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SYNTHESIS AND REACTIONS OF 2-PHENYLAMINO, 6,8-DIBROMO-3,1-BENZOXAZIN-4-ONE AND 4(3H)QUINAZOLIN-4-ONE DERIVATIVES

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ABSTRACT

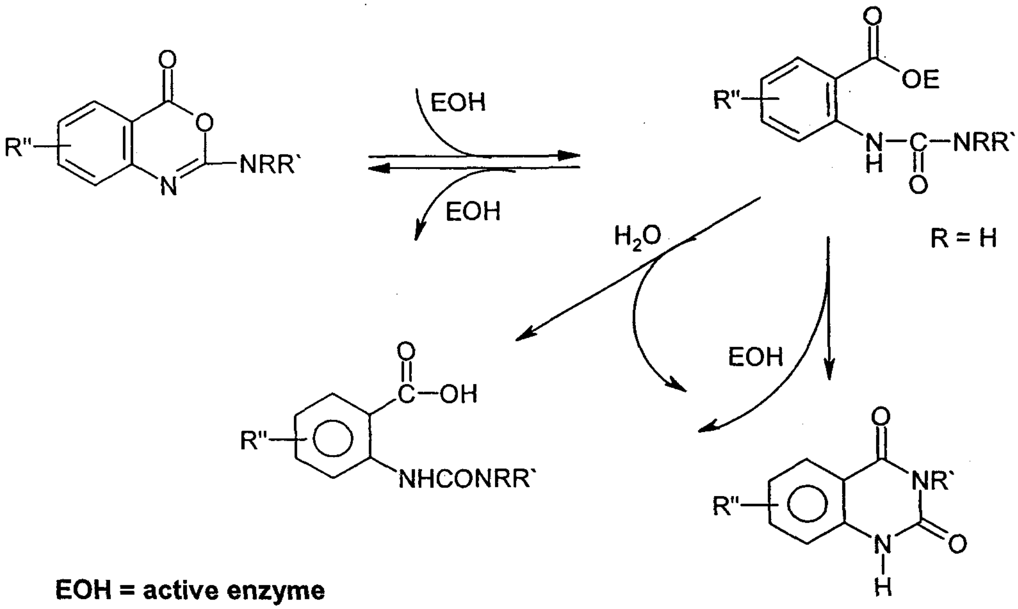
2-Phenylamino-6,8-dibromo-4H-3,1 -benzoxazinone has been reacted with nitrogen nucleophües, such as hydrazine hydrate, amines and formamide. and yielded 4(3H)quinazolin-one derivatives; and with sulphur nucleophiles and yielded the corresponding thioesters. The behaviour of aminoquinazoli-none and 4(3H)quinazolinone towards carbon elecIrophiles under different conditions has been described.

KEYWORDS: 2-Phenilamino-6,8-dibromo-4H-3,1-benzoxazinone , quinazolinone derivatives, nitrogen nucleophiles, sulfur nucleophiles, carbon electrophiles.

INTRODUCTION

U. Neumann et. al.(1) have investigated the inhibition of chymotrypsin-like and elastase-like serine proteases by 4H-3,l-benzoxazinones. Such compounds have recently been showvn to be active in vivo after intratracheal administration(2). Benzoxazinones temporarily inhibit the catalytic activity of serine proteases by accumulation of a catalytically inactive acyl-enzyme intermediate (Scheme 1). The rates of acylation and deacylation as well as the compound selectivity is determined both by substituents at the benzene unit and the 2-substituent at benzoxazinone moiety. Potent benzoxazinone inhibitors for human leukocyte elastase (HLE)[3], human Cathepsin G, and bovine chymotrypsin(4) have been described. Introduction of 2-amino substituent is a successful strategy to improve the chemical stability of benzoxazinones(3-5).

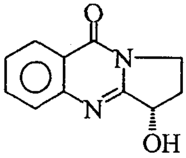
Reaction of 2-amino-4H-3,l-benzoxazinones with serine proteases. (Formation of acyl-enzyme).



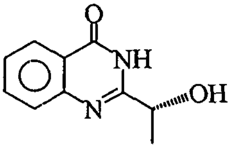
Scheme 1

On the other hand, like wise, many fused pyrimidines such as quinazolines have been reported, anti-inflammatory(6,7), antimicrobial(8), and anticancer (9,10) activities. Moreover, several quinazolinone derivatives were synthesized as potential antimicrobial(11), anticancer(12) and antimalarial(13) agents.

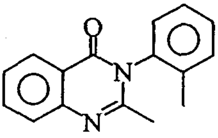
3H-Quinazoline-4-one is a frequently encountered unit in natural products such as L-vasicinone14), chrysogine(15) and drugs such as methaqualone(16), febrifugine and isofebrifugine. Molecules based on quinazoline and quinazolinone exhibit a multitude of interesting pharmacological activities(17-19).



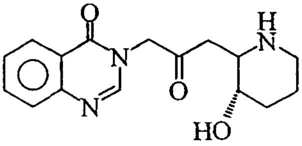
L-vasicinone



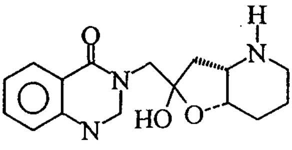
chrysogine



methaqualone



febrifugine



isofebrifugine

Aforementioned findings prompted the authors to synthesise a varieties of the quinazolinone derivatives via the interaction of the benzaxazinone derivative 1 with different nitrogen nucleophiles, with the aim of obtaining more precise information about the course of the reaction and some interesting pharmaceutical compounds.

RESULTS AND DISCUSSION

Interaction of 3,5-dibromoanthranilic acid with phenyl iso-cyanate in boiling toluene afforded 2-phenylamino-6,8-dibromo 4H-3,l-benzoxazinone (1). The structure of the compound 1 was inferred from its IR spectrum which reveals strong absorption bands at 1646, 1749 and 3286 cm^{-1} attributable to $\nu_{C=N}$, $\nu_{C=O}$, and ν_{NH} respectively. Electron impact fragmentation of compound 1 exhibits the molecular ion peak m/e, M$^+$ (394, 43.5%), M$^+$+l (396, 78.2%) and M$^+$+2 (398, 41.8%).

