Research Article

The Reactivity of 2-Ethoxy-4-Chloroquinazoline and Its Use in Synthesis of Novel Quinazoline Derivatives

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The behavior of 2-ethoxy-4-chloroquinazoline **2** towards various nitrogen nucleophiles, namely: thiosemicarbazide, sodium azide, glucosamine, ethanol, and hydrazine hydrate has been discussed. Also, the behavior of 4-(2-ethoxyquinazolin-4-yl)thiosemicarbazide towards one-carbon, for example, ethyl chloroformate, and two-carbon donors, for example, ethyl chloroacetate and diethyl oxalate has been investigated. On the other hand, new 5-ethoxy-2-substituted[1,2,4]-triazolo-[1,5-*c*]quinazoline derivatives have been obtained by ring closure accompanied with Dimroth rearrangement through the interaction of compound **2** with hydrazides of acetic, benzoic, crotonic, cinnamic, 2-furoic, and phthalimidoacetic acids. Structures of the novel products were confirmed by elemental, IR, MS, and ¹H-NMR spectral analyses.

1. Introduction

Quinazolines are a big family of heterocyclic compounds, which have shown broad variety of biological activity profiles [1, 2], for example, analgesic, narcotic, diuretic, antihypertensive, antimalarial, sedative, hypoglycaemic, antibiotic, antitumoral, and many others. It has been found [3] that the biological activity strongly depends on the type and place of the substituents in their molecules.

Out of the wide substitution patterns known, 4-aminoquinazolines are useful as fungicides [4, 5], anti-inflammatory [6, 7], anticancer [8, 9], antimicrobial, and antihypertensive agents [10, 11]. Some 4-anilinoquinazolines have been found to be potential and highly selective inhibitors of human immunoglobulin E [12] and epidermal growth factor receptor tyrosine kinase [13] which regulates the cell growth and proliferation, so they can work as potent antiallergic or anticancer agents, respectively. Among the broad synthetic pathways for aminoquinazoline preparation [14, 15] the substitution of chlorine atom in 4-chloroquinazolines by amines is the shortest and cheapest one. On the other hand, it is well known that heterocycle-bearing N-glycosides play a significant role as inhibitors, for example,

the tetrazole-bearing N-glycosides used as SGLT2 inhibitors [16] where their hypoglycemic activity is tested *in vivo* by mice oral glucose tolerance test (OGTT). In the current paper we report the synthesis of 4-aminoquinazoline-bearing N-glycosides in a similar way, with exception of the endocyclic 2° nitrogen atom attached to the glucose moiety.

2. Results and Discussion

In many syntheses of quinazoline derivatives the 4-chloroquinazoline exhibits a very important key intermediate due to its reactivity towards many types of nucleophiles, especially the nitrogen and oxygen nucleophiles [17–19]. The stepwise synthesis of 4-chloro-2-ethoxyquinazoline **2** starts with aminolysis of 2-ethoxy(4*H*)-3,1-benzoxazin-4-one affording 2-ethoxy-4(3*H*)quinazolinone **1** followed by the chlorination by phosphorus oxychloride in boiling water bath (Scheme 1) [20–22].

Compound **2** interacted with thiosemicarbazide in boiling acetic acid affording the open-chain intermediate **3** which was reacted, as a good substrate for one-carbon and two-carbon donors, with ethyl chloroformate, diethyl oxalate,

SCHEME 1: Synthetic pathway for compound 2.

4: Y = $=C(OEt)-$; X = Cl; Z = $OEt/C_5H_5N/4h$

5: Y = $-CO-CO-$; X = Z = $OEt/EtOH/2h$

6: Y = $-CO-CH_2-$; X = OEt ; Z = $Cl/EtOH/10h$

SCHEME 2: Synthetic pathway for compounds 4–6.

and ethyl chloroacetate giving open products that cyclized, in turn, affording the new 4-triazolo- and 4-triazinoquinazoline products 4–6, respectively (Scheme 2).

Treatment of compound 2 with sodium azide in acetic acid (Scheme 3) gave derivative 7 whose analogues are believed to have antimicrobial and anti-inflammatory activities [23–25].

