SYNTHESIS AND REACTIONS OF 2-(4-BROMOPHENYL)-4H-3,1-BENZOXAZINE-4-ONE

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Keywords: Benzoxazin-4-one, 2,3-disubstituted quinazolin-4-one, glycine

A new series of 2,3-disubstituted quinazolin-4(3H)-one derivatives was synthesized via nucleophilic attack at C(2)of the corresponding key starting material 2-(4-bromophenyl)-4H-3,1-benzoxazin-4-one (Scheme 5). The reaction proceeded via amidinium salt formation (Scheme 3) rather than via an N-acyl anthranilamide. The structure of the prepared compounds were elucidated by physical and spectral data like FT-IR, ^{1}H-NMR, and mass spectroscopy.

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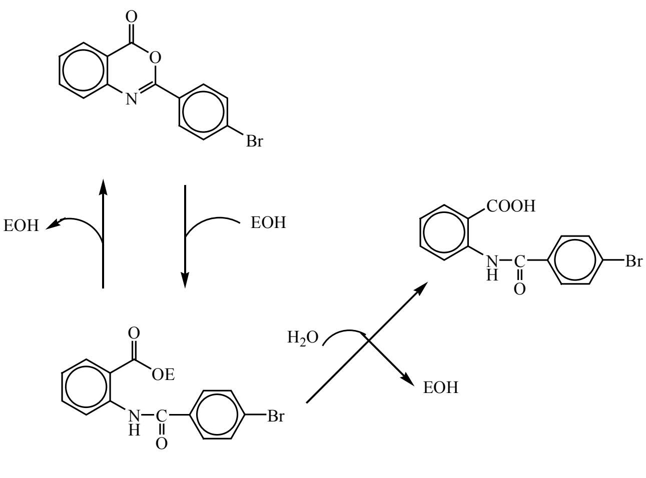
Introduction

Due to their interesting biological and other properties, 4H-3,1-benzoxazin-4-one derivatives are an important class of compounds.[1-4] Like other heterocyclic compounds, they are used directly or indirectly in many industrial research, and clinical applications. They can be used as starting material for different clinically used 4-quinazolone derivatives.[5-9] Benzoxazinone derivatives are also used as antiphlogistic drugs.[2-10] Anthalexine, another compound of this type, finds use as an antifungal and antibacterial agent.[11-14] Several 4H-3,1-benzoxazin-4-ones have been demonstrated to be an alternate inhibitors of human leukocyte elastase (HLE), forming acyl- enzyme intermediate during catalysis. It was demonstrated that electron withdrawal at position 2 gives better inhibition because acylation rates are increased. 4H-3,1-Benzoxazin-4-ones was shown to be active in vivo after intracheal administration. Benzoxazinones temporarily inhibit the catalytic activity of serine protease by accumulation of a catalytically inactive acyl-enzyme intermediate (Scheme1). The rates of acylation and deacylation, as well as compound selectivity, are determined by substitution at the benzene ring unit and the 2-substituent.

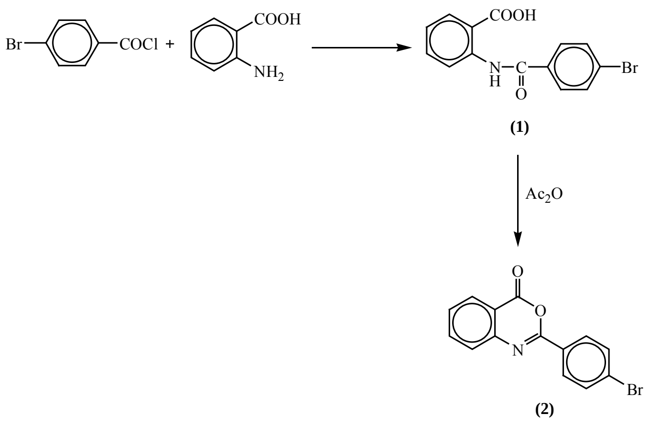


Scheme 1.

According to the reaction of 2-(4-bromophenyl)-4H-3,1-benzoxazin-4-one with serine protease (formation of acyl-enzyme, with a possible way of deacylation), prompted us to synthesis the 2-(4-bromophenyl)-4H-3,1-benzoxazin-4-one **2,** which posses an electron withdrawal group at position 2.