When compound 1 was allowed to react with hydrazine hydrate in boiling ethanol it yielded 2-phenylamino-3-amino-6,8-dibromo-4(3H)-quinazolinone (2). Its IR spectrum exhibits absorption at 1617, 1666, 3203, 3250 and 3305 cm$^{''1}$ attributable to $\nu_{C=N}$, $\nu_{C=O}$ and ν_{NH} respectively.

Electron impact fragmentation of compound 2 exhibits m/e (333, 32.4%), (335, 63.6%) and (337, 31.2%) attributable to (M$^+$ -CeH$_5$) with proton transfer.

When compound 1 was allowed to react with formamide and/or ammonium acetate yielded 2-phenylamino-6,8-dibromo-4(3H)-quina-zolinone (3). IR spectrum of compound 3 revealed strong absorption bands at 1691, 3075 and 3193 cm^{-1} attributable to $\nu_{C=O}$ and ν_{NH} respectively. Electron impact of compound 3 exhibits m/e at (302, 49.4%), (304, 100%) and (306, 48.8%) corresponding to (M$^+$-NH$_2$) with hydrogen transfer. The 'H-NMR spectrum of compound 3 in DMSO-d$_6$ exhibits signals at § ppm 5.8(s, 3H, NH protons which disappear when spectrum runs in D$_2$O) and 8.17-8.3 (m, 2H, ArH).

Interaction of the compound 1 with 2-chloroaniline in boiling ethanol afforded 2-amino-3-(2-chlorophenyl)-6,8-dibromo-4(3H)-quinazolinone (4a). The reaction takes place via heteroring opening followed by cyclization with elimination of the phenyl group. IR spectrum of compound 3a exhibits strong absorption at 1678, 3249, 3360 and 3467 attributable to $\nu_{C=O}$, ν_{NH} hydrogen bonded and unbonded respectively. Electron impact reveals m/e at (429, 1.7%), (431, 1.8%) and (433, 4.4%) attributable to M$^+$, M$^+$+l and M$^+$+2 and agreed well with isotopic abundance of bromine and chlorine.

Similarly compound 1 undergoes heteroring opening with isobutylamine to give 2-amino-3-isobutyl-6,8-dibromo-4(3H)-quinazo-linone (4b). IR spectrum of 4b reveals strong absorption bands at 1670, 3100 and 3214 due to $v_{C=O}$ and v_{NH} respectively.

Compound 1 reacts with semicarbazide in boiling pyridine and yielded 4-phenyl-5-amino-1,2,4-triazolo[2,3-b]-6,8-dibromo-4(3H)-quinazolinone (5). IR spectrum reveals strong absorption at 1620, 1670, 3200 and 3300 cm'^{1} attributable to $v_{C=N}$, $v_{C=O}$ and v_{NH} respectively. The 'H-NMR spectrum of compound 5 in acetone d_6 shows signals at δ ppm 5 8 (s, 2H, NH) and 7.8-8.2 (m, 7H, ArH). Its electron impact shows m/e at (357, 58.7%), (359, 100%) and
(361, 58.7%) attributable to the molecular ion peak with loss of phenyl group and hydrogen transfer.

On the other hand, when compound 1 was allowed to react with thiosemicarbazide in boiling pyridine, it yielded 2-phenylamino-3-thiocarbamoylamino-6,8-dibromo-4(3H)-quinazolinone (6). Its IR spectrum reveals strong absorption bands at 1370, 1670, 3172, 3277 and 3338 cm^{-1} due to $v_{C=S}$, $v_{C=O}$ and v_{NH} respectively.

The benzoxazinone derivative 1 undergoes heteroring opening upon treatment with piperidine in boiling ethanol gives 2-(N-piperidino-carbonyl)-4,6-dibromo-N-(phenylcarbamoyl)aniline (7). IR spectrum of compound 7 exhibits strong absorption bands at 1675, 3246, 3359 and 3469 cm^{-1} attributable to $v_{C=O}$ and v_{NH} hydrogen bonded and unbonded respectively.

This investigation also deals with the hitherto unknown reaction of aliphatic and aromatic mercaptans with the benzoxazinone 1. Thus, when compound 1 was allowed to react with 2-aminothiophenol in dry toluene it gives 2-phenylcarbamoyl-amino-3,5-dibromo-(2-amino)phenylthiobenzoate (8). IR spectrum of compound 8 exhibits strong absorption bands at 1611, 1692, 3073, 3100, 3180 and 3222 due to $v_{C=O}$ and v_{NH} respectively.

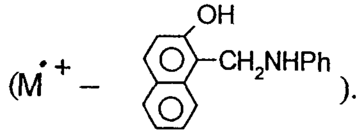
Similarly, when compound 1 was submitted to react with thio-glycolic acid in dry toluene it afforded 2-phenylcarbamoyl amino-3,5-dibromocarboxymethylthiobenzoate (9). IR spectrum of compound 9 revealed strong absorption bands at 1665, 1713, 3180, 3265 and broad basin peak at 3380 cm^{-1} attributable to v_{max} of carbonyl groups, v_{NH} and v_{OH} respectively.

In this investigation the authors used 3-aminoquinazolinone derivative 2 as a key starting material for synthesis of a diverse of 3-substituted quinazolinone derivatives and annulated fused quinazolinone compounds Scheme 2.

When compound 2 was allowed to react with diethylmalonate it yielded 2-phenylamino-3-ethoxycarbonylacetylamino-6,8-dibromo-4(3H)-quinazolinone (10).

IR spectrum of compound 10 reveals strong absorption at 1668, 1696, 1731, 3210 and 3300 cm^{-1} attributable to v_{max} of three carbonyl groups and v_{NH}.

