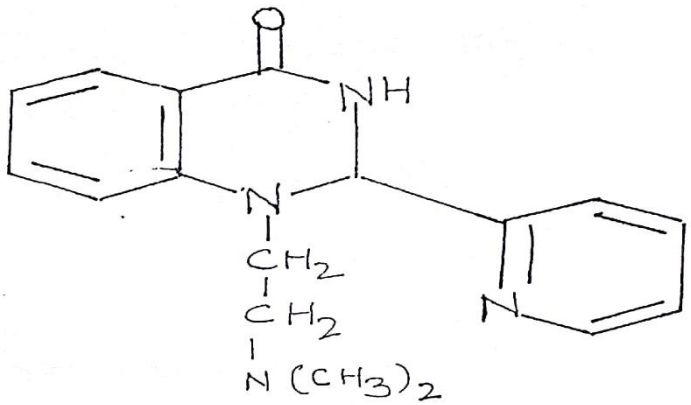
Febrifungie (IV)

Low antihistamine activity was observed in 4-N'-alkyl- 2', 2'-dialkyl- aminoethyl aminoquinazoline (V) but the activity was highly specific and the compounds had no antiacetyl choline activity.



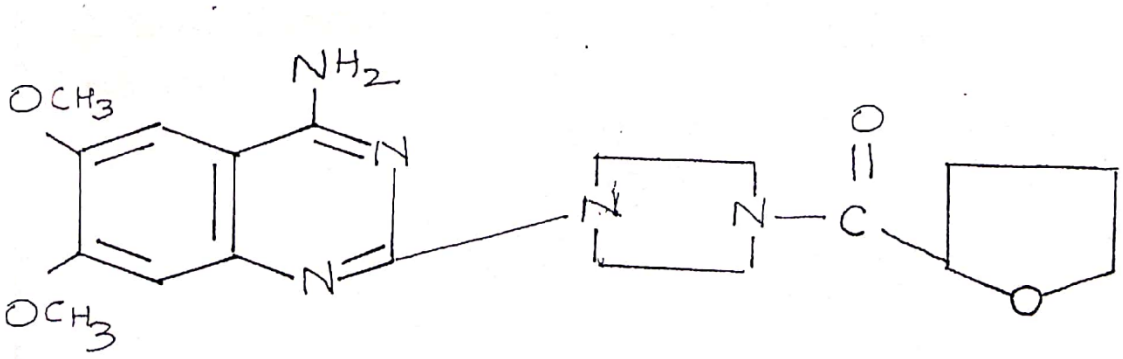
(V)

Among various 1, 2, 3, 4 - tetrahydro - 4 - oxoquinazolines; 1, 2' -dimethylamino - ethyl - 1, 2, 3, 4 - tetrahydro - 4 - oxo - 2, 2'- pyridyl quinazolines (VI) showed the highest specific antihistamine activity *in vivo* and *in vitro*. It had low toxicity with almost complete absence of sedating side effects.



(VI)

Prazosin (VII), a quinazoline derivative is used as antihypertensive drug acting by vesodilation.



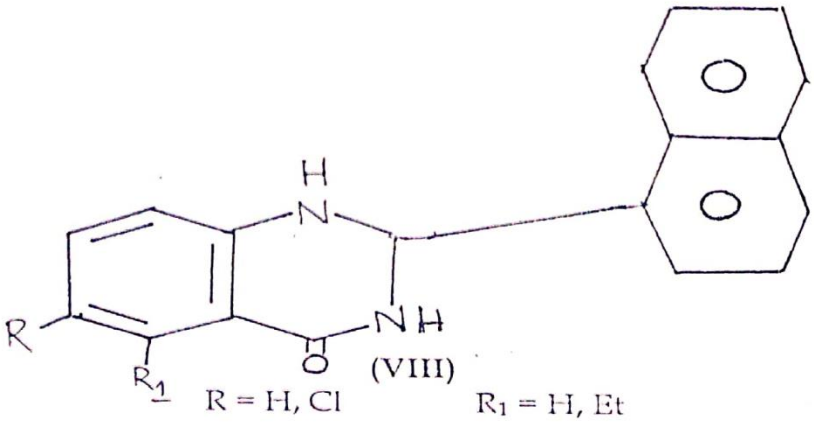
Prazosin (VII)

Several derivative of oxo-quinazoline had shown antibacterial activity. Several oxo-, thio-, chloro- and nitro quinazolines have been incorporated into the vitamin B molelcule by replacing the 5,6-dimethyl benzimidazole moiety and possessed cobalamine activity. 3,4- Dihydro -3-hydroxy - 4 - oxo quinazolines was found useful in protection from radiation damage. Several hydrazino quinazoline condensation product are reported as inhibitors for human type tuberculosis bacillus and have compared with standard such as Streptomycin and Tibione.

