Chemical and Process Engineering Research
ISSN 2224-7467 (Paper) ISSN 2225-0913 (Online)
Vol.15, 2013

Synthesis and Reactivity of 6-Iodo-4*H*-3,1-Benzoxazin-4-one Towards Nitrogen Nucleophiles and Their Antimicrobial Activities.

Abdel-Monem. M. F. Eissa, Kouser. A. Hebash, Mohamed. Abo Riya and Sherif. I. M. Ramadan*

Chemistry Department, Faculty of Science, Benha University, Benha, Egypt
*Author to whom correspondence should be addressed;
E-Mail: sherif.ibrahim@fsc.bu.edu.eg ;
Tel.: +2-0111-6872078.

Abstract

In attempt to find new pharmacological active molecules, we synthesized 6-iodo-4*H*-3,1-benzoxazin-4-one and allowed it to react with some nitrogen nucleophiles namely; hydroxylamine hydrochloride, hydrazine hydrate, fomamide, aliphatic amine, aromatic amines, aralkyl amine, different amino acids, heteryl amines, ethanolamine and sodium azide to afford annelated quinazolinone derivatives and other related systems. The synthesized compounds were characterized with the help of spectroscopic techniques including IR, ^{1}H-NMR and Mass spectra. Also their antimicrobial activities were screened against different strains of bacteria and fungi.

Keywords: 6-Iodo-4*H*-3,1-benzoxazin-4-one; quinazolinone derivatives; nitrogen nucleophiles; antimicrobial activity .

Introduction

The chemistry of heterocyclic compounds has been an interesting field of study for long time [1]. Benzoxazinone derivatives are regarded as remarkable candidates for biological applications [2], where 4*H*-3,1-benzoxazinone derivatives have shown antiphlogistic [3], antibacterial, antifungal [4-7], antimuscular contractor and hypnotic activities [8-10]. Also, benzoxazinones showed antiplatelet aggregation activity [11], antidiabetic and hypolipidaemic activity [12].

4*H*-3,1-benzoxazin-4-ones have attracted considerable attention as inhibitors of serine proteases by enzyme acylation due to the nucleophilic attack of the active site serine on the lactone carbon [13-14], and also new benzoxazinones were tested for their inhibitory activity towards human leukocyte elastase [15-16].

In addition to their pharmaceutical and biological application, benzoxazinone showed some important industrial applications in the synthesis of polymeric material [17], optical bleaching agents [18] and cosmetics [19]. On the other hand 4*H*-3,1 benzoxazin-4-ones are valuable starting materials for the synthesis of a variety of 2,3-disubstituted quinazolin-4-ones [20-24], where the chemistry and biological activities of quinazolin-4(3*H*)-ones and derivatives have been reviewed comprehensively in the literature [25].

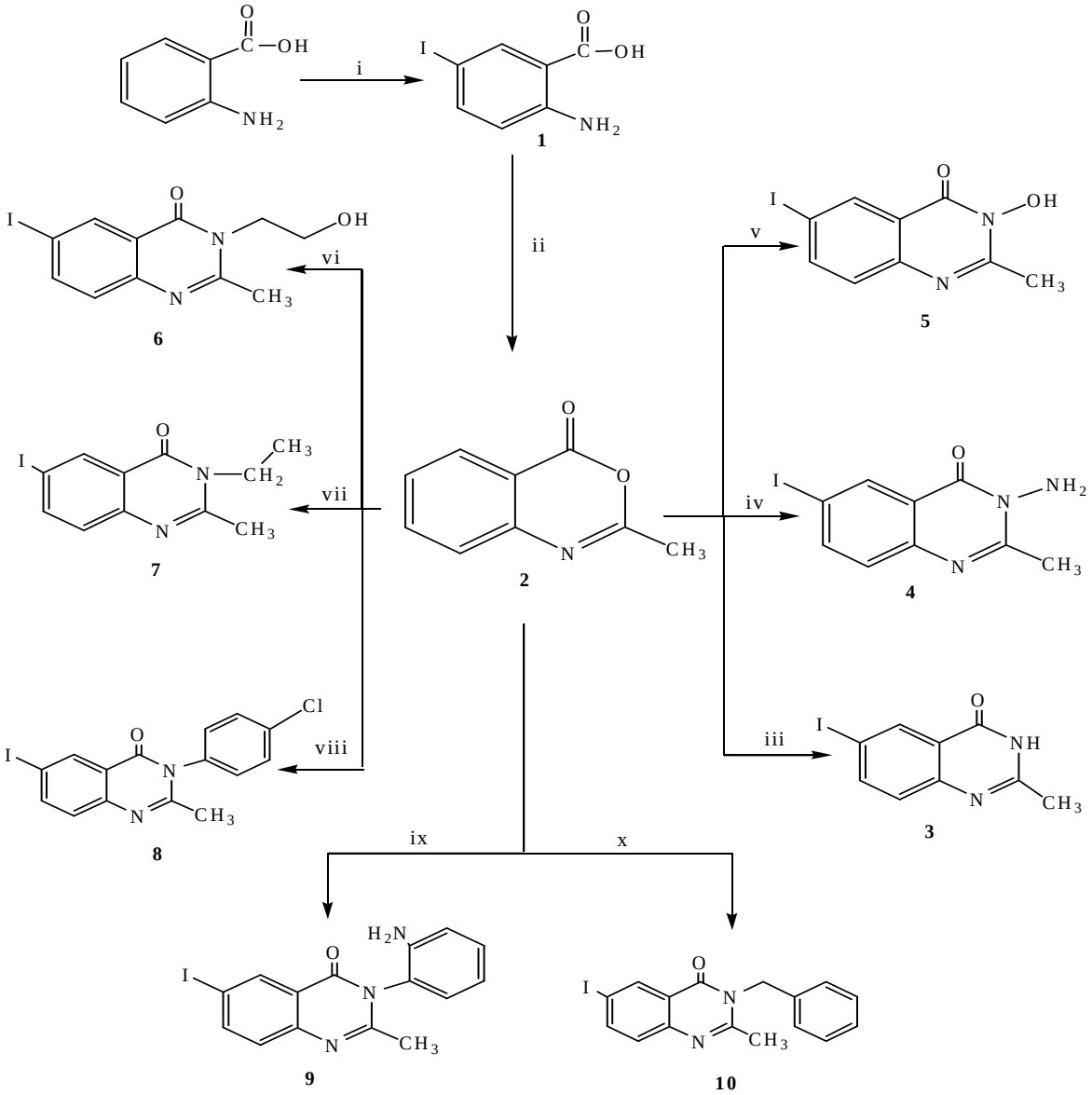
Based on the above facts, herein we search for new members, new and versatile methodologies for synthesis of 4*H*-3,1-benzoxazin-4-one derivatives, studying their behavior towards nitrogen nucleophiles and screening their biological activities.

