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Synthesis of novel quinazolinone and fused quinazolinones

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ABSTRACT

A number of novel quinazolinone derivatives have been synthesized using the readily obtainable 2-[(1*Z*,3*E*)-1-benzamido-4-phenyl-1,3-butadien-1-yl]-3,1-benzoxazin-4(*H*)one (**1**) via the reaction with different nitrogen nucleophiles such as azines, Schiff's base, primary aromatic amines, diamines, hydrazine hydrate and hydroxylamine.

1. Introduction

Benzoxazinones (BAS) are natural products that are present in Gramineae [1] and represent part of the plant defense system against pests, including insects, bacteria and fungi [2,3]. Several studies on the acute toxic effects of BAS in insects and bacteria have been published [4-8]. Quinazolinone alkaloids possess a diverse range of biological activities including cytotoxicity [9], anti-inflammatory [10], anticancer, antimicrobial, anticonvulsant [11-15] and cardiovascular activity [16,17]. These compounds also act as cardiotonic, antihistaminic, antifungal, antiviral, antimycobacterial and antimalarial agents [18-24] and they have demonstrated psychotropic, hypnotic and a range of other central nervous system (CNS) effects [25-27]. In view of their natural occurrence, biological activities and utility as synthetic intermediates [28-33], we report here the synthesis of novel benzoxazinone and quinazolinone derivatives starting from the readily obtainable 2-[(1*Z*,3*E*)-1-benzamido-4-phenyl-1,3-butadien-1-yl]-3,1-benzoxazin-4(*H*)one (**1**) which prepared via the reaction of oxazolone derivative with anthranilic acid in boiling acetic acid according to the published procedure [34].

2. Experimental

All melting points were taken on Griffin and Geory melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP1200 spectrophotometer using KBr Wafer technique. ^{1}H NMR spectra were determined on a Varian Gemini 200 MHz using TMS as internal standard (chemical shifts in δ-scale). EI-MS were measured on a Shimadzu-GC-MS operating at 70 eV. ^{13}C NMR spectra were measured on Jool 75 MHz. Elemental analyses were carried out at the Microanalytical unit, Faculty of Science, Ain Shams University by using Perkin-Elmer 2400 CHN elemental analyzer and satisfactory analytical data (± 0.4) were obtained for all compounds. The homogeneity of the synthesized compounds was controlled by TLC [Using TLC aluminum sheets silica gel F_{254} (Merck)].

2.1. 2-[(1Z,3E)-1-benzamido-4-phenyl-1,3-butadien-1-yl]-3,1-benzoxazin-4(H)-one (1)

A mixture of 4-cinnamylidene-2-phenyl-Δ^2-oxazol-5-one (2.73 g, 0.01 mol) and anthranilic acid (1.37 g, 0.01 mol) in acetic acid (20 mL) and freshly distilled acetic anhydride (10 mL) was refluxed for 10 hrs until no more substrate (TLC). The reaction mixture was poured on water (100 mL) and stirred for 20 min. The yellow solid separated was collected by filtration, washed with water several times, then with sodium bicarbonate solution (10%, 40 mL). The solid was filtered off, washed with water, dried and then recrystallized from ethanol to give **1** as lemon yellow crystals. Yield: 64%. M.p.: 84-86 °C. FT-IR (KBr, cm^{-1}): 3292 ν(NH), 1771 ν(C=$O_{δ\text{-lactone}}$), 1678 ν(C=O_{amide}), 1642 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 8.90 (s, 1H, NH, exchangeable with D_2O), 8.08-7.40 (m, 14$H_{arom.}$), 7.10-5.60 (m, 3H). ^{13}C NMR (200 MHz, $CDCl_3$): 167.1 (CO_{amide}), 160.1 (C_4), 158.2 (C_2), 133.7 (C_4'), 134.1 (C_5), 130.1 (C_7), 128.6 (C_6), 127.2 (C_8), 126.3 (C_3'), 120.3 (C_1'), 109.3 (C_2'), 133.2, 128.1, 126.6, 130.2 (phenyl of benzamido group), 135.0, 128.3, 127.7, 128.2 (phenyl at C_4'). MS (EI, m/z (%)): 394 ($M^{+\cdot}$, 22.2), 366 (18.9), 289 (40.3), 147 (100), 105 (80.2), 77 (36.7). Anal. Calcd. for $C_{25}H_{18}N_2O_3$ (394): C, 76.14; H, 4.59; N, 7.1. Found: C, 75.92; H, 4.66; N, 7.06%.