Treatment of the quinazolinone 2 with aromatic aldehydes namely, cinnamaldehyde, 4-N,N-dimethylaminobenzaldehyde and/or 2-hydroxy-l-naphthaldehyde afforded 4-pheny-5-aryl-l,2,4-triazolo-[2,3-b]-6,8-dibromo-4(3H)-quinazolinone (lla-c). IR spectrum of 11a reveals strong absorption at 1610, 1666, 2907 and 3079 due to $v_{C=N}$, $v_{C=O}$, and VCH respectively the reaction possibly takes place through non isolated intermediate arylidene amino derivative followed by cyclisation and dehydrogenation yielded the more thermo-dynamically stable annulated quinazolinone. I.R. spectrum of compound llb reveals strong absorption at 1592, 1674 due to $v_{C=N}$, $v_{C=O}$, respectively. The ^{1}H-NMR spectrum of compound llb in DMSO exhibits signals at δppm 3.5(s, 6H, $N(CH_3)_2$), 7.7-8.57(m, 6H, ArH). The ^{1}H-NMR spectrum of compound 11c in DMSO exhibits signals at 7.2-8.81 (m, 13H, ArH), 9.62 (s, 1H, OH). Electron impact pattern of compound 11c shows m/e at M^+(316, 45.1%), M^+ +1(318,100%), M^+ +2(320, 58.7%) attributable to



When the aminoquinazolinone 2 was submitted to react with acetylacetone afforded the bridgehead nitrogen compound 12. Formation of compound 12 involving condensation of acetylacetone with amino group followed by ring closure and deaçetonyiaiiftcu. IR spectrum of 12 revealed strong absorption at 1607, 1703 and devoid any band for v_{NH}. Such IR data agreed well with the proposed structure.

Treatment of the quinazolinone 2 vvith diacetyl in the boiling ethanol yielded 5,6-dimethyltriazino(2,3-b)-6,8-dibromo-4(3H)-quinazolinone (13). Formation of 13 takes place via condensation followed by elimination of the phenol molecule yielding the more thermodynamically stable compound. IR spectrum of compound 13 revealed strong absorption bands at 1697 and 2922 attributable to $v_{C=O}$ and v_{CH} respectively.

Interaction of aminoquinazolinone derivative 2 with phenyliso-cyanate in boiling ethanol gives 2-phenylamino-3-phenylcarbamoyl-amino-6,8-dibromo-4-(3H)-quinazolinone (14). IR spectrum of compound 14 exhibits strong absorption bands at 1672, 3095, 3225 and 3298 attributable to $v_{C=O}$ and v_{NH} respectively.

When the quinazolinone 3 was submitted to react with ethyl-chloroacetate in refluxing dioxan in the presence of potassium carbonate as a catalyst yielded 3-ethoxycarbonylmethyl-6,8-dibromo-4(3H)-quinazolinone (15). Isolation of compound 15 as a sole product suggesting that the lactam form (ketoform) is the predominant one(20), (ketoform is more stable than the enol form by about 10 k cal/mol). The reaction takes place via SN^2 mechanism followed by loss of aniline molecule. IR spectrum of compound 15 exhibits strong absorption bands at 1605, 1687 and 1730 attributable to $\nu_{C=N}$ and ν_{max} of two carbonyl groups and devoid any band for ν_{NH}. Electron impact pattern of compound 15 shows m/e at (388, 41.9%), (390, 80%) and (392, 39.2%).

Hydrazinolysis of compound 15 in boiling ethanol yielded 3-aminocarbamoylmethyl-6,8-dibromo-4(3H)-quinazolinone (16). IR spectrum of 16 exhibits strong absorption bands at 1645, 1677, 3065, 3254 and 3342 cm^{-1} due to ν_{max} of two carbonyl groups and ν_{NH} respectively. Electron impact pattern shows m/e (374, 2.1%), (376, 4.5%) and (378, 2%).

Interaction of the aminocarbamoyl derivative 16 with phenyl-isocyanate gives 3-phenylthiocarbamoylaminocarbamoylmethyl-6,8-dibromo-4(3H)-quinaolinone (17). IR spectrum of compound 22 reveals strong absorption at 1607, 1675, 1696, 3072, 3200, 3307, 3427 attributable to $\nu_{C=N}$, ν_{max} of carbonyl groups ν_{NH} bonded and unbonded respectively.

Treatment of compound 17 with heating sodium hydroxide yielded 3-(3-mercapto-4-phenyl-1,2,4-triazole-5-yl)methyl-6,8-dibromo-4(3H)-quinazolinone (18).

Its IR spectrum exhibits absorption bands at 1607, 1677, 3359, 3467 attributable to $\nu_{C=N}$, $\nu_{C=O}$ and ν_{NH} respectively.

Interaction of the aminocarbamoyl derivative 16 with carbon disulphide in the presence of potassium hydroxide yielded the potassium salt of dithioic acid 19 which reacts with methyl iodide and gives 3-thiomethoxythiocarboxyaminocarbamoylmethyl-6,8-dibromo-4(3H)-quinazolinone (20), its IR spectrum reveals absorption bands at 1606, 1684, 3068, 3200, 3427 attributable $\nu_{C=N}$, $\nu_{C=O}$ and ν_{NH} respectively.

When compound 16 was allowed to react with potassium thiocyanate it afforded 3-thiocarbamoylaminocarbamoylmethyl-6,8-dibromo-4(3H)-quinazolinone (21). Its IR spectrum reveals absorption at 1659, 1694, 3072, 3277, 3382 due to $\nu_{C=O}$ and ν_{NH} respectively.