Quinazolones derivatives as anti-fertility agents:

Quite early in the study of steroidal anti-fertility agents, it was realized that continuous long-term administration of drug is associated with side effects, due to hormonal imbalance. It was therefore that development of nonhormonal compounds possessing anti fertility activity is a major research area. In search of such compounds, various non-steroidal heterocyclic anti-fertility agents were developed. Various quinazolinones derivatives are reported as anti-fertility agents.

Reif and Ericson el al[31] have synthesized 2-(l-naphthyl)-2,3-dihydro-4(IH)- quinazolinones (VIII) reported to inhibit fertility in male mammals.

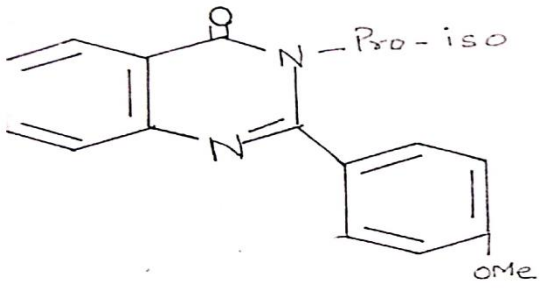


(VIII)

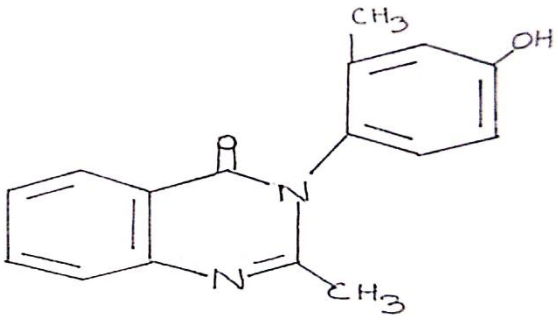
R = H, Cl R_1 = H, Et

Saxena et al[32] also observed that if 4(3H) quinazolinones fed orally at 30mg/kg to rats from days 1 to 7 of pregnancy, only 2- (p-anisyl-3-isopropyl -3, 4 - dihydro - quinazolin - 4 one) (IX) inhibited pregnancy to the extent of 60 percent at 30 mg/k' dose. Among 20 quinazolin ones, fed to rats at 30mg/kg/day on days 1-7 of pregnancy 2-methyl - 3 - (4 - hydroxy - 2 - methylphenyl) - 4 (3H) - quinazolinone (IX) caused 60 percent inhibition of pregnancy.[33]

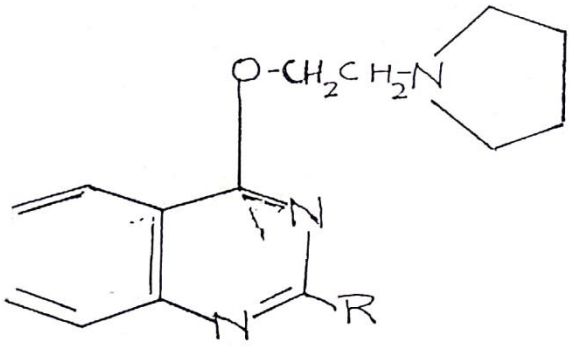
Manhas et al[34] also synthesized several quinazolino derivatives (Xl-XIl) incorporating trans stiblene moiety for anti-implantation activity but none of the compound turned out to be very effective.



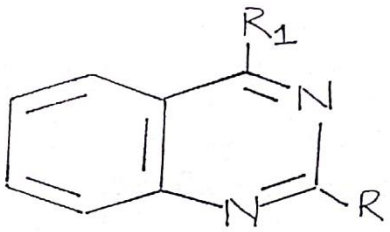
IX



X



(XI)



(XII)

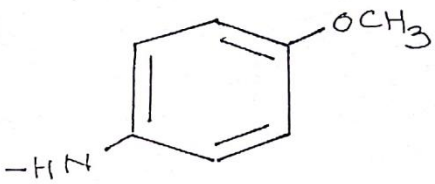
a, - $C_6H_4OCH_3$ (4)

b, - C (Ph) = CH C_6 H_4 OCH_3 (4)

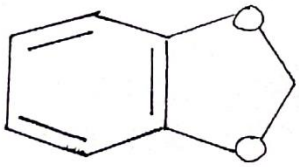
c, - C (C_6H_3 $(OCH_3)_2$ 3,4] =·CHPh

R= C_6H_4OMe (4)