2.2. 2-[(2Z,4E)-2-benzamido-5-phenylpenta-2,4-dienamido]-N-p-tolylbenzamide (2)

Method 1: To a solution of **1** (1.2 g, 0.003 mol) in dry benzene (20 mL), 4-chlorobenzylidene-4-methylaniline (0.65 g,

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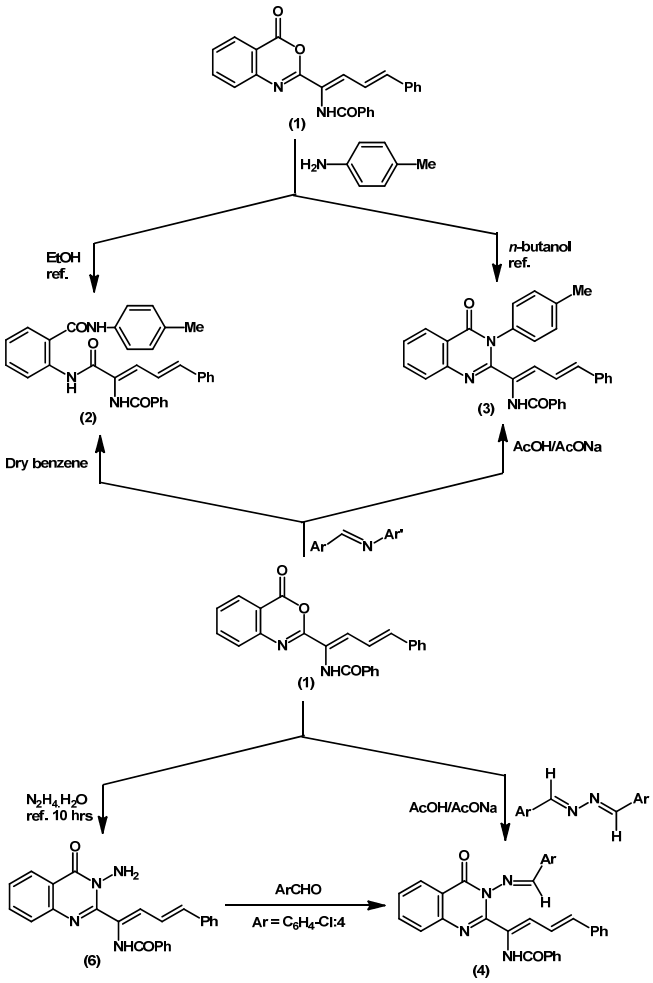


Scheme 1

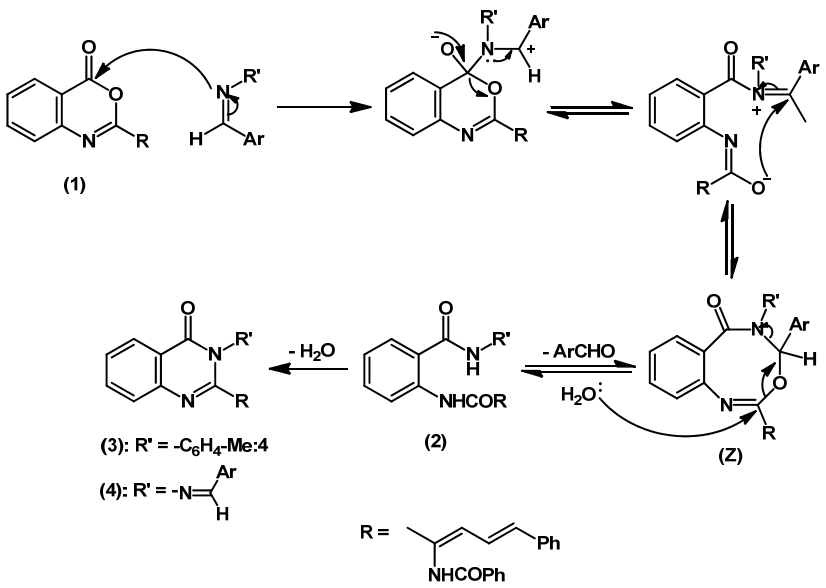
0.003 mol) was added and then the reaction mixture was heated under reflux for 6 hrs (TLC). The solid formed after cooling was filtered off, dried and then recrystallized from benzene to give **2** as yellowish-white crystals (Scheme 1 and 2). Yield: 55%. M.p.: 176-178 °C. FT-IR (KBr, cm^{-1}): 3314, 3216 ν(NH), 1678, 1663, 1658 ν($C=O_{amides}$). ^1H NMR (200 MHz, $CDCl_3$): 10.33 (br. s., 2H, exchangeable with D_2O), 9.6 (s, 1H, exchangeable with D_2O), 8.4-7.4 (m, $18H_{arom.}$), 7.1-6.7 (m, 3H), 2.3 (s, 3H). MS (EI, m/z (%)): 502 ($M^{+\cdot}$+1, 22.6), 501 ($M^{+\cdot}$, 100), 395 (70.1), 276 (16.2), 105 (90.2), 91 (30.1), 77 (76.2). Anal. Calcd. for $C_{32}H_{27}N_3O_3$ (501): C, 76.64; H, 5.38; N, 8.38. Found: C, 76.34; H, 5.22; N, 8.75%.

