

Reactivity of 2-Ethoxyquinazolin- 4-yl hydrazine and its Use in Synthesis of Novel Quinazoline Derivatives of Antimicrobial Activity

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Abstract: The reactions of 2-ethoxy-4-hydrazinoquinazoline 2 with diethyl oxalate and ethyl chloroacetate gave 6-ethoxy-2*H*-[1,2,4] triazino [4,3-*c*] quinazoline-3,4-dione 3 and 6-ethoxy-2,3-dihydro-4*H*-[1,2,4] triazino [4,3-*c*] quinazolin-4-one 4 respectively. A series of 5-ethoxy-2-*X*-[1, 2, 4] triazolo [1, 5-*c*] quinazolines 5a-d was also produced by reacting 2 with the acid chlorides namely: benzoyl, crotonyl, cinnamyl and 2-furoyl chlorides via Dimroth rearrangement. Also, 2 reacted with ethyl chloroformate giving 6. Condensation of 2 with acetone gave Schiff base 7, and with monosaccharides gave the sugar hydrazones 8a-e which was thereafter acetylated giving the corresponding 9a-e. Cyclization of 8a-e by iron(III) chloride gave triazoloquinazolines 10a-e acyclic *C*-nucleosides which, by acetylation, afforded 11a-e. All products were confirmed by elemental, IR, MS, and ¹H-NMR analysis. Products 8-11 were chosen for biological screening test against gram (+ ive) and gram (- ive) bacteria.

Keywords: Iminamine, Triazoloquinazoline, Sugar Hydrazones, *C*-Nucleosides

1. Introduction

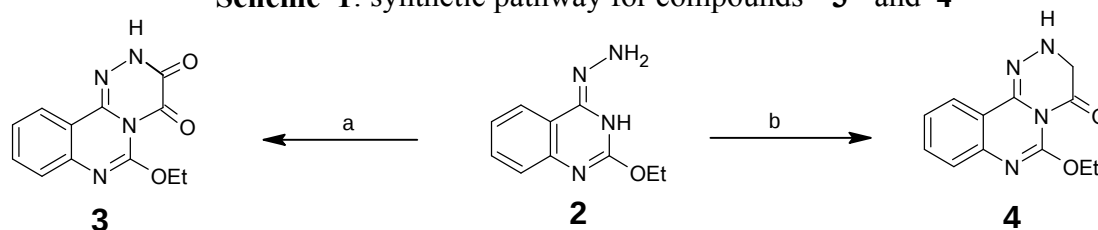
Quinazolines are a big family of heterocyclic compounds, which have shown broad variety of biological activity profiles, e. g. analgesic, antiinflammatory, antipyretic [1, 2], antimicrobial [3], anticonvulsant [4], anticancer [5], antitumoral [6], antihypertensive [7], antimalarial [8], diuretic [9], antidiabetic [10], antihistamine/sedative [11], antibiotic [12] and many others. Heterocycle-bearing *N*-glycosides are well known to play a significant role as inhibitors. An example is the tetrazole-bearing *N*-glycosides used as SGLT2 inhibitors [13], where their hypoglycemic activity is tested *in vivo* by mice oral glucose tolerance test (OGTT). Moreover, sugar hydrazones exhibit remarkable biological activity [14]. Herein we report the synthesis of hydrazones of *D*-exoses and *D*-pentoses with 4-hydrazinoquinazoline and the screening of their antimicrobial potentials.

2. Result and Discussion

Recently, it was reported that 4-substituted-aminoquinazolines are exploited as potent antitumor compounds [15]. The 4-hydrazinoquinazolines resemble primary amines in being good substrates for aldehydes, ketones, alkyl and acid halides, anhydrides, etc. Therefore, they play a significant role in the synthesis of biologically active products [16]. The tautomeric behavior of hydrazinoquinazoline is used whenever necessary. For example, any necessary cyclization prior to product formation requires the presence of iminamine rather than hydrazine - form (Chart 1).

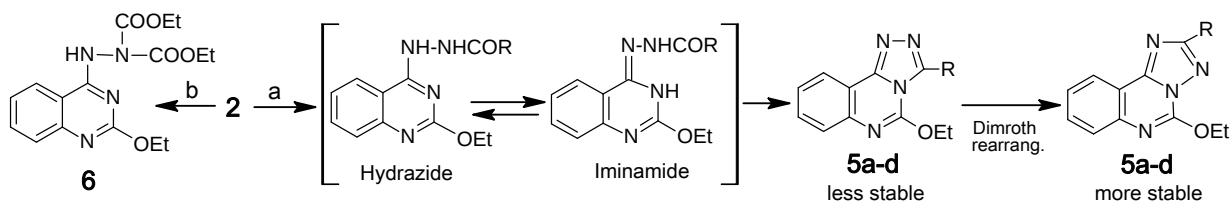
Chart 1: Tautomeric phenomenon of compound **2**

Compound **2** reacted with diethyl oxalate and with ethyl chloroacetate in boiling ethanol to giving products **3** and **4** respectively (Scheme 1). The reaction possibly started with a nucleophilic attack of NH_2 of hydrazine moiety on $\text{C}=\text{O}$ of the ester group through a tetrahedral mechanism intermediate to yield a fleeting acyl derivative followed by 1,3-tautomerism and ring closure via $\text{S}_\text{N}2$ mechanism.

Scheme 1: synthetic pathway for compounds **3** and **4**

(a) $\text{EtOOC-COOEt} / \text{EtOH}$; (b) $\text{Cl-CH}_2\text{COOEt} / \text{EtOH}$.

Similarly, compound **2** was reacted with acid halides namely: benzoyl, crotonyl, cinnamyl and furoyl chlorides in dry CHCl_3 and K_2CO_3 giving the 2-acyl-1-(2-ethoxyquinazolin-4-yl)hydrazine derivatives, which tautomerized into the iminamide form upon heating and then underwent cyclization and Dimroth rearrangement affording the more stable derivatives **5a-d** respectively (Scheme 2). Compound **2** was also reacted with ethyl chloroformate in dry pyridine affording derivative **6**.

