Use of 2-Ethoxy(4H)-3,1-benoxazin-4-one as a Precursor for Synthesis of Quinazoline and Quinazolinone Starting Materials

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Abstract:
The interactions of 2-ethoxy(4H)-3,1-benoxazin-4-one (1) with various nitrogen nucleophiles such as ammonium acetate, hydrazine hydrate, ethanolamine, p-phenylenediamine, o-phenylenediamine, o-tolidine, dapsone, 2-aminophenol, 4-aminophenol, 4-aminobenzoic acid and 2-aminonicotinic acid have been discussed. The reactions of 2-thoxy-(3H)-quinazolin-4-one with ethyl chloroformate, phosphorus pentasulfide, chloroacetyl chloride and phosphorus oxychloride have also been investigated. Similar reactions of 2-ethoxy-4-chloroquinazoline with hydrazine hydrate and thiosemicarbazide have been introduced. Aminolysis of the 2-ethoxy group in some of the thiadiazoloquinazolinone derivatives has been attempted. The interactions of these aminolized derivatives and the 3-aminoquinazolinone with chloroacetyl chloride have been studied. All of the synthesized derivatives have been used in a wide range as starting materials for the synthesis of novel quinazoline and/or quinazolinones which have biological activity. The structures of all these products, obtained by heterocyclic ring opening and ring closure, were inferred by the IR, MS, 1H NMR spectral as well as elemental analyses.

Keywords: Aminothiadiazole, Benzoxazin-4-one, N-nucleophile, quinazoline, quinazolin-4-one, thiosemicarbazide.

1. Introduction
3,1-Benzoxazin-4-ones can be considered as semiacid anhydrides which undergo many of the reactions of true acid anhydrides, but at a slower rate. This special reactivity allows this class of compounds to be useful as antimicrobial (Mathew et al. 2010), anti-platelet aggregation (Pritchard et al. 2007), human leukocyte elastase inhibitors (Pei-Wen Hsieh et al. 2005), receptor agonist active (Ward et al. 2007), receptor antagonist active (Deswal et al. 2006, ohno et al. 2006, Kern et al. 2007, Powell et al. 2007, Bromidge et al. 2009), pesticides (Shakil et al. 2010), tissue culture protective and in vivo model of neurodegeneration (Wang et al. 2010) and improve the umbilical vein endothelial cells (Dong et al. 2010). On the other hand, in recent years, there has been an increasing interest in the chemistry of 4(3H)-quinazolinones because of their biological importance. Many of them show antifungal (Bartroli et al. 1998), antibacterial (Shiba et al. 1997), anticancer (Abdel-Hamid et al. 1997), anti-inflammatory (Barker 1995), anticonvulsant (Bekhit et al. 1998), immunotrophic (Gursoy et al. 1995), hypolipidemic (Nawrocka et al. 1997), antitumor (Kurogi et al. 1996), antiulcer (Hame et al. 1996), analgesic (Terashima et al. 1995),
antiproliferative activities (Raffa et al. 1999) and inhibitory effects (Baek et al. 1998) for thymidylate synthase and poly(ADP-ribose) polymerase (PARP) (Griffin et al. 1998). The 4(3H)-quinazolinones can act as semicyclic amides or iminols, due to the tautomeric phenomenon they have. Their reactions in either form with alkyl or acyl halides are perhaps the most interesting due to the large number of heterocycles that are obtained either directly or through further transformations of the initially formed products. Also quinazolines are a big family of heterocyclic compounds, which have shown broad variety of biological activity profiles (Jhone 1982, Brown 1996), e.g. analgesic, narcotic, diuretic, antihypertensive, antimalarial, sedative, hypoglycaemic, antibiotic, antitumoral and many others. It has been found (Armarego 1967) 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 (Nakagami et al. 1982, Haley 1994) anti-inflammatory (Palanki et al. 1999, Myers et al. 1998) anticancer (Baker 1999) anti-microbial and anti-hypertensive agents (Nauta 1976, Mizogami et al. 1986). Some 4-anilinoquinazolines have found to be potential and highly selective inhibitors of human immunoglobulin E (Berger et al. 2001) and epidermal growth factor receptor tyrosine kinase (Bridges 2001) which regulates the cell growth and proliferation, so they work as potent antiallergic or anticancer agents, respectively. Among the broad synthetic pathways for aminoquinazoline preparation (Katritzky et al. 1996 and 2000) 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, e.g. the tetrazole-bearing N-glycosides used as SGLT2 inhibitors (Gao et al. 2010) where their hypoglycemic activity is tested in vivo by mice oral glucose tolerance test (OGTT). In the current article 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 this paper we used the 2-ethoxy(4H)-3,1-benzoxazin-4-one (1) to synthesize novel quinazoline and quinazolinone derivatives having active functional groups which make their parent compounds important to be used as starting materials for novel derivatives. This advantage will be revealed by the functional group (or groups) residing on position 2 of the benzoxazinone ring, on positions 2 and 3 of the quinazolin-4-one ring and positions 2 and 4 of the quinazoline ring. Thus, the fusion of compound 1 with ammonium acetate gave the quinazolin-4-one 4 (Scheme 1).

\[
\text{Scheme 1: synthetic pathway for compound 2}
\]

The structure of compound 2 was inferred by its \( ^1H \) NMR spectrum that showed a singlet at \( \delta \ 12.30 \) which is attributable for NH group.
Compound 1 reacted with hydrazine hydrate in boiling ethanol to give 3-aminoquinazolinone 3 (Scheme 2).