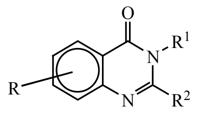
Results and discussion

The benzoxazinone derivative **1** was obtained via the interaction of 4-benzoyl chloride with anthranilic acid in pyridine, afforded the corresponding anthranil. The desired product **2** was obtained via ring closure of **1** with acetic anhydride (Scheme2).



Scheme 2.

Considering the structure of 4-H-3,1-benzoxazin 4-one derivatives, there are two available sites for nucleophilic attack (C-2 and C-4), i.e. two different sites with partial positive charge that can lead to the opening of the oxazinone moiety by different nucleophiles. In most cases, reclosure of the heterocyclic part of the molecule is favored and provides a new compound with interesting biological properties.[15,16] The **2** is considered as a key starting material for the synthesis of many heterocyclic system**s.** 3H-Quinazolin-4-one (**3**) is a frequently encountered unit in natural products such as L-vasicineone (**4**)**,**[17,18] chrysogine (**5**)**,**[19] and drugs as methqualone (**6**)**,**[20] febrifungine (**7**)**,** and isofebrifungine (**8**). The latter two compounds are potent but toxic antimalarial drugs. Molecules based on quinazoline and quinazolinone exhibit a multitude of interesting pharmacological,[21] including anticonvulsant, antibacterial, and antidiabetic activity.[22,23]



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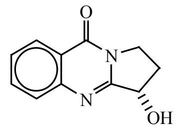

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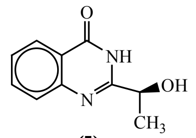

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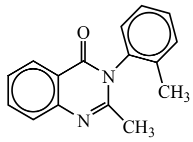

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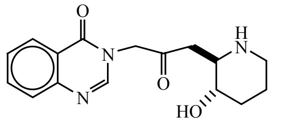

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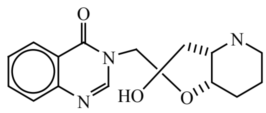
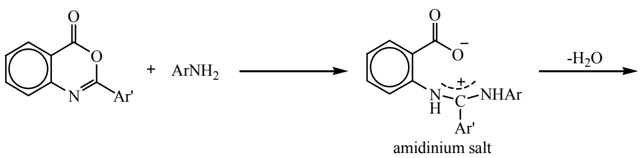
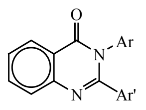


(8)

The aim of the present work is to synthesis quinazolin-4(3H)-one derivatives via interaction of benzoxazinone derivative **2** with nitrogen nucleophiles.

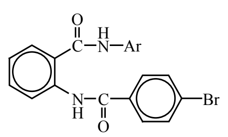
Thus, when **2** was submitted to react with formamide in boiling oil bath yielded 2-(4-bromo)-4(3H)-quinazolin-4-one (**9**). It was reported that 4H-3,1-benzoxazin-4-one derivatives react with semicarbazide (hydrazine-carboxamide) in boiling glacial acetic acid, afforded 2-propyl[1,2,4]triazolo[1,5-c]quinazolin-2(3H)-one.[24] Thus, upon treatment of **2** with hydrazine carboxamide in pyridine afforded 2-(4-bromophenyl)-[1,2,4]triazolo[1,5-c]quinazolin-2(3H)-one **(10).** The reaction took place via hetero ring opening at C-4 followed by double ring closure to yield the desired product.





(12)

a) Ar = C_6H_5
b) $C_6H_5CH_2$
c) $C_6H_4(CH_3)$.p
d) C_6H_4COOH.p
e) 2-C_6H_4N



(13)

Scheme 3.

Heating **2** in neat hydrazine hydrate afforded 3-amino-2(4-bromophenyl)quinazolin-4(3H)-one **(11a)** while upon hydrazinolysis with phNHNH$_2$ provided the quinazolinone **11b**.