When compound 16 was submitted to react with 4-methoxy-benzaldehyde and 2-hydroxy-l-naphthaldehyde in boiling ethanol, it afforded 3-(2-aryl-1,3,4-oxadiazole-5-yl)methyl-6,8-dibromo-4(3H)-quinazolinone (22a and b) respectively. The reaction takes place via formation of the fleeting intermediate 22' followed by cyclization via addition of enolic hydroxyl group to azaolefinic double bond. IR spectra of compound 22 revealed strong absorption in the region 1676-1683, 3070-3190 and 3450 cm^{-1} attributable to $\nu_{C=O}$ and ν_{NH} or OH.

Behaviour of some synthesized organic compounds toward organisms.

The behaviour of the synthesized organic compounds as antibacterial has been investigated at the Medical Mycology Lab. The Regional Center for Mycology and Biotechnology, Alazhar University.

The results show the effectively of compounds 2 against Escherichia coli at concentration 1,2.5 and 5 mg/ml and against Pseudomonas aeruginosa at concentration 5 mg/ml and the ineffectivety against Bacillus subtilis and Staphylococcus aurous.

For compound 3 the results show its ineffectivety against the bacteria, Sa, Pa, Bs and Ec.

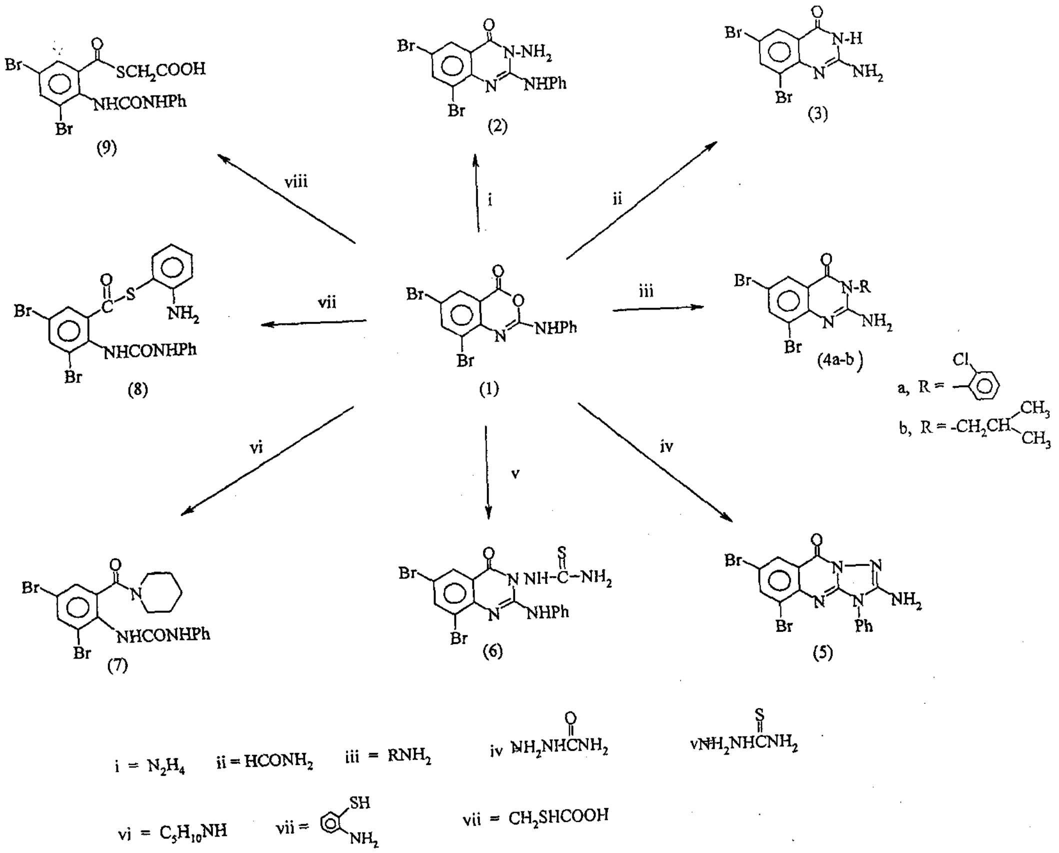
For compound 11b its effective against Bs at concentration 2.5 mg/ml and against Ec at concentration 5 mg/ml.

For compound 17 it is effective against Ec at conc. 1 m gm/ml and against Bs, Pa at concentration 5 m gm/ml and ineffective against Sa.

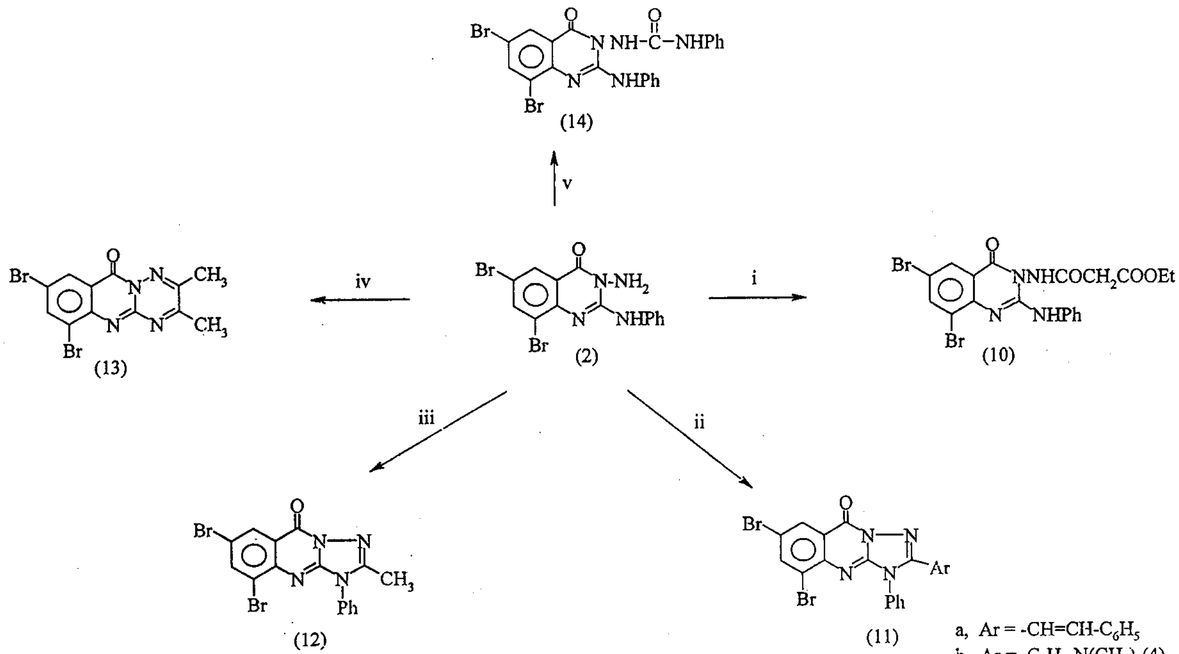
For compound 22a it is active against Ec at conc. 2.5 mg/ml and inactive against Sa, Pa and Bs.