The structure of compound 3 was assigned by its $^1$H NMR spectrum that showed a singlet at $\delta$ 2.00 which is attributable for amino group.

Compound 1 was interacted with 2-aminoethanol in boiling ethanol to afford compound 4 which on heating above its melting point (120-121 °C) yielded the desired product 4a (Scheme 3).

The elemental analyses and spectroscopic data for 4 and 4a were consistent with the assigned structures and isolation of 4 ruled out an abnormal nucleophilic addition to C-2 to form an amidine salt that subsequently dehydrates to give the desired product 4a (Dong et al 2010).

Compound 1 was reacted with $p$-phenylenediamine in boiling ethanol affording compound 5 (Scheme 4).

The structure of 5 was confirmed by microanalytical and spectral analysis.

Compound 1 was reacted with $o$-phenylenediamine in warming ethanol affording compound 6 (Scheme 5). Heating compound 6 above its melting point afforded compound 6a with traces of compound 6b.
The $^1$H NMR spectrum of 6a devoid any band for the carbonyl group whereas the $^1$H NMR of 6b devoid any band for the ethoxy group.

Compound 1 was reacted with o-tolidine in boiling ethanol to give compound 7 (Scheme 6).

![Scheme 6: synthetic pathway for compound 7]

The structure of compound 7 was assigned by its mass spectrum and elemental analysis.

Compound 1 was reacted with dapsone in boiling ethanol to give compound 8 (Scheme 7).

![Scheme 7: synthetic pathway for compound 8]

The structure of compound 8 was assigned by its mass spectrum and elemental analysis.

Compound 1 was reacted with 2-aminophenol in boiling ethanol to give compound 9 (Scheme 8).

![Scheme 8: synthetic pathway for compounds 9]

Compound 1 was reacted with 4-aminophenol in boiling ethanol to give compound 10 (Scheme 9).
The structures of compounds 9 and 10 were confirmed by microanalytical and spectral analysis.

Compound 1 was reacted with 4-aminobenzoic acid in boiling ethanol to give compound 11 (Scheme 10).

Compound 1 was reacted with 2-aminonicotinic acid in boiling ethanol to give compound 12 (Scheme 11).

The structures of products 11 and 12 were inferred by microanalytical and spectral analysis. The IR spectra for 11 and 12 showed absorption bands in the range 1704-1705 attributable to $\nu_{\text{max}}$ of C=O groups of acids.

Compound 2 was reacted with ethyl chloroformate in dry pyridine to give compound 13 (Scheme 12).

The IR spectrum devoid any band of NH but rather revealed an absorption band at 1762 attributable to $\nu_{\text{max}}$ of C=O group of ester.

Compound 2 was reacted with phosphorus pentasulfide in dry xylene to give compound 14 (Scheme 13).
The IR spectrum devoid any band of C=O in the carbonyl region but rather revealed an absorption band at 1319 attributable to $\nu_{\text{max}}$ of C=S group.

Compound 2 was reacted with phosphorus oxychloride in water bath to give compound 15 (Scheme 14).

The IR spectrum devoid any band of C=O in the carbonyl region.

Compound 15 was reacted with hydrazine hydrate in boiling ethanol to give compound 16 (Scheme 15).

The IR spectrum revealed an absorption band in the range 3250-3300 attributable to $\nu_{\text{max}}$ of NH$_2$ group.

Compound 15 was heated with thiosemicarbazide in AcOH / fused NaOAc to give product 17 (Scheme 16).

The IR spectrum revealed an absorption band at 1381 attributable to $\nu_{\text{max}}$ of C=S group.
Compound 1 was heated with thiadiazole derivatives in boiling AcOH/fused NaOAc affording compounds 18a-c (Scheme 17).

\[
\begin{align*}
\text{1} & \text{AcOH} \xrightarrow{\text{fused NaOAc}} \text{18a-c}
\end{align*}
\]

**Scheme 17**: synthetic pathway for compounds 18a-c

The structures of 18a-c were assigned by their mass spectra and elemental analysis.

Compounds 18a-c were fused with ammonium acetate or formamide to give products 19a-c (Scheme 18).

\[
\begin{align*}
\text{18a-c} & \text{HCONH}_2 \xrightarrow{\text{fusion / 2 h}} \text{19a-c}
\end{align*}
\]

**Scheme 18**: synthetic pathway for compounds 19a-c

The \(^1\text{H}\) NMR spectrum devoid any band of ethoxy group.

Compounds 19a-c were reacted with chloroacetyl chloride in pyridine to give products 20a-c (Scheme 19).

\[
\begin{align*}
\text{19a-c} & \text{ClCH}_2\text{COCl} \xrightarrow{\text{Pyridine / r.t.}} \text{20a-c}
\end{align*}
\]

**Scheme 19**: synthetic pathway for compounds 20a-c

Compound 3 was reacted with chloroacetyl chloride in pyridine to give compound 21 (Scheme 20).

\[
\begin{align*}
\text{3} & \text{ClCH}_2\text{COCl} \xrightarrow{\text{Pyridine / r.t.}} \text{21}
\end{align*}
\]

**Scheme 20**: synthetic pathway for compound 21

The \(^1\text{H}\) NMR spectra for 20 and 21 always revealed singlets at \(\delta 8.00\) and 8.11 for the amidicNH.
Experimental

All melting points recorded are uncorrected. The IR spectra were recorded on a Pye Unicam SP1200 spectrophotometer using KBr wafer technique. The $^1$H-NMR spectra were determined on a Varian FT-200, Brucker AC-200 MHz spectrophotometry experiment using TMS as an internal standard. Chemical shifts ($\delta$) 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(4H)–3,1–benzoxazin–4–one 1 was prepared according to methods available in the literature (Krantz et al 1990) and was immediately used after preparation, prior to each synthesis to avoid moisture.