Glucosamine is one of the constituents of chitin, chitosan, and mucopolysaccharides and has important biomedical applications, including pharmaceutical preparations for treating cartilage diseases of joints [26–30]. Such preparations include often glucosamine hydrochloride or sulfate and chondroitin sulfate. In this paper we invented reaction of the 4-chloroquinazoline 2 with glucosamine hydrochloride in the presence of sodium bicarbonate in methanol to afford product 8 (α and β anomers) (Scheme 4). Structures of 8 ($\alpha + \beta$) were assigned by TLC and 1H -NMR spectra. The 1H -NMR spectra for 8 ($\alpha + \beta$) showed H-1 doublets at 5.05 and 4.80 ppm, characteristic for the α and β anomers, respectively [31]. Moreover, the TLC data obtained at room temperature including silica gel and a mixture of ethyl acetate:hexane (3:1) indicated that derivative 8 presented two spots, with R_f value for β anomer being double that for α .

Recently, it was reported that 4-substituted-aminoquinazolines are exploited as potent antitumor compounds (human breast carcinoma cell line in which EGFR is highly expressed) [32]. Herein we synthesized 4-hydrazinoquinazoline 9 by reacting compound 2 with hydrazine hydrate in boiling ethanol (Scheme 5). During the synthesis of product 9, variable quantities of derivatives 10 and 11 were also obtained as shown by mass spectral data. Product 11, in

its hydrochloride form, was obtained due to the reaction of derivative 2 with absolute ethanol during synthesis of derivative 9.

Also, as a good substrate for one-carbon donors, product 2 reacted with acid hydrazides, namely: acetic, benzoic, crotonic, cinnamic, furoic, and phthalimidoacetic hydrazides affording first the 2-acylated-1-(2-ethoxyquinazolin-4-yl) hydrazine products which, on heating, rearranged giving the imidamide tautomer (Scheme 6) and then cyclized losing water to give the triazoloquinazolines 12a–f, respectively. Whereas the literature indicates the possibility for the Dimroth rearrangement [33], we have been unable to unambiguously verify the structures of 12, and the proposed structures are on the basis of mass spectral fragments observed.

For each compound the mass spectrum showed a molecular ion peak for the parent compound and ion peaks for fragments, which showed no indication for molecular ion peaks to be attributed to nitrogen gas or aziridine residues in the 5-ethoxy-3-X[1,2,4]triazolo[4,3-c]quinazoline fragmentation but the fragments detected included the diazireno[1,3-c]quinazoline residue, confirming that a single nitrogen atom was lost in 5-ethoxy-2-methyl[1,2,4]triazolo[1,5-c]quinazoline fragmentation.

3. Experimental

All melting points recorded are uncorrected. The IR spectra were recorded on a Pye Unicam SP 1200 spectrophotometer using KBr wafer technique. The 1H -NMR spectra were determined on a Varian FT-200, Bruker AC-200 MHz spectrophotometry experiment using TMS as an internal

SCHEME 3: Synthetic pathway for compound 7.

SCHEME 4: Synthetic pathway for compound 8 anomers.

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).

The 2-ethoxy(4*H*)-3,1-benzoxazin-4-one was prepared according to methods available in the literature [34] and was immediately used after preparation, prior to each synthesis to avoid moisture.

3.1. 2-Ethoxy-4(3*H*)quinazolinone 1. 2-ethoxy(4*H*)-3,1-benzoxazin-4-one (0.01 mol) and ammonium acetate (0.01 mol) were fused using an oil bath for 2 h. The mixture was poured into an ice/water mixture and stirred. The beige white precipitate that separated out was filtered, washed, dried, and then crystallized from ethanol affording beige white crystals of quinazolinone 1. M.p. 155–156 °C; yield 85%; Elemental analysis for $C_{10}H_{10}N_2O_2$ (M.wt. 190); Found: C, 63.16; H, 5.26; N, 14.74; Calcd: C, 63.22; H, 5.18; N, 14.72; IR ν (cm^{-1}) 1671 (C=O), 3229 (NH); MS: m/z $[M+H]^+$ 190 (58%); 1H -NMR (DMSO- d_6) δ 1.19 (t, 3H; CH_3 of ethoxy $J = 7.4$ Hz), 4.29 (q, 2H; CH_2 of ethoxy $J = 7.4$), 7.31–8.17 (4Xd, 4H; ArH), 12.30 (br s, 1H, NH).