The results are summarized in (Table 2).

Sa : *Staphylococcus aurous.*
Pa : *Pseudomonas aeruginosa.*
Bs : *Bacillus subtilis.*
Ec : *Escherichia coli.*


Br
SCH2COOH
NHCONHPh
(9)
N-NH2
NHPh
(2)
N-H
NH2
(3)
viii
i
ii
NH2
S
C
(8)
vii
O
NHPh
(1)
iii
N-R
(4a-b)
a, R = Cl
b, R = -CH2CH CH3 CH3
vi
v
iv
N
(7)
NH-C-NH2
(6)
Ph
(5)
i = N2H4
ii = HCONH2
iii = RNH2
iv NH2NHCNH2
v NH2NHCNH2
vi = C5H10NH
vii = SH NH2
vii = CH2SHCOOH

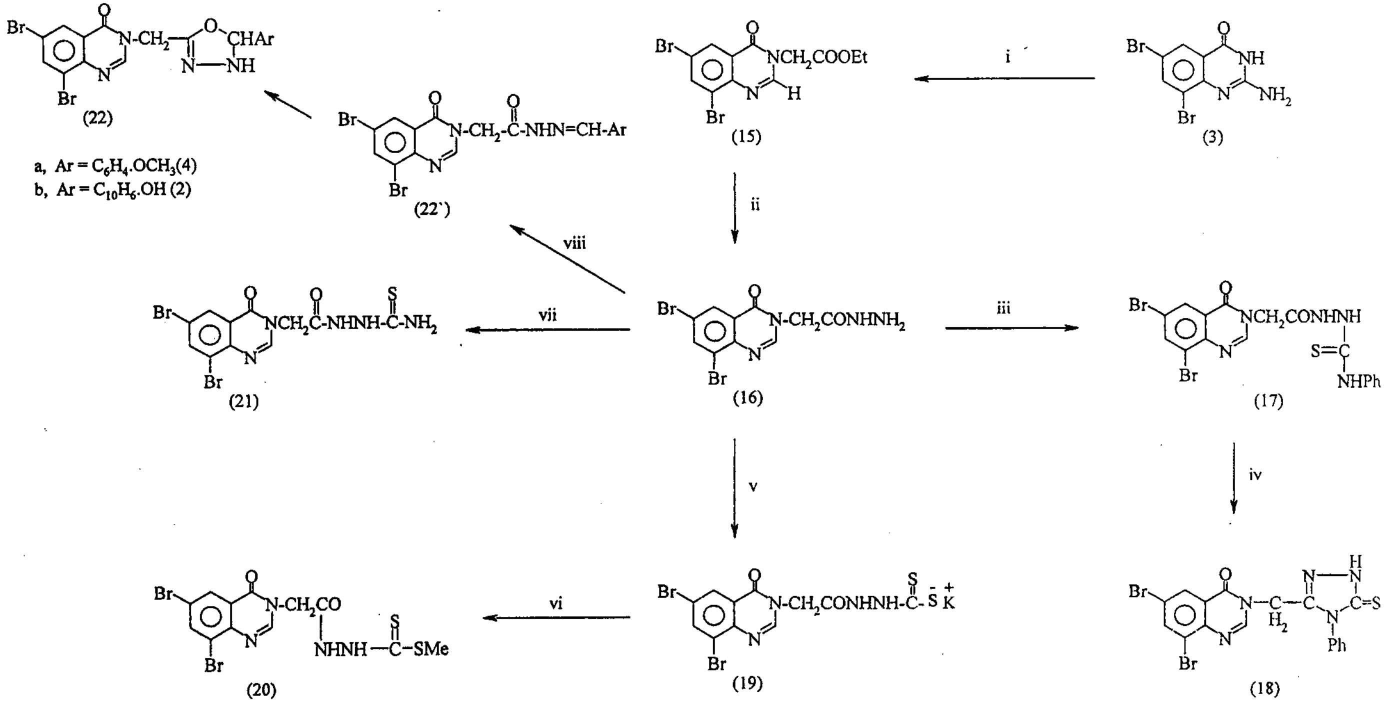
(Scheme 2)



a, Ar = -CH=CH-C_6H_5
b, Ar = C_6H_4-$N(CH_3)_2$(4)
c, Ar = $C_{10}H_6OH$(2)

i = $CH_2(COOEt)_2$ ii = ArCHO iii = $CH_3COCH_2COCH_3$ iv = $CH_3COCOCH_3$ v = Ph-N=C=O

(Scheme 3)



i = $ClCH_2COOEt / K_2CO_3$ / Dioxan ii = N_2H_4 iii = PhN=C=S iv = NaOH

v = $CS_2/KOH/C_2H_5OH$ vi = CH_3I vii = KSCN/Conc. HCl/H_2O viii = ArCHO

(Scheme 4)

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were carried out in the Microanalytical Center, Cairo University, Egypt. IR spectra were recorded in (KBr) disks on Shimadzu FTIR 8101 PC and ^{1}H-NMR spectra recorded on a Varian 300 MHz in ($CDCl_3$) or (DMSO-d_6) as solvents, (Chemical shifts in δ ppm) using TMS as internal Standard. The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometer at 70 e.v. Homogeneity of all compounds synthesized was checked by TLC. Characterization data of the various compounds prepared are given in (Table 1).