2- Ethoxy-4(3H)quinazolinone 2. 2-ethoxy(4H)-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 yellowish white precipitate that separated out was filtered, washed, dried, and then crystallized from ethanol to give off-white crystals of compound 2. M.p. 155-156°C; yield 85 %; Anal. for C$_{16}$H$_{16}$N$_2$O$_2$ (m.w. 190); Found: C, 63.16; H, 5.26; N, 14.74; Calcd: C, 63.22; H, 5.18; N, 14.72; IR $\nu$ (cm$^{-1}$) 1671 (C=O), 3229 (NH); MS: m/z (int. %) [M+H]+ 190 (58%); $^1$H-NMR (DMSO-d$_6$) $\delta$ 1.19 (t, 3H; OCH$_2$CH$_3$), J = 7.4 Hz), 4.29 (q, 2H; OCH$_2$CH$_3$, J = 7.4 Hz), 7.31-8.17 (4d, 4H; ArH), 12.30 (br s, 1H, NH).

3-Amino-2-ethoxyquinazolin-4(3H)-one 3. 2-ethoxy-4H-3,1- benzoxazin-4-one (0.01 mol) was heated under reflux with hydrazine hydrate (0.02 mol) in ethanol (20 mL) for 3 h. The mixture was cooled, filtered and crystallized from ethanol as off-white needles; yield 68 %; m.p. 172-173 °C. Anal. for C$_{16}$H$_{16}$N$_2$O$_2$ (m.w. 205); Found: C, 58.59; H, 5.42; N, 20.56; Calcd: C, 58.53; H, 5.37; N, 20.49; IR $\nu$ (cm$^{-1}$) 1671 (C=O), 1528 (C=N); 3389 (NH); 3443 (CH); MS: m/z (int. %) [M+H]+ 205 (78.3); $^1$H-NMR (DMSO-d$_6$) $\delta$ 1.14 (t, 3H; OCH$_2$CH$_3$), 4.33 (q, 2H; OCH$_2$CH$_3$), 7.29-8.19 (m, 4H; ArH), 2.0 (s, NH, amine).

Synthesis of Compounds 4 and 4a

A mixture of compound 1 and ethanolamine (0.01mol each) in boiling ethanol (30 mL) was refluxed for 3h. Concentration of the solvent left a white precipitate of compound 4 which was crystallized from ethanol to affording off-white crystals. Heating of 4 above its melting point yielded the corresponding product 4a.

2-Ethoxycarbonylamino(β-hydroxyethyl)benzamide 4. Yellowish white crystals from ethanol; m.p. 120-121 °C; yield 80 %; Anal. for C$_{16}$H$_{16}$N$_2$O$_4$ (m.w. 252); Found: C, 57.21; H, 6.29; N, 11.13; Calcd: C, 57.14; H, 6.35; N, 11.11; IR $\nu$ (cm$^{-1}$) 1636 (C=O), 1737 (C=O), 3069 (CH), 3130 (NH), 3342 (OH); MS: m/z (int. %) [M+H]+ 252 (42.3).

2-Ethoxy–3-(2-hydroxyethyl)quinazolin–4–one 4a. Light brown crystals; m.p. 108-109 °C; yield 75 %; Anal. for C$_{16}$H$_{16}$N$_2$O$_3$ (m.w. 234); Found: C, 61.05; H, 5.98; N, 12.03; Calcd: C, 61.54; H, 5.98; N, 11.97; IR $\nu$ (cm$^{-1}$) 1660 (C=O), 3340 (OH); MS: m/z (int. %) [M+H]+ 234 (58.0), 236 (12.8), 190 (100), 192 (22.3); 174 (22.3), 176 (12.4); $^1$H-NMR (DMSO-d$_6$) $\delta$ 1.19 (t, 3H; OCH$_2$CH$_3$), J = 7.4 Hz), 3.52 (m, 2H, 2'-H), 4.32 (q, 2H; OCH$_2$CH$_3$, J = 7.4Hz), 4.13 (m, 1H, 1'-H), 5.72 (s, br., OH), 7.41- 8.16 (4 d, 4H; ArH).

2-Ethoxy-3-(4-aminophenyl)quinazolin-4-one 5. A mixture of compound 1 (0.01 mol) and p-phenylene diamine (0.01 mol) in boiling ethanol (30 mL) was refluxed for 3 h. Concentration of the solution gave a solid which was filtered, washed, dried and then crystallized from ethanol to give blue crystals of product 5; m.p. 105-106 °C; yield 80 %. Anal. for C$_{16}$H$_{16}$N$_2$O$_2$ (m.w. 278); Found: C, 69.22; H, 4.16; N, 15.08; Calcd: C, 69.06; H, 4.32; N, 15.10; IR $\nu$ (cm$^{-1}$) 1635 (C=N), 1670 (C=O), 3225 (NH). MS: m/z (int. %) [M+H]+ 278 (55.0), 280 (18.2), 191 (100), 193 (31.7), 175 (32.1), 177 (0.8), 157 (4.7), 159 (0.6), 130 (52.4), 132
Reactions of Compound 1 with o-phenylene diamine:

A mixture of compound 1 and o-phenylenediamine (0.01 mol each) was slightly warmed in ethanol (30 mL) for 15 min. The precipitate that separated out was filtered, washed, dried and then crystallized from ethanol to give light blue crystals of product 6. Heating product 6 above its melting point gave dark blue residue of unstable melting point. Crystallization of the residue, using different ratios of benzene/ethanol, enabled the products 6a and 6b to be isolated. The purity of products was checked by different melting points and TLC.