Result and discussion

6-Iodo-2-methyl-benzo[3,1]oxazin-4-one **(2)** was prepared by refluxing 5-Iodoanthranilic acid **(1)** with acetic anhydride and its chemical structure was elucidated by its IR spectrum which showed absorption band at 1620, 1760 cm^{-1} attributable to C=N and C=O respectively. The benzoxazinone derivative was allowed to react with different nitrogen nucleophiles to afford new quinazolinone derivatives of biological interest. Thus, the reaction of compound **2** with formamide, produced the corresponding 6-iodo-2-methyl-3*H*-quinazolin-4-one **(3)**, while hydrazinolysis of benzoxazinone **2** in boiling ethanol afforded 3-amino-6-iodo-2-methyl-3*H*-quinazolin-4-one **(4)**, ***Scheme 1***.

Treatment of **2** with hydroxylamine hydrochloride in boiling pyridine gave 3-hydroxy-6-iodo-2-methyl-3*H*-quinazolin-4-one **(5)**. Also, refluxing benzoxazinone derivative **2** with ethanol amine in boiling acetic acid and anhydrous sodium acetate yielded 3-(2-hydroxy-ethyl)-6-iodo-2-methyl-3H-quinazolin-4-one **(6)**.

Moreover, when compound **2** was subjected to react with different amines *namely*; ethyl amine (aliphatic amine), 4-chloroaniline , o-phenyl- enediamine (aromatic amines) and benzyl amine (aralkyl amine) in boiling acetic acid produced 3-ethyl-6-iodo-2-methyl-3*H*-quinazolin-4-one **(7)** , 3-(4-chlorophenyl)-6-iodo-2-methyl-3*H*-quinazolin-4-one **(8)**, 3-(2-aminophenyl)-6-iodo-2-methyl-3*H*-quinazolin-4-one **(9)** and 3-benzyl-6-iodo-2-methyl-3*H*-quinazolin-4-one **(10)** respectively. Formation of compounds **7-10** takes place via hetero-ring opening followed by cyclization, ***Scheme 1***.



Scheme 1: (i) I_2, KOH, AcOH, stirring 2h; (ii) Ac_2O, reflux 2h; (iii) Formamide, reflux 2h; (iv) $N_2H_4.H_2O$, EtOH, reflux 3h; (v) $NH_2OH.HCl$, pyridine, reflux 5h; (vi) $NH_2CH_2CH_2OH$, AcOH/AcONa, reflux 3h; (vii) $CH_3CH_2NH_2$, EtOH, reflux 5h; (viii) 4-Chloroaniline, EtOH, reflux 6h; (ix) *o*-Phenylenediamine, AcOH/AcONa, reflux 2h; (x) Benzylamine, AcOH, reflux 6h.

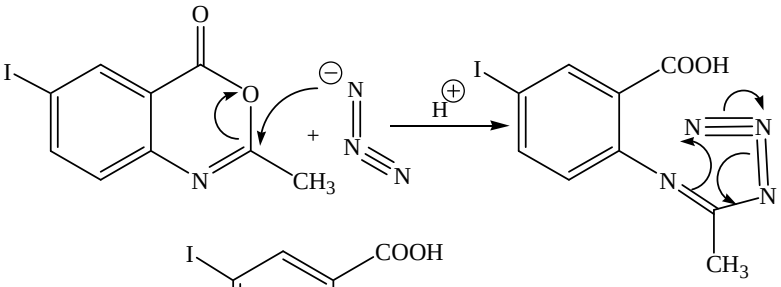
In a similar manner, condensation of compound **2** with semicarbazide hydrochloride, thiosemicarbazide and sulphanilic acid (in boiling pyridine), afforded urea derivative **11a**, thiourea derivative **11b** and benzenesulfonic acid derivative **(12)** respectively, ***Scheme 2***.

