Behavior of 6-Iodobenzoxazinone towards some Nitrogen nucleophiles and evaluation of 4(3H) - Quinazolinones derivatives as potential Antimicrobial agents.

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Abstract: The present work deals with synthesis of new quinazolinone derivatives of biological interest, via the reaction of 6 - iodo - 4H - 3, 1 - benzoxazin **2** with some nitrogen nucleophiles namely; 2 - aminopyridine, glycine, o- phenylene diamine, ethylene diamine , ethanolamine and made hydrazinolysis of benzoxazinone **2** in boiling butanol afforded 3 - amino - 6 - iodo - 2 - phenyl -3H- quinazolin – 4 – one (**6**), the formed compounds characterized through its elemental analysis, melting point, IR, Mass, ^{1}H-NMR as well as studying the bilogical evaloation of synthsisted compounds as antimicrobial.
[M. A. El-Hashash, Assy, M. G, Aly A. Aly, Abdel Aziz, A. E. **Behavior of 6-Iodobenzoxazinone towards some Nitrogen nucleophiles and evaluation of 4(3H) - Quinazolinones derivatives as potential Antimicrobial agents.** *Nat Sci* 2016;14(5):76-84]. ISSN 1545-0740 (print); ISSN 2375-7167 (online). http://www.sciencepub.net/nature. 11. doi:10.7537/marsnsj14051611.

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

1. Introduction

The reported synthesis of new series of benzoxazinone [1] that have biological and pharmacological activities [2], such as anticonvulsant [3-5], antihistaminic [6], antihypertensive [7-8], analgsic [9-10], anti-inflammatory [11], antimicrobial [12-14], antifungal [15-16], antibacterial [17], antimuscular contractor and hypnotic activities [18], antiplatlet aggrgation activity [19], antidiabetic and hypolipidaemic activity [20], benzoxazinones were tested for their inhibitory activity towards human leukocyte elastase [21-22], antimalarial, anticancer, anti-HIV [23-24].

In addition to their pharmaceutical and biological application, benzoxazinone showed some important industrial application in the synthesis of polymeric material [25], optical bleaching agents [2] and cosmetics [26]. On other hand 4H-3,1-benzoxazin-4-ones as starting materials for the synthesis of varity of 2,3-disubstituted quinazolin-4-ones [27], where the chemistry and bilogical activities of quinazolin-4(3H)-ones and derivatives have been reviwed comprehensively in the literature [28].

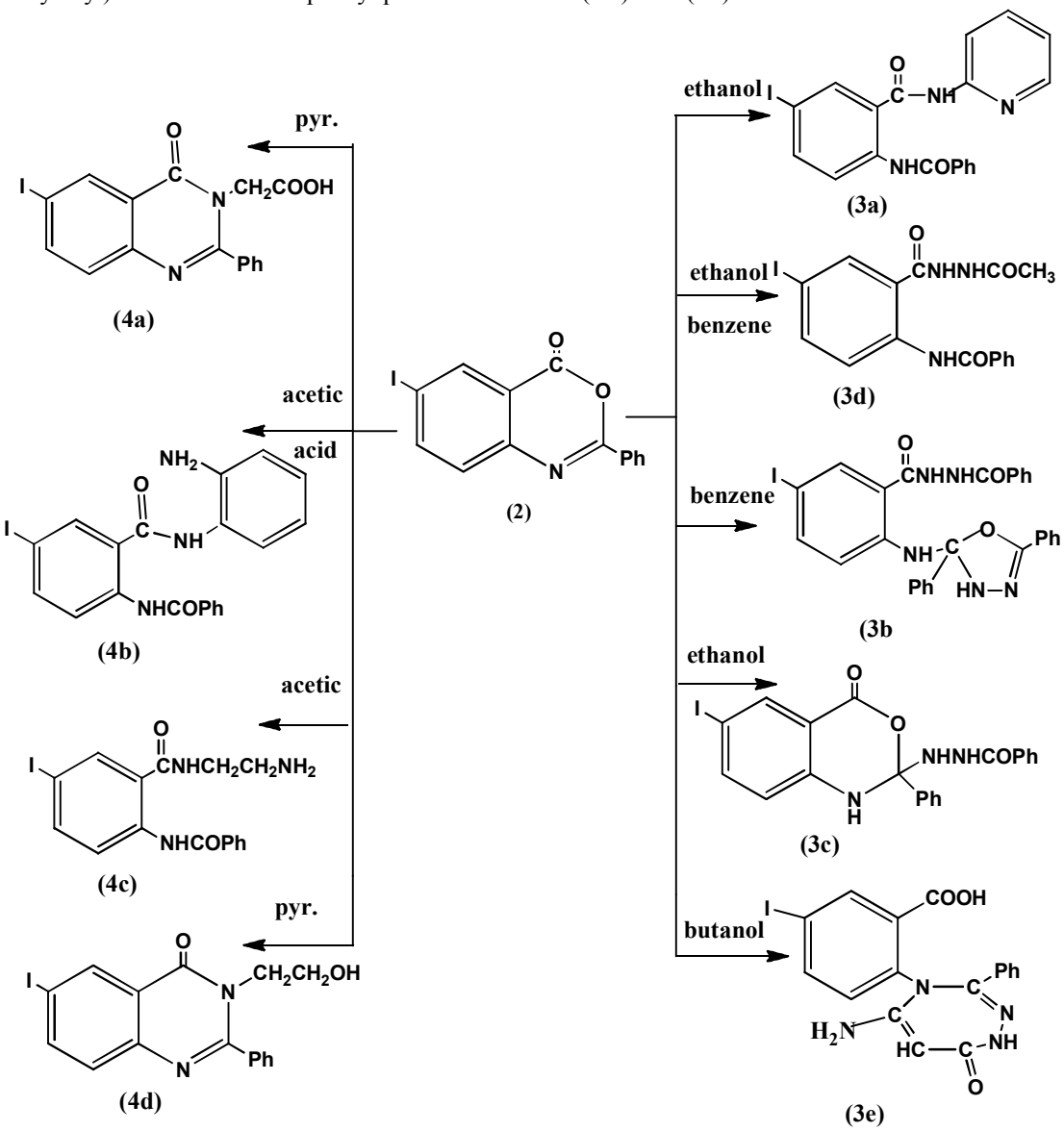
Based on above facts, we search for new members and methologies for synthesis of 4H-3, 1-benzoxazin-4-one derivatives, studying their behavior towards nitrogen nucleophiles and screening their biological activities. Have stimulated us to synthesize some new derivatives of these classes of compounds with the hope of obtaining new structures with enhanced potency of finding new applications. Also we aimed to incorporate a sterically bulky group such phenyl group in position - 2 to detact its role in the nature and ease of reaction of these compounds.