3-(2-aminophenyl)-2-ethoxyquinazolin-4(3H)-one 6. M.p. 105-106 ºC; yield 80 %. Anal. for C19H12N3O2 (m.w. 278); Found: C, 69.22; H, 4.16; N, 15.08; Calcd: C, 69.06; H, 4.32; N, 15.10; IR u (cm^-1) 1635 (C=N), 1670 (C=O), 3225 (NH). MS: m/z (int. %) [M+H]^+ 278 (55.0), 280 (18.2), 191 (100), 193 (31.7), 175 (32.1), 177 (0.8), 157 (4.7), 159 (0.6), 130 (52.4), 132 (0.3), 93 (0.9), 95 (0.1), 78 (0.2), 80 (0.1); ^1H-NMR (DMSO-d6) δ 1.22 (t, 3H; OCH3), 2.21 (t, 3H; OCH3), 4.47 (q, 2H: OCH2CH3, J = 6.9 Hz), 5.12 (s, 2H, NH2), 6.70-7.43 (m, 4H; Ph-H), 7.47-8.19 (m, 4H, quinazolone).

2-Ethoxy benzimidazo-[1,2-c]quinazoline 6a. M.p. 191-192 ºC; yield 85 %. Anal. for C16H13N3O (m.w. 263); Found: C, 73.02; H, 4.94; N, 15.98; Calcd: C, 73.00; H, 4.94; N, 15.97; IR u (cm^-1) 1607 (C=N). MS: m/z (int. %) [M+H]^+ 263 (66.0), 265 (17.3), 187 (44.8), 189 (4.8), 175 (28.4), 177 (11.1), 157 (3.3), 159 (0.1), 130 (78.9), 132 (12.4), 78 (2.4), 80 (0.1); ^1H-NMR (DMSO-d6) δ 1.22 (t, 3H; -OCH2CH3, J = 7.1 Hz), 4.31 (q, 2H; OCH2CH3, J = 7.1), 7.52-7.92 (m, 4H, benzimidazole), 7.62-8.55 (2m, 4H; quinazoline).

Benzimidazo[2,1-b]quinazolin-5(1H)-one 6b. M.p. 202-203 ºC; yield 23 %. Anal. for C17H15N3O (m.w. 235); Found: C, 71.56; H, 3.85; N, 17.91; Calcd: C, 71.49; H, 3.83; N, 17.87; IR u (cm^-1) 1607 (C=N). MS: m/z (int. %) [M+H]^+ 235 (26.0), 237 (1.8); ^1H-NMR (DMSO-d6) δ 7.52-7.92 (m, 4H, PhH), 7.62-8.55 (2m, 4H; quinazoline), 6.88 (br s, 1 H, NH).
A mixture of compound 1 and ω-hydroxyaniline or ρ-hydroxyaniline (0.01 mol each) in 40 mL of boiling ethanol was refluxed for 3 h. The obtained precipitate was heated in a round bottom flask (25 mL) in an oil bath at 160 °C for 30 minutes. After cooling the products were crystallized from the proper solvent to give the corresponding quinazolinones 9 and 10, respectively.

2-Ethoxy-3-(2-hydroxyphenyl)quinazolin-4-one 9. Dark brown crystals from light petroleum (100-120 °C); m.p. 89-90 °C; yield 80 %; Anal. for C_{16}H_{14}N_{2}O_{3}: C, 67.31; H, 4.73; N, 9.89; Calcd: C, 67.60; H, 4.93; N, 9.86; IR ν (cm⁻¹) 1669 (C=O), 2988 (OH); MS: m/z (%) [M+H]^+ 284 (48.0), 286 (6.3), 191 (100), 193 (43.3), 175 (18.2), 177 (0.1), 157 (4.7), 159 (1.2), 130 (67.1), 132 (63.3); ¹H-NMR (DMSO-d₆) δ 1.22 (t, 3H; -OCH₂CH₃, J = 7.4 Hz), 4.36 (q, 2H; -OCH₂CH₃, J = 7.4 Hz), 5.55 (s, H; OH), 6.76 – 7.67 (m, 4H; Ph-H), 7.30 – 8.19 (m, 4H, quinazolinone).

2-Ethoxy-3-(4-hydroxyanisol)-quinazolin-4-one 10. Dark brown crystals from benzene: m.p. 105-106 °C; yield 80 %; Anal. for C_{16}H_{14}N_{2}O₃ (m.w. 284): Found: C, 67.42; H, 4.70; N, 9.81; Calcd: C, 67.60; H, 4.93; N, 9.86; IR ν (cm⁻¹) 1671 (C=O), 2992 (OH); MS: m/z (%) [M+H]^+ 284 (43.0), 286 (16.3), 191 (100), 193 (52.3), 175 (20.8), 177 (0.1), 157 (4.3), 159 (0.5), 130 (57.4), 132 (7.9); ¹H-NMR (DMSO-d₆) δ 1.22 (t, 3H; -OCH₂CH₃, J = 7.4 Hz), 4.35 (q, 2H; -OCH₂CH₃, J = 7.4 Hz), 5.35 (s, H; OH), 6.68-7.69 (m, 4H; Ph-H), 7.43-8.19 (m, 4H, quinazolinone).