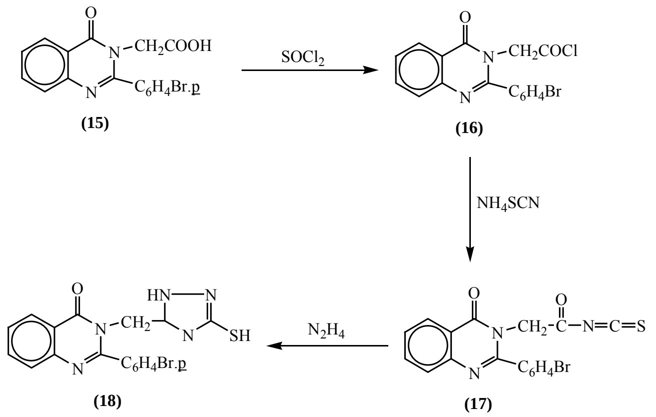
When aniline, benzylamine, and substituted aniline namely: 4-methylaniline (p-toluidine), 4-aminobenzoic acid, and 2-aminopyridine reacted with **2,** the 3-aryl-2-(4-bromophenyl) quinazolin- 4(3H)-one derivatives **12a-e** were obtained (Scheme2). One can interpret these results as follows:

The N-nucleophile attack **2** in a fashion in which the amino group first undergoes H-bonding to the N-atom of the heterocyclic ring, then the amino group reacts by nucleophilic addition at the "azavinylic" C-2 forming an inner amidinium salt which subsequently dehydrated giving **12a-e** (Scheme 3).

The elemental analysis and spectroscopic datae for **12** are consistent with the assigned structures. No isolation of 2-(4-bromobenzoylamino)benzamide derivatives **13** ruled out the nucleophilic addition to C-4.

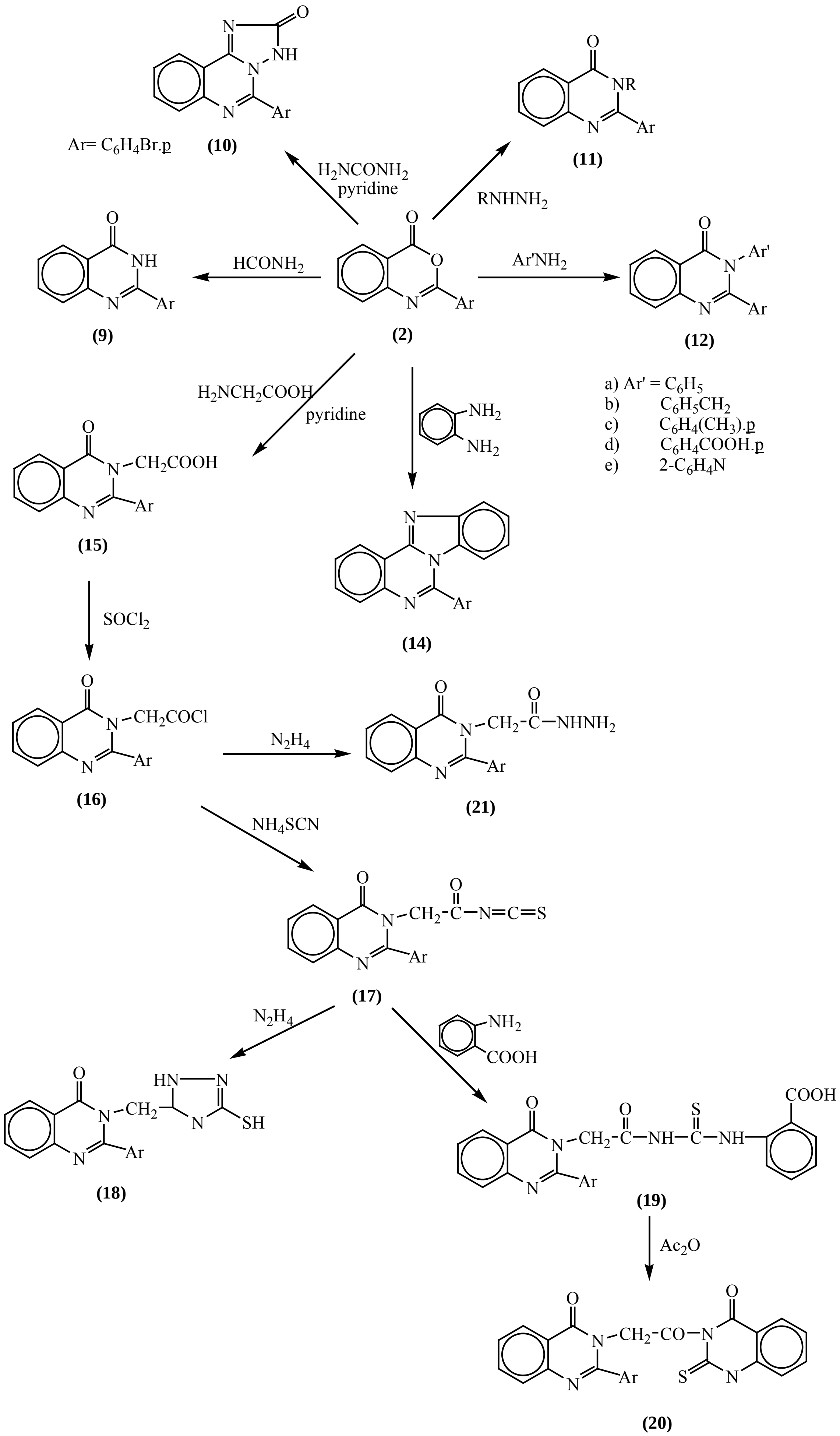
Fusion of **2** with o-phenylene diamine in an oil bath afforded 2-(4-bromophenyl)benzimidazolo[1,2-c]quinazoline **(14),** also when it was allowed to react with glycine in boiling pyridine, it gave [2-(4-bromophenyl)-4-oxoquinazolin-3-yl]acetic acid (**15)**.