3.2. 4-Chloro-2-ethoxyquinazoline 2. A mixture of 2-Ethoxy-4(3*H*)quinazolinone 1 (0.01 mol), phosphorus oxychloride (10 mL) was heated using water bath for 30 min. The excess oxychloride was removed under reduced pressure, and crushed ice (20 g) was added to the residue. The separated solid was filtered, washed with water, dried, and crystallized from chloroform affording the product 2; yield 64%; m.p. 180–182 °C. *Anal.* for $C_{10}H_9N_2OCl$ (M.wt. 208.5); Found: C, 57.45; H, 4.31; N, 13.42; Cl, 17.00; Calcd: C, 57.55; H, 4.3; N, 13.43; Cl, 17.02; IR ν (cm^{-1}) 1622 (C=N); MS: m/z $[M+H]^+$ 208.5; 1H -NMR (DMSO- d_6) δ 1.17 (t, 3H, CH_3 of ethoxy $J = 7.4$ Hz), 4.19 (q, 2H, CH_2 of ethoxy $J = 7.4$), 7.13–8.28 (4d, 4H, ArH).

3.3. 4-(2-Ethoxyquinazolin-4-yl)thiosemicarbazide 3. Refluxing a mixture of the quinazoline 2 and thiosemicarbazide (0.01 mol each) in acetic acid/fused sodium acetate (30 mL/2 g) for 3 h and pouring the solution onto ice/water left a white solid. The latter was filtered, washed with water, dried, and crystallized from ethanol affording white crystals of compound 3; yield 74%; m.p. 128–130 °C. *Anal.* for $C_{11}H_{13}N_5OS$ (M.wt. 263); Found: C, 53.38; H, 5.19; N, 28.39; Calcd: C, 53.44; H, 5.26; N, 28.34; IR ν (cm^{-1}) 1381 (C=S), 1620 (C=N), 3418, 3250 (NH and NH_2). MS: m/z $[M+H]^+$ 263 (77%). 1H -NMR (DMSO- d_6) δ 1.20 (t, 3H; CH_3 of ethoxy $J = 7.2$ Hz), 4.15 (q, 2H; CH_2 of ethoxy $J = 7.2$), 7.44–8.06 (4d, 4H, ArH), 8.41–9.34 (2 br. s, 4H, 2 NH and NH_2).

3.4. 5-Ethoxy-1-(2-ethoxyquinazolin-4-yl)-1,2-dihydro-3*H*-1,2,4-triazole-3-thione 4. Quinazolinone 3 (0.01 mol) was heated under reflux with ethyl chloroformate (0.01 mol) in dry pyridine (30 mL) for 3 h. The excess solvent was removed by distillation, and the solution was left to cool down and then poured into an ice/HCl mixture with stirring to obtain the crude product which was filtered off, thoroughly washed with cold water, dried, and crystallized from ethanol affording product 4; brown crystals (m.p. 239–241 °C). Yield 67%; *Anal.* for $C_{14}H_{15}N_5O_2S$ (M.wt. 317); Found: C, 52.81; H, 4.51; N, 22.22; Calcd: C, 52.99; H, 4.73; N, 22.08; IR ν (cm^{-1}) 1273 (C=S), 1619 (C=N), 2992 (CH), 3314 (sec NH); MS: m/z $[M+H]^+$ 317; 1H -NMR (DMSO- d_6) δ 1.23 (t, 3H, CH_3 of ethoxy $J = 7.4$ Hz), 1.19 (t, 3H, CH_3 of ethoxy of triazole), 4.16 (q, 2H, CH_2 of ethoxy $J = 7.4$ Hz), 4.41 (q, 2H, CH_2 of ethoxy of triazole), 7.55–8.83 (m, 4H, ArH), 7.83 (br, 1H, NH), and 8.34 (br, 1H, NH).

3.5. 1-(2-Ethoxyquinazolin-4-yl)-3-thioxo-1,2,4-triazinane-5,6-dione 5. A mixture of compound 3 (0.01 mol) and diethyl oxalate (0.01 mol) in absolute ethanol (20 mL) was heated

SCHEME 5: Synthetic pathway for compounds 9–11.