2-Phenylamino-6,8-dibromo-4H-3,l-benzoxazinone (1).

A mixture of 3,5-dibromo anthranilic acid (2.95 g, 0.01 mol) and phenyl isocyanate (1.19 g, 0.01 mol) in dry toluene (30 ml) was refluxed for 2 hr. The solid that separated after cooling, filtered off, dried and crystallized from toluene to afford the benzoxazine 1.

2-Phenylamino-3-amino-6,8-dibromo-4(3H)-quinazolinone *12).*

A mixture of benzoxazinone (3.96 g, 0.01 mol) and hydrazine hydrate (1 g, 0.02 mol) was heated under reflux in absolute ethanol (30 ml) for 3 hr.

The reaction mixture was concentrated. The solid that was separated out, filtered off, dried and then recrystallized from butanol to afford quinazolinone 2.

2-Amino-6,8-dibromo-4(3H)-quinazolinone (3).

A solution of benzoxazinone 1 (3.96 g, 0.01 mol) in formamide (15 ml) was refluxed for 2 hr. The reaction mixture after cooling was poured onto ice/H_2O. The solid separated was filtered, dried and recrystallized from the dioxan to give 3.

2-Amino-3-(2-chlorophenyl)-6,8-dibromo-4(3H)-quinazolinone (4a).

A mixture of benzoxazinone 1 (3.96 g, 0.01 mol) and 2-chloro-aniline (1.28, 0.01 mol) was refluxed in ethanol (30 mi) for 6 hr. The reaction mixture was concentrated. The solid that separated filtered off, dried and then recrystallized from toluene to afforded the quinazolinone 4a.

2-Amino-3-(isobutyl)-6,8-dibromo-4(3H)-quinazolinone (4b).

A mixture of benzoxazinone 1 (3.96 g, 0.01 mol) and isobutyl-amine (0.73 g, 0.01 mol) was refluxed in absolute ethanol 30 mi for 6 hr. The reaction mixture was concentrated. The solid that separated was filtered off, dried and then recrystallized from toluene to afford the quinazolinone 4b.

4-Phenyl-5-amino-1,2,4-triazolo[2,3-b]-6,8-dibromo-4(3H)-quinazolinone (5).

A mixture of benzoxazinone 1 (3.96 g, 0.01 mol) and semicarbazide (0.75 g, 0.01 mol) in boiling pyridine (20 ml) for 4 hr. The reaction mixture after cooling was poured into crushed ice/HCl. The solid separated filtered off, dried and crystallized from the toluene to give 5.

2-Phenylamino-3-thiocarbamoylamino-6,8-dibromo-4(3H)-quinazolinone (6).

A mixture of benzoxazinone 1 (3.96 g, 0.01 mol) and thio-semicarbazide (0.91 g, 0.01 mol) in boiling pyridine (20 ml) for 4 hr. The reaction mixture after cooling was poured into crushed ice/HCl. The solid separated filtered off, dried and crystallized from the ethanol to give 6.

2-(N-piperidinocarbonyl)-4,6-dibromo-N(phenylcarbamoyl] aniline (7).

A solution of benzoxazinone 1 (3.96 g, 0.01 mol) and piperidine (0.85 g, 0.01 mol) in ethanol (30 ml) was heated under reflux for 4 hr. The solid separated on cooling was crystallized from toluene to give 7.

2-Phenylcarbamoyl-amino-3,5-dibromo-(2-aminophenyl) thio benzoate (8).

A solution of benzoxazinone 1 (3.96, 0.01 mol) and 2-amino-thiophenol (1.88 g, 0.015 mol) in dry toluene was stirred for 3 hr. The solid separated was flittered off, washed by dry toluene, dried and crystallized from the Pet. 80-100 to give 8.

2-phenylcarbamoylamino-3,5-dibromocarboxymethyl-thiobenzoat (9).

A solution of benzoxazinone 1 (3.96 g, 0.01 mol) and thiogli-colic acid (1.38 g, 0.015 mol) in dry toluene (30 ml) was stirred for 3 hr. The solid separated was filtered off, washed by toluene, dried and crystallized from the dioxan to give 9.

2-Phenylamino-3-ethoxycarbonylacetylamino-6,8-dibromo-4(3H)-quinazolinone (10).

A mixture of quinazolinone 2 (4.1 g, 0.01 mol) and diethylmalonate (10 ml) was refluxed for 4 hr. after cooling, the solid was filtered off, washed with methanol, dried and crystallized from the butanol to give 10.

4-phenyl-5-aryl-1,2,4-triazolor2,3-bl-6,8-dibromo-4(3H)-guinazolinone (lla-c).

A mixture of the quinazolinone 2 (4.1 g, 0.01 mol) and aromatic aldehydes namely cinnimaldehyde (1.6 g, 0.012 mol), 4-N,N-dimethylaminobenzaldehyde (1.7 g, 0.012 mol) and/or 2-hydroxy-1-naphthaldehyde (2.07 g, 0.012 mol) in absolute ethanol (50 ml) containing (1 ml) pipridine and refluxed for 4 hr. The crystalline solid was obtained collected by filtration, dried and recrystallized from toluene, butanol and dioxan to give lla, llb and 1lc respectively.

l-Phenyl-2-methyltriazol(4,5-b)-6,8-dibromo-4(3Hl-quinazolinone (12).

A mixture of quinazolinone 2 (4.1 g, 0.01 mol) and acetyl acetone (5 mi) was refluxed for 2 ½ hr. after cooling the precipitate was filtered off washed with cold ethanol, dried and crystallized from toluene to give 12.