2.1 Result And Discussion

In continuation of our efforts to develop the synthesis and reactivity of benzoxazinone derivatives toward nitrogen and oxygen nucleophilic reagents, we reported herein the reaction of 6–iodo–2–phenyl–4H–3,1– benzoxazin– 4– one (**2**) afforded new quinazolinone derivatives of bilogical interest. Thus the reaction of compond **2** with 2–aminopyridine, acetic acid hydrazide in boiling ethanol or benzene it yielded the corresponding 2–benzamido–5–iodo–N–pyridin–2–yl)benzamide (**3a**), N–[2–(2–acetylhydrazincarbonyl)–4–iodophenyl]benzamide (**3b**) respectively, when benzoxazinone **2** reacted with benzoic acid hydrazide in boiled benzene it yielded N-benzoyl-2-(2,5-diphenyl-2,3-dihydro-1,3,4-oxadiazol-2-yl)amino-5-iodobenzohydrazide (**3c**), when the compound **2** reacted with, benzoic acid hydrazide in boiled ethanol it afforded N'–(6–iodo–4–oxo–2–phenyl–2,4–dihydro–1H– benzo[d] [1,3]oxazin–2–yl)benzohydrazide (**3d**), with cyanoacetic acid hydrazide it yielded triazepene derivative (**3e**).

Also benzoxazinone **2** reacted with nutrogen nucleophiles such as glycine, 0 - phenylene diamine, ethylene diamine in glacial acetic acid yielded 2–phenyl–3–carboxymethyl– 5–iodoquinazolinone (**4a**), N–(2–aminophenyl)–2–benzamido–5–iodobenzamide (**4b**) and N–(2–aminoethyl)–2–benzamido–5–iodobenzamide (**4c**) respectively. Also benzoxazinone **2** reacted with ethanol amine in pyridine yielded, 3–

(2–hydroxyethyl) –6–iodo–2–phenylquinazolin– 4(3H)–one (**4d**). **Scheme 1**.

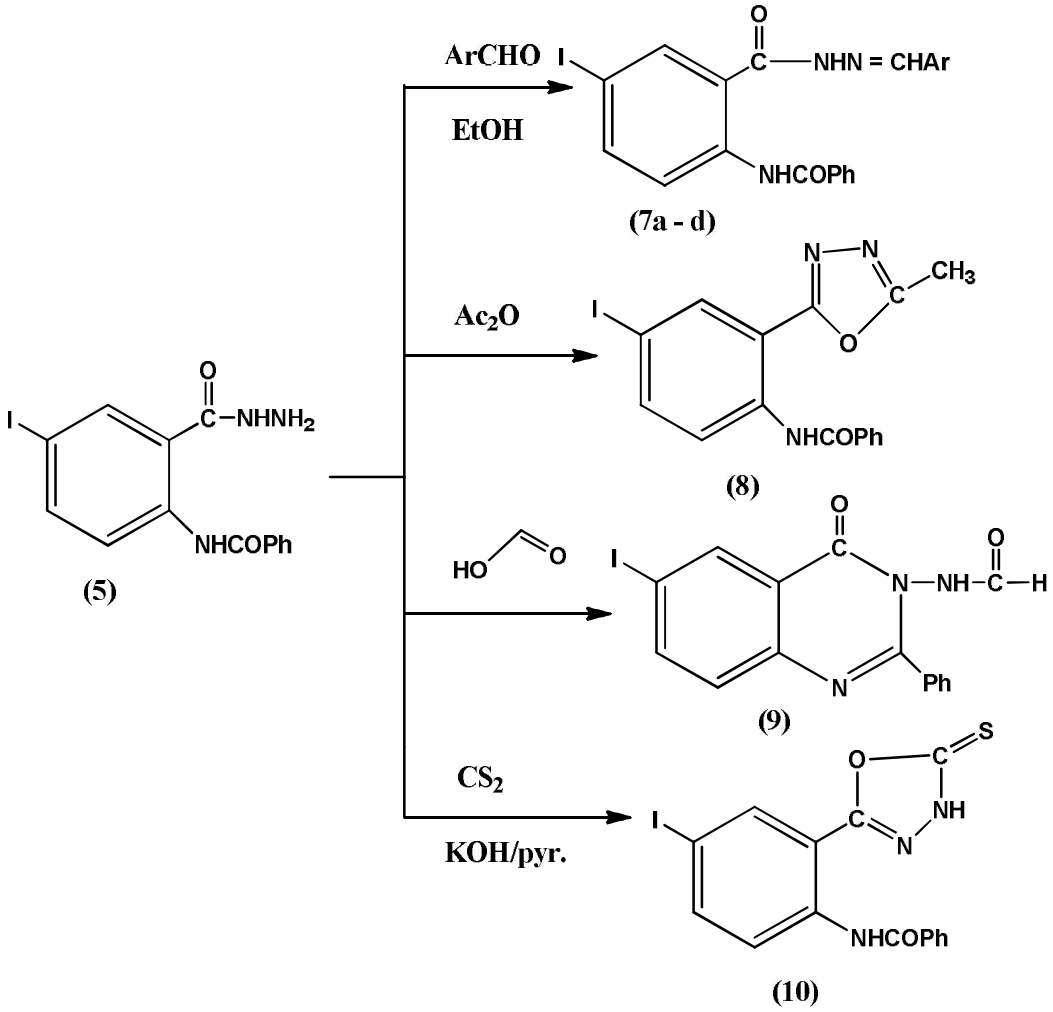


Schem1

While hydrazinolysis of benzoxazinone **2** in boiled ethanol afforded 2– benzamido–5– iodobenzoylhydrazide (**5**), while hydrazinolysis of compound **2** in boiling butanol yielded quinazolinone derivative (**6**).