SCHEME 6: Synthetic pathway for compounds 12a–f.

under reflux for 2 h. The excess ethanol was distilled-off, and the separated solid was dried and crystallized from ethanol affording white crystals of product **5**; yield 78%; m.p. 228–230°C. *Anal.* for C₁₃H₁₁N₅O₃S (M.wt. 317); Found: C, 49.08; H, 3.56; N, 22.01; Calcd: C, 49.21; H, 3.47; N, 22.08; IR ν (cm⁻¹) 1319 (C=S), 1622 (C=N), 1640 (C=O), 3316 (sec NH); MS: m/z [M+H]⁺ 317 (72%). ¹H-NMR (DMSO-d₆) δ 1.27 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 4.19 (q, 2H, CH₂ of ethoxy J = 7.4), 7.54–8.83 (4Xd, 4H, ArH), 7.62 (br, 1H, NH), and 8.13 (br, 1H, NH).

3.6. 1-(2-ethoxyquinazolin-4-yl)-3-thioxo-1,2,4-triazinan-5-one 6. A mixture of **3** (0.01 mol) and ethyl chloroacetate (0.01 mol) in absolute ethanol (25 mL) was heated under reflux for 10 h. The solid that separated after cooling and crystallization from dioxane gave **6**; brown crystals (m.p. 196–199°C). Yield 66%. *Anal.* for C₁₃H₁₃N₅O₂S (M.wt. 303); Found: C, 51.44; H, 4.14; N, 23.02; S, 10.78; Calcd: C, 51.49; H, 4.29; N, 23.10; S, 10.56; IR ν (cm⁻¹) 1276 (C=S), 1622 (C=N), 1671 (C=O), 2990 (CH), 3316 (sec NH); MS: m/z [M+H]⁺ 303; ¹H-NMR (DMSO-d₆) δ 1.20 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 4.08, 4.31 (2 d, 2H, CH₂CO), 4.15 (q, 2H, CH₂ of ethoxy J = 7.4), 7.43–7.87 (m, 4H, ArH), 7.82 (br, 1H, NH), and 8.35 (br. s, 1H, NH).

3.7. 5-Ethoxy-*s*-tetrazolo-[1,5-*c*]quinazoline 7. A mixture of quinazoline **2** (0.01 mol) and sodium azide (0.01 mol) in acetic acid (15 mL) was heated under reflux for 2 h. The solvent

was evaporated under vacuum, and the separated solid was filtered, washed with water, dried, and recrystallized from ethanol affording off-white needles of compound **7** (m.p. 168–170°C). Yield 63%. *Anal.* for C₁₀H₉N₅O (M.wt. 215); Found: C, 55.76; H, 4.14; N, 32.62; Calcd: C, 55.81; H, 4.18; N, 32.56; IR ν (cm⁻¹) 1622 (C=N); MS: m/z [M+H]⁺ 215; ¹H-NMR (DMSO-d₆) δ 1.16 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 4.31 (q, 2H, CH₂ of ethoxy J = 7.4), 7.55–8.53 (4d, 4H, ArH).

3.8. 2-[N-(2-Ethoxyquinazolin-4-yl)-2-deoxy-D-glucose 8(α+β). A mixture of compound **2** and glucosamine hydrochloride (0.01 mol each) in methanol/sodium bicarbonate mixture (20 mL/0.025 mol) was stirred at 50°C for 12 h. The reaction mixture was filtered, washed, and dried affording a white solid. Purification was performed using column chromatography (3:1, EtOAc:Hexane), and the resultant white solid was later on recrystallized using dichloromethane, diethyl ether, hexane solvents affording the crystalline products **8(α+β)**.

3.9. Anomer 8α. Yield 14%. *Anal.* for C₁₆H₂₁N₃O₆ (M.wt. 351); Found: C, 55.21; H, 6.01; N, 11.92; Calcd: C, 54.70; H, 5.98; N, 11.96; IR ν (cm⁻¹) 1622 (C=N); 2852, 2922 (CH, CH₂); 3315 (OH); MS: m/z [M+H]⁺ 351; ¹H-NMR (DMSO-d₆) δ 1.20 (t, 3H; CH₃ of ethoxy J = 6.8 Hz), 3.22–3.91 (m, 6H; H-2', H-3', H-4', H-5', H-6'a, and H-6'b), 3.71 (m, 1'-OH, 3'-OH, 4'-OH), 4.13 (q, 2H; CH₂ of ethoxy J = 6.8),

5.05 (d, 1H; H-1', $J = 6.5$), 4.92 (s, 6'-OH), 7.41–7.85 (m, 4H; ArH); 9.38 (bs, 1H, NH).