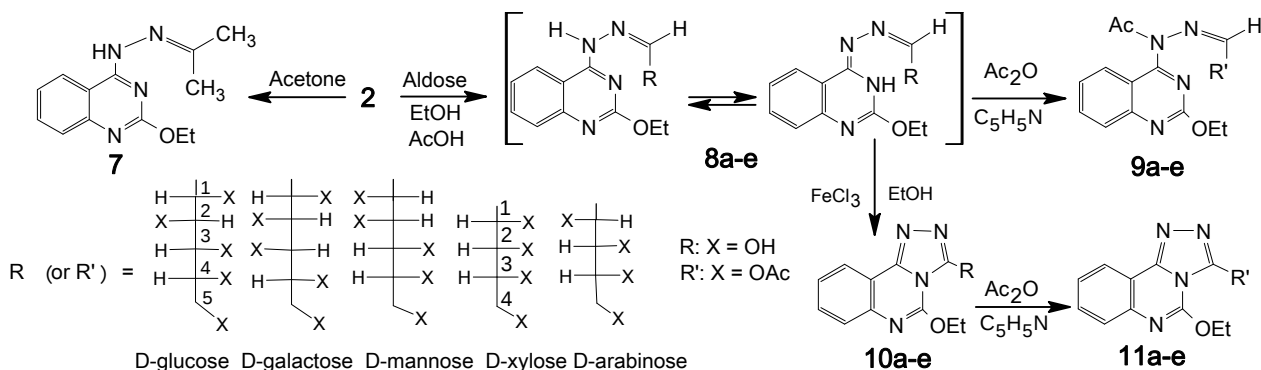
Scheme 2: synthetic pathway for compounds **5a-d**

(a) $\text{RCOCl} / \text{CHCl}_3 / \text{K}_2\text{CO}_3$; R: - Ph; - $\text{CH}=\text{CH-CH}_3$; - $\text{CH}=\text{CH-Ph}$; furan-2-yl; (b) $\text{ClCOOEt} / \text{pyridine}$.

Compound **2** was reacted with acetone affording derivative **7**, whose mass spectrum showed a molecular ion peak at m/z 244,246 whereas the ^1NMR spectrum showed a singlet at δ 2.40 ppm characteristic for CH_3 groups of the hydrazone. A number of sugar hydrazones **8a-e** were prepared by condensation of compound **2** with equimolar amounts of D-aldohexoses and D-aldopentoses namely: glucose, galactose, mannose, xylose and arabinose, respectively in boiling ethanol and drops of acetic acid as a catalyst (Scheme 3). Their IR spectra revealed characteristic absorption bands at $3459\text{-}3135\text{ cm}^{-1}$ attributed to OH and NH groups. Acetylation of these hydrazones **8a-e** by acetic anhydride in pyridine at room temperature afforded the corresponding per-acetyl products **9a-e**, whose IR spectra revealed disappearance of the bands of OH groups and appearance of absorption bands in the carbonyl group frequency region at $1711\text{-}1725\text{ cm}^{-1}$ and $1673\text{ - }1692\text{ cm}^{-1}$ due to the OAc and NAc groups, respectively. The $^1\text{H-NMR}$ spectra showed signals corresponding to O-acetyl groups in addition to NAc groups; whereas no signals could be found for NH groups confirming that per-O- and N-acetylation had taken place. The

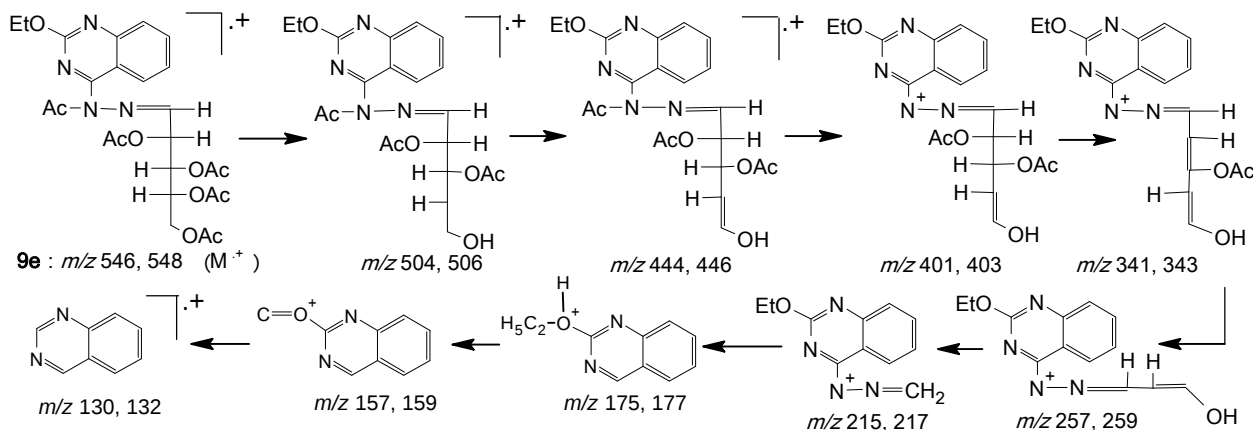
spectra also confirmed the presence of the HC=N proton as a doublet at δ 6.55-6.74 ppm low field in addition to the rest of alditol-1-yl side chain.

Scheme 3: synthetic pathway for compounds 7 - 11



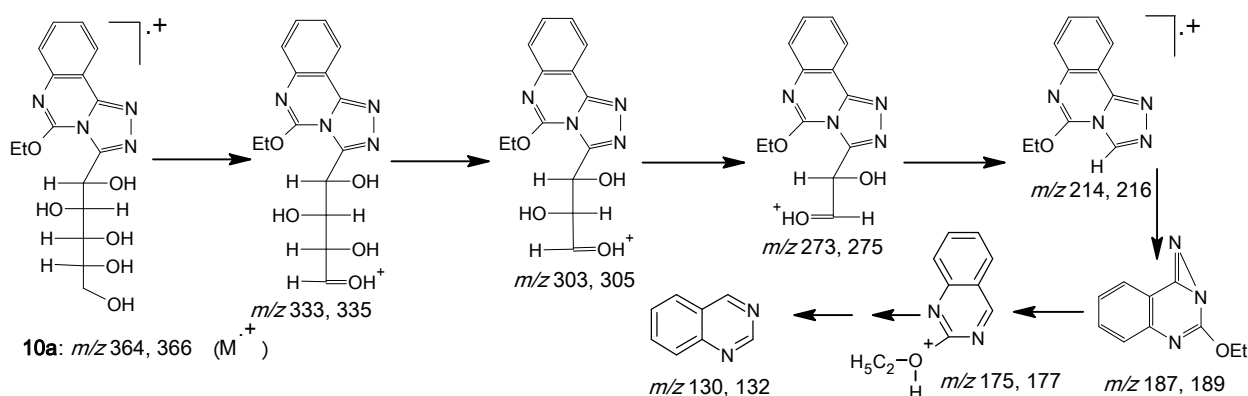
The mass spectral data of 9e showed a molecular ion peak at m/z 546, 548 which agreed with the molecular formula $C_{25}H_{30}N_4O_{10}$. The ion at m/z 215, 217 confirmed a loss of sugar residue from the molecular ion. The fragment at m/z 175, 177 referred to quinoxaline ring (Scheme 4).