4-[2-Ethoxy-4-quinazol-3-yl]benzoic acid 11. A mixture of compound 1 (0.01 mol) and p-aminobenzoic acid in boiling butanone (30 mL) was refluxed for 3 h. Concentration of the solution gave a solid which was washed, filtered, dried and then crystallized from ethanol affording derivatives 11 as light brown crystals of m.p. 151-152 °C; yield 80 %; Anal. for C₁₇H₁₂N₂O₄ (m.w. 310): Found: C, 65.44; H, 4.72; N, 9.00; Calcd: C, 65.80; H, 4.52; N, 9.03; IR ν (cm⁻¹) 1675, 1705 (2xC=O), 3355 (chelated OH); MS: m/z (%) [M+H]^+ 310 (63.0), 312 (28.2), 191 (100), 193 (27.8), 175 (34.3), 177 (0.6), 130 (59.3), 132 (0.2), 122 (1.8), 124 (0.2), 78 (0.1), 80 (0.1); ¹H-NMR (DMSO-d₆) δ 1.22 (t, 3H; -OCH₂CH₃, J = 6.9 Hz), 4.36 (q, 2H; -OCH₂CH₃, J = 7.4 Hz), 7.40-8.00 (m, 4H; Ph-H), 7.43-8.19 (m, 4H, quinazolinone), 10.6 (1H, acid proton).

2-[2-Ethoxy-4-oxoquinazolin-3(4H)-yl]pyridine-3-carboxylic acid 12. A mixture of benzoxazine 1 (0.01 mol) and 2-amino nicotinic acid (0.01 mol) in boiling butanone (30 mL) was refluxed for 6 h. Concentrating the solution gave a solid which was washed, filtered, dried and then crystallized from ethanol affording the quinazolinone 12 as brown crystals; m.p. 298-300 °C; yield 80 %; Anal. for C₁₆H₁₂N₂O₄ (m.w. 311): Found: C, 61.58; H, 4.26; N, 13.20; Calcd: C, 61.74; H, 4.18; N, 13.50; IR ν (cm⁻¹) 1669, 1704 (2xC=O), 3255 (chelated OH); MS: m/z (%) [M+H]^+ 311 (36.0), 313 (19.5), 191 (100), 193 (28.6), 175 (61.8), 177 (7.6), 157 (5.2), 159 (1.1), 130 (58.2), 132 (0.6), 123 (0.7), 125 (0.2), 79 (0.7), 81 (0.1); ¹H-NMR (DMSO-d₆) δ 1.22 (t, 3H; -OCH₂CH₃, J = 6.9 Hz), 4.37 (q, 2H; -OCH₂CH₃, J = 6.9 Hz), 7.44-8.20 (m, 4H; quinazolinone), 6.97, 7.87, 8.41 (m, 3H; H-4, H-5, H-6, pyridine moiety).

3-Ethoxycarbonyl-2-ethoxyquinazolin-4-one 13. Compound 2 (0.01 mol) was heated under refluxed with ethyl chloroformate (0.01 mol) in 50 mL of dry pyridine for 4h. The excess solvent was distilled off and the solution was left to cool and then poured onto ice with stirring to obtain a crude product, which was filtered off, thoroughly washed with cold water, and dried and crystallized from benzene affording products 13 as white crystals; m.p. 177-178 °C; yield 92 %. Anal. for C₁₆H₁₂N₂O₄ (m.w. 262): Found: C, 59.65; H, 5.39; N, 10.68; Calcd: C, 59.54; H, 5.34; N, 10.69; IR ν (cm⁻¹) 1672, 1762 (2xC=O); MS: m/z (%) [M+H]^+ 262 (88.5); ¹H-NMR (DMSO-d₆) δ 1.19 (t, 3H; -OCH₂CH₃, J = 7.4 Hz), 1.15 (t, 3H, CH₃, COOCH₂CH₃), 4.24 (q, 2H, CH₂, COOCH₂CH₃), 4.34 (q, 2H; -OCH₂CH₃, J = 7.4 Hz), 7.43-8.17 (m, 4H, ArH).

2-Ethoxy-4(3H)quinazolin-4-thione 14. A solution of compound 2 and P₂S₅ (0.03 mol each) in dry xylene (50 mL) was boiled for 6 h. The reaction mixture was filtered while hot and then concentrated. The product
separated on cooling was crystallized from ethanol to give the product 14. Brown crystals of m.p. 137-138 °C; yield 65 %. Anal. for C₉H₁₀N₂O₂ (m.w. 206); Found: C, 58.15; H, 4.81; N, 13.52; S, 15.53; Calcd: C, 58.25; H, 4.85; N, 13.59; S, 15.53; IR ν (cm⁻¹) 1319 (C=S), 1597 (C=N), 3137 (NH); MS: m/z (int. %) [M+H]+ 206 (55.7); 1H-NMR (DMSO-d₆) δ 1.19 (t, 3H, -OCH₃CH₂, J = 7.4 Hz), 4.39 (q, 2H, -OCH₂CH₃, J = 7.4 Hz), 7.29-7.67 (m, 4H, ArH), 12.3 (br s, 1H, NH).