3.10. Anomer 8β. Yield 18%. *Anal.* for $C_{16}H_{21}N_3O_6$ (M.wt. 351); Found: C, 55.92; H, 5.93; N, 11.98; Calcd: C, 54.70; H, 5.98; N, 11.96; IR ν (cm^{-1}) 1619 (C=N); 2871, 2918 (CH, CH₂); 3341 (OH); MS: m/z $[M+H]^+$ 351; ¹H-NMR (DMSO- d_6) δ 1.19 (t, 3H; CH₃ of ethoxy $J = 6.8$ Hz), 3.19–3.92 (m, 6H; H-2', H-3', H-4', H-5', H-6'a, and H-6'b), 3.76 (m, 1'-OH, 3'-OH, 4'-OH), 4.15 (q, 2H; CH₂ of ethoxy $J = 6.8$ Hz), 4.80 (d, 1H; H-1', $J = 6.5$), 4.88 (s, 6'-OH), 7.41–7.85 (m, 4H; ArH); 9.42 (bs, 1H, NH).

3.11. Reaction of 4-chloro-2-ethoxyquinazoline 2 with hydrazine. An emulsion of product **2** (0.01 mol) and hydrazine hydrate (0.05 mol) in benzene (15 mL) was stirred for 2 h. The benzene-insoluble gum obtained was treated and washed with water, dried, and recrystallized from ethanol giving reddish brown crystals of product **9**. Evaporation of solvent, from the benzene-soluble fraction gave a residue that was rinsed with water and dried. Recrystallization of the residue from absolute ethanol gave a mixture containing product **10** according to mass spectrum. Evaporation of the ethanolic mother liquor, extraction of the resulting residue with chloroform, evaporation of solvent and treatment of the residue with ether afforded product **11** as hydrochloride. The presence of halogen was verified by a green flame with a copper wire.

3.11.1. 2-Ethoxyquinazolin-4-ylhydrazine 9. 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), 4.17 (q, 2H, CH₂ of ethoxy $J = 7.4$), 7.40–8.06 (m, 4H, ArH), 8.65 (br. s, 3H, NH and NH₂).

3.11.2. (4Z,4'Z)-4,4'-(1Z,2Z)-hydrazine-1,2-diylidenebis(2-ethoxy-3,4-dihydroquinazoline) 10. Yield 24%; m.p. 204–206°C. *Anal.* for $C_{20}H_{20}N_6O_2$ (M.wt. 376); Found: C, 86.84; H, 5.26; N, 22.26; Calcd: C, 86.96; H, 5.32; N, 22.34; IR ν (cm^{-1}) 1635 (C=N), 3160 (NH); MS: m/z $[M+H]^+$ 376; ¹H-NMR (DMSO- d_6) δ 1.17 (t, 6H, 2CH₃ of 2 ethoxy $J = 7.4$ Hz), 4.44–4.54 (q, 4H, 2 CH₂ of 2 ethoxy $J = 7.4$), 7.18–7.71 (m, 8H, ArH), 9.65 (br. s, 2H, 2NH).

3.11.3. 2,4-Diethoxyquinazoline hydrochloride 11. Yield 42%; m.p. 181–182°C. *Anal.* for $C_{12}H_{15}ClN_2O_2$ (M.wt. 254.5); Found: C, 56.62; H, 5.96; Cl, 14.51; N, 9.88; Calcd: C, 56.58; H, 5.89; N, 9.82; Cl, 14.46; IR ν (cm^{-1}) 1619 (C=N); MS: m/z $[M+H]^+$ 254.5; ¹H-NMR (DMSO- d_6) δ 1.14 (t, 3H, CH₃ of 4-ethoxy $J = 7.4$ Hz), 1.20 (t, 3H, CH₃ of 2-ethoxy $J = 7.4$ Hz), 4.19 (q, 2H, CH₂ of 2-ethoxy $J = 7.4$), 4.22 (q, 2H, CH₂ of 4-ethoxy $J = 7.4$), 7.53–8.82 (m, 4H, ArH).

3.12. General Procedure for the Synthesis of Compounds 12a–f. A mixture of equimolar amounts of compound **2** and the acid hydrazides namely: acetic, benzoic, crotonic, cinnamic,

furoic, and phthalimidoacetic hydrazides (0.01 mol) was heated on an oil bath for 3 h (6 h in the case of phthalimidoacetic hydrazides). The precipitate that separated out was filtered, washed, dried, and then crystallized from ethanol affording crystals **12a–f**, respectively.