Scheme 4: MS data interpretation of compound 9a



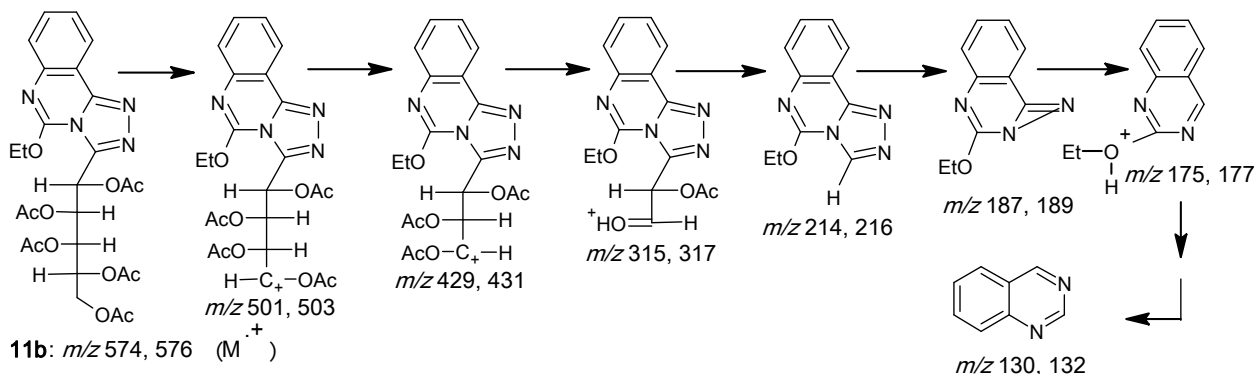
The oxidative cyclization of the hydrazones 8a-e with ethanolic iron (III) chloride afforded the triazolo[4,3-a]quinoxalines 10a-e. The oxidation must have taken place by an electrophilic attack of the hard acid site of ferric chloride on the hardest basic site of sugar hydrazones 8a-e followed by an elimination of hydrogen chloride and formation of possibly a nitrilimine that undergoes 1,5-electrocyclization to give 10a-e. The IR spectra showed bands at 3240-3488 cm^{-1} (OH) and the mass spectral data of 10a showed a molecular ion peak at m/z 364 and 366 and an ion peak at m/z 214 and 216 presumably attributable to the triazoloquinoxaline ring (Scheme 5).

Scheme 5: MS data interpretation of compound 10a



The ^1H -NMR spectrum of compound 10c showed a doublet at low field at δ 5.22 ppm assigned to H-1, followed by the rest of the alditol-1-yl chain at higher field. The spectrum of 10e is similar, showing a doublet at low field at δ 5.03 ppm for H-1. Acetylation of 10a-e by acetic anhydride in pyridine at room temperature gave polyacetoxyalkyl derivatives 11a-e, whose IR spectra showed only one absorption band in the C=O frequency region (OA). The OAc groups were confirmed by the ^1H -NMR spectra showing singlets at δ 2.03-2.19. The doublets at δ 5.74-6.02 were attributed to H-1. The mass spectra of products 11b and 11d showed molecular ion peaks at m/z 574, 576 and 501, 503 (Scheme 6) which, on combination with the elemental analysis, led to the assignment of their molecular formulas $\text{C}_{26}\text{H}_{30}\text{N}_4\text{O}_{11}$ and $\text{C}_{23}\text{H}_{26}\text{N}_4\text{O}_9$ respectively. In addition, the characteristic fragment at m/z 214,216 was shown attributable to the triazoloquinazoline ring.

Scheme 6: MS data interpretation of compound 11b



2.1 Antimicrobial Activity

All compounds were screened for their antimicrobial activity. Compounds 8-11 were tested against gram-positive bacteria *Staphylococcus aureus*, *Streptobacillus moniliformis* and *Bacillus subtilis* and gram-negative bacteria *E. coli*, *Streptobacillus moniliformis* and *Pseudomonas aeruginosa* species applying the agar plate diffusion method. The screening results (Table 1) indicated that all the tested products exhibited antimicrobial activities against one or more type of bacteria. Almost all triazoloquinazoline products 10a-e and 11a-e showed more inhibition against the gram positive bacteria specially *Streptobacillus* than the gram negative one.

<Table 1>

2.2 Experimental

All melting points recorded are uncorrected. The IR spectra were recorded on a Pye Unicam SP1200 spectrophotometer using KBr wafer technique. The ^1H -NMR spectra were determined on a Varian FT-200 or Bruker AC-200 MHz instrument using TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. The mass spectra were determined using MP model NS-5988 and Shimadzu single focusing mass spectrometer (70 eV). All the solvents used were of HPLC/AnalaR grade. All reagents were used as received from Alfa Aesar.

Synthesis of 2-Ethoxyquinazolin-4-ylhydrazine 1.

An emulsion of 4-chloro-2-ethoxyquinazoline 1 (0.01mol) and hydrazine hydrate (0.05 mol) in benzene (15 mL) was stirred for 2h. The benzene-insoluble gum obtained was treated and washed with water, dried and crystallized from ethanol affording reddish brown crystals of product 2. Evaporation of solvent from the benzene-soluble fraction afforded a residue which was rinsed with water and air dried. Crystallization of the residue from absolute ethanol afforded product 2.

2-Ethoxyquinazolin-4-ylhydrazine 2.