Reaction of hydrazide **5** with aromatic aldehydes yielded the corresponding hydrazones (**7a**

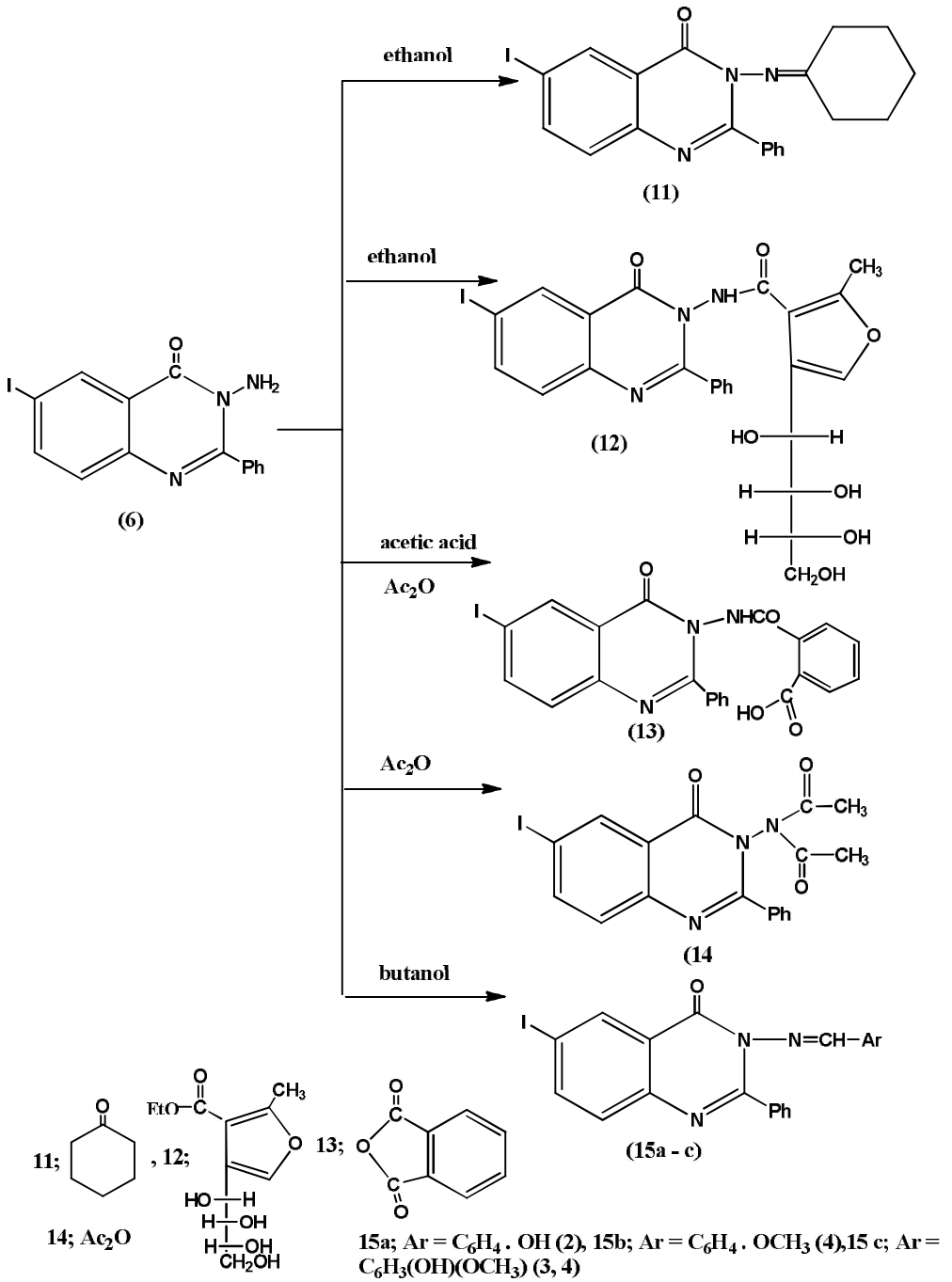
– d), hydrazide **5** react with acetic anhydride it yielded N–(4–Iodo–2– (5–methyl–1,3,4–oxadiazol–2–yl)phenyl)benzamide (**8**), hydrazide **5** reacted with formic acid to yield N-(6–iodo–4–oxo– 2–phenylquinazolin–3(4H)–yl)formamide (**9**) and hydrazide **5** reacted with carbon disulphide in pyridine it yielded N–[4–Iodo–2 –(5–thioxo–4,5–dihydro–1,3,4–oxadiazole–2–yl)phenyl]benzamide (**10**). **Scheme 3**.