Furthermore, when compound **2** was submitted to react with various heteryl amines *viz* 4-aminoantipyrine (in boiling ethanol), 2-aminothiazole, 2-aminopyridine (in boiling pyridine), 2-amino-6-methoxybenzothiazole and 2-amino-5,6-dimethoxybenzimidazole (in boiling acetic acid), it produced 3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-6-iodo-2-methyl-3*H*-quinazolin-4-one **(13a)**, 6-iodo-2-methyl-3-thiazol-2-yl-3*H*-quinazolin-4-one **(13b)**, 6-iodo-2-methyl-3-pyridin-4-yl-3H-quinazolin-4-one **(13c)**, 6-

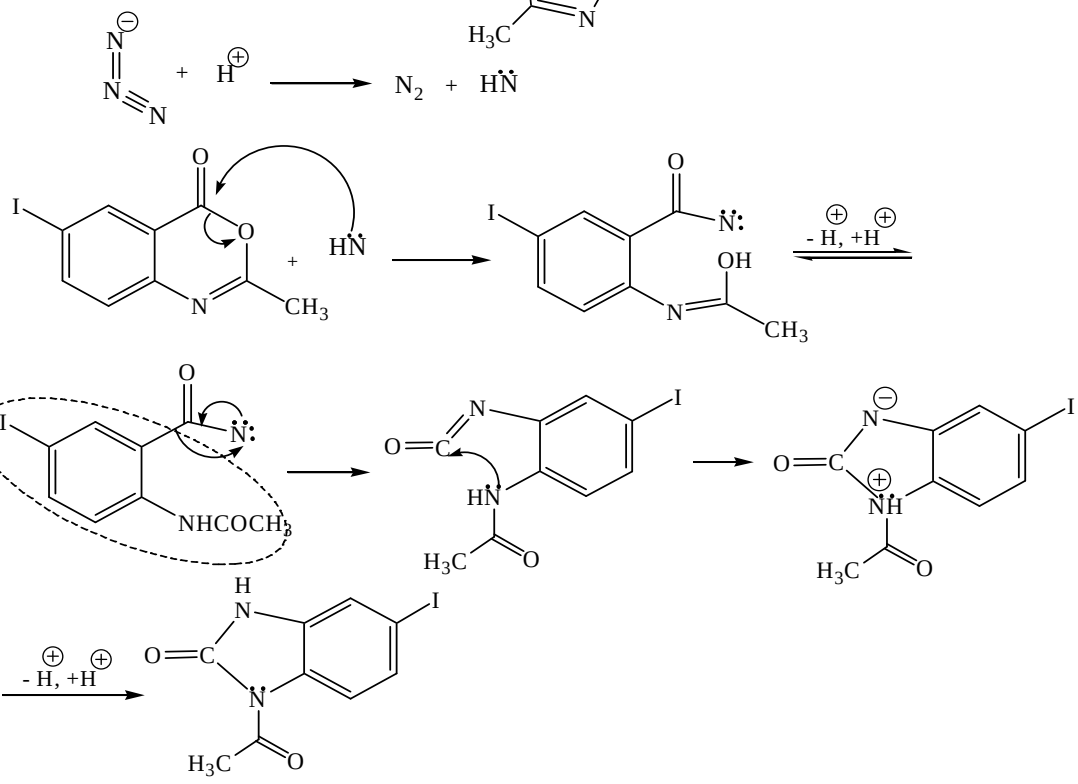
iodo-3-(6-methoxybenzothiazol-2-yl)-2-methyl-3*H*-quinazolin-4-one **(13d)** and 3-(5,6-dimethylbenzothiazol-2-yl)-6-iodo-2-methyl-3*H*-quinazolin-4-one **(13e)** respectively, ***Scheme 2***.

As an extension of this synthetic route, the behavior of compound **2** towards sodium azide in boiling acetic acid was investigated to afford two compounds 5-iodo-2-(5-methyl-tetrazol-1-yl)-benzoic acid **(14)** and 1-acetyl-5-iodo-1,3-dihydro-benzoimidazol-2-one **(15)** which were separated through fractional distillation. The reaction may proceed via the following two pathways:

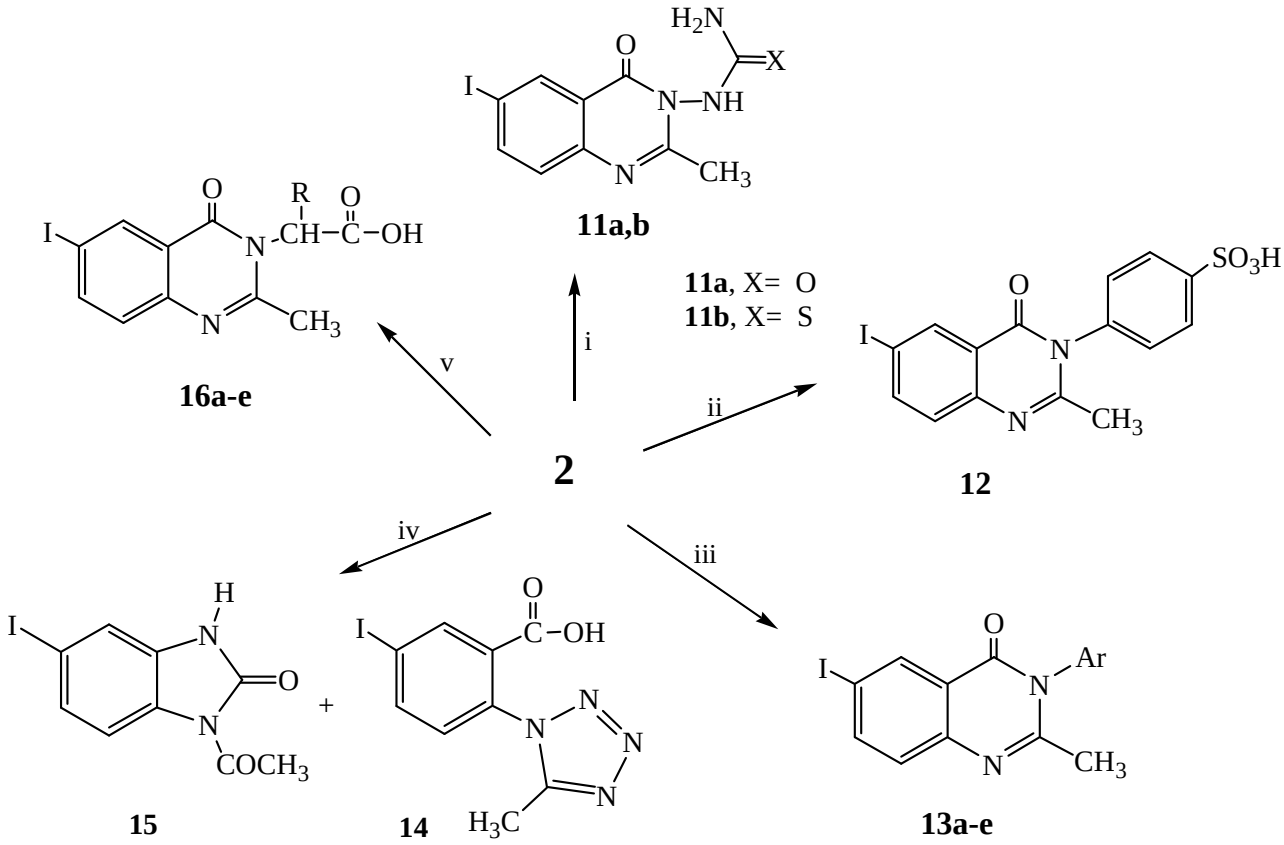
Pathway A:

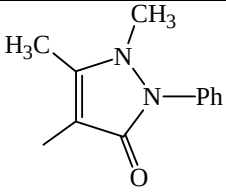
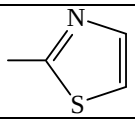
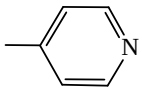
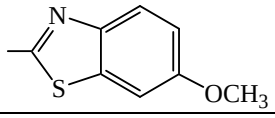
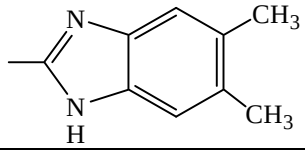
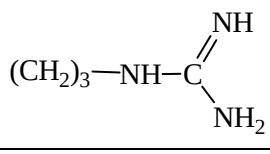


Pathway B:



Finally, the reactivity of benzoxazinone derivative **2** towards a series of amino acids was reported. Thus, the reaction of **2** with glycine, alanine, L-serine, DL-valine and L-arginine (in boiling pyridine) furnished (6-iodo-2-methyl-4-oxo-4*H*-quinazolin-3-yl)acetic acid **(16a)**, 2-(6-iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)propionic acid **(16b)**, 3-hydroxy-2-(6-iodo-2-methyl-4-oxo-4*H*-quinazolin-3-yl)propionic acid **(16c)**, 2-(6-iodo-2-methyl-4-oxo-4*H*-quinazolin-3-yl)-3-methylbutyric acid **(16d)** and 5-guanidino-2-(6-iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)pentanoic acid **(16e)** respectively, ***Scheme 2***.



Compd. No	Ar	Compd. No	R
13a		**16a**	H
13b		**16b**	CH_3
13c		**16c**	CH_2OH
13d		**16d**	$CH(CH_3)_2$
13e		**16e**	

Scheme 2: (i) $NH_2NHCXNH_2$, pyridine, reflux 5h; (ii) Sulphanilic acid, pyridine, reflux 6h; (iii) Heterylamine, reflux 3-5h; (iv) NaN_3, AcOH, reflux 3h; (v) Amino acid, pyridine, reflux 8h.

I

All melting points are uncorrected and were determined by the open capillary method using Gallen Kamp melting point apparatus. FTIR spectra (KBr disk) were recorded on a Nicolet Magna IR model 550 spectrophotometer. Mass spectra were recorded on a Shimadzu GCMS-QP 1000EX instrument (70 ev EI mode). ^{1}H-NMR spectra were determined on Brucker Wpsy 200 MHz spectrometer with TMS as internal reference with chemical shifts expressed as δ ppm. All microanalysis were carried out at Micro Analytical Unit, Faculty of Science, Cairo University, Egypt.