When **15** was treated with thionyl chloride on a heated water bath, yielded the corresponding acid chloride **16** as a fleeting (not isolated) intermediate, followed by a reaction with ammonium thiocyanate yielding the [2-(4-bromophenyl)-4-oxoquinazolin-3-yl]acetyl isothiocyanate (**17)** which on turn reacted with hydrazine hydrate giving 2-(4-bromophenyl)-3-[(3-mercapto-1H-1,2,4-triazolo-5-yl)methyl]-4(3H)-quinazolin-4-one **(18).**



Scheme 4.

Similarily, **17** reacted with anthranilic acid, yielded 2-{[2-(4-bromophenyl)]-4-oxo-quinazolin-3-yl}acetyl thiocarbamoyl amino benzoic acid **(19)**. Treatment of **19** with boiling acetic anhydride afforded 2-(4-bromophenyl)-3-[2-oxo-2(4-oxo-2-thioxo-1,4-dihydroquinazolin-3(2H)-yl)ethyl]-4(3H)-quinazolin-4-one (**20).** Interaction of **16** with hydrazine hydrate in boiling toluene afforded 2-[2-(4-bromophenyl)-4-oxoquinazolin-3-yl]acetohydrazide **(21)**.


Ar= C6H4Br.p
(10)
(11)
H2NCONH2
pyridine
RNHNH2
HCONH2
Ar'NH2
(9)
(2)
(12)
H2NCH2COOH
pyridine
a) Ar' = C6H5
b) C6H5CH2
c) C6H4(CH3).p
d) C6H4COOH.p
e) 2-C6H4N
(15)
SOCl2
(14)
(16)
N2H4
(21)
NH4SCN
(17)
N2H4
(18)
(19)
Ac2O
(20)

Experimental Part

All melting points recorded are uncorrected and are determined on Gallen Kamp apparatus. The IR were recorded on Perkin Elmer 398 spectrophotometer, ^{1}H-NMR spectra were recorded on Varian Gemini, 300 MH_z instrument. MS spectra were obtained on Shimadzu, GCMS QP 1000 Ex mass spectrophotometer (70 eV). Micro analytical data were obtained from the microanalytical center at Cairo University, Giza, Egypt.

2-(4-Bromobenzoyl)aminobenzoic acid (1)

A solution of o-aminobenzoic acid (1.37 g, 0.01 mol) in dry pyridine (3 ml) was treated with a solution of 4-bromobenzoyl chloride (0.01 mol) in dry pyridine (3 ml) drop by drop with stirring for 15 minutes. The reaction mixture was poured onto ice/HCl. The solution that separated was filtered off and recrystallized from ethanol: **1,** yield (80 %), colourless crystals, m.p.190 °C. IR(KBr): 1660 (C=O amide), 1680 (C=O of acid), 3220 (NH), 3300, (OH, basin peak) cm^{-1} . ^{1}H-NMR (DMSO-d_6): 6.98-8.11 (m, 8H, Ar-H), 9.2 (s, 1H, NH, D_2O exchangeable) 12.11 (s, 1H, OH, D_2O exchangeable). MS (319, 321, M^+, M^++2). Anal.: calcd for $C_{14}H_{10}BrNO_3$: C 52.32, H 3.34, N 4.37, Br 24.95; found: C 52.52, H 3.14, N 4.57, Br 24.57.