Yield 68%; m. p. 156-158°C. *Anal.* for $C_{10}H_{12}N_4O$ (M. wt. 204); Found: C, 58.86; H, 5.78; N, 27.45; Calcd: C, 58.82; H, 5.88; N, 27.45; IR ν (cm^{-1}) 1620 (C=N), 3160 (NH), 3250, 3300 (NH₂); MS: m/z $[M+H]^+$ 204; ¹H-NMR (DMSO- d_6) δ 1.18 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 4.19 (q, 2H, CH₂ of ethoxy J = 7.4), 4.95 (br. s, 3H, NH and NH₂), 7.43 - 8.08 (m, 4H, ArH).

6-ethoxy-2H-[1,2,4]triazino[4,3-c]quinazoline-3,4-dione 3.

A mixture of 2 (2.04 g, 0.01 mol) and diethyl oxalate (1.46 g, 0.01 mol) in boiling ethanol (30 mL) was heated under reflux for 10 h. After cooling the separated solid was collected and recrystallized from THF to give white crystals of 3; m. p. 237-239 °C; yield 58 %. *Anal.* for $C_{12}H_{10}N_4O_3$ (M. wt. 258); Found: C, 54.21; H, 3.56; N, 21.89; Calcd: C, 55.81; H, 3.88; N, 21.71; IR ν (cm^{-1}) 1680-1690 (C=O), 3275 (sec NH); MS: m/z $[M+H]^+$ 258 (77%). ¹H-NMR (DMSO- d_6) δ 1.21 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 4.38 (q, 2H, CH₂ of ethoxy J = 7.4), 7.21 - 8.13 (m, 5H, ArH and NH), 10.20 (s, 1H, NH, exchangeable).

6-ethoxy-2H-[1,2,4]triazino[4,3-c]quinazolin-3(4H)-one 4.

A mixture of 2 (2.04 g, 0.01 mol) and ethyl chloroacetate (1.22 g, 0.01 mol) in boiling ethanol (35 mL) was heated under reflux for 10 h. The solid that separated after cooling was recrystallized from dioxane affording light brown crystals of 4; m. p. 213-216 °C; yield 58 %. *Anal.* for $C_{12}H_{12}N_4O_2$ (M. wt. 244); Found: C, 58.85; H, 4.53; N, 23.02; Calcd: C, 59.02; H, 4.92; N, 22.95; IR ν (cm^{-1}) 1675 (C=O), 2993 (CH), 3312 (sec NH); MS: m/z $[M+H]^+$ 244; ¹H-NMR (DMSO- d_6) δ 1.19 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 3.94, 4.30 (m, 2H, CH₂CO), 4.30 (q, 2H, CH₂ of ethoxy J = 7.4), 7.01 - 8.31 (m, 5H, ArH and NH of triazine), 9.96 (s, 1H, NH, exchangeable).

Synthesis of 5-ethoxy-2-substituted[1,2,4]triazolo[1,5-c]quinazoline 5a-d.

To a solution of derivative 2 (0.01mol) in dry chloroform (100 mL) containing anhydrous K₂CO₃ (1g) the acid chloride namely: benzoyl, crotonyl, cinnamyl and furoyl chlorides (0.015 mol) was added slowly. After the addition was complete, the mixture was stirred at room temperature for 30 min and then heated on a steam bath for 1h. The mixture was filtered, evaporated and the crude product was collected and crystallized from the proper solvent affording product 5a-d.

5-Ethoxy-2-phenyl[1,2,4]triazolo[1,5-c]quinazoline 5a.

Colorless needles from ethanol; m. p. 168 -170°C; yield 68%. *Anal.* for $C_{17}H_{14}N_4O$ (M. wt. 290); Found: C, 70.17; H, 4.91; N, 19.38; Calcd: C, 70.34; H, 4.83; N, 19.31; IR ν (cm^{-1}) 1622 (C=N), 3050 (CH); MS: m/z $[M+H]^+$ 290 (32.2), 292 (12.3), 214 (100), 216 (23.5), 174 (43.8), 176 (8.2), 78 (13.2), 80 (0.3); ¹H-NMR (DMSO- d_6) δ 1.19 (t, 3H, CH₃ of ethoxy J = 7.4), 4.33 (q, 2H, CH₂ of ethoxy J = 7.4), 7.57-8.10 (m, 5H, phenyl), 7.62 - 8.65 (m, 4H, ArH).

5-Ethoxy-2-[(1E)-prop-1-en-1-yl][1,2,4]triazolo[1,5-c]quinazoline 5b.

Brown white crystals from ethanol; m. p. 223-225 °C; yield 71%. *Anal.* for $C_{14}H_{14}N_4O$ (M. wt. 254); Found: C, 66.28; H, 5.31; N, 22.23; Calcd: C, 66.14; H, 5.51; N, 22.05; IR ν (cm^{-1}) 1635 (C=N), 3050 (CH); MS: m/z $[M+H]^+$ 254 (48.2), 256 (14.2), 174 (100), 176 (38.1); ¹H-NMR (DMSO- d_6) δ 1.21 (t, 3H, CH₃ of ethoxy J = 7.4), 1.67 (t, 3H, CH₃), 4.31 (q, 2H, CH₂ of ethoxy J = 7.4 Hz), 6.13 (d, H, CH_{trans}), 6.70 (d, H, CH_{trans}), 7.53 - 8.21 (m, 4H, ArH).

5-Ethoxy-2-[(E)-2-phenylethenyl][1,2,4]triazolo[1,5-c]quinazoline 5c.

Off-white crystals from ethanol; 153 - 155 °C; yield 62%. *Anal.* for $C_{19}H_{16}N_4O$ (M. wt. 316); Found: C, 72.84; H, 5.19; N, 17.76; Calcd: C, 72.15; H, 5.06; N, 17.72; IR ν (cm^{-1}) 1633 (C=N), MS: m/z $[M+H]^+$ 316 (29.3), 318 (12.8), 174 (100), 176 (41.1), 103 (12.7), 105 (0.8); ¹H-NMR (DMSO- d_6) δ 1.2 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 4.38 (q, 2H, CH₂ of ethoxy J = 7.4), 7.09, 7.48 (2d, 2H, of two olefin protons), 7.4-7.6 (m, 5H, PhH), 7.67-8.71 (m, 4H, quinazoline).

5-Ethoxy-2-(furan-2-yl)[1,2,4]triazolo[1,5-c]quinazoline 5d.