3.12.1. 5-ethoxymethyl[1,2,4]triazolo[1,5-c]quinazoline 12a. Colorless needles from ethanol. Yield 58%; m.p. 158–160°C. *Anal.* for $C_{12}H_{12}N_4O$ (M.wt. 228); Found: C, 63.28; H, 5.32; N, 24.64; Calcd: C, 63.16; H, 5.26; N, 24.56; IR ν (cm^{-1}) 1619 (C=N), 2992 (CH); MS: m/z $[M+H]^+$ 228 (78.3), 230 (12.3), 215 (61.9), 217 (9.2), 203 (43.7), 205 (2.4), 188 (1.6), 190 (0.5), 143 (100), 145 (0.2), 130 (0.2), 132 (0.1); ¹H-NMR (DMSO- d_6) δ 1.20 (t, 3H, CH₃ of ethoxy $J = 7.4$ Hz), 2.52 (s, 3H, CH₃), 4.27 (q, 2H, CH₂ of 2-ethoxy $J = 7.4$), 7.48–8.02 (m, 4H, ArH).

3.12.2. 5-ethoxy-2-phenyl[1,2,4]triazolo[1,5-c]quinazoline 12b. 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), 215 (100), 217 (23.5), 203 (12.1), 205 (6.4), 188 (18.5), 190 (9.2), 143 (83.8), 145 (8.2), 130 (3.1), 132 (0.1), 77 (13.2), 79 (0.3); ¹H-NMR (DMSO- d_6) δ 1.19 (t, 3H, CH₃ of ethoxy $J = 7.4$), 4.35 (q, 2H, CH₂ of ethoxy $J = 7.4$), 7.55–8.08 (m, 5H, phenyl), 7.65–8.62 (4d, 4H, ArH).

3.12.3. 5-ethoxy-2-[(1E)-prop-1-en-1-yl][1,2,4]triazolo[1,5-c]quinazoline 12c. Brownish 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), 215 (100), 217 (29.5), 203 (22.2), 205 (9.5), 188 (16.9), 190 (6.3), 143 (88.6), 145 (38.1), 130 (4.5), 132 (0.1); 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 $J = 7.4$), 6.10, 6.70 (2d, 2H, 2CH_{trans}), 7.53–8.21 (m, 4H, ArH).

3.12.4. 5-ethoxy-2-[(E)-2-phenylethenyl][1,2,4]triazolo[1,5-c]quinazoline 12d. Brownish 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), 215 (100), 217 (21.8), 203 (19.3), 205 (8.7), 188 (13.7), 190 (4.3), 143 (67.3), 145 (18.3), 130 (2.5), 132 (0.1), 104 (1.1), 106 (0.1); ¹H-NMR (DMSO- d_6) δ 1.20 (t, 3H, CH₃ of ethoxy $J = 7.4$), 4.36 (q, 2H, CH₂ of ethoxy $J = 7.4$), 7.09 (d, 1H, CH_{trans}), 7.47 (d, 1H, CH_{trans}), 7.39–7.60 (m, 5H, Ph-H), 7.47–8.63 (m, 4H, ArH).

3.12.5. 5-ethoxy-2-(furan-2-yl)[1,2,4]triazolo[1,5-c]quinazoline 12e. 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), 215 (100), 217 (29.5), 203 (21.3), 205 (11.3), 188 (16.9), 190 (6.3), 143

(88.6), 145 (38.1), 130 (4.5), 132 (0.1), 68 (1.2), 70 (0.1); $^1\text{H-NMR}$ (DMSO-d_6) δ 1.20 (t, 3H, CH_3 of ethoxy $J = 7.4$ Hz), 4.29 (q, 2H, CH_2 of ethoxy $J = 7.4$), 6.76 (q, 1H, $J = 3.6$ Hz, $J = 1.6$, Furan-H), 7.43 (q, 1H, $J = 4.4$, Furan-H), 7.85 (q, 1H, $J = 1.6$ Hz, Furan-H), 7.54–8.02 (m, 4H, ArH).