7a, Ar= C_6H_5; 7b = C_6H_4 .OH(2), 7c, Ar= C_6H_4 .(OCH_3), 7d, Ar = C_6H_4 .(OH)(OCH_3)(3,4)

Scheme 3

Finally reaction of 3–Amino– 6– iodo–2–phenyquinazolin–4–one (**6**), with cyclohexanone, 3–ethoxycarbonyl–2– methyl–4(1,2,3,4)–tetrahydroxybutylfuran in boiled ethanol it yielded 3–(cyclohexylideneamino)–6–iodo–2–phenylquinazolin– 4(3H)–one (**12**), quinazolinone derivative (**13**), benzoylation of aminoquinazolinone **6** with phthalic anhydride the acyl product 2–[(6–iodo–4–oxo–2–phenyl–quinazolin–4(3H)–yl)carbamoyl] benzoicacid (**14**) formed, interstingly reaction of compound **6** with acetic anhydride afforded N–acetyl–N–(6–iodo–4–oxo–2–phenylquinazolin–3(4H)–yl]acetamide(**15**) and finally compound **6** reacted with schiff bases to afforded phenylquinazolinone derivatives (**16a – c**), **Scheme 4**.



Scheme 4

2.2 Antibacterial, Antifungal and Antiyeast Activation of the Synthesized Compounds

The antimicrobial activities of the synthesized compounds were determined in vitro using the hole plate and filter paper disc method which considered the most commonly used technique for determining sensitivity of chemotherapeutic agents. Compounds were dissolved in 10% DMSO at different concentrations (125, 250, 500 µg/ml). Agar plates were inoculated uniformly from fresh broth culture of Gram –ve bacteria (Escherichia coli), Gram +ve bacteria (Staphylococcus aureus), fungi (Aspergillus flavus), and yeast (Candida albicans). The disk were inubated at 28ºC for 24h, and the formed inhibition zones were diffused into the agar from the disk (this refers to the organism was inhibited by material) and were measured in mm.

Bacterial media: Nutrient agar and broth (PH 7.0), Peptone (0.5g), Beef extract (0.3g), Agar (15.0g) and distilled water (1000.0 ml).

Funal media: $MgSO_4$ (0.5g); KCl (0.5g); Sucrose (30.0g); $FeSO_4$ (0.01g); $NaNO_3$ (3.0g), K_2HPO_4 (1.0g); Agar (15.0g) and distilled water (1000.0 ml).

Table 1: Antimicrobial activity of some synthesized compounds.

Compound	Bacteri		Fungi	Yeast
Control: DMSO	Escherichia coli (G^-)	Staphylococcus aureus (G^+)	Aspergillus flavus (fungus)	Candidaalbicans (fungus)
5b	0.0	0.0	0.0	0.0
8	0.0	12	0.0	0.0
3b	0.0	0.0	0.0	0.0
3c	15	17	0.0	11
3e	14	16	0.0	12
10	15	22	0.0	0.0

- G: Gram reaction.
- Solvent: DMSO.

Conclusion

Based on the results of the inhibition zoon in table 2 revealed that trizole 5 – Iodo – 2 – (5 – phenyl – tetrazol – 1 – yl) benzoic acid **10** and trizepin2 –(5 – amino – 7– oxo – 3 – phenyl – IH - 1, 2, 4 – triazepin – 4(7H) – yl) – 5 – iodobenzoic acid **3e** showed promosing antimicrobial activity while benzohydrazide N' – (6 – Iodo – 4 – oxo – 2 – phenyl – 2, 4 dihydro – 1H – benzo [d][1, 3] oxazin – 2 – yl) benzohydrazide (**3c**) & N – benzoyl – 2 – (2, 5 – diphenyl – 2, 3 – dihydro – 1, 3, 4 – oxadiazol – 2 – yl) amino – 5 – iodobenzo – hydrazide (**3e**) exhibited high antibacterial and antifungai activities. Compounds N – Phenyl – 2 – Benzamido – 5 – iodo - benzoylhydrazide (**5b**), N – (4 – Iodo – 2 – (5 – methyl – 1, 3, 4 – oxadiazol – 2 – yl) phenyl)benzamide (**8**) exhibited no antimicrobial activity.

1. Experimental

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 Nicolet Magna IR model 550 spectrophotometer. Mass spectra were recorded on Shimadzu GCMS – QP 1000EX instrument (70 ev EI mode). ^{1}HNMR spectra were determined on Brucher Wpsy 200 MHz spectrometer with TMS as internal reference with chemical shifts expressed as ^{TM}ppm. All microanalysis were carried out at Micro Analytical Unit, Faculty of Science, Cairo Univerisity, Egypt.

3.1 6–Iodo–2–phenyl–4H–3, 1– Benzoxazin–4–one (2)

Benzoxazinone has been synthesized by following. A mixture of 2 -Benzamido -5 - iodobenzoic acid **1**(0.01mole) and acetic anhydride (0.02 mole) was refluxed for 1 - 2h. The mixture was cooled, evaporated and the residue was washed with H_2O afforded the compound **2**. IR (KBr) (ν, cm^{-1}): 1755 (ν C = O), 1607 (C=N), ^{1}HNMR (DMSO – d_6): δ (ppm): 8.39 (s, 1H, ArH), 8.26 – 8.17 (m, 3H, ArH), 7.68 – 7.48 (m, 4H, ArH). MS, m/z (%): 349 ($M^{\cdot +}$, 75), 305 (20), 105 (100), 77 (100), 51 (35). Colour: white, M.P.: 173-174ºC, Yield: 80%. Anal. Calcd. For (C14H8NO2I, 349.12): C, 48.16; H, 2.31; N, 4.01. Found: C, 48.36; H, 2.40; N, 4.44.

General method for reaction of benzoxazinone 2 with nitrogen nucleophiles namely 2-aminopyridine, benzoic acid hydrazide in benzene, or in ethanol, acetic acid hydrazide in benzene or ethanol andcyanoacetic acid (3a-e).

3.2.1 2–benzamido-5–Iodo–N–(pyridin–2–yl)benzamide (3a)

A mixture of benzoxazinone **2** (0.01 mole), and 2 – aminopyridine (0.01mole) was boiled in ethanol (30 mL) for 5hr. After cooling, the reaction mixture was poured into crushed ice. The solid that was deposited was filtered off, dried, IR (KBr) (vmax, cm^{-1}): exhibits strong absorption bands at 3335 (NH), 1642, 1681 (C = O). Colour: white, M.P.: 199 - 200ºC, Yield: 55%, Recrystallized from: benzene. Anal.calcd. For $C_{19}H_{14}N_3O_2I$, 443.24): C, 51.49; H, 3.18; N, 9.48. Found: C, 51.53; H, 3.32; N, 9.52.