White crystals from benzene; 163-164°C; yield 68%. *Anal.* for $C_{15}H_{12}N_4O_2$ (M. wt. 280); Found: C, 64.38; H, 4.31; N, 20.07; Calcd: C, 64.29; H, 4.29; N, 20.00; IR ν (cm^{-1}) 1619 (C=N), MS: m/z $[M+H]^+$ 280 (33.2), 282

(12.4), 174 (100), 176 (31.3), 60 (0.8), 61 (0.1); $^1\text{H-NMR}$ (DMSO- d_6) δ 1.2 (t, 3H, CH_3 of ethoxy $J = 7.4\text{Hz}$), 4.2 (q, 2H, CH_2 of ethoxy $J = 7.4$), 6.79(dd, 1H, $J = 3.6\text{Hz}$, $J = 1.6$, Furan-H), 7.29(d, 1H, $J = 4.4\text{Hz}$, Furan-H), 7.76(d, 1H, $J = 1.6\text{Hz}$, Furan-H), 7.5 - 8.2 (m, 4H, ArH).

1-(2-Ethoxyquinazolin-4-yl)-2-bis(ethoxycarbonyl) hydrazine 6.

A mixture of 2 (0.01 mol) and ethyl chloroformate (0.02 mol) in dry pyridine (20 mL) was heated at boiling water bath for 4 h. The solvent was evaporated under vacuum, the residue was cooled and crystallized from ethanol giving colorless needles of 6; m.p. 123-125 °C; yield 52 %. *Anal.* $\text{C}_{16}\text{H}_{20}\text{N}_4\text{O}_5$ (M.wt. 348); Found: C, 55.27; H, 5.83; N, 16.08; Calcd: C, 55.17; H, 5.75; N, 16.09; IR ν (cm^{-1}) 1250 (C-O), 1622 (C=N), 1731 (C=O), 2986 (C-H); MS: m/z $[\text{M}+\text{H}]^+$ 348 (31.5), 350 (14.1), 275 (2.8), 277 (13.2), 187 (0.8), 189 (0.2), 174 (100), 176 (39.4), 74 (0.7), 75(0.1); $^1\text{H-NMR}$ (DMSO- d_6) δ 1.11-1.25 (t, 9H, 3 CH_3 of ethoxy), 4.15-4.25(q, 6H, 3 CH_2 of ethoxy), 8.5-8.8(m, 4H, ArH), 10.05(s, 1H, NH).

2-ethoxy-4-hydrazinoquinazoline Acetone hydrazone 7.

A solution of crude 2 (0.01 mol) in acetone was left to stand for several days when the solvent had evaporated to give a solid from which the hydrazone 7 (80%) was isolated by chromatography on silica gel (30 g, 2.5% absolute ethanol-chloroform). Crystallization from hexane gave product 7 as colorless solid that turned deep yellow on exposure to light and air; m. p. 115 -116 °C; yield 85 %. *Anal.* for $\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}$ (M. wt. 244); Found: C, 63.98; H, 6.61; N, 22.95; Calcd: C, 63.93; H, 6.56; N, 22.95; IR ν (cm^{-1}) 1634 (C=N), 2993 (CH), 3243 (sec NH); MS: m/z $[\text{M}+\text{H}]^+$ 244 (33.1), 246 (12.6), 215 (100), 217 (19.6), 174 (55.8), 176 (1.2); $^1\text{H-NMR}$ (DMSO- d_6) δ 1.13 (t, 3H, CH_3 of ethoxy $J = 7.4$), 2.4 (3H, s, $-\text{N}=\text{C}-\text{CH}_3$), 4.23(q, 2H, CH_2 of ethoxy $J = 7.4$), 7.1-8.3(m, 4H, ArH), 8.3(br. s, 1H, NH).

General procedure for the synthesis of sugar (2-ethoxyquinazolin-4-yl) hydrazones 8a-e.

To a suspension of 2-Ethoxy-4-hydrazinoquinazoline 2 (0.01 mol) in ethanol (30 ml), was added a solution of selected sugar (D-glucose, D-galactose, D-mannose, D-xylose and D-arabinose (0.01 mol)) in water (10 ml) and few drops of glacial acetic acid. The mixture was heated under reflux until reaction was judged complete by TLC (2-6 h). The solid product formed upon cooling was filtered off, washed with the minimum amount of ethanol, dried and finally crystallized from ethanol to afford the corresponding hydrazones 8a-e.

2-ethoxy-4-hydrazinoquinazoline-D-glucose hydrazone 8a.

Yield 62 % (from ethanol); m. p. 212 - 214 °C; *Anal.* for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_6$ (M. wt. 366); Found: C, 52.66; H, 6.16; N, 15.41; Calcd: C, 52.46; H, 6.01; N, 15.30; IR ν (cm^{-1}) 1615 (C=N), 3225 - 3417 (OH, NH); MS: m/z $[\text{M}+\text{H}]^+$ 366; $^1\text{H-NMR}$ (DMSO- d_6) δ 1.17 (t, 3H, CH_3 of ethoxy $J = 7.4$), 4.17 (q, 2H, CH_2 of ethoxy $J = 7.4$), 7.1- 8.3 (m, 4H, ArH), 8.33 (br. s, 1H, NH).

2-ethoxy-4-hydrazinoquinazoline-D-galactose hydrazone 8b.

Yield 88% (from DMF/ethanol); m. p. 193-195 °C; *Anal.* for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_6$ (M. wt. 366); Found: C, 52.56; H, 6.23; N, 15.48; Calcd: C, 52.46; H, 6.01; N, 15.30; IR ν (cm^{-1}) 1615 (C=N), 3135-3391 (OH and NH); MS: m/z $[\text{M}+\text{H}]^+$ 366; $^1\text{H-NMR}$ (DMSO- d_6) δ 1.13 (t, 3H, CH_3 of ethoxy $J = 7.4$ Hz), 4.21 (q, 2H, CH_2 of ethoxy $J = 7.4$), 7.3 - 8.2 (m, 4H, ArH), 8.37 (br. s, 1H, NH).

2-ethoxy-4-hydrazinoquinazoline-D-mannose hydrazone 8c.