3.12.6. 2-[(5-ethoxy[1,2,4]triazolo[1,5-c]quinazolin-2-yl)methyl]-1H-isoindole-1,3(2H)-dione **12f**. Brown crystals from DMF; m.p. 286–288°C; yield 72%. *Anal.* for $\text{C}_{20}\text{H}_{15}\text{N}_5\text{O}_3$ (M.wt. 373); found: C, 58.72; H, 3.66; N, 16.31; Calcd: C, 58.20; H, 3.46; N, 16.17; IR ν (cm^{-1}) 1631 ($\text{C}=\text{N}$), 1727, 1776 ($\text{C}=\text{O}$). MS: m/z [$\text{M}+\text{H}$] $^+$ 373 (58.0), 375 (31.2), 215 (44.1), 217 (27.8), 203 (24.5), 205 (13.6), 188 (26.1), 190 (16.2), 161 (33.3), 163 (21.1), 147 (18.7), 149 (9.8), 143 (11.1), 145 (6.2), 130 (0.6), 132 (0.2), 122 (2.2), 124 (1.1), 78 (0.2), 80 (0.1); $^1\text{H-NMR}$ (DMSO-d_6) δ 1.19 (t, 3H; CH_3 of ethoxy $J = 7.1$), 4.37 (q, 2H; CH_2 of ethoxy), 5.55 (s, 2H; CH_2 , phthalimidomethyl), 7.55–8.03 (m, 4H, quinazol.), 7.73–7.87 (m, 4H, phthalimido moiety).

Conflict of Interests

The authors declare no conflict of interests.

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References

- [1] S. Jhone, "Search for pharmaceutically interesting quinazoline derivatives: efforts and results (1969–1980)," in *Progress in Drug Research*, E. Jucker, Ed., vol. 26, pp. 259–341, Birkhäuser, Basel, Switzerland, 1982.
- [2] D. J. Brown, *The Chemistry of Heterocyclic Compounds*, John Wiley & Sons, New York, NY, USA, 1996.
- [3] W. Armarego, *Fused Pyrimidines: Part I—Quinazolines*, Interscience Publishers, New York, NY, USA, 1967.
- [4] K. Nakagami, S. Yokoi, K. Nishimura et al., "Aminoquinazoline compounds useful as agricultural fungicides," US Patent 4323680, 1982.
- [5] G. J. Haley, "Substituted quinazoline fungicidal agents," US Patent 5373011, 1994.
- [6] M. Palanki and M. Suto, "Quinazoline analogs and related compounds and methods for treating inflammatory conditions," US Patent 5939421, 1999.
- [7] M. R. Myers, A. Spada, M. Maguire et al., "Aryl and heteroaryl quinazoline compounds which inhibit CSF-1R receptor tyrosine kinase," US Patent 5714493, 1998.
- [8] A. J. Baker, "Quinazoline derivatives," US Patent 5932574, 1999.
- [9] A. J. Baker, "Quinazoline derivatives," US Patent 5942514, 1999.
- [10] W. T. Nauta, "4-Amino-pyrimidine derivatives," US Patent 3980650, 1976.
- [11] S. Mizogami, H. Hiranuma, T. Sekiya, and M. Hanazuka, "Quinazoline derivatives and pharmaceutical composition thereof," US Patent 4607034, 1986.
- [12] M. Berger, B. Albrecht, A. Berces, P. Ettmayer, W. Neruda, and M. Woisetschlager, "S(+)-4-(1-phenylethyl-amino)quinazolines as inhibitors of human immunoglobuline E synthesis: potency is dictated by stereochemistry and atomic point charges at N-1," *Journal of Medicinal Chemistry*, vol. 44, no. 18, pp. 3031–3038, 2001.
- [13] A. J. Bridges, "Chemical inhibitors of protein kinases," *Chemical Reviews*, vol. 101, no. 8, pp. 2541–2571, 2001.
- [14] A. R. Katritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry II*, Pergamon, Oxford, UK, 1996.
- [15] A. R. Katritzky and A. F. Pozharski, *Handbook of Heterocyclic Chemistry*, Pergamon, New York, NY, USA, 2nd edition, 2000.
- [16] Y. L. Gao, G. L. Zhao, W. Liu et al., "Design, synthesis and in vivo hypoglycemic activity of tetrazole-bearing N-glycosides as SGLT2 inhibitors," *Indian Journal of Chemistry—Section B*, vol. 49, no. 11, pp. 1499–1508, 2010.
- [17] M. S. Mohamed, M. K. Ibrahim, A. M. Alafify, S. G. Abdel-Hamide, and A. M. Mostafa, "Synthesis and anti-inflammatory evaluation of some new quinazoline derivatives," *International Journal of Pharmaceutics*, vol. 1, no. 3, pp. 261–266, 2005.
- [18] V. B. Kurteva, V. N. Zlatanova, and V. D. Dimitrov, "Solvent-free synthesis of a series of differently N-substituted 4-amino-2-methylquinazolines under microwave irradiation," *Arkivoc*, vol. 2006, no. 1, pp. 46–56, 2006.
- [19] A. A. Aly, "Synthesis and antimicrobial activity of some annealed quinazoline derivatives," *Journal of the Chinese Chemical Society*, vol. 54, no. 2, pp. 437–446, 2007.
- [20] T. George et al., "Synthesis of substituted quinazolines: part II—use of diethyl oxalate in quinazoline synthesis," *Indian Journal of Chemistry*, vol. 9, pp. 1077–1080, 1971.
- [21] P. M. Chandrika, T. Yakaiah, B. Narsaiah et al., "Synthesis leading to novel 2,4,6-trisubstituted quinazoline derivatives, their antibacterial and cytotoxic activity against thp-1, hl-60 and a375 cell lines," *Indian Journal of Chemistry—Section B*, vol. 48, no. 6, pp. 840–847, 2009.
- [22] E. A. Arnott, L. C. Chan, B. G. Cox, B. Meyrick, and A. Phillips, "POCl₃ chlorination of 4-quinazolones," *Journal of Organic Chemistry*, vol. 76, no. 6, pp. 1653–1661, 2011.
- [23] M. Kumar and V. H. Bhaskar, "Synthesis, characterization and biological evaluation of some derivatives of Ethyl-4-hydrazino-3, 4-dihydroquinazoline -2-carboxylate," *Journal of Pharmacy Research*, vol. 3, no. 1, pp. 60–62, 2010.
- [24] R. A. Al-Salahi, "Synthesis and reactivity of [1,2,4]triazolo-annealed quinazolines," *Molecules*, vol. 15, no. 10, pp. 7016–7034, 2010.
- [25] T. Sambaiah, A. Ankush, S. Rajinder, H. L. Henry, and H. Peiyong, "Preparation of tetrazoloquinoline derivatives as inhibitors of HCV," *Chemical Abstracts*, vol. 142, Article ID 373704, 2005.
- [26] *The Merck Index*, Merck & Co., Whitehouse Station, NJ, USA, 14th edition, 2006.
- [27] A. R. Ray and D. K. Singh, "Biomedical applications of chitin, chitosan, and their derivatives," *Journal of Macromolecular Science—Polymer Reviews*, vol. 40, no. 1, pp. 69–83, 2000.
- [28] K. C. Gupta and M. N. V. Ravi Kumar, "An overview on chitin and chitosan applications with an emphasis on controlled drug release formulations," *Journal of Macromolecular Science—Polymer Reviews*, vol. 40, no. 4, pp. 273–308, 2000.
- [29] O. L. Shanmugasundaram, "Chitosan coated cotton yarn and its effect on antimicrobial activity," *Journal of Textile and Apparel, Technology and Management*, vol. 5, no. 3, 1 pages, 2006.