4-Chloro-2-ethoxyquinazoline 15. A solution of 2-ethoxy-4(3H)quinazolinone 1 (0.01 mol) in phosphorus oxychloride (20 mL) was heated on a water bath at 70 °C for 2 h. The reaction mixture was then cooled and diluted with ice/water and the resulting precipitate was collected by filtration and recrystallized from CHCl₃ chloroform giving product 15 as light brown crystals; m.p. 180-182 °C; yield 85 %. Anal. For C₉H₈N₂O₂Cl (m.w. 208.5); Found: C, 57.45; H, 4.31; N, 13.42; Cl, 17.00; Calcd: C, 57.55; H, 4.30; N, 13.43; Cl, 17.02; IR ν (cm⁻¹) 1622 (C=N); MS: m/z (int. %) [M+H]+ 208.5 (57.9); 1H-NMR (DMSO-d₆) δ 1.19 (t, 3H, -OCH₃CH₂, J = 7.4 Hz), 4.19 (q, 2H, -OCH₂CH₃, J = 7.4 Hz), 7.49-8.86 (m, 4H, ArH).

2-Ethoxyquinazolin-4-ylhydrazine 16. An emulsion of product 15 (0.01mol) 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 crystallized from ethanol giving redish brown crystals of product 16. Yield 68 %; m. p. 156-158 °C. Anal. For C₁₀H₁₀N₂O₂ (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 (NH); MS: m/z [M+H]+ 204; 1H-NMR (DMSO-d₆) δ 1.18 (t, 3H, CH₃ of ethoxy J = 7.4 Hz), 4.17 (q, 2H, CH₂ of ethoxy J = 7.4 Hz), 7.40 - 8.06 (m, 4H, ArH), 8.65 (br. s, 3H, NH and NH₂).

4-(2-Ethoxyquinazolin-4-yl)thiosemicarbazide 17. A mixture of the quinazoline 15 and thiosemicarbazide (0.01 mol each) was heated under reflux in acetic acid / fused sodium acetate (30 mL / 2 g) for 3 h. Pouring the solution onto ice/water left a white solid which was filtered, washed with water, dried and recrystallized from ethanol giving white crystals of compound 17; yield 74 %; m. p. 128 -130 °C. Anal. For C₁₀H₁₀N₂O₂ (m.w. 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 NH₂). MS: m/z [M]+ 263 (77%). 1H-NMR (DMSO-d₆) δ 1.20 (t, 3H; CH₃ of ethoxy J = 7.2 Hz), 4.15 (q, 2H; CH₂ of ethoxy J = 7.2), 7.44-8.06(4d, 4H, ArH), 8.41 - 9.34 (2 br. s, 4H, 2NH and NH₂).

Synthesis of Compounds 18a-c

A mixture of compound 1 (0.01 mol) and the aminothiadiazole derivatives 2-phenyl-5-aminothiadiazole, 2-cinnamyl-5-aminothiadiazole and 2-phthalimidomethyl-5-aminothiadiazole (0.01 mol) was heated under reflux in boiling acetic acid / fused sodium acetate (30 mL / 2 g) for 3 h. The solution was poured into an ice / water mixture, stirred and left to settle down affording a white solid. The resulting solid was filtered, washed, dried and finally recrystallized from the proper solvent affording the derivatives 18a-c.

5-[2-Ethoxy-quinazolone-3-yl]-2-phenylthiadiazole 18a. Brown crystals from DMF; m. p. 172-173 °C; yield 85 %. Anal. for C₁₀H₁₀N₂O₂S (m.w. 350); Found: C, 61.88; H, 4.04; N, 16.08; S, 9.17; Calcd: C, 61.71; H, 4.00; N, 16.00; S, 9.14; IR ν (cm⁻¹) 1630 (C=N), 1669 (C=O). MS: m/z (int. %) [M]+ 350 (78.0), 352 (31.1), 191 (100), 193 (23.7), 157 (4.4), 159 (0.1), 175 (49.5), 177 (9.7), 162 (38.2), 164 (3.6), 130 (61.2), 132 (4.1), 103 (1.8), 105 (0.2), 78 (0.7), 80 (0.1); 1H-NMR (DMSO-d₆) δ 1.22 (t, 3H; -OCH₂CH₃, J = 7.1 Hz), 4.40 (q, 2H; -OCH₂CH₃, J = 7.1 Hz), 7.41 - 7.94 (m, 5H, Ph-H), 7.44 - 8.20 (m, 4H, quinazolinone).

5-[2-Ethoxy-quinazolone-3-yl]-2-cinnamylthiadiazole 18b. Brown crystals from DMF; m. p. 289-290 °C; yield 85 %. Anal. for C₂₀H₁₆N₄O₂ (m.w. 376); Found: C, 68.99; H, 4.72; N, 16.00; S, 9.03; Calcd:
The quinazolinone thiadiazole derivative 18a-c was heated under reflux with formamide (0.01 mol each) for 3 h. The mixture was poured onto ice/water mixture with stirring leaving a white material to separate out and then begin to solidify forming gum. This material was washed with water, filtered and crystallized from ethanol as off-white needles of 19a-c.