Yield 77% (from DMF/ethanol); m. p. 222-224°C; *Anal.* for $\text{C}_{16}\text{H}_{22}\text{N}_4\text{O}_6$ (M. wt. 366); Found: C, 52.42; H, 6.04; N, 15.37; Calcd: C, 52.46; H, 6.01; N, 15.30; IR ν (cm^{-1}) 1618 (C=N), 3232-3459 (OH and NH); MS: m/z $[\text{M}+\text{H}]^+$ 366; $^1\text{H-NMR}$ (DMSO- d_6) δ 1.15 (t, 3H, CH_3 of ethoxy $J = 7.4$ Hz), 4.23 (q, 2H, CH_2 of ethoxy $J = 7.4$), 7.0 - 8.1 (m, 4H, ArH), 8.29 (br. s, 1H, NH).

2-ethoxy-4-hydrazinoquinazoline-D-ribose hydrazone 8d.

Yield 61% (from DMF/ethanol); m. p. 217-219 °C; *Anal.* for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_5$ (M. wt. 336); Found: C, 53.68; H, 6.04; N, 16.57; Calcd: C, 53.57; H, 5.95; N, 16.67; IR ν (cm^{-1}) 1616 (C=N), 3210-3439 (OH and NH); MS: m/z $[\text{M}+\text{H}]^+$ 336; $^1\text{H-NMR}$ (DMSO- d_6) δ 1.13 (t, 3H, CH_3 of ethoxy $J = 7.4$ Hz), 4.23 (q, 2H, CH_2 of ethoxy $J = 7.4$), 7.1- 8.2 (m, 4H, ArH), 8.52 (br. s, 1H, NH).

2-ethoxy-4-hydrazinoquinazoline-D-arabinose hydrazone 8e.

Yield 63% (from ethanol); m. p. 197-198 °C; *Anal.* for $\text{C}_{15}\text{H}_{20}\text{N}_4\text{O}_5$ (M. wt. 336); Found: C, 53.62; H, 5.98; N, 16.63; Calcd: C, 53.57; H, 5.95; N, 16.67; IR ν (cm^{-1}) 1613 (C=N), 3230-3414 (OH and NH); MS: m/z $[\text{M}+\text{H}]^+$ 336; $^1\text{H-NMR}$ (DMSO- d_6) δ 1.11 (t, 3H, CH_3 of ethoxy $J = 7.4$ Hz), 4.19 (q, 2H, CH_2 of ethoxy $J = 7.4$), 7.2- 8.3 (m, 4H, ArH), 8.33 (br. s, 1H, NH).

Synthesis of per-O-acetylsugar [1-acetyl-1-(2-ethoxyquinazolin-4-yl)] hydrazones 9a-e.

A cold solution of 8a-e (0.02 mol) in dry pyridine (50 mL) was treated with Ac₂O (50 mL). The mixture was kept overnight at room temperature, with occasional shaking, and then poured onto crushed ice, and the residue was collected by filtration, washed repeatedly with water, dried and recrystallized from ethanol affording product 9a-e.

2,3,4,5,6-Penta-O-acetyl-D-glucose[1-acetyl-1-(2-ethoxyquinazolin-4-yl)] hydrazones 9a.

Yield 58 %; m. p. 63 - 64 °C; *Anal.* for C₂₈H₃₄N₄O₁₂ (M. wt. 618); Found: C, 54.41; H, 5.56; N, 9.01; Calcd: C, 54.37; H, 5.50; N, 9.06; IR ν (cm⁻¹) 1608 (C=N), 1673 (NAc), 1718 (OAc); MS: m/z [M+H]⁺ 618; ¹H-NMR (DMSO-d₆) δ 1.13 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 2.02, 2.04, 2.10 (3s, 15H, 5 OAc), 2.50 (s, 3H, NAc), 4.1(q, 2H, CH₂ of ethoxy J = 7.4), 4.15 (dd, 1H, H-6'), 4.26 (dd, 1H, H-6), 5.02-5.10 (m, 1H, H-5), 5.44-5.55 (m, 2H, H-4, H-3), 5.62 (dd, 1H, H-2), 6.74 (d, 1H, H-1), 7.11-8.23 (m, 4H, ArH).

2,3,4,5,6-Penta-O-acetyl-D-galactose[1-acetyl-1-(2-ethoxyquinazolin-4-yl)] hydrazones 9b.

Yield 80 %; m. p. 158 -160 °C; *Anal.* for C₂₈H₃₄N₄O₁₂ (M. wt. 618); Found: C, 54.43; H, 5.53; N, 9.03; Calcd: C, 54.37; H, 5.50; N, 9.06; IR ν (cm⁻¹) 1633(C=N), 1692(NAc), 1722(OAc); MS: m/z [M+H]⁺ 618; ¹H-NMR (DMSO-d₆) δ 1.13 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 1.96, 1.99, 2.02, 2.03, 2.08, 2.09 (5s, 15H, 5OAc), 2.47(s, 3H, NAc), 3.88(dd, 1H, H-6'), 4.1(q, 2H, CH₂ of ethoxy J = 7.4), 4.28 (dd, 1H, H-6), 5.38-5.88 (m, 4H, H-5, H-4, H-3, H-2), 6.55 (d, 1H, H-1), 7.15- 8.33 (m, 4H, ArH).

2,3,4,5,6-Penta-O-acetyl-D-mannose[1-acetyl-1-(2-ethoxyquinazolin-4-yl)] hydrazones 9c.

Yield 63 %; m. p. 58 - 60 °C; *Anal.* for C₂₈H₃₄N₄O₁₂ (M. wt. 618); Found: C, 54.40; H, 5.51; N, 9.02; Calcd: C, 54.37; H, 5.50; N, 9.06; IR ν (cm⁻¹) 1615(C=N), 1682(NAc), 1711(OAc); MS: m/z [M+H]⁺ 618; ¹H-NMR (DMSO-d₆) δ 1.13 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 2.05, 2.06, 2.10 (3s, 15H,5OAc), 2.52 (s, 3H, NAc), 4.11(q, 2H, CH₂ of ethoxy J = 7.4), 4.14 (dd, 1H, H-6'), 4.28 (dd, 1H, H-6), 5.22-5.40 (m, 1H, H-5), 5.42 (d, 1H, H-4), 5.54 (dd, 1H, H-3), 5.66 (dd, 1H, H-2), 6.68 (d, 1H, H-1), 7.00 - 8.13 (m, 4H, ArH).

2,3,4,5-Tetra-O-acetyl-D-ribose[1-acetyl-1-(2-ethoxyquinazolin-4-yl)] hydrazones 9d.