3.2.2N–benzoyl–2–(2,5–diphenyl–2,3–dihydro–1,3,4–oxadiazol–2–yl)amino–5–iodobenzo–hydrazide (3b)

A mixture of benzoxazinone **2** (0.01 mole), and benzoic acid hydrazide (0.01mole) in boiled benzene (20 mL) was heated under reflux for 3hr. The reaction mixture was cooled and solid that obtained was dried, and recrystallized from ethanol to give **3b**. IR (KBr) (vmax, cm^{-1}): 3200, 3400 (NH) bonded, 1631 (C = O). ^{1}H – NMR (DMSO - d_6): δ, ppm:δ7.5-7.94 (m, 18H, ArH's), 10.49 (s, 4H, NH, D_2O exchangable). Colour: brown, M.P. : 158 - 160ºC, Yield: 70%, Recrystallized

from: ethanol. Anal.calcd. for $C_{28}H_{22}N_5O_3I$, 603.41): C, 55.73; H, 3.67; N, 11.61. Found: C, 55.85; H, 3.82; N, 11.72.

3.2.3N'–(6–Iodo–4–oxo–2–phenyl–2,4-dihydro–1H–benzo[d][1,3]oxazin–2–yl)benzohydrazide (3c)

When the reaction of the benzoxazinone **2** (0.01 mole) with benzoic acid hydrazide (0.01mole) was conducted in boiling ethanol (20 mL) anstead of benzene was heated under reflux for 3hr. The reaction mixture was cooled and solid that obtained was dried, and recrystallized from ethanol to give **3c**. IR (KBr)(νmax, cm^{-1}): 3379 (NH), 1754 (C = O). ^1H – NMR (DMSO – d_6): δ, ppm: δ 7.44 - 7.99 (m, 13H, ArH), 8.50 (s, 1H, NH), 10.48 (s, 1H, NH) and 12.07 (s, 1H, NH, D_2O exchangable). Colour: gray, M.P.: 180 - 182ºC, Yield: 72%, Recrystallized from: ethanol. Anal.calcd. for $C_{21}H_{16}N_3O_3I$, 485.27): C, 51.98; H, 3.32; N, 8.66. Found: C, 46.03; H, 3.50; N, 8.72.

3.2.4N–[2–(2–acetylhydrazincarbonyl)–4–iodophenyl]benzamide (3d)

A mixture of benzoxazinone **2** (0.01 mole), and acetic acid hydrazide (0.01mole), in boiled ethanol or benzene (20 mL), was heated under reflux for 3hr. The reaction mixture was cooled and solid that obtained was dried, and recrystallized from ethanol to give **3c**. IR (KBr) (νmax, cm^{-1}): 3214, 3290, 3315 and 3434 (NH) bonded and non bonded respectively, 1678, 1621 (C = O). Colour: white, M.P.: 168 - 170ºC, Yield: 65%, Recrystallized from: ethanol. Anal.calcd. For $C_{18}H_{18}N_5O_3I$, 479.27): C, 45.11; H, 3.79; N, 14.61. Found: C, 45.23; H, 3.82; N, 14.72.

3.2.52–(5–amino–7–oxo–3–phenyl–IH-1,2,4–triazepin–4(7H)–yl)–5–iodobenzoic acid (3e)

A mixture of benzoxazinone **2** (0.01 mole), and cyanoacetic acid hydrazide (0.01 mole) in (20 mL) butanol, was heated under reflux for 3hr. The reaction mixture was cooled and solid that obtained was dried, and recrystallized from ethanol to give triazepene derivative **3e**. IR (KBr) (νmax, cm^{-1}): 2586, 3429 due to (νc=N) and (NH) and chelated OH group, 1600, 1700 (νC = O). the reaction takes place via heteroring opening at C_2 followed by cyclisation to give the desired product. Colour: white, M.P. : 138 - 140ºC, Yield: 80%, Recrystallized from: ethanol. Anal.calcd. For $C_{17}H_{13}N_4O_3I$, 448.21): C, 45.55; H, 2.92; N, 12.50. Found: C, 45.63; H, 3.02; N, 12.72.

General method of reaction of benzoxazinone 2 with glycine, o-phenylene diamine, ethylene diamine and ethanol amine (4a-d).

3.3.12–phenyl-3–carboxymethyl–5–Iodoquinazolinone (4a)

A mixture of benzoxazinone **2** (0.01 mole), and glycine (0.01mole), (0.5g) sodium acetate as catalysis in (20 mL) boiling glacial acetic acid, was heated under reflux for 6hr. 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 **4a**. IR (KBr) (νmax, cm^{-1}): 3446 (broad peak, chartarized to OH),1726,1657 (νC = O). Colour: white, M.P.: 288 - 290ºC, Yield: 62%, Recrystallized from: ethanol. Anal.calcd. For $C_{16}H_{11}N_2O_3I$, 406.17): C, 47.31; H, 2.73; N, 6.90. Found: C, 47.43; H, 2.82; N, 7.02.

3.3.2N–(2–aminophenyl)–2–benzamido–5–iodobenzamide (4b)

A mixture of benzoxazinone **2** (0.01 mole),ando–phenylene–diamine (0.01mole) in glacial acetic acid (30 mL) was refluxed for 3hr. The solid that separated out, after cooling, was filtered off, dried, and recrystallized from suitable solvent to give **4b**. IR (KBr) (νmax, cm^{-1}): 3384, 3415, 3496 due to (NH) bonded and non bonded, 1610, 1671 (C = O). Colour: white, M.P.: 180 - 182ºC, Yield: 62%, Recrystallized from: ethanol. Anal.calcd. For $C_{20}H_{16}N_3O_2I$, 457.26): C, 52.53; H, 3.53; N, 9.19. Found: C, 52.73; H, 3.62; N, 9.32.