2-Amino-5-iodobenzoic acid (1)

This compound was prepared according to the method of Klemme and Hunter. A solution of anthranilic acid (25 g) in water (500 mL) containing potassium hydroxide (15 g) was added to a solution of iodine (46.5 g) in water (250 mL) having potassium hydroxide (24.75 g). To this solution, glacial acetic acid (100 mL) was added and the reaction mixture immediately diluted with water (120 mL), a solid separated was filtered, washed with sodium bisulphate (25 mL) and purified by recrystallization from a mixture of methanol/ water. Yield (86.8%); m.p. 210 °C.

6-Iodo -2-methyl-4H-3,1-benzoxazin-4-one (2)

Benzoxazinone has been synthesized by following the procedure of Bogert and Seil. A mixture of **1** (0.01 mole) and acetic anhydride (0.02 mole) was refluxed for 1-2 h. The mixture was cooled, evaporated and the residue was washed with H_2O and recrystallized from ethanol to afford the compound **2**. Yield (75%), m.p. 155 °C; **IR** (ν/cm^{-1}): 3012 (C-H aromatic), 2925 (C-H aliphatic), 1760 (C=O), 1620 (C=N). **MS**: m/z 287 [M$^+$]. **^{1}H NMR** ($CDCl_3$): δ = 7.32-7.10 (m, 3H, ArH), 1.61(s, 3H, CH_3), Anal. calcd for $C_9H_6NO_2I$: C, 37.63; H, 2.09; N, 4.88%. Found: C, 37.78; H, 2.39; N, 5.09.

6-Iodo-2-methyl-3H-quinazolin-4-one (3)

A solution of benzoxazinone **2** (2.87 g, 0.01 mole) in formamide (15 mL) was refluxed for 2h. The reaction mixture after cooling was poured onto ice/H_2O. The solid separated was filtered, dried, and recrystallized from dioxan to give compound **3**. Yield (77.5%), m.p. 272 °C; **IR** (ν/cm^{-1}): 3316, 3160 (NH), 3019 (C-H aromatic), 2919 (C-H aliphatic), 1678 (C=O), 1615 (C=N). **MS**: m/z 286 [M$^+$]. Anal. calcd for $C_9H_7IN_2O$: C, 37.79; H, 2.47; I, 44.36; N, 9.79.

3-Amino-6-iodo-2-methyl-3H-quinazolin-4-one (4)

A mixture of benzoxazinone **2** (2.87 g, 0.01 mole) and hydrazine hydrate (1 g, 0.02 mole) was heated under reflux in absolute ethanol (30 mL) for 3 h. The reaction mixture was concentrated. After cooling, the solid was separated out, filtered off, dried, and then recrystallized from ethanol to afford quinazolinone **4**. Yield (80%), m.p. 158 °C; **IR** (ν/cm^{-1}): 3284, 3194 (NH_2), 3046 (C-H aromatic), 1660 (C=O), 1596 (C=N). **MS**: m/z 301 [M$^+$]. Anal. calcd for $C_9H_8IN_3O$: C, 35.90; H, 2.68; I, 42.15; N, 13.96.

3-Hydroxy-6-iodo-2-methyl-3H-quinazolin-4-one (5)

A mixture of benzoxazinone **2** (2.87 g, 0.01 mole) and hydroxylamine hydrochloride (2.1 g, 0.03 mole) in pyridine (20 mL) was heated under reflux for 3h. The reaction mixture, after cooling, was poured into ice/HCl. The solid that obtained was filtered off, dried and recrystallized from ethanol to give 5. Yield (65%), m.p. 215 °C; **IR** (ν/cm^{-1}): 3429 (OH), 1659 (C=O), 1600 (C=N). **MS**: m/z 302[M$^+$], 304[M$^+$+2]. Anal. calcd for $C_9H_7IN_2O_2$: C, 35.79; H, 2.34; I, 42.01; N, 9.27.

3-(2-Hydroxy-ethyl)-6-iodo-2-methyl-3H-quinazolin-4-one (6).

An equimolar mixture of compound **2** and ethanol amine in glacial acetic acid and anhydrous sodium acetate (0.5 g) was refluxed for 3 h. The reaction mixture was cooled and poured onto cold water. The solid obtained was filtered off and recrystallized from benzene to give **6**. Yield (64%), m.p. 240 °C; **IR** (ν/cm^{-1}) : 3441, 3235 (OH), 2917 (C-H aliphatic), 1655(C=O), 1582 (C=N), **^{1}H-NMR (**DMSO**)**: δ = 7.8-8.2 (s, 3H, ArH), 2.5 (t, 2H, CH_2), 2.1 (s, 3H, CH_3), 1.9 (t, 2H, CH_2), 10.9 (s, 1H, OH). Anal. calcd for $C_{11}H_{11}IN_2O_2$: C, 40.02; H, 3.36; I, 38.44; N, 8.49.