Method 2: *p*-Toluidine (0.32 g, 0.003 mol) was added to a stirred solution of **1** (1.2 g, 0.003 mol) in ethanol (20 mL) and the reaction mixture was refluxed for 2 hrs (TLC). Evaporation of the excess ethanol left a crude pale yellow product which recrystallized from benzene to give **2**; yield 86.3% (identity m.p, mixed m.p, TLC).

2.3. 2-[(1Z,3E)-1-benzamido-4-phenyl-1,3-butadien-1-yl]-3-(4-methylphenyl) quinazolin-4(H)-one (3)

Method 1: A mixture of **1** (3.49 g, 0.01 mol), Schiff's base (4-chlorobenzylidene-4-methylaniline) (2.3 g, 0.01 mol) and anhydrous sodium acetate (2 g, 0.024 mol) in acetic acid (30 mL) was heated under reflux for 6 hrs, then the reaction mixture was allowed to cool. The cooled mixture was stirred with water (100 mL) for 15 min. and the solid formed was filtered off, dried and recrystallized from ethanol to give **3** as orange crystals (Scheme 1 and 2). Yield: 55%. M.p.:127-129 °C. FT-IR (KBr, cm^{-1}): 3278 ν(NH), 1722 ν(C=O), 1650 ν($C=O_{amide}$), 1632 ν(C=N). ^1H NMR (200 MHz, $CDCl_3$): 9.4 (s, 1H, exchangeable with D_2O), 8.5-7.3 (m, $18H_{arom.}$), 7.1-6.6 (m, 3H), 2.3 (s, 3H). ^{13}C NMR (200 MHz, $CDCl_3$): 167.8 (CO_{amide}), 163.4 (CO), 159.6 (C_2), 138.1, 123.6, 122.3, 110.2 (C_1- C_4butadiene), 21.4 (CH_3), 135.6, 129.7, 128.5, 127.9 (p-tolyl), 135.2, 128.6, 128.5, 128.1, 126.9 (C_4- phenyl), 133.2, 132.1, 128.1, 127.5 (phenyl ring of benzamido group). MS (EI, m/z (%)): 483 ($M^{+\cdot}$, 70.3), 393 (18.6), 236 (66.3), 105 (100), 77 (46.2). Anal. Calcd. for $C_{32}H_{25}N_3O_2$ (483): C, 79.50; H, 5.17; N, 8.69. Found: C, 79.34; H, 5.32; N, 8.45%.

Method 2: Compound **1** (1.2 g, 0.003 mol) was heated with p-toluidine (0.32 g, 0.003 mol) in refluxing *n*-butanol (20 mL) for 10 hrs (TLC). The reaction mixture was concentrated and the deposited solid after cooling was collected by filtration and recrystallized from ethanol to give **3**; yield 64% (identity m.p, mixed m.p, TLC, IR).