Yield 52 %; m. p. 92 - 93 °C; *Anal.* for C₂₅H₃₀N₄O₁₀ (M. wt. 546); Found: C, 54.97; H, 5.54; N, 10.29; Calcd: C, 54.94; H, 5.49; N, 10.26; IR ν (cm⁻¹) 1619 (C=N), 1682 (NAc), 1725 (OAc); MS: m/z [M+H]⁺ 546; ¹H-NMR (DMSO-d₆) δ 1.91, 1.94, 2.00, 2.19 (4s, 12H, 4OAc), 1.13 (t,3H, CH₃ of ethoxy J = 7.4 Hz), 2.51 (s, 3H, NAc), 4.15 (q, 2H, CH₂ of ethoxy J = 7.4), 4.22 (dd, 1H, H-5'), 4.39 (dd, 1H, H-5), 5.38 - 5.40 (m, 1H, H-4), 5.78 (dd, 1H, H-3), 6.01 (dd, 1H, H-2), 6.59 (d, 1H, H-1), 7.10- 8.32 (m, 4H, ArH).

2,3,4,5-Tetra-O-acetyl-D-arabinose[1-acetyl-1-(2-ethoxyquinazolin-4-yl)] hydrazones 9e.

Yield 67 %; m. p. 108-111 °C; *Anal.* for C₂₅H₃₀N₄O₁₀ (M. wt. 546); Found: C, 54.95; H, 5.52; N, 10.27; Calcd: C, 54.94; H, 5.49; N, 10.26; IR ν (cm⁻¹) 1610 (C=N), 1682 (NAc), 1715 (OAc); MS: m/z [M+H]⁺ 546 (42.9), 548 (14.3), 504 (10.5), 506 (3.4), 444 (25.0), 446 (8.2), 401 (13.3), 403 (4.4), 341 (17.6), 343 (5.8), 257 (40.5), 259 (13.4), 215 (100), 217 (33.3), 175 (16.2), 177 (5.3), 157 (2.8), 159 (0.9), 130 (58.3), 132 (0.1).

General method for preparing 1-(alditol-1-yl) - 5-ethoxy[1,2,4]triazolo[1,5-c] quinazoline 10a-e.

A 2 M solution of iron (III) chloride in EtOH (2 mL) was added dropwise to a boiling solution of 8a-e (0.01 mol) in ethanol (50 mL). Heating was continued for 10 min and the mixture was then kept overnight at room temperature. The product was filtered, washed repeatedly with water, air dried and recrystallized from EtOH affording product 10a-e.

1-(D-gluco-pentitol-1-yl)-5-ethoxy[1,2,4]triazolo[1,5-c] quinazoline 10a.

Yield 90 %; m. p. 85-87 °C; *Anal.* for C₁₆H₂₀N₄O₆ (M. wt. 364); Found: C, 52.79; H, 5.52; N,15.43; Calcd: C, 52.75; H, 5.49; N, 15.38; IR ν (cm⁻¹) 1613 (C=N), 3240-3454 (OH); MS: m/z [M+H]⁺ 364 (14.4), 366 (4.8), 333 (0.3), 335 (0.1), 303 (0.6), 305 (0.2), 273 (0.6), 275 (0.2), 214 (100), 216 (33.4), 187 (59.8), 189 (19.6), 175(6.2), 177 (2.1), 157 (2.5), 159 (0.5), 130(63.4), 132 (0.1).

1-(D-galacto-pentitol-1-yl)-5-ethoxy[1,2,4]triazolo[1,5-c] quinazoline 10b.

Yield 85 %; m. p. 80 °C; *Anal.* for C₁₆H₂₀N₄O₆ (M. wt. 364); Found: C, 52.77; H, 5.56;N, 15.48; Calcd: C, 52.74; H, 5.49; N, 15.38; IR ν (cm⁻¹) 1619 (C=N), 3340-3450 (OH);

1-(D-manno-pentitol-1-yl)-5-ethoxy[1,2,4]triazolo[1,5-c] quinazoline 10c.

Yield 75 %; m. p. 101-102°C; *Anal.* for $C_{16}H_{20}N_4O_6$ (M. wt. 364); Found: C, 52.82; H, 5.59; N, 15.53; Calcd: C, 52.74; H, 5.49; N, 15.38; IR ν (cm^{-1}) 1615 (C=N), 3290-3466 (OH); 1H -NMR (DMSO- d_6) δ 3.97-4.20 (m, 2H, H-5', H-5), 4.40 (dd, 1H, H-4), 4.62 (dd, 1H, H-3), 5.03 (t, 1H, H-2), 5.22 (d, 1H, H-1), 7.10- 8.32 (m, 4H, ArH).

1-(D-ribo-pentitol-1-yl)-5-ethoxy[1,2,4]triazolo[1,5-c] quinazoline 10d.

Yield 68 %; m. p. 128 °C; *Anal.* for $C_{15}H_{18}N_4O_5$ (M. wt. 334); Found: C, 53.92; H, 5.43; N, 16.81; Calcd: C, 53.89; H, 5.39; N, 16.77; IR ν (cm^{-1}) 1623 (C=N), 3310 - 3444 (OH); MS: m/z $[M+H]^+$ 334 (21.1), 336 (7.0), 303 (3.5), 305 (1.1), 273 (0.6), 275 (0.2), 214 (9.9), 216 (3.2), 187 (100), 189 (33.2), 175 (5.4), 177 (1.1), 157 (1.8), 159 (0.3), 130(56.4), 132 (0.1).

1-(D-arabino-pentitol-1-yl)- 5-ethoxy[1,2,4]triazolo[1,5-c] quinazoline 10e.

Yield 63 %; m. p. 108 °C; *Anal.* for $C_{15}H_{18}N_4O_5$ (M. wt. 334); Found: C, 53.97; H, 5.46; N, 16.88; Calcd: C, 53.89; H, 5.39; N, 16.77; IR ν (cm^{-1}) 1619 (C=N), 3320-3480 (OH); 1H -NMR (DMSO- d_6) δ 3.49-3.75 (m, 2H, H-4', H-4), 4.18-4.39 (m, 2H, H-3, H-2), 5.03 (d, 1H, H-1), 7.1-8.3 (m, 4H, ArH).