3-Ethyl-6-iodo-2-methyl-3H-quinazolin-4-one (7)

An equimolar mixture of **2** (2.87 g, 0.01 mole) and ethylamine (aliphatic amine) (0.45 g, .01 mole) in ethanol (30 mL) was refluxed for 5 h. The solid that separated after concentrating and cooling was recrystallized from toluene to give compound **7**. Yield (82%), m.p. 196 °C; **IR** (ν/cm^{-1}): 2926 (C-H aliphatic), 1671 (C=O), 1605

(C=N), **^{1}H-NMR** (DMSO): δ = 7.4-8.2 (m, 3H, ArH), 2.5 (s, 3H, CH_3), 2.1 (q, 2H, CH_2), 1.2 (t, 3H, CH_3). Anal. calcd for $C_{11}H_{11}IN_2O$: C, 42.06; H, 3.53; I, 40.40; N, 8.92.

3-(4-Chloro-phenyl)-6-iodo-2-methyl-3H-quinazolin-4-one (8)
A mixture of benzoxazinone **2** (2.87 g, 0.01 mole) and 4-chloro aniline (0.01 mole) was refluxed in ethanol (30 mL) for 6 h. The reaction mixture was concentrated. The solid that separated was filtered off, dried, and then recrystallized from toluene to afford **8**. Yield (64%), m.p. 138°C; **IR** (ν/cm^{-1}): 3068(C-H aromatic), 2925 (C-H aliphatic), 1670 (C=O), 1602 (C=N). **MS**: m/z 396 [M$^+$], 398 [M$^+$ + 2]. Anal. Calcd for $C_{15}H_{10}ClIN_2O$: C, 45.43; H, 2.54; Cl, 8.94; I, 32.00; N, 7.06.

3-(2-Amino-phenyl)-6-iodo-2-methyl-3*H*-quinazolin-4-one (9)
A mixture of benzoxazinone **2** (2.87 g, 0.01 mole) and *o*-phenylene- diamine (1.08 g, 0.01 mole) in glacial acetic acid (30 mL) and (0.5 g) anhydrous sodium acetate was refluxed for 2 h. The solid that separated out, after cooling, was filtered off, dried, and recrystallized from benzene to give **9**. Yield (90%), m.p. 238 °C; **IR** (ν/cm^{-1}): 3233, 3117 (NH_2), 2871 (C-H aliphatic), 1655 (C=O), 1581 (C=N), **MS**: m/z 379 [M$^+$ + 2]. Anal. calcd for $C_{15}H_{12}IN_3O$: C, 47.77; H, 3.21; I, 33.65; N, 11.14.

3-Benzyl-6-iodo-2-methyl-3H-quinazolin-4-one (10)
An equimolar mixture of benzoxazinone **2** (2.87 g, 0.01 mole) and benzyl amine (1.07 g, 0.01 mole) in glacial acetic acid (20 mL) was refluxed for 6h. The solid that separated after concentration and cooling was recrystallized from acetic acid to give **10**. Yield (89%), m.p. 232 °C; **IR** (ν/cm^{-1}) : 2928 (C-H aliphatic), 1676 (C=O), 1606 (C=N). **^{1}H-NMR** (DMSO): δ = 7.8-8.2 (m, 8H, ArH), 2.5 (s, 2H, CH_2) and 2.1 (s, 3H, CH_3). Anal. calcd for $C_{16}H_{13}IN_2O$: C, 51.08; H, 3.48; I, 33.73; N, 7.45.

General procedure for preparation of compounds 11a,b
A mixture of benzoxazinone **2** (2.87 g, 0.01 mole), semicarbazide hydrochloride (0.75 g, 0.01 mole), and/or thiosemicarbazide (0.91 g, 0.01 mole) was boiled in pyridine (20 mL) for 4-6 h. After cooling, the reaction mixture was poured into ice/HCl. The solid that was deposited was filtered off, dried and recrystallized from ethanol to afford (**11a**) and (**11b**) respectively.

(6-Iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)urea (11a)
Yield (65%), m.p. (200-202 °C); **IR** (ν/cm^{-1}): 3430, 3235 (NH_2), 2868 (C-H aliphatic), 1684, 1651 (two C=O group), 1580 (C=N). **MS**: m/z 344 [M$^+$], 345 [m$^+$ + 1]. Anal. calcd for $C_{10}H_9IN_4O_2$: C, 34.90; H, 2.64; I, 36.88; N, 16.28.

(6-Iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)thiourea (11b)
Yield (53%), m.p. 198 °C; **IR** (ν/cm^{-1}): 3423, 3235 (NH_2, NH), 1684 (C=O), 1381 (C=S). **MS**: m/z 361 [M$^+$]. Anal. calcd for $C_{10}H_9IN_4OS$: C, 33.35; H, 2.52; I, 35.23; N, 15.56; S, 8.90 .

4-(6-Iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)benzenesulfonic acid (12)
An equimolar mixture of benzoxazinone **2** (2.87 g, 0.01 mole) and sulphanilic acid (0.01 mole) in pyridine (20 mL) was refluxed for 5h. After cooling, the reaction mixture was poured into ice/HCl. The solid separated was filtered off, dried, and recrystallized from ethanol to give **12.** Yield (77%), m.p. 220°C; ; **IR** (ν/cm^{-1}) : 3495, 3233 (OH), 2873 (C-H aliphatic), 1683 (C=O), 1653 (C=N). **MS**: m/z 445 [M$^+$ + 3]. Anal. calcd for $C_{15}H_{11}IN_2O_4S$: C, 40.74; H, 2.51; I, 28.70; N, 6.33; S, 7.25.