3.3.3N–(2–aminoethyl)–2–benzamido–5–iodobenzamide (4c)

A mixture of benzoxazinone **2** (0.01 mole), and ethylene diamine (0.01mole) in glacial acetic acid (30 mL) was refluxed for 3hr. The solid that separated out, after cooling, was filtered off, dried, and recrystallized from suitable solvent to give **4c**. IR (KBr) (νmax, cm^{-1}): 3104, 3311 and 3420 due to (νNH), 1684, 1631 (νC = O). Colour: white, M.P.: 276 - 278ºC, Yield: 60%, Recrystallized from: ethanol. Anal.calcd. For $C_{16}H_{16}N_3O_2I$, 409.22): C, 46.96; H, 3.94; N, 10.27. Found: C, 47.03; H, 4.02; N, 10.72.

3.3.4 3–(2–Hydroxy–ethyl)–6–iodo–2–phenylquinazolin–4(3H)–one (4d)

A mixture of benzoxazinone **2** and ethanol amine (20 mL) and pyridine 3 drops was refluxed for 6hr. The reaction mixture was cooled and poured onto cold water. The solid that separated out, was filtered off, dried, and recrystallized from ethanol to give **4d**. IR (KBr) (νmax, cm^{-1}): 3444 (broad) due to (νNH), 1659 (νC = O). Colour: white, M.P.: 196 - 198ºC, Yield: 80%, Recrystallized from: ethanol. Anal.calcd. for $C_{16}H_{13}N_2O_2I$, 392.19): C, 49.00; H, 3.34; N, 7.14. Found: C, 49.13; H, 3.42; N, 7.22.

4 2 – Benzamido – 5 – iodobenzoylhydrazide (5)

A mixture of **2** (0.01 mole) and hydrazines namely, hydrazine hydrate, in boiling ethanol (30 mL) was refluxed for 3h. The solid seprated after concentration of ethanol was filtered off, and recrystallized from a suitable solvent to give (**5**). IR (KBr) (νmax, cm^{-1}): revealed strong absorption bands at 3300, 3250 (NH), 1685, 1640 (C = O). ^1H – NMR (DMSO – d_6): δ, ppm: δ 12.45 (br, 1H, NH), 8.48 - 8.46 (d, 1H, ArH), 8.10 (s, 1H, ArH), 7.95 – 7.88 (m, 3H, ArH), 7.78 – 7.40 (m, 3H, ArH), 5.67 (s, 1H, NH), 4.77 (br, 2H, NH, D_2O exchagable). m/z (%): 381

(M^+, 23), 287 (38), 237 (26), 173 (23), 127 (31), 77 (52), 55 (100). Colour: white, M.P. : 204 - 206 ºC, Yield: 70%, Recrystallized from: ethanol. Anal.calcd. For $C_{14}H_{12}N_3O_2I$, 381.17): C, 44.11; H, 3.17; N, 11.02. Found: C, 44.18; H, 2.99; N, 10.98.

General procedure for reaction of hydrazide 5 with aromatic aldehydes, acetic acid, formic acid, carbon di sulphid.

4.1 General procedure for preparation of compounds 7a – d:

A mixture of hydrazide **5** (0.01 mole), and aromatic aldehydes namely, benzaldehyde, 2-hydroxybenzaldehyde, 4 – methoxybenzaldehyde and 3-hydroxy-4-methoxybenzaldehyde (0.01mole) in ethanol (30 mL) was refluxed for 5hr. The reaction mixture was allowed to cool and seprated products was filtered, dried and recrystallized from ethanol to afforded the corresponding hydrazones **7a – c**.

4.1.1 N–(2 –(2–benzylidenehydrazinecarbonyl)– 4–iodophenyl)benzamide (7a)

IR (KBr) (νmax, cm^{-1}): 1646 – 1656, 1675 - 1660(C = O), and 3413 – 3440, 3273 – 3220, 3197 - 3180 (νNH)**.** Colour: white, M.P. : 162 - 164ºC, Yield: 65%, Recrystallized from: ethanol. Anal.calcd. For $C_{21}H_{16}N_3O_2I$, 469.28): C, 53.75; H, 3.44; N, 8.95. Found: C, 53.80; H, 3.50; N, 9.02.

4.1.2N-(2-(2-(2-hydroxy-benzylidene)hydrazinecarbonyl)-4-iodophenyl)benzamide (7b).

IR (KBr) (νmax, cm^{-1}): 1656 and 3446 (νC=O) and (νOH), Mass m/e: 485(M+2), (100%). ^1H – NMR (DMSO – d_6): δ, ppm: δ 12.27 – 11.00 (s, 3H,2NH), 8.68- 6.9 (m, 13H, ArH'S), 4.26 (s, 1H, OH). Colour: white, M.P.: 148 - 150ºC, Yield: 70%, Recrystallized from: ethanol. Anal.calcd. for $C_{21}H_{16}N_3O_3I$, 485.27): C, 51.98; H, 3.32; N, 8.66. Found: C, 52.03; H, 3.41; N, 8.71.

4.1.3N-(2-(2-(2-hydroxy-4-methoxybenzylidene)hydrazinecarbonyl)-4-iodophenyl)benzamide (7c).

IR (KBr) (νmax, cm^{-1}): revealed strong absorption bands in the region 1675-1639 (ν C=O) and 3422 (ν OH), Mass (m/e): 515 (M+1), (100). ^1H – NMR (DMSO – d_6): δ, ppm: δ3.8(s,3H,OCH_3),5.6 (s, 1H,NH,D_2O exchangable), 7.02-8.46 (m,8H,ArH and azamethine proton), 11.95 (s,1H,2NH), 9.59-9.87(s,2H, OH). Colour: white, M.P. : 223 - 225ºC, Yield: 65%, Recrystallized from: benzene. Anal.calcd. For $C_{22}H_{18}N_3O_4I$, 515.30): C, 51.28; H, 3.52; N, 8.15. Found: C, 51.34; H, 3.64; N, 8.23.