Preparation of 1-(penta-O-acetylsugar-1-yl)-5-ethoxy-1,2,4-triazolo[1,5-c] quinazoline 11a-e

A cold solution of 10a-e (0.002 mol) in dry pyridine (10 mL) was treated with Ac_2O (6 mL), and the mixture was kept overnight at room temperature, with occasional shaking, and then poured onto crushed ice, and the residue was collected by filtration, washed repeatedly with water, dried and recrystallized from ethanol affording product 11a-e.

1-(1,2,3,4,5-penta-O-acetyl-D-glucopentitol-1-yl)-5-ethoxy-1,2,4-triazolo[1,5-c] quinazoline 11a.

Yield 78 %; m. p. 71 °C; *Anal.* for $C_{26}H_{30}N_4O_{11}$ (M. wt. 574); Found: C, 54.42; H, 5.26; N, 9.83; Calcd: C, 54.36; H, 5.23; N, 9.76; IR ν (cm^{-1}) 1650 (C=N), 1725 (OAc); 1H -NMR (DMSO- d_6) δ 1.99, 2.01, 2.03 (3s, 12H, 4OAc), 3.98 (dd, 1H, H-5'), 4.30 (dd, 1H, H-5), 5.30-5.52 (m, 3H, H-4, H-3, H-2), 5.86 (d, 1H, H-1), 7.26-8.30 (m, 4H, ArH).

1-(1,2,3,4,5-penta-O-acetyl-D-galactopentitol-1-yl)-5-ethoxy-1,2,4-triazolo[1,5-c] quinazoline 11b.

Yield 81 %; m. p. 66 °C; *Anal.* for $C_{26}H_{30}N_4O_{11}$ (M. wt. 574); Found: C, 54.39; H, 5.24; N, 9.79; Calcd: C, 54.36; H, 5.23; N, 9.76; IR ν (cm^{-1}) 1619(C=N), 1719(OAc); MS: m/z $[M+H]^+$ 574 (19.3), 576 (6.3), 501 (27.4), 503(9.1), 429(31.7), 431 (10.5), 315 (9.5), 317 (3.2), 214 (100), 216 (33.3), 187 (59.8), 189 (19.9), 175(5.4), 177 (2.1), 157 (1.3), 159 (0.2), 130 (48.4), 132 (0.1).

1-(1,2,3,4,5-penta-O-acetyl-D-mannopentitol-1-yl)-5-ethoxy-1,2,4-triazolo[1,5-c]quinazoline 11c.

Yield 63 %; m. p. 76 °C; *Anal.* for $C_{26}H_{30}N_4O_{11}$ (M. wt. 574); Found: C, 54.41; H, 5.27;N, 9.81; Calcd: C, 54.36; H, 5.23; N, 9.76; IR ν (cm^{-1}) 1639 (C=N), 1745 (OAc); 1H -NMR (DMSO- d_6) δ 1.96, 1.99, 2.03, 2.08(4s, 12H, 4OAc), 3.90(dd, 1H, H-5'), 4.32 (dd, 1H, H-5), 5.30-5.53 (m, 3H, H-4, H-3, H-2), 5.76 (d, 1H, H-1), 7.15-8.31(m, 4H, ArH).

1-(1,2,3,4-tetra-O-acetyl-D-ribosepentitol-1-yl)-5-ethoxy-1,2,4-triazolo[1,5-c] quinazoline 11d.

Yield 58 %; m. p. 71 °C; *Anal.* for $C_{23}H_{26}N_4O_9$ (M. wt. 502); Found: C, 54.94; H, 5.22; N, 11.14; Calcd: C, 54.98; H, 5.18; N, 11.16; IR ν (cm^{-1}) 1629 (C=N), 1731 (C=O); MS: m/z $[M+H]^+$ 502 (21.3), 504 (7.1), 430 (17.6), 432 (5.8), 358 (21.4), 360 (7.1), 286(16.9), 288(5.6), 214 (100), 216 (33.2), 187(8.4), 189(2.8), 175(5.8), 177(1.9), 157(1.6), 159 (0.1), 130 (59.3), 132 (0.1). 1H -NMR (DMSO- d_6) δ 1.13 (t, 3H, CH_3 of ethoxy J = 7.4), 2.03, 2.06, 2.08 (3s, 12H, 4OAc), 4.05 (dd, 2H, H-4', H-4), 4.35-4.55 (m, 1H, H-3), 5.56(dd, 1H, H-2), 5.74 (d, 1H, H-1), 7.1 - 8.3 (m, 4H, ArH).

1-(1,2,3,4-tetra-O-acetyl-D-arabinopentitol-1-yl)-5-ethoxy-1,2,4-triazolo[1,5-c] quinazoline 11e. Yield 67%; m. p. 98°C; *Anal.* for $C_{23}H_{26}N_4O_9$ (M. wt. 502); Found: C, 54.92; H, 5.24; N, 11.19; Calcd: C, 54.98; H, 5.18; N, 11.16; IR ν (cm^{-1}) 1618 (C=N); 1H -NMR (DMSO- d_6) δ 1.13 (t, 3H, CH_3 of ethoxy J = 7.4), 1.81, 1.86, 1.91, 2.19 (4s, 12H, 4 OAc), 4.22 (dd, 2H, H-4', H-4), 5.35 - 5.41 (m, 1H,H-3), 5.76 (dd, 1H, H-2), 6.02 (d, 1H, H-1), 7.17 - 8.32 (m, 4H, ArH).

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Authors' Statement

Competing Interests

The authors declare no conflict of interest.

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Table 1. Antimicrobial activity

Compd No	Gram-positive Bacteria			Gram-negative Bacteria		
	Staphy- lococcussp	Strepto- bacillussp	Bacillus- subtillissp	Esch- colisp	Strepto- bacillusssp	Pseudo- monassp
8a	-	+	-	-	-	-
8b	-	+	-	-	-	-
8c	-	+	+	-	-	-
8d	-	+	-	-	-	-
8e	-	+	-	-	-	-
9a	-	+	+	-	+	-
9b	-	+	+	+	-	-
9c	-	+	+	-	-	+
9d	-	+	-	+	-	-
9e	-	+	+	+	-	+
10a	-	+	+	+	-	-
10b	-	+	+	+	+	+
10c	-	++	++	+	+	+
10d	+	+++	++	+	-	-
10e	+	+	+	+	-	-
11a	-	+++	++	+	+	+
11b	-	++	+	+	-	-
11c	-	++	+	+	-	-
11d	+	+	+	+	-	-
11e	-	++	+	+	-	-