2-(4-Bromophenyl)-4H-3,1-benzoxa-4-one (2)

A suspension of aminobenzoic acid derivative **1** (3.2 g, 0.01 mol) in freshly distilled acetic anhydride (10 ml) was heated under reflux for 1 h, and then was concentrated. The solid that was separated was crystallized from benzene: **2,** yield (75 %), pale yellow crystals m.p. 166 °C. IR (KBr): 1617 (C=N), 1762 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 6.88-8.92 (m, 8H, Ar-H). MS: 301, 303 (M^+, M^++2). Anal.: calcd for $C_{14}H_8$ Br NO_2: C 55.62, H 2.68, N 4.55, Br 26.45; found: C 55.55, H 2.56, N 4.36, Br 26.64.

2-(4-Bromophenyl)-4(3H)-quinazolin-4-one (9)

A mixture of **2** (3.02 g, 0.01 mol) and formamide (10 ml) was heated under reflux for 2 h, after cooling, the reaction mixture was poured onto water. The precipitate that separated was filtered off and crystallized from ethanol: **9,** yield (70 %), m.p. 276 °C. IR(KBr): 1602 (C=N), 1676 (C=O), 3122 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 6.99-8.11 (m, 8H, Ar-H), 10.89 (s, 1H, NH, D_2O exchangeable). Anal.: calcd for $C_{14}H_9BrN_2O$: C 55.81, H 2.95, N 9.03, Br 26.37; found: C 55.51, H 2.75, N 9.45, Br 26.37.

2-(4-Bromophenyl)[1,2,4]triazolo[1,5-c]quinazolin-2(3H) -one(10)

A mixture of **2** (3.02 g, 0.01 mol) and semicarbazide (0.01 mol) in pyridine (15 ml) was heated under reflux for 3 h. The reaction mixture after cooling was poured onto ice/HCl. The solid that separated was filtered off and crystallized from ethanol: **10,** yield (65 %) m.p. 128 °C. IR(KBr): 1599 (C=N), 1680 (C=O), 3321 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 6.80-8.11 (m, 8H, Ar-H), 9.2 (s, 1H, NH, D_2O exchangeable). Anal.: calcd for $C_{15}H_9BrN_4O$: C 52.65, H 2.94, N 16.37, Br 23.35; found : C 52.55, H 2.74, N 16.57, Br 23.55.

3-Amino and 3-phenylamino-2(4-bromophenyl)quinazolin-4(3H)-one (11a and 11b)

A mixture of **2** (3.02 g , 0.01 mol) and hydrazine hydrate and/or phenylhydrazine (0.015 mol) in n-butanol (10 ml) was heated under reflux for 3 h. The solid that separated after cooling was filtered off and crystallized from butanol for **11a** and xylene for **11b.**

3-Amino-2-(4-bromophenyl)quinazolin-4(3H)-one (11a): yield (61 %), m.p. 188 °C. IR(KBr): 1637 (C=N), 1668 (C=O), 3217, 3311 (NH) cm^{-1}. M.S: 315, 317 (M^+, M^++2). Anal.: calcd for $C_{14}H_{10}BrN_3O$:C 53.18, H 3.18, N 13.29, Br 25.27; found: C 53.28, H 3.18, N 3.18, Br 25.17.

3-Phenylamino-2-(4-bromophenyl)quinazolin-4(3H)-one (11b): yield (55%), m.p. 144 °C. IR(KBr): 1683 (C=O), 3249 (NH) cm^{-1}. Anal.: calcd for $C_{20}H_{14}BrN_3O$: C 61.24, H 3.59, N 10.71, Br 20.37; found: C 61.34, H 3.49, N 10.51, Br 20.37.