5-[[2-Ethoxyquinazolone-3-yl]-2-phenylamidomethylthiadiazole] 18c. Brown crystals from DMF; m.p. 303-304 °C; yield 85 %. Anal. for C_{20}H_{18}N_{2}O_{3}S (m.w. 433): found: C, 58.72; H, 3.66; N, 16.31; S, 7.42; Calcd: C, 58.20; H, 3.46; N, 16.17; S, 7.39. IR ν (cm⁻¹) 1631 (C=N), 1670, 1727, 1776 (3xC=O). MS: m/z (int. %) [M+H]⁺ 433 (58.0), 435 (22.8), 245 (36.4), 247 (3.4), 191 (100), 193 (56.1), 186 (78.0), 188 (12.7), 175 (30.1), 177 (8.1), 157 (0.1), 147 (8.3), 149 (0.3), 130 (48.3), 132 (6.4), 122 (4.5), 124 (0.2), 78 (0.3), 80 (0.1); ¹H-NMR (DMSO-d₆) δ 8.20 (t, 3H; -OCH₂CH₃, J = 7.1 Hz), 4.43 (q, 2H; -OCH₂CH₃, J = 7.1 Hz); 7.42-8.20 (4d, 4H, quinazolinone), 7.35 - 7.45 (m, 5H, Ph-H), 7.20, 7.47 (2d, 2H, J = 15.8 Hz, olefinic-H).

Synthesis of Compounds 19a-c

The quinazolinone thiadiazole derivative 18a-c was heated under reflux with formamide (0.01 mol each) for 3 h. The mixture was poured onto ice/water mixture with stirring leaving a white material to separate out and then begin to solidify forming gum. This material was washed with water, filtered and crystallized from ethanol as off-white needles of 19a-c.

5-[[2-Amino-4-oxoquinazolin-3(4H)-yl]-2-phenylthiadiazole] 19a. Yield 73 %, m.p. 243-245 °C. Anal. for C_{21}H_{18}N_{2}O_{3}S (m.w. 350); found: C, 61.76; H, 4.04; N, 16.02; S, 9.17; Calcd: C, 61.71; H, 4.00; N, 16.00; S, 9.14; IR ν (cm⁻¹) 1669 (C=O), 1531 (C=N); 3330 (NH); 3444 (CH); MS: m/z (int. %) [M+H]⁺ 350 (72.3); ¹H-NMR (DMSO-d₆) δ 2.11 (s, 2H, NH₂); 7.28-7.77 (m, 4H, quinazolinone), 7.41-7.93 (m, 5H, Ph-H).

5-[[2-Amino-4-oxoquinazolin-3(4H)-yl]-2-cinnamylthiadiazole] 19b. Yield 78 %, m.p. 262-263 °C. Anal. for C_{21}H_{18}N_{2}O_{3}S (m.w. 376); found: C, 63.87; H, 4.27; N, 14.91; S, 8.53; Calcd: C, 63.83; H, 4.26; N, 14.89; S, 8.51; IR ν (cm⁻¹) 1670 (C=O), 1529 (C=N); 3392 (NH); 3443 (CH); MS: m/z (int. %) [M+H]⁺ 376 (78.3); ¹H-NMR (DMSO-d₆) δ 2.04 (s, NH, NH₂), 7.20, 7.47 (2d, 2H, J = 15.8 Hz, olefinic-H), 7.34-7.44 (m, 5H, Ph-H), 7.30-7.77 (m, 4H, quinazolinone).

2-[[5-(2-Amino-4-oxoquinazolin-3(4H)-yl)-1,3,4-thiadiazol-2-yl]methyl]-1H-isindole-1,3(2H)-dione 19c. Yield 68 %, m.p. 272-273 °C. Anal. for C_{21}H_{18}N_{2}O_{3}S (m.w. 404); found: C, 56.49; H, 2.99; N, 20.83; S, 7.95; Calcd: C, 56.44; H, 2.97; N, 20.79; S, 7.92; IR ν (cm⁻¹) 1671, 1730, 1790 (3xC=O), 1528 (C=N); 3389 (NH); 3443 (CH); MS: m/z (int. %) [M+H]⁺ 404 (78.3); ¹H-NMR (DMSO-d₆) δ 2.00 (s, 2H, NH₂), 7.29-8.19 (m, 4H, ArH), 7.30-7.77 (m, 4H, quinazolinone).

Synthesis of Compounds 20a-c

Compound 19a-c (0.01 mol) was dissolved in 50 mL of dry toluene and cooled to 15 °C. To this solution was added drop wise an equimolar amount of chloroacetyl chloride with frequent stirring. The temperature of the reaction was brought slowly to room temperature an then the solution was heated under reflux for 4h. The excess toluene was distilled off and the resultant precipitate was filtered, washed repeatedly with dry toluene, dried and crystallized from aqueous dioxane affording compounds 20a-c.

2-Chloro-N-[3-(5-phenyl-1,3,4-thiadiazol-2-yl)-4-oxo-3,4-dihydroquinazolin-2-yl]acetamide 20a. White crystals from dioxane; m.p. 163-164°C, yield 77 %. Anal. For C_{13}H_{12}ClN_{2}O_{3} (m.w. 397.5); found: C, 54.38; H, 3.05; Cl, 8.96; N, 17.66; S, 8.08; Calcd: C, 54.34 ; H, 3.02; Cl, 8.93; N, 17.61; S, 8.05; IR ν (cm⁻¹) 3230 (N-H), 3023 (Ar-H), 2995 (C=H₂), 1668, 1699 (CO), 763 (CCl); MS: m/z (int. %) [M+H]⁺ 397.5...
(68.4); ^1H-NMR (DMSO-d$_6$) δ 4.41 (s, 2H, CH$_2$Cl), 8.11 (s, 1H, NH), 7.38-7.93 (m, 4H, Ph-H) 7.21-8.19 (m, 4H, quinazolinone).