3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-6-iodo-2-methyl-3H-quinazolin-4-one (13a)
A mixture of benzoxazinone **2** (2.87 g, 0.01 mole) and 4-aminoantipyrine (3.048 g, 0.015 mole) in absolute ethanol (30 mL) was heated under reflux for 3 h. The reaction mixture was concentrated. The solid was separated out after cooling, filtered off, dried, and recrystallized from ethanol to afford **13a** : yield (77%), m.p. 94°C; **IR** (ν/cm^{-1}) : 2928 (C-H aliphatic), 1676 (C=O), 1606 (C=N). **MS**: m/z 472 [M$^+$], 474 [M$^+$ + 2]. Anal. calcd for $C_{20}H_{17}IN_4O_2$: C, 50.86; H, 3.63; I, 26.87; N, 11.86.

General procedure for preparation of compounds 13b,c

A mixture of benzoxazinone **2** (2.87 g, 0.01 mole), 2-aminothiazole (0.01 mole) and/or 4-aminopyridine (0.01 mole) was boiled in pyridine (20 mL) for 5 h. After cooling, the reaction mixture was poured into crushed ice/HCl. The solid that was deposited was filtered off, dried, and recrystallized from suitable solvent.

6-Iodo-2-methyl-3-thiazol-2-yl-3H-quinazolin-4-one (13b)

Yield (62%), m.p. 225 °C; **IR** (ν/cm^{-1}): 2873 (C-H aliphatic), 1685 (C=O), 1580 (C=N), **MS**: m/z 369 [M^{+}]. Anal . calcd for $C_{12}H_8IN_3OS$: C, 39.04; H, 2.18; I, 34.37; N, 11.38; S, 8.69.

6-Iodo-2-methyl-3-pyridin-4-yl-3H-quinazolin-4-one (13c)

Yield (70%), m.p. 205°C; **IR** (ν/cm^{-1}): 3234(NH_2), 2873 (C-H aliphatic), 1686 (C=O), 1651, 1580 (C=N), Anal. calcd for $C_{14}H_{10}IN_3O$: C, 46.30; H, 2.78; I, 34.95; N, 11.57.

General procedure for preparation of compounds 13d,e

An equimolar mixture of benzoxazinone **2** (2.87 g, 0.01 mole), 2-amino-6-methoxybenzothiazole (0.01 mole) and/or 2-amino-5,6-dimethylbenz- imidazole (0.01 mole) in glacial acetic acid (20 mL) was refluxed for 5 h. The solid that separated after cooling was filtered, dried and recrystallized from acetic acid to give **13d** and **13e** respectively.

6-Iodo-3-(5-methoxy-benzothiazol-2-yl)-2-methyl-3H-quinazolin-4-one (13d)

Yield (87%), m.p. 228°C; **IR** (ν/cm^{-1}): 2938 (C-H aliphatic), 1689 (C=O), 1653, 1572 (C=N), **MS**: m/z 449 [M^{+}], 359[m^{+} + 2] Anal. calcd for $C_{17}H_{12}IN_3O_2S$: C, 45.45; H, 2.69; I, 28.25; N, 9.35 S, 7.14.

3-(5,6-Dimethyl-benzothiazol-2-yl)-6-iodo-2-methyl-3H-quinazolin-4-one (13e)

Yield (91%), m.p. 270 °C; **IR** (ν/cm^{-1}): 3320, 3122(NH), 2917(C-H aliphatic), 1649 (C=O), **MS**: m/z 430 [M$^{+\cdot}$], Anal. calcd for $C_{18}H_{14}IN_3OS$: C, 48.33; H, 3.15; I, 28.37; N, 9.39; S, 7.17.

5-Iodo-2-(5-methyl-tetrazol-1-yl)benzoic acid (14) and 1-Acetyl-5-iodo-1,3-dihydro-benzoimidazol-2-one (15)

A mixture of benzoxazinone **2** (2.87 g, 0.01 mole) and sodium azide (0.01 mole) in glacial acetic acid was heated under reflux for 3h. Then after cooling, the reaction mixture was poured into water, the solid that separated out , filtered, dried, and fractionally distilled with light petroleum to give **15** while the insoluble part was crystallized from ethanol and afforded the tetrazole derivative **14**.

14: yield (51%), m.p. 250°C; **IR** (ν/cm^{-1}) : 3495, 3233 (OH), 2873 (C-H aliphatic), 1683 (C=O), 1653 (C=N), **^{1}H-NMR (**DMSO): δ = 7.8-8.2 (m, 3H, ArH), 2.1 (s, 3H, CH3), 10.9 (s, 1H, OH), Anal. calcd for $C_9H_7IN_4O_2$: C, 32.75; H, 2.14; I, 38.45; N, 16.97.