Scheme 2

Method 3: Compound **2** (1.5 g, 0.003 mol) was heated on an oil-bath at 200 °C for 1 hr and left at room temperature to cool. The resulting melt was triturated with boiling ethanol and concentrated then left to cool. The solid formed was filtered off, dried and recrystallized from ethanol to give **3** as orange crystals; yield 71%, which show no depression when admixed with **3**.

2.4. 3-(4-chlorobenzylidene)amino-2-[(1Z,3E)-1-benzamido-4-phenyl-1,3-butadien-1-yl]quinazolin-4(H)-one (4)

A mixture of **1** (0.01 mol), 4-chlorobenzalazine (2.76 g, 0.01 mol) and anhydrous sodium acetate (2 g) in glacial acetic acid was heated under reflux for 10 hrs (TLC). The reaction mixture was poured into ice-cooled water and the solid deposited was filtered off, dried and then recrystallized from ethanol to give **4** as pale yellow crystals (Scheme 1 and 2). Yield: 32.2%. M.p.: 202-204 °C. FT-IR (KBr, cm^{-1}): 3293 ν(NH), 1711 ν(C=O), 1652 ν($C=O_{amide}$), 1626 ν(C=N). ^1H NMR (200 MHz, DMSO-d_6): 9.2 (s, 1H, exchangeable with D_2O), 8.3 (s, 1H), 8.1-6.9 (m, $18H_{arom.}$), 6.36 (m, 3H). MS (EI, m/z (%)): 533 (M+2, 4.3), 531 ($M^{+\cdot}$, 12.7), 393 (32.3), 146 (100), 105 (92.8), 77 (62.4). Anal. Calcd. for $C_{32}H_{23}ClN_4O_2$ (530.5): C, 72.38; H, 4.33; N, 10.55; Cl, 6.69. Found: C, 72.48; H, 4.13; N, 10.45; Cl, 6.83%.

2.5. 2-[N-(2Z,4E)-1-benzamido-1-oxo-5-phenylpenta-2,4-dien-2-yl]amino benzoic acid hydrazide (5)

To a solution of **1** (1.2 g, 0.003 mole) in absolute ethanol (30 mL), hydrazine hydrate (0.003 mol, 80%) was added dropwise with stirring at room temperature for 2 hrs (TLC). The separated solid was filtered off, dried and recrystallized from benzene to give **5** as colourless crystals (Scheme 3). Yield: 81.3%. M.p.: 132-134 °C. FT-IR (KBr, cm^{-1}): 3540, 3331, 3232 ν(NH_2, NH), 1683 ν(C=O), 1650 ν(C=O). ^1H NMR (200 MHz, $CDCl_3$): 9.3 (br.s, 1H, exchangeable with D_2O), 9.0 (br.s, 2H, exchangeable with D_2O), 8.04-7.20 (m, $14H_{arom.}$), 6.9 (br.s, 3H), 4.2 (br.s, 2H, exchangeable with D_2O). MS (EI, m/z (%)): 426 ($M^{+\cdot}$, 23.6), 395 (33.1), 367 (60.4), 178 (100), 105 (90.2), 77 (66.1). Anal. Calcd. for $C_{25}H_{22}N_4O_3$ (426): C, 70.42; H, 5.16; N, 13.14. Found: C, 70.42; H, 5.40; N, 13.09%.

2.6. 3-amino-2-[(1Z,3E)-1-benzamido-4-phenyl-1,3-butadien-1-yl]quinazolin-4(H)-one(6)