4.1.4 N – (4 – iodo - 2 – (2 - (4 – methoxybenzylidene) phenyl) benzamide (7d)

IR (KBr) (νmax, cm^{-1}): revealed strong absorption band at 1674(ν C=O) and 3424 (ν NH), Mass (m/e): 499(100%). ^1H – NMR (DMSO – d_6): δ, ppm: δ11.93 (s.1H,NH), 12.01(s, 1H, NH), 7.02-8.46(m,13H, ArH), 3.29-3.30(d, 1H,OCH_3). Colour: white, M.P.: 220 - 222ºC, Yield: 70%, Recrystallized from: ethanol. Anal.calcd. for $C_{22}H_{18}N_3O_3I$, 499.30): C, 52.92; H, 3.63; N, 8.42. Found: C, 53.02; H, 3.70; N, 8.50.

4.2 N–(4–Iodo–2–(5– methyl – 1, 3, 4 – oxadiazol – 2 – yl) phenyl) benzamide (8)

A mixture of compound **5** (0.01 mole), and acetic anhydride (15mL) was refluxed for 3hr. After cooling, the reaction mixture was poured into water. The solid obtained was washed with water several times and crystallized from ethanol to afford **8**. IR (KBr) (νmax, cm^{-1}): Strong peak at 1755 (νC = O), and devoid any band for (νNH). Colour: white, M.P.: 204 - 206ºC, Yield: 55%, Recrystallized from: ethanol. Anal.calcd. for $C_{16}H_{12}N_3O_2I$, 405.19): C, 47.43; H, 2.99; N, 10.37. Found: C, 47.48; H, 3.03; N, 10.45.

4.3 6 N-(6– iodo–4 – oxo– 2– phenylquinazolin–3(4H)–yl)formamide (9)

A mixture of compound **5** (0.01 mole), and formic acid (20 mL) was refluxed for 3hr. After cooling, the reaction mixture was poured into water. The solid obtained and crystallized from ethanol to afford **9**. IR (KBr) (νmax, cm^{-1}): 1700, 1647 (νC = O), and 3429, 3112 for (νNH). ^1H – NMR (DMSO – d_6): δ, ppm: δ 12.05 (s, 1H, NH), 8.52 – 7.55 (m, 9H, ArH, C=OH). Colour: brown, M.P.: 242 - 244ºC, Yield: 70%, Recrystallized from: benzene. Anal.calcd. for $C_{15}H_{10}N_3O_2I$, 391.16): C, 46.06; H, 2.58; N, 10.47. Found: C, 46.15; H, 2.64; N, 10.52.

4.4 N–[4–iodo–2–(5–thioxo–4,5–dihydro–1,3,4–oxodiazol–2–yl)phenyl]benzamide (10)

A mixture of compound **5** (0.01 mole), and carbon disulphid (0.01 mole), and (0.5g) potassium hydroxide as abase was boiled in (20mL) ethanol for 6hr. Inwater bath. The reaction mixture was poured into peaker to evaporate the solvent, after concentration the solid seprated , crystallised from ethanol to give **10**. IR (KBr) (νmax, cm^{-1}): 1617, 1652, 3390, 3281 for (νC = N), (νC = O) and (νNH) respectively. ^1H – NMR (DMSO – d_6): δ, ppm: δ 4.13 (s, 1H, NH, D_2O exchangable), 7.57 – 8.62 (m, 8H, ArH), 12.12 (s, 1H, NH, D_2O exchangable). Mass EIMS showed (m/z) 426 (M^++2), (100%). Colour: green, M.P.: 209 - 212ºC, Yield: 65%, Recrystallized from: Methanol/ Ethanol. Anal.calcd. for $C_{15}H_{10}IN_3O_2S$, 423.23): C, 42.57; H, 2.38; N, 9.93. Found: C, 42.61; H2.46; N, 10.09.

5 3 –Amino–6–iodo–2–phenyquinazolin–4–one (6)

A mixture of **2** (0.01 mole) and hydrazines namely, hydrazine hydrate, in boiling butanol (30 mL) was refluxed for 5hr. The solid seprated after concentration of butanol was filtered off, and recrystallized from a suitable solvent to give (**6**). IR (KBr) (νmax, cm^{-1}): 3310, 3270 (NH), 1665 (C = O). ^1H – NMR (DMSO – d_6): δ, ppm: δ 8.46 – 8.45 (d,

1H, ArH), 8.13 - 8.12 (d, 1H, ArH), 7.82 – 7.79 (m, 2H, ArH), 7.52 – 7.44 (m, 4H, ArH), 5.67 (s, 2H, NH_2). M/z (%): 363 (M^+, 2), 349 (9), 285 (2), 105 (100). Colour: white, M.P.: 146 - 148ºC, Yield: 75%, Recrystallized from: Toluene/Ethanol. Anal.calcd. for $C_{14}H_{10}N_3OI$, 363.15): C, 46.30; H, 2.77; N, 11.57. Found: C, 46.48; H, 2.80; N, 11.62.

General method for reaction of aminoquinazolinone 6 with cyclohexanone, furan derivative, phthalic anhydride, acetic anhydride, aromatic aldehydes (15a-c).

5.1 3–(cyclohexylideneamino)–6–iodo–2–phenylquinazolin–4(3H)–one (11)

A mixture of compound **6** (0.01 mole), and cyclohexanone (0.01mole) in boiled benzene (20 mL) was refluxed for 3hr. The reaction mixture was cooled, Tthe solid that separated out, was filtered off, dried, and recrystallized from ethanol to give **11**. IR (KBr) (νmax, cm^{-1}): 1671 (νC = O) and devoid any band for νNH. Colour: white, M.P.: 118 - 120ºC, Yield: 52%, Recrystallized from: benzene. Anal.calcd. for $C_{20}H_{18}N_3OI$, 443.28): C, 54.19; H, 4.09; N, 9.48. Found: C, 54.24; H, 4.12; N, 9.55.