2-Chloro-N-[4-oxo-3-{5-[(E)-2-phenylethenyl]-1,3,4-thiadiazol-2-yl}-3,4-dihydroquinazolin-2-yl]acetamide 20b. White crystals from dioxane; m.p. 171-173°C, yield 81 %. Anal. For C$_2$H$_4$ClN$_2$O$_5$S (m.w. 423.5); Found: C, 56.71; H, 3.33; Cl, 8.40; N, 16.55; S, 7.58; Calcd: C, 56.67; H, 3.31; Cl, 8.38; N, 16.53; S, 7.56; IR υ (cm$^{-1}$) 3205 (N-H), 3010 (Ar-H), 2935 (CH$_2$), 1666, 1694, (CO), 775 (CCI); MS: m/z (int. %) [M+H]$^+$ 423.5 (73.4); ^1H-NMR (DMSO-d$_6$) δ 4.41 (s, 2H, CH$_2$Cl), 8.00 (s, 1H, NH), 7.20, 7.47 (2 d, 2 H, olefin-H), 7.28-7.45 (m, 4H, cinnamyl moiety), 7.27-8.14 (m, 4H, quinazolinone).

2-Chloro-N-[3-{5-[(1,3-dioxo-1,3-dihydro-2H-isoinodol-2-yl)methyl]-1,3,4-thiadiazol-2-yl}-4-oxo-3,4-dihydroquinazolin-2-yl]acetamide 20c. White crystals from dioxane; m.p. 179-181°C, yield 73 %. Anal. for C$_2$H$_4$ClN$_2$O$_5$S (m.w. 480.5); Found: C, 52.48; H, 2.74; Cl, 7.43; N, 14.57; S, 6.71; Calcd: C, 52.44; H, 2.71; Cl, 7.39; N, 14.48; S, 6.66; IR υ (cm$^{-1}$) 3205 (N-H), 3010 (Ar-H), 2935 (CH$_2$), 1666, 1694, 1776 (CO), 775 (CCI); MS: m/z (int. %) [M+H]$^+$ 480.5 (73.4); ^1H-NMR (DMSO-d$_6$) δ 4.60 (s, 2H, CH$_2$Cl), 8.00 (s, 1H, NH), 7.25-7.85 (m, 4H, quinazolinone), 7.96-8.03 (m, 4H, phthalimido moiety).

2-Chloro-N-(2-ethoxy-4-oxoquinazolin-3(4H)-yl)acetamide 21. Compound 3 (0.01 mol) was dissolved in 50 mL of dry toluene and cooled to 15 °C. To this solution was added drop wise an equimolar amount of chloroacetyl chloride with frequent stirring. The temperature of the reaction was brought slowly to room temperature and then the solution was heated under reflux for 4 h. The excess toluene was distilled off and the resultant precipitate was filtered, washed repeatedly with dry toluene, dried and then crystallized from aqueous dioxane as white crystals of compound 21, m.p. 149-151 °C, yield 73 %. Anal. for C$_3$H$_4$ClN$_2$O$_3$S (m.w. 281.5); Found: C, 51.15; H, 4.26; N, 14.92; Cl, 12.61; Calcd: C, 51.22; H, 4.29; N, 14.99; Cl, 12.66; IR υ (cm$^{-1}$) 3205 (N-H), 3010 (Ar-C), 2935 (CH$_2$), 1666, 1694 (CO), 1568, 1328 (CN), 775 (CCI); MS: m/z (int. %) [M+H]$^+$ 281 (73.4); ^1H-NMR (DMSO-d$_6$) δ 1.15 (t, 3H, OCH$_2$CH$_3$), 4.31 (s, 2H, CH$_2$Cl), 4.43 (q, 2H, OCH$_2$CH$_3$), 8.0 (s, 1H, NH), 7.28-8.20 (m, 4H, ArH).

3-Chloroacetyl-2-ethoxyquinazolin-4-one 22. Compound 2 (0.01 mol) was refluxed with chloroacetyl chloride (0.01 mol) in 50 mL of dry pyridine for 4 h. The excess solvent was distilled off and the solution was left to cool and then poured onto ice with frequent stirring till a crude product was obtained. The latter was filtered off, thoroughly washed with cold water, dried and crystallized from ethanol affording brownish white crystals of derivative 8; m.p. 152-153 °C; yield 85 %. Anal. for C$_3$H$_4$ClN$_2$O$_3$S (m.w. 266.5); Found: C, 54.52; H, 5.69; N, 7.92; Cl, 13.32; Calcd: C, 54.54; H, 5.68; N, 7.95; Cl, 13.28; IR υ (cm$^{-1}$) 1668, 1717 (2 C=O), 2823 (CH); MS: m/z (int. %) [M+H]$^+$ 266.5 (77.3); ^1H-NMR (DMSO-d$_6$) δ 1.2 (t, 3H, -OCH$_2$CH$_3$), J = 7.4 Hz), 4.36 (q, 2H, -OCH$_2$CH$_3$), J = 7.4 Hz), 4.29 (d, 2H, CH$_2$Cl), 7.45-8.20 (m, 4H, ArH).

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**References**


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