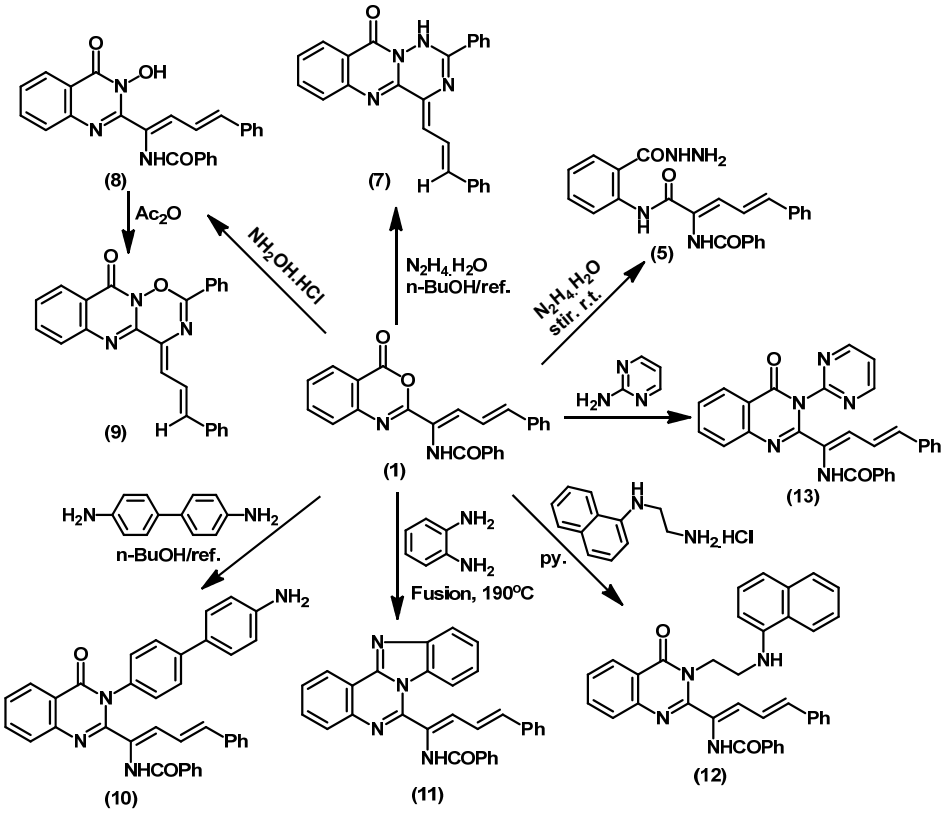
A mixture of **1** (0.01 mol), hydrazine hydrate (0.03 mol, 80%) in absolute ethanol (30 mL) was refluxed for 10 hrs (TLC). Evaporation of excess ethanol left a crude product which filtered off, dried and recrystallized from toluene to give **6** as pale yellow crystals (Scheme 1 and 2). Yield: 61.2%. M.p.: 174-176 °C. FT-IR (KBr, cm^{-1}): 3392, 3273, 3172 ν(NH_2), 1705, 1662 ν(C=O), 1621 ν(C=C). ^1H NMR (200 MHz, $CDCl_3$): 9.1 (br.s, 1H, exchangeable with D_2O), 8.7 (br.s, 2H, exchangeable with D_2O), 8.04-7.20 (m, $14H_{arom.}$), 6.8 (br.s, 3H). MS (EI, m/z (%)): 408 ($M^{+\cdot}$, 40.2), 393 (70.6), 145 (100), 105 (90.6), 77 (70.3). Anal. Calcd. for $C_{25}H_{20}N_4O_2$ (408): C, 73.52; H, 4.9; N, 13.72. Found: C, 73.38; H, 5.02; N, 13.83%.

2.7. Reaction of 6 with aromatic aldehydes

Compound **6** (1.2 g, 0.003 mol) was dissolved in absolute ethanol (30 mL) and *p*-chlorobenzaldehyde (0.42 g, 0.003 mol) was added dropwise with stirring at room temperature for 30 min., then the reaction mixture was refluxed for 3 hrs (TLC). Evaporation of the solvent left a crude product which filtered off, dried and recrystallized from ethanol to give **4** (identity m.p, mixed m.p, TLC, IR).

2.8. 1,2,3-triazino[6,1-b]quinazolin-10(4H)-one (7)

To a stirred solution of **1** (0.01 mol) in *n*-butanol (20 mL), hydrazine hydrate (0.03 mol, 80%) was added and the reaction mixture was refluxed for 16 hrs (TLC). The excess solvent was evaporated under reduced pressure. The residual was triturated with benzene to afford a solid product which filtered off, dried and recrystallized from dioxane to give **7** as yellow crystals (Scheme 3). Yield: 62.4%. M.p.: 147-149 °C. FT-IR (KBr, cm^{-1}): 3286 ν(NH), 1716 ν(C=O), 1643 ν(C=N). ^1H NMR (200 MHz, $CDCl_3$): 8.9 (br.s, 1H, exchangeable with D_2O), 8.1-7.0 (m, $14H_{arom.}$), 6.8 (br.s, 3H). MS (EI, m/z (%)): 390 ($M^{+\cdot}$, 22.1), 313 (16.7), 287 (23.4), 161 (100), 77 (48.3). Anal. Calcd. for $C_{25}H_{18}N_4O$ (390): C, 76.92; H, 4.61; N, 14.35. Found: C, 77.04; H, 4.93; N, 14.66%.



