Synthesis, Antimicrobial and Anti-inflammatory Activity of Some New Benzoxazinone and Quinazolinone Candidates

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Received November 14, 2015; accepted December 9, 2015; advance publication released online December 22, 2015

Heterocycles containing benzoxazinone and quinazolinone moieties have great importance in medicinal chemistry. They are of considerable interest on account of the diverse range of biological properties such as antimicrobial, herbicidal, anti-inflammatory, anticancer, antibacterial, anti-fungal, central nervous system (CNS), antimalarial, antitumor, and adenosine receptor antagonistic activities.1–14 In continuation of our interest in the synthesis of some of heterocyclic nitrogen compounds having biological and pharmacological activities,15–25 and through our program26–29 aiming to explore the chemical reactivity of the oxazinone moiety present in 4(1H)-3,1-benzoxazin-4-one derivatives, we have decided to synthesize a series of novel 3-substituted quinazolin-4(3H)-one which underwent a reaction with primary and secondary amines, and hydrazine hydrate to give compounds 3, 4 and 5, respectively. Treatment of 2 with hydroxylamine hydrochloride, formamide and/or NaN₃/AcOH afforded compounds 7, 8, 11 and 12, respectively. Also, compound 2 reacted with maleic anhydride, aromatic hydrocarbons and/or active methylene compounds to produce compounds 13, 15a–e and 16, respectively. Most of the newly synthesized compounds showed significant antimicrobial and anti-inflammatory activities comparable to ampicillin, mycostatin and indomethacin positive controls.

Key words benzoxazinone; quinazolinone; imidazole; tetrazole; antimicrobial; anti-inflammatory

Results and Discussion

Chemistry  N-[α-Benzoylaminocinnamoyl]-3,5-dibromoanthranilic acid (1) was synthesized in a good yield by the treatment of a solution of 3,5-dibromoanthranilic acid (0.01 mol) in pyridine with equimolecular amount of 2-phenyl-4-(phenyl methane)-5(4H)-oxazole. The structure of compound 1 was confirmed by elemental analysis and spectral data (Experimental). On refluxing the acid 1 with acetic anhydride, the title compound 2 was obtained in 59% yield as a result of ring closure (Chart 1). Structure of 4(1H)-3,1-benzoxazin-4-one derivative 2 was elucidated from its analytical data, IR (showed νC=O at 1749 cm⁻¹ which is characteristic for the benzoxazinone moiety) and 1H-NMR spectrum which displayed peaks at δ 6.71 for CH=, 7.28–7.77 (10, Ar-H), 8.20, 8.37 (2s, 2H, Ar-H benzoxazinone), 10.22 exchangeable with D₂O for NH. The 13C-NMR spectrum contained 14 signals; the most important, at δ 118.10, 120.30 and 161.60, 163.40 ppm for (C=C) and (C=O). Its mass spectrum displayed the expected molecular ion peaks at m/z 526 (4.8%), 528 (10.1%) and 530 (5.1%).

When compound 2 was heated with primary amines such as aniline, t-butyl amine, benzyl amine and/or phenyl hydrazine in boiling ethanol, afforded the corresponding N-[α-benzoylaminocinnamoyl]-3,5-dibromo-anthranilic acid amides and hydrazide 3a–d, respectively. Similarly, secondary amines (piperidine and/or morpholine) reacted with 2 yielding N-[α-benzoylaminocinnamoyl]-3,5-dibromo-anthranilic acid piperidine and morpholide 4a and b respectively (Chart 1). Analytical and spectral data for 3a–d and 4a, b were in agreement with the proposed structures (Experimental).

On the other hand, hydrazinolysis of 2 with hydrazine hydrate in refluxing n-butanol gave the 3-aminoquazolinone derivative 5. The IR spectrum showed three bands at 3429, 3230 and 3110 cm⁻¹, corresponding to the NH₂ and NH groups. Also, the 1H-NMR spectrum indicated the presence of a broad singlet peak at δ 4.86 ppm integrated for two exchangeable protons (NH₂ group). Its mass spectrum gave the molecular ion peaks at m/z 540 (8.6%), 528 (17.7%) and 5530 (9.1%). When compound 5 was subjected to condensation with benzaldehyde in boiling ethanol, Schiff’s base 6 was obtained. Similarly, hydroxyl amine hydrochloride reacted with 2 producing the 3-hydroxyquinazolinone derivative 7 (Chart 2). Fusion of the benzoxazinone 2 with ammonium acetate...
afforded the quinazolin-4-one derivative 8, which was also obtained by refluxing 2 in excess formamide. The existence of compound 8 in the lactam–lactim tautomeric equilibrium was proved through its reaction with acetic anhydride where it underwent N-acetylation (through the lactam form) to give compound 9, but, it upon alkylation with ethyl chloroacetate the ester 10 was formed (through the lactim form) (Chart 2). The $^1$H-NMR spectra of compounds 9