- [30] I. F. Amaral, P. L. Granja, and M. A. Barbosa, "Chemical modification of chitosan by phosphorylation: an XPS, FT-IR and SEM study," *Journal of Biomaterials Science, Polymer Edition*, vol. 16, no. 12, pp. 1575–1593, 2005.
- [31] M. Bem, F. Badea, C. Draghici et al., "4-(D-Glucosamino)-7-nitrobenzoxadiazole: synthesis, anomers, spectra, TLC behavior, and applications," *Arkivoc*, vol. 2008, no. 2, pp. 218–234, 2008.
- [32] K. Abouzid and S. Shouman, "Design, synthesis and in vitro antitumor activity of 4-aminoquinoline and 4-aminoquinazoline derivatives targeting EGFR tyrosine kinase," *Bioorganic and Medicinal Chemistry*, vol. 16, no. 16, pp. 7543–7551, 2008.
- [33] S. I. Kovalenko and O. V. Karpenko, in *Proceedings of the 10th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-10)*, November 2006.
- [34] A. Krantz, R. W. Spencer, T. F. Tam et al., "Design and synthesis of 4H-3,1-benzoxazin-4-ones as potent alternate substrate inhibitors of human leukocyte elastase," *Journal of Medicinal Chemistry*, vol. 33, no. 2, pp. 464–479, 1990.