5.2 2–Methyl–5–(1,2,3,4–tetrahydroxy–butyl)–furan–3–carboxylicacid(6– iodo–2– phenyl–4–oxo–4H–quinazolin– 3–yl)amide (12)

A mixture of compound **6** (0.01 mole), and 2 – methyl – 5 – (1, 2, 3, 4 – tetrahydroxy – butyl) – furan – 3 – carboxylic acid ethyl ester (0.01mole) in a bsolute ethanol (25 mL) was refluxed for 6hr. After cooling, the collected solid crystallized from ethanol to afford quinazolinone derivative **12**. IR (KBr) (νmax, cm^{-1}): 1680, 3123, 3196, 3270, 3327, 3382, 3441 attributed to ν C=O, νNH and νOH. ^1H – NMR (DMSO – d_6): δ, ppm: δ 12.40 – 10.24 (s, 2H, NH), Mass (m/z): 591(M+1),(100%). Colour: brown, M.P.: 198 - 200ºC, Yield: 60%, Recrystallized from: ethanol. Anal.calcd. for $C_{24}H_{30}N_3O_7I$, 599.42): C, 48.09; H, 5.04; N, 7.01. Found: C, 48.23; H, 5.18; N, 7.12.

5.3 2-[(6-iodo-4-oxo-2-phenyl-quinazolin-4(3H)-yl) carbamoyl]benzoicacid (13).

A mixture of compound **6** (0.01 mole), and phthalic anhydride (0.01mole) in acetic acid anhydride (10 mL) and glacial acetic acid (10 mL) was heated under reflux for 3hr. The reaction mixture was allowed to cool then poured into water. The solid was seprated out filtered off, dried, and recrystallized from ethanol to afford **13**. IR (KBr) (νmax, cm^{-1}): 1628, 1664 (νC = O), 3212, 3308, 3420 attributed to νNH and νOH respectively. Colour: brown, M.P.: 164 - 166ºC, Yield: 70%, Recrystallized from: ethanol. Anal.calcd. For $C_{22}H_{14}N_3O_4I$, 511.27): C, 51.68; H, 2.76; N, 8.22. Found: C, 51.76; H, 2.84; N, 8.36.

5.4 N–acetyl–N–(6–iodo–4–oxo–2–phenylquinazolin–3(4H)–yl)acetamide (14)

A mixture of compound **6** (0.01 mole), and acetic anhydride (15mL) was refluxed for 3hr. After cooling, the reaction mixture was poured into water. The solid obtained was washed with water several times and crystallized from ethanol to afford **14**. IR (KBr) (νmax, cm^{-1}): 1698, 1743(νC = O) and devoid any band for νNH. Colour: white, M.P.: 139 - 141ºC, Yield: 55%, Recrystallized from: ethanol. Anal.calcd. for $C_{18}H_{14}N_3O_3I$, 447.23): C, 48.34; H, 3.16; N, 9.40. Found: C, 48.55; H, 3.28; N, 9.62.

5.5.1 General procedure for preparation of compounds 15a – c:

A mixture of compound **6** (0.01 mole), and aromatic aldehydes namely, salicyaldehyde, anisaldehyde and vaniline (0.01mole) in ethanol (30 mL) was refluxed for 5hr. The reaction mixture was allowed to cool and seprated products was filtered, dried and recrystallized from ethanol to produce schiff bases **15a** &**15b** and **15c** respectively.

5.5.2 3–(2–hydroxybenzylideneamino)–6–iodo–2–phenylquinazolin–4(3H)–one (15a)

IR (KBr) (νmax, cm^{-1}): 1673 (νC=O) and 3329, 2915 (νOH). M/z (%): 467 (M^+, 3), (100%), ^1H – NMR (DMSO – d_6): δ, ppm: δ4.29 (s,1H,OH), 6.87-8.5 (m, 12H,ArH). Colour: white, M.P.: 213 - 215ºC, Yield: 70%, Recrystallized from: ethanol. Anal.calcd. for $C_{22}H_{14}N_3O_2I$, 467.26): C, 53.98; H, 3.02; N, 8.99. Found: C, 54.05; H, 3.20; N, 9.08.

5.5.33–(4–methoxybenzylideneamino)–6–iodo–2–phenylquinazolin–4(3H)–one (15b)

IR (KBr) (νmax, cm-1): 1671.02(νC = O). Mass, m/z (%): 481 (M^+, 1), 481 ((100%). Colour: white, M.P. : 224 - 226ºC, Yield: 75%, Recrystallized from: ethanol. Anal.calcd. for $C_{22}H_{16}N_3O_2I$, 481.29): C, 54.90; H, 3.35; N, 8.73. Found: C, 55.00; H, 3.42; N, 8.81.

5.5.43–(4–methoxy–3–hydroxybenzylidene–amino)–6–iodo–2–phenylquinazolin – 4(3H) – one (15c)

IR (KBr) (νmax, cm-1): revealed strong absorption bands in the region 1661, 1666 (νC = O), and 3424 (νOH).Mass (m/e): 497,(100%). ^1H – NMR (DMSO – d6): δ, ppm: δ 3.82 (s, 1H, OCH_3, D_2O exchangable), 7.03 – 8.80 (m, 7H, ArH and azamethine proton), 8.14(s, 1H, OH). Colour: white, M.P.: 230 - 232ºC, Yield: 75%, Recrystallized from: ethanol. Anal.calcd. for $C_{22}H_{16}N_3O_3I$, 497.29): C, 53.14; H, 3.24; N, 8.45. Found: C, 53.23; H, 3.32; N, 8.52.

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4/6/2016