3-Aryl-2-(4-bromophenyl)quinazolin-4(3H)-ones, (12a-12e)

A solution of **2** (3.02 g, 0.01 mol) and aromatic amines namely; aniline, benzylamine, p-toluidine, p-aminobenzoic acid, and 2-aminopyridine (0.01 mol) in ethanol (40 ml) was heated under reflux for 3 h. The solids that separated after cooling were crystallized from toluene for **12a,** n-butanol for **12b** and **12c** ethanol for **12d** and xylene for **12e.**

3-Phenyl-2-(4-bromophenyl)quinazolin-4(3H)-one (12a): yield (60 %), m.p. 136 °C, IR(KBr): 1618(C=N), 1675 (C=O) cm^{-1}. Anal.: calcd for $C_{20}H_{13}BrN_2$: C 63.67, H 3.47, N 7.42, Br 21.18; found: C 63.47, H 3.37, N 7.42, Br 21.38.

3-Benzyl-2-(4-bromophenyl)quinazolin-4(3H)-one (12b): yield (65 %) m.p. 132 °C. IR(KBr): 1615 (C=N), 1680 (C=O) cm^{-1}. Anal.: calcd for $C_{21}H_{15}BrN_2O$: C 64.46, H 3.86, N 7.15, Br 20.24; found: C 64.56 , H 3.66, N 7.13, Br 20.42.

3-(4-Methylphenyl-2-(4-bromophenyl)quinazolin-4(3H)-one (12c) : yield (65%), m.p.148 °C. IR(KBr): 1615 (C=N), 1680 (C=O) cm^{-1}. Anal.: calcd for $C_{21}H_{15}BrN_2O$: C 64.46, H 3.86, N 7.15, Br 20.24; found: C 64.24, H 3.96, N 7.25, Br 20.44.

4-[4-Oxo-2-(4-bromophenyl)quinazolin-4(3H)-yl]benzoic acid (12d): yield (65%), m.p.186 °C.IR (KBr) γ : 1620 (C=N), 1680, 1687(C=O), 3200 (basin peak chelated OH cm^{-1}. ^{1}H-NMR (d_6) DMSO): 7.11-8.99 (m, 12H, Ar-H), 12.5 (s, 1H, OH, D_2O exchangeable). Anal. Calcd $C_{21}H_{13}BrN_2O_3$: C 43.39, H 2.25, N 4.81, Br 13.75; found: C 43.59, H 2.45, N 4.61, Br 13.64.

3-(Pyridin-2-yl)-2(-4-bromophenyl)quinazolin-4(3H)-one (12e) : yield (55%). m.p. 140 °C, IR (KBr) γ : 1620 (C=N), 1687 (C=O) cm^{-1}. Anal. Calcd for $C_{19}H_{12}BrN_3O$: C 60.33, H 3.19, N 7.15, Br 21.12; found : C 60.13, H 3.29, N 11.42, Br 21.42.

2-(4-Bromophenyl-benzimidazolo[1,2-C]quinazoline (14)

A mixture of **2** (3.02 g, 0.01 mol) and o-phenylene diamine (1.5 g, 0.01 mol) was heated in oil bath at 160 °C for 2 h. The reaction product was treated with water and the solid that obtained was crystallized from ethanol. **14:** yield (77 %). m.p. 230 °C. IR(KBr): 1620 (C=N) cm^{-1}. MS. 373, 375 (M^+, M^++2). Anal.: calcd for $C_{20}H_{12}BrN_3$: C 64. 81, H 3.23, N 11.22, Br 21.35; found: C 64.28, H 3.13, N 11.08, Br 21.15.

[2-(4-Bromophenyl)-4-oxoquinazolin-3-yl]acetic acid (15)

A mixture of **2** (3.02 g, 0.01 mol) and glycine (0.015 g, 0.01 mol) in pyridine (20 ml) was heated under reflux for 2 h. The reaction mixture was poured on ice/HCl, the solid that separated was filtered off and crystallized from methanol. **15:** yield **(** 67 %) m.p. 174 °C. IR(KBr): 1610 (C=N), 1683 (C=O cyclic amide, 1722 (C=O of carboxylic), 3365 (basin peak chelated OH) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.49 (s, 2H, methylene protons 7.18-8.66 (m, 8H, Ar-H), 12.26 (s, broad, 1H, OH, D_2O exchangeable). Anal.: calcd for $C_{16}H_{11}Br\ N_2O_3$: C 53.50, H 3.08, N 7.79, Br 27.25; found: C 53.40, H 3.18, N 7.59, Br 27.35.