5,6-Dimethyltriazino-(2,3-b)-6,8-dibromo-4(3H)-quinazolinone (13).

A mixture of quinazolinone 2 (4.1 g, 0.01 mol) and diacetyl (0.86 g, 0.01 mol) in ethanol (30 ml) was refluxed for 3 hr. The solid that separated after concentrated and cooling was filtered off, dried and crystallized from toluene to give 13.

2-Phenylamino-3-phenylcarbamoylamino-6,8-dibromo-4(3H)-quinazolinone (141.

A mixture of quinazolinone 2 (4.1g, 0.01 mol) and phenyl isocyanate (1.19 g, 0.01 mol) in ethanol (30 ml) was refluxed for 2 hr. The solid separated was filtered off, dried and crystallized from D.M.F to give 14.

3-Ethoxycarbonylmethyl-6,8-dibromo-4(3H)-quinazolinone (15).

A mixture of quinazolinone 3 (3.19 g, 0.01 mol), ethyl chloroacetate (4.9 g : 0.04 mol) and anhydrous potassium carbonate (5.5 g : 0.04 mol) in dioxin (50 ml) was heated under reflux for 24 hr. The reaction mixture was concentrated, filtered off, dried and recrystallized from benzene to afford quinazolinone 15.

3-Aminocarbamoylmethyl-6,8-dibromo-4(3H)-quinazolinone (16).

A mixture of quinazolinone 15 (3.9 g : 0.01 mol) and hydrazine hydrate (1.0 g : 0.02 mol) in absolute ethanol (30 ml) was heated under reflux for 3 hr. The reaction mixture was concentrated, filtered off, dried and crystallized from dioxan to give 16.

3-Phenylthiocarbamoylaminocarbamoylmethyl-6,8-dibromo-4(3H)-quinazolinone (17).

An equimolecular quantity of amino carbamoyl derivative 16 (3.76 : 0.01 mol) and phenyl isothiocyanate (1.35 g : 0.01 mol) in dioxin (40 ml) was refluxed for 6 hr. on cooling at room temperature, the fine crystals which was appeared. Filtered off and recrystallized from ethanol to give 17.

3-(3-Mercapto-4-phenyl-1,2,4-triazole-5-yl)methyl-6,8-dibromo-4(3H)-quinazolinone (18).

Quinzolinone 17 (10.22 g : 0.07 mol) was refluxed in sodium hydroxide solution (4%, 25 ml) for 3 hr. The resulting solution was treated with charcoal, filtered and cooled. The filtrate was acidified with hydrochloric acid to pH 5-6. The solid which appeared was filtered, dried and recrystallized from ethanol to give 18.

3(Dithiocarboxyaminocarbamoylmethyl)-6,8-dibromo-4(3H)-quinazolinone potassium salt (19).

Carbon disulphide (11.4 g, 0.15 mol) was added dropwise to an ice/cold solution of 16(3.76 g, 0.01 mol) in alc. KOH (5.6 g, 0.1 mol in 5 ml C_2H_5OH). The whole mixture stirred at r.t. for 2 hr. (50 ml) dry ether was added, the separated solid was filtered off to give 19.

3-Thiomethoxythiocarboxyaminocarbamoyl methyl-6,8-dibromo-4(3H)-quinazolinone (20).

Methyl iodide (1.42 g : 0.01 mol) was added to a stirred solution of the potassium salt 19 (4.90 : 0.01 mol) in (50 ml) of water, after one hour the white solid was filtered, washed with water and recrystallized from toluene to give 20.

3-Thiocarbamoylaminocarbamoylmethyl-6,8-dibromo-4(3H)-quinazolinone (21).

A suspension of 16 (3.76 : 0.01 mol), potassium thiocyanate (1.94 g : 0.02 mol), hydrochloric acid (10 ml) and water (200 mi) was refluxed for 3 hr. The white solid that appeared on cooling was filtered, dried and recrystallized from methanol to give 21.

3-(2-Aryl-1,3,4-oxadiazole-5-yl)methyl-6,8-dibromo-4(3H)-quinazolinone (22a and b).

A mixture of quinazolinone 16 (3.76 g : 0.01 mol) and p-anisaldehyde (1.63 g : 0.012 mol) and/or 2-hydroxy-l-naphthaldehyde (2.1 g : 0.012 mol) in absolute ethanol (50 ml) containing (1 ml) pipredine was refluxed for 3 hr. The solid formed was filtered off and recrystallized from dioxan and D.M.F to give 22a and 22b respectively.

Table (1): Characterisation and physical data for synthesised compounds.

Compd. No.	M.p.°C	* Solvent colour	Formula M. Wt.	Analysis % Calc./Found			
				C	H	N	Br/Cl/S
1	276	Toluene Yellow	$C_{14}H_8N_2O_2Br_2$ (396)	42.42 42.40	2.02 2.10	7.07 7.00	40.40 40.43
2	252	Butanol White	$C_{14}H_{10}N_4OBr_2$ (410)	40.98 40.99	2.44 2.47	13.66 12.57	39.02 38.98
3	Over 300	Dioxan Pale brown	$C_8H_5N_3OBr_2$ (319)	30.09 29.97	1.57 1.60	13.17 13.23	50.16 50.00
4a	224	Toluene White	$C_{14}H_8N_3OBr_2Cl$ (429.5)	39.12 39.20	1.86 1.83	9.78 9.65	37.25/8.27 37.00/8.29
4b	218	Toluene White	$C_{12}H_{13}N_3OBr_2$ (375)	38.40 38.37	3.47 3.50	11.20 11.22	42.67 43.00
5	222	Toluene Brown	$C_{15}H_9N_5OBr_2$ (435)	41.38 41.50	2.07 2.12	16.09 15.00	36.78 36.41
6	196	Ethanol White	$C_{15}H_{11}N_5OSBr_2$ (469)	38.38 38.11	2.35 2.46	14.93 15.01	34.12/--/6.82 34.00/--/6.85
7	172	Toluene White	$C_{20}H_{19}N_3O_2Br_2$ (493)	48.68 48.50	3.85 4.00	8.52 8.50	32.45 32.50
8	160	Pet. 8-100 White	$C_{20}H_{15}N_3O_2SBr_2$ (521)	46.07 45.98	2.88 2.61	8.06 8.00	30.71/--/6.14 30.24/--/6.30
9	216	Dioxan White	$C_{16}H_{12}N_2O_4SBr_2$ (480)	40.00 39.15	2.50 2.60	5.83 5.75	33.33/--/6.67 32.80/--/6.62
10	230	Butanol White	$C_{19}H_{16}N_4O_4Br_2$ (524)	43.51 43.12	3.05 2.97	10.68 10.14	30.53 30.50
11a	244	Toluene Fir prick	$C_{23}H_{14}N_4OBr_2$ (522)	52.87 53.13	2.68 2.55	10.73 10.92	30.65 31.04
11b	266	Butanol Deep yellow	$C_{23}H_{17}N_5OBr_2$ (539)	51.21 50.89	3.15 3.14	12.99 12.96	29.68 29.50