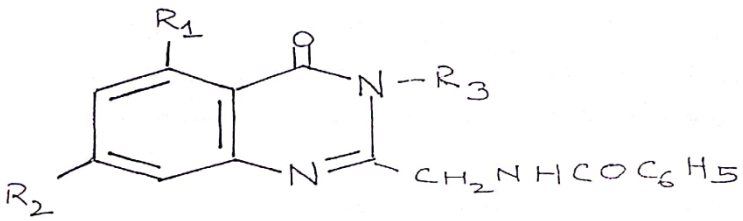
R_1= SMe,



d,



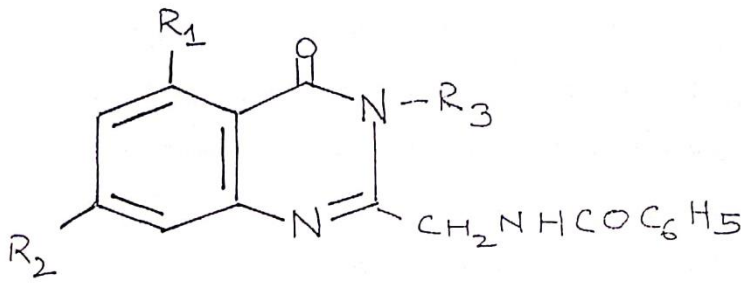
A number of 2- hippuryl-3-arylquinazoIinone (Xlll) were tested for anti implantation activity in rats[35]. The tested compounds has no significant anti-implantation activity at the oral dosage of 20mg/kg/day; all the tested animals became pregnant.



(XIII)
R= Ph, $PhCH_2$, Cyclohexyl

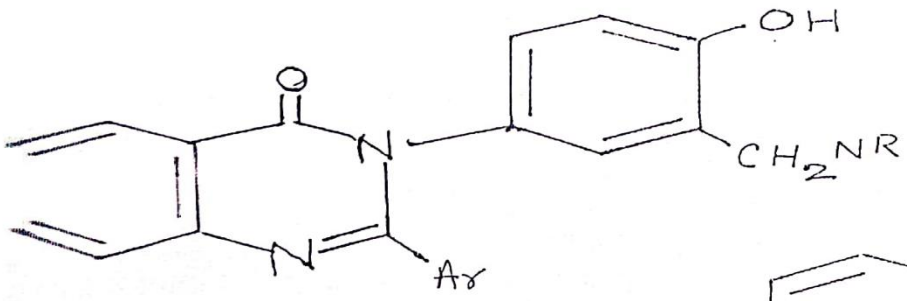
In view of diverse biological activities associated with quinazolones, 2,3,6 and 2,3,7- trisubstituted benzoxazines (XIV) and 2,3,6,7- tetrasubstituted quinazolones (XV) were synthesised as contraceptive agents but none of them exhibited any significantactivity.[36]

Several quinazolin-4-one derivatives have been reported to exhibit appreciable anti-fertility activity. These provided the necessary lead for the synthesis of 2- phenyl-3- (3-aminomethyl-4-hydroxy phenyl) -quinazolinones (XVI) and 2- phenyl/3, 4, 5 - trimethoxy - 3 - (2-methoxy/3,4,5 tri methoxy phenyl) - 6 - substituted quinazolin-4-ones (XVII) as possible anti-fertility agents. All the compounds were found ineffective[373]. In connection of above approach, several other compounds such as 2- (N,N- disubstituted diaminomethyl)-3- (2-pyridyl)- 4 (3H) quinazolones (XVIII) were also prepared as contraceptive agents but none of these compounds showed any significant activity at an oral dose level of 25 mg/kg body weight[37b].

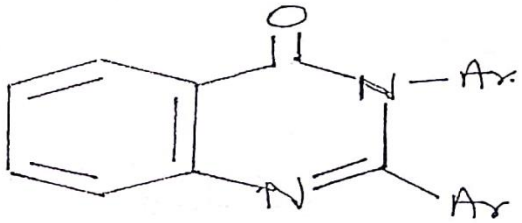


(XIII)
R= Ph, $PhCH_2$, Cyclohexyl

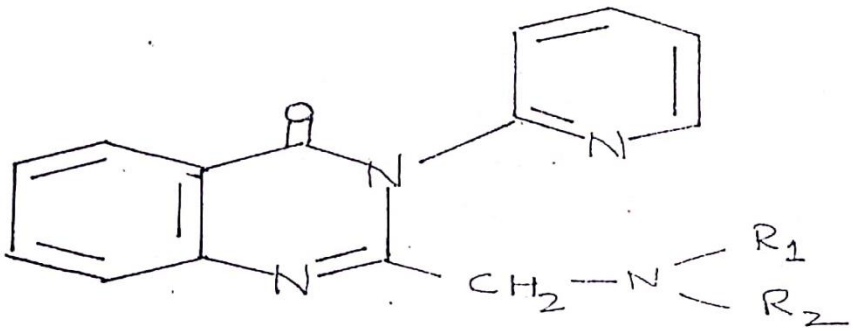
Some fused quinazoline derivative such as 10,12- disubstituted [1,4]-benzoazino [3,4-d] quinazolin -8-ones (XIX) were preapred and evaluated for their contra gestational activity. These compounds were marginally effective at the dose level of 25 mg/kg. body eight of theanimal.[37b]



(XVI)
NR= Dimethylamino,
N- Phenylpiperazino



(XVII)
X= H, Br.
Ar = Phenyl, 3,4,5 - Trimethoxy phenyl



(XVIII)
NR_1, R_2 = Diethylamino, Pyrrolidino, Morpholino

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