Scheme 3

2.9. 3-hydroxy-2-[(1Z,3E)-1-benzamido-4-phenyl-1,3-butadien-1-yl]quinazolin-4(H)-one (8)

A mixture of **1** (0.01 mol), hydroxylamine hydrochloride (2.1 g, 0.02 mol) in pyridine (30 mL) was heated under reflux for 12 hrs (TLC). The cooled mixture was acidified with ice cold hydrochloric acid and the separated solid was filtered off, dried and recrystallized from dioxane to give **8** as pale yellow crystals (Scheme 3). Yield: 43%. M.p.: 217-219 °C. FT-IR (KBr, cm^{-1}): br. 3436, 3217 ν(NH, OH), 1697, 1672 ν(C=O), 1612 ν(C=C). ^{1}H NMR (200 MHz, DMSO-d_6): 9.3 (br.s, 1H, exchangeable with D_2O), 8.6 (br.s, 1H, exchangeable with D_2O), 7.9-7.0 (m, 14$H_{arom.}$), 6.7 (br.s, 3H). MS (EI, m/z (%)): 409 ($M^{+\cdot}$, 21.3), 392 (76.3), 105 (100), 77 (66.3). Anal. Calcd. for $C_{25}H_{19}N_3O_3$ (409): C, 73.34; H, 4.64; N, 10.26. Found: C, 73.08; H, 4.63; N, 10.17%.

2.10. 1,2,5-oxadiazino[3,2-b]quinazolin-10(4H)-one derivative (9)

Compound **8** (1 g, 0.002 mol) and freshly distilled acetic anhydride (10 mL) was heated under reflux for 2 hrs (TLC). The cooled reaction mixture was poured onto ice-water and stirred for 0.5 hr and the crude solid obtained was filtered off, dried and recrystallized from dioxane to give **9** as a light brown crystals (Scheme 3). Yield: 0.68 g, 71.5%. M.p.: 194-196 °C. FT-IR (KBr, cm^{-1}): 1731 ν(C=O), 1634 ν(C=N), 1610 ν(C=C), 980, 940 ν(NO). ^{1}H NMR (200 MHz, $CDCl_3$): 8.1-7.3 (m, 14$H_{arom.}$), 6.9-6.6 (m, 3H). MS (EI, m/z (%)): 391 ($M^{+\cdot}$, 17.3), 314 (41.2), 288 (100), 77 (36.1). Anal. Calcd. for $C_{25}H_{17}N_3O_2$ (391): C, 76.72; H, 4.34; N, 10.74. Found: C, 76.33; H, 4.08; N, 10.47%.

2.11. 3-(4-aminobiphenyl-4-yl)-2-[(1Z,3E)-1-benzamido-4-phenyl-1,3-butadien-1-yl]quinazolin-4(H)-one (10)

A mixture of **1** (1.2 g, 0.003 mol) and benzidine (0.55 g, 0.003 mol) in *n*-butanol (30 mL) was refluxed for 12 hrs (TLC). The reaction mixture was concentrated and the solid separated after cooling was filtered off, washed several times with diluted methanol, dried and recrystallized from ethanol to give **10** as a yellowish-green crystals (Scheme 3). Yield: 72%. M.p.: 130-132 °C. FT-IR (KBr, cm^{-1}): br. centered at 3358 ν(NH_2), 1742 ν(C=O), 1692 ν(C=O), 1621 ν(C=N). ^{1}H NMR (200 MHz, $CDCl_3$): 9.1 (br.s, 1H, exchangeable with D_2O), 8.4-7.3 (m, 22$H_{arom.}$), 6.77 (br.s, 3H), 4.6 (br.s, 2H, exchangeable with D_2O). MS (EI, m/z (%)): 560 ($M^{+\cdot}$-1, 12.9), 313 (10.6), 210 (15), 184 (28.7), 105 (100), 77 (70.2). Anal. Calcd. for $C_{37}H_{28}N_4O_2$ (561): C, 79.14; H, 4.99; N, 9.98. Found: C, 79.08; H, 4.71; N, 10.15%.