Table 1. (cont ...)

Compd. No.	M.p.°C	* Solvent colour	Formula M. Wt.	Analysis % Calc./Found			
				C	H	N	Br/Cl/S
11c	Over 300	Dioxan Yellow	$C_{25}H_{14}N_4O_2Br_2$ (562)	53.38 53.56	2.49 2.63	9.96 9.90	28.47 28.37
12	162	Toluene Brown	$C_{16}H_{10}N_4OBr_2$ (434)	44.24 44.15	2.30 2.32	12.90 12.79	36.87 36.85
13	216	Toluene Brown	$C_{12}H_8N_4OBr_2$ (384)	37.50 37.44	2.08 1.92	14.58 14.55	41.67 41.72
14	260	D.M.F White	$C_{21}H_{15}N_5O_2Br_2$ (529)	47.64 47.90	2.84 2.76	13.23 13.34	30.25 30.32
15	176	Benzen White	$C_{12}H_{10}N_2O_3Br_2$ (390)	36.92 37.02	2.56 2.63	7.18 7.21	41.03 40.72
16	Over 300	Dioxan White	$C_{10}H_8N_4O_2Br_2$ (376)	31.91 31.90	2.13 2.15	14.89 14.90	42.55 42.57
17	Over 300	Ethanol Pale yellow	$C_{17}H_{13}N_5O_2SBr_2$ (511)	39.92 39.89	2.54 2.63	13.70 13.59	31.31/--/6.26 31.43/--/6.15
18	224	Ethanol White	$C_{17}H_{11}N_5OSBr_2$ (493)	41.38 41.37	2.23 3.20	14.20 14.22	32.45/--/6.49 32.47/--/6.52
19	-	Salt Pale yellow	$C_{11}H_7N_4O_2S_2KBr_2$ (490)	26.94 26.50	1.43 1.41	11.43 11.47	32.65/--/13.06 32.55/--/12.99
20	238	Toluene White	$C_{12}H_{10}N_4O_2S_2Br_2$ (466)	30.90 31.02	2.15 2.11	12.02 11.98	34.33/--/13.73 34.20/--/13.81
21	Over 300	Methanol White	$C_{11}H_9N_5O_2SBr_2$ (435)	30.34 30.31	2.07 2.12	16.09 16.18	36.78/--/7.36 36.82/--/7.40
22a	Over 300	Dioxan Pink	$C_{18}H_{14}N_4O_3Br_2$ (494)	43.72 43.61	2.83 2.81	11.34 11.32	32.39 32.40
22b	Over 300	D.M.F. Deep yellow	$C_{21}H_{14}N_4O_3Br_2$ (530)	47.55 47.51	2.64 2.50	10.57 10.57	30.19 30.31

Table (2) : Relative activity of the some compounds against Gram + ve and Gram – ve bacteria

organisms / Samples	Gram + ve bacteria						Gram – ve bacteria					
	Staphylococuus aureus			Pseudomonas aerugranosa			Bacillus subtillis mg/l			Escherichia coli		
	5	2.5	1	5	2.5	1	5	2.5	1	5	2.5	1
2	0	0	0	+	0	0	0	0	0	+	+	+
3	0	0	0	0	0	0	0	0	0	0	0	0
11(b)	0	0	0	0	0	0	+	+	0	+	0	0
17	0	0	0	+	0	0	+	0	0	+	+	+
22(a)	0	0	0	0	0	0	0	0	0	+	+	0
St.	++	++	++	+++	+++	++	+++	+++	++	++	++	++

- St. = Reference standard; Chloramphenicol was used as a standard antibacterial agent.
- The test was done using the diffusion agar technique.
- Well diameter: 0.6 cm … (100 ul of each conc. was tested).
- Inhibition values = 0.1 – 0.5 cm beyond control = + ; Inhibition values = 0.6 – 1.0 cm beyond control = ++ ;
- Inhibition values = 1.1 – 1.5 cm beyond control = +++ ; 0 = Not detected.

2-FENİLAMİNO-6,8-DİBROM-3,1 BENZOKSAZİN-4-ON VE 4(3H)KİNAZOLİN-4-ON TÜREVLERİNİN SENTEZİ VE REAKSİYONLARI

ÖZET

2-Fenilamino-6,8-dibrom-4H-3,1-benzoksazinin Hidrazin Hidrat, aminler ve formamit gibi azotlu nüklefillerle reaksiyonundan 4(3H)kinozolinon türevleri, kükürtlü nükrefillerle reaksiyonundan ise karşılığı olan tiyoester türevleri oluşmuştur. Amino kinozolinon ve 4(3H) kinozolinonun karbon elektrofillerine karşı davranışı farklı şartlar altında incelenmiştir.

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