[2-(4-Bromophenyl)-4-oxoquinazolin-3-yl]acetyl isothiocyanate(17)

A mixture of **8** (3.59 g, 0.01 mol) and thionyl chloride (10 ml) was heated on water bath for 2 h. Excess of thionyl chloride was removed by distillation under reduced pressure, a semisolid product was obtained treated with a solution of ammonium thiocyanate (1.5 g, 0.02 mol) in dry acetone (30 ml) with stirring for 30 min. The solid that separated after distillation of acetone was crystallized from dimethylformamide. **17:** yield (60 %), m.p. 150 °C. IR (KBr): 1620 (C=N), 1675 (C=O) cm^{-1}. Anal.: calcd for $C_{17}H_{10}Br\ N_3O_2S$: C 49.12, H 3.34, N 14.32, Br 20.42, S 8.06; found: C 49.22, H 3.34, N 14.11, S 7.85, Br 20.22

[2-(4-Bromophenyl)-3[(3-mercapto-1H-1,2,4-triazolo-5-yl)methyl]-(3H)quinazolin-4-one(18)

A mixture of **17** (2 g, 0.005 mol) and hydrazine hydrate (0.01 mol) was refluxed in dry benzene (30 ml) for 3 h. The solid that separated after cooling was filtered off and crystallized from ethanol. **18:** yield (57 %), m.p. 167 °C. IR(KBr): 1671 (C=O), 2567 (SH), 3243 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 4.22 (s, 2H, methylene protons), 5.53 (s, 1H, SH D_2O exchangeable), 9.88 (s, 1H, NH, D_2O exchangeable). Anal.: calcd for $C_{17}H_{12}Br\ N_5OS$: C 49.27, H 2.90, N 16.90, S 7.73, Br 19.10; found: C 49.67, H 2.71, N 16.55, S 7.93, Br 19.55.

2-{[2-(4-Bromophenyl)-4-oxoquinazolin-3-yl]acetylthiocarbamoyl}aminobenzoic acid (19)

A mixture of **17** (2 g, 0.005 mol) and anthranilic acid(1.37 g, 0.01 mol) in dry acetone (30 ml) was heated under reflux for 3 h. The solid that separated after distillation of acetone was diluted with water and filtered off and crystallized from benzene. **19:** yield (70 %), m.p. 183 °C. IR(KBr): 1665, (C=O), 3182 (NH), 3380 chelated (OH) cm^{-1}. Anal.: calcd for $C_{24}H_{17}BrN_4O_4S$: C 49.48, H 2.91, N 16.90, S 5.95, Br 19.28; found: C 49.84, H 2.71, N 16.70, S 5.53, Br 19.48.

2-(4-Bromophenyl)-3-[2-oxo-2(4-oxo-2thioxo-1,4-dihydroquinazolin-3(2H)-yl)ethyl]-4(3H)-quinazolin-4-one (20)

A solution of **19** (2.65 g, 0.005 mol) in freshly distilled acetic anhydride (10 ml) was heated on water bath for 2 h.The solid that separated after cooling was crystallized from ethanol: yield (52 %), m.p.166 °C. IR(KBr): 1241 (C=S), 1630, 1680 (C=O), 3180 (NH) cm^{-1}. ^{1}H-NMR (DMSO-d_6): 2.8 (s, 2H, CH_2), 7.2-8.8 (m, 2H, Ar-H), (s, 1H, NH, D_2O exchangeable). Anal.: calcd. for $C_{24}H_{15}Br\ N_4O_3S$: C 53.64, H 3.18, N 10.42, S 6.16,Br 14.86; found: C 53.74,H 3.38,N 10.62, S 6.36, Br 14.76.

2-[2(4-Bromophenyl)-4-oxoquinazolin-3-yl]acetohydrazide (21)

A solution of the acid chloride (0.01 mol) and hydrazine hydrate (0.015 mol) in toluene (30 ml) was heated under reflux for 2 h.

The solid that separated after cooling was filtered off and crystallized from ethanol: **21** yield (63 %), m.p. 168 °C. IR(KBr): 1590 (C=N), 1683 (C=O), 3200, 3280 (NH) cm^{-1}. Anal.: calcd for $C_{16}H_{13}BrN_4O_2$: C 55.61, H 2.72, N 10.80, Br 15.41; found: C 55.34, H 2.52, N 10.75, Br 15.21.

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