2.12. Benzimidazolo[1,2-c]quinazoline derivative (11)

A mixture of **1** (1.2 g, 0.003 mol) and *o*-phenylenediamine (0.65 g, 0.006 mol) was heated with stirring on an oil-bath for 6 hrs at 190 °C. The crude product was triturated with water then filtered off, washed several times with diethyl ether, dried and recrystallized from benzene-ethanol to give **11** as a light brown crystals (Scheme 3). Yield: 0.86 g, 61.4%. M.p.: 210-212 °C. IR (KBr, cm^{-1}): 3310 ν(NH), 1668 ν(C=O_{amide}), 1622 ν(C=N), 1606 ν(C=C). ^{1}H NMR (200 MHz, DMSO-d_6): 8.9 (br.s, 1H, exchangeable with D_2O), 8.4-6.8 (m, 21$H_{arom.}$ + olefinic protons). MS (EI, m/z (%)): 466 ($M^{+\cdot}$, 3.9), 365 (16.9), 350 (13.6), 261 (17.6), 105 (100), 77 (81.6). Anal. Calcd. for $C_{31}H_{22}N_4O$ (466): C, 79.83; H, 4.72; N, 12.02. Found: C, 79.66; H, 4.64; N, 12.21%.

2.13. Quinazolin-4(H)-one derivative (12)

To a solution of **1** (0.01 mol) in pyridine (30 mL), *N*-(1-naphthyl)ethane-1,2-diamine hydrochloride (3.3 g, 0.015 mol) was added and the reaction mixture was heated under reflux for 10 hrs (TLC). The cooled reaction mixture was acidified with cold dilute hydrochloric acid. The solid deposited was filtered off, dried and recrystallized from toluene to give **12** as pale yellow crystals (Scheme 3). Yield: 83%. M.p.: 200-202 °C. IR (KBr, cm^{-1}): br. 3420, 3302 ν(NH), 1738 ν(C=O), 1668 ν(C=O), 1600 ν(C=C). ^{1}H NMR (200 MHz, DMSO-d_6): 8.9 (br.s, 1H, exchangeable with D_2O), 8.4-7.1 (m, 21$H_{arom.}$), 7.0-6.1 (m, 3H), 3.6 (m, 2H), 3.4 (t, 2H, J = 4.6 Hz). MS (EI, m/z (%)): 435 ($M^{+\cdot}$ – $C_{10}H_7$, 12.7), 393 (70.2), 145 (17.8), 105 (100), 77 (76.8). Anal. Calcd. for $C_{37}H_{30}N_4O_2$ (562): C, 79.0; H, 5.34; N, 9.96. Found: C, 79.13; H, 5.0; N, 9.66 %.

2.14. 3-(pyrimidin-2-yl)-2-[(1Z,3E)-1-benzamido-4-phenyl-1,3-butadien-1-yl]quinazolin-4(H)-one (13)

A mixture of **1** (0.01 mol) and 2-aminopyrimidine (1.4 g, 0.015 mol) was heated with stirring on an oil-bath for 4 hrs at 200 °C. The reaction mixture was triturated with dilute methanol and the separated solid was filtered off, washed several times with diethyl ether, dried and recrystallized from ethanol to give **13** as a light brown crystals (Scheme 3). Yield: 68%. M.p.: 166-167 °C. IR (KBr, cm^{-1}): 3264 ν(NH), 1711, 1672 ν(C=O), 1638 ν(C=N), 1608 ν(C=C). ^{1}H NMR (200 MHz, $CDCl_3$): 9.0 (s, 1H, exchangeable with D_2O), 8.7-7.12 (m, 17$H_{arom.}$), 6.8-6.5 (m, 3H). MS (EI, m/z (%)): 472 ($M^{+\cdot}$+1, 20.2), 393 (66.1), 105 (100), 77 (60.1). Anal. Calcd. for $C_{29}H_{21}N_5O_2$ (471): C, 73.88; H, 4.45; N, 14.86. Found: C, 73.62; H, 4.37; N, 14.58%.