15: yield (21%), m.p. 170 °C; **IR** (ν/cm^{-1}): 3232 (NH), 2922 (C-H aliphatic), 1760, 1681 (C=O), 1636 (C=N), **MS**: m/z 305 [M^{+} + 3]. Anal. calcd for $C_9H_7IN_2O_2$: C, 35.79; H, 2.34; I, 42.01; N, 9.27.

General procedure for preparation of compounds 16a-e

A mixture of benzoxazinone **2** (2.87 g, 0.01 mole), glycine (0.75 g, 0.01 mole), alanine (0.01 mole), L-serine (0.01 mole), DL-valine (0.01 mole) or L-arginine (0.01 mole) in pyridine (15 mL with few drops of water) was heated under reflex for 8 h. The reaction mixture was cooled and poured into crushed ice/ HCl. The solid that obtained was washed, dried, and recrystallized from suitable solvent to yield **16a-e** respectively.

(6-Iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)acetic acid (16 a)

Yield (42%), m.p. 120 °C; **IR** (ν/cm^{-1}): 3435, 3235 (OH), 2870 (C-H aliphatic), 1685, 1651 (two C=O group), 1579 (C=N). Anal. calcd for $C_{11}H_9IN_2O_3$: C, 38.39; H, 2.64; I, 36.88; N, 8.14.

2-(6-Iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)-propionic acid (16b)

Yield (45%), m.p. 204 °C; **IR** (ν/cm^{-1}): 3424, 3235 (OH), 2922 (C-H aliphatic), 1686, 1651 (two C=O group), 1580 (C=N). **MS**: m/z 358 [M^{+} + 1], 359[M^{+} + 2]. Anal. calcd for $C_{12}H_{11}IN_2O_3$: C, 40.24; H, 3.10; I, 35.44; N, 7.82.

3-Hydroxy-2-(6-iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)propionic acid (16c)

Yield (58%), m.p. 206 °C; **IR** (ν/cm^{-1}): 3435, 3235 (OH), 2921 (C-H aliphatic), 1685, 1651 (two C=O group), 1580 (C=N). Anal. calcd for $C_{12}H_{11}IN_2O_4$: C, 38.52; H, 2.96; I, 33.92; N, 7.49.

2-(6-Iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)-3-methylbutyric acid (16d)
Yield (39%), m.p. 212 °C; **IR** (ν/cm^{-1}): 3436, 3235 (OH), 2873 (C-H aliphatic), 1686, 1651 (two C=O group), 1579 (C=N). **MS**: m/z 386 [M^{+}], 388, [M^{+} + 2]. Anal. calcd for $C_{14}H_{15}IN_2O_3$: C, 43.54; H, 3.91; I, 32.86; N, 7.25.

5-Guanidino-2-(6-iodo-2-methyl-4-oxo-4H-quinazolin-3-yl)pentanoic acid (16e)
Yield (51%), m.p. 202 °C; **IR** (ν/cm^{-1}): 3235 (OH), 2873 (C-H aliphatic), 1685, 1651 (two C=O group), 1579 (C=N). Anal. calcd for $C_{15}H_{18}IN_5O_3$: C, 40.65; H, 4.09; I, 28.63; N, 15.80.

Antimicrobial activity

The antimicrobial activity of some synthesized compounds were determined in vitro using hole plate and filter paper disk methods [28]. A variety of species of gram-positive bacteria (*Bacillus megathorium*) and gram-negative bacteria (*Escherichia coli*) in addition to some fungal plant pathogens (Mucor and Aspergillus flavus) were used. The tested compound were dissolved in DMSO, and different concentration have been chosen (100, 200, 300µg/mL). The minimum inhibitory concentration (MIC) of some of the tested compounds was measured by twofold serial dilution method.

Comparative studies of the prepared compounds and standard drug were also carried out. Tetracycline and Amphotercin B were used as standard drugs for antibacterial and antifungal activity respectively. The results are illustrated in **Table 1**. The investigation of antibacterial and antifungal screening data revealed that most of the tested compounds showed moderate to good activity compared to standard drugs used.

Table 1: Antimicrobial activity of the synthesized compounds

Compd. No	*Gram +ve bacteria*		*Gram –ve bacteria*		*Fungi*			
	Bacillus megathorium		**Escherichia coli**		**Mucor**		**Aspergillus flavus**	
	A	MIC	A	MIC	A	MIC	A	MIC
3	+	100	+++	200	--	--	--	--
4	+	100	--	--	--	--	--	--
6	++	100	--	--	--	--	--	--
8	++	100	--	--	--	--	--	--
9	+	100	++	300	--	--	--	--
10	++	300	+	100	--	--	--	--
11b	+++	100	+	200	+++	200	+	200
12	+	100	--	--	--	--	--	--
13a	+	100	+	300	--	--	--	--
13b	+++	100	--	--	--	--	--	--
13d	++	100	--	--	--	--	+	100
14	+	200	++	100	--	--	--	--
16d	++	100	--	--	++	300	--	--
Tetracycline	+++	100	+++	100	--	--	--	--
Amphotercin B	--	--	--	--	+++	100	+++	100

A = Antimicrobial activity of tested compounds; MIC = Minimum inhibitory concentration; -, inactive; + > 5 mm, slightly active; ++ > 7 mm, moderately active; +++ > 10 mm, highly active.

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