3. Results and discussion

Benzoxazinones can be considered as semi acid anhydride and they undergo many reactions of true acid anhydrides [35,36]. Acid anhydrides react with Schiff's bases and azines to give products depending upon reaction conditions. The reaction in many cases involved the displacement of arylidene group of the imine molecule. The present investigation was to involve the reaction of compound **1** with Schiff's bases and azines.

The interaction of equimolecular amounts of **1** and 4-chlorobenzylidene-4-methylaniline in dry benzene under reflux yielded 2-substituted amino-*N*-(4-methyl-phenyl)benzamide (**2**). However, when the reaction was conduced in glacial acetic acid containing catalytic amount of anhydrous sodium acetate, 3-(4-methylphenyl)-2-substituted quinazolin-4(H)-one (**3**) was obtained in quantitative yield. The structures of **2** and **3** were rigidly established beside the microanalytical and spectral data by identity with authentic samples (m.p, mixed m.p, TLC) prepared from the reaction of **1** with *p*-toluidine in refluxing ethanol or *n*-butanol and by heating **2** above its melting point to give **3** (Scheme 1).

When **1** was allowed to react with 7-chlorobenzalazine in glacial acetic acid containing catalytic amount of anhydrous sodium acetate, 3-(4-chlorobenzylidene)amino-2-substituted quinazolin-4(H)-one (**4**) was isolated as the sole product, which indicates the displacement of one arylidene group during the reaction conditions.

A possible explanation for the reaction of **1** with the Schiff's base and azine is formulated in Scheme 2. The reaction of **1** with the Schiff's base and azine proceeded via the formation of the intermediate (*Z*) which gave rise to **2**. Analogous intermediate (*Z*) have been reported for the reaction products of imines with succinic and maleic anhydrides [35].

When **1** was stirred with hydrazine hydrate (80%) in absolute ethanol at room temperature for one hour, the hydrazide derivative **5** was obtained. Whereas, the same reaction under relfux for 3 hrs afforded the 3-aminoquinazolin-4(*H*)-one derivative **6**, whose structure was substantiated beside the correct microanalytical and spectroscopic data by treatment compound **6** with *p*-chlorobenzaldehyde in refluxing ethanol to give the quinazolinone derivative **4** (Scheme 1). On the other hand, treatment of **1** with hydrazine hydrate (80%) in boiling *n*-butanol yielded the 1,2,4-triazino[6,1-*b*]quinazolin-10(4*H*)-one derivative **7**, whose structure was confirmed from the analytical and spectral data (c.f. Exp.). Similarly, the reaction of **1** with hydroxyl amine in order to obtain another heterocyclic ketone containing oxadiazine nucleus have been studied. Thus, treatment of **1** with hydroxyl amine hydrochloride in refluxing pyridine afforded 3-hydroxy-2-substituted quinazolin-4*H*-one **8**, which spontaneously recyclized in freshly distilled acetic anhydride to give the desired 1,2,5-oxadiazino[3,2-*b*]quinazolin-4(*H*)-one derivative **9** (Scheme 3).

It was reported [37] that the rate of addition of amines to the semiacid anhydride is a function of both electronic as well as steric factors and the overall rate is of course affected by ring substituents that influence the electrophilicity at position-2, so addition to the more electrophilic center at position-4 may occur faster. The molarity of amines and reaction time [38] are not the sole factors necessary for cyclization of the anilide derivatives to the corresponding 3-substituted quinazoline derivatives. However, the reaction of **1** with benzidine in *n*-butanol furnished the cyclized product **10**. Fusion of **1** with *o*-phenylenediamine in an oil-bath at 190 °C afforded the benzimidazolo[1,2-*c*]quinazoline derivative **11**. Furthermore, refluxing **1** with *N*-(1-naphthyl)ethylene-diamine hydrochloride in pyridine yielded the quinazolin-4(*H*)-one derivative **12**. Upon treatment of **1** with 2-aminopyridine in boiling ethanol or *n*-butanol, **1** was recovered unchanged. However, heating **1** with 2-aminopyridine in an oil-bath at 200 °C gave the quinazolin-4(*H*)-one derivative **13** (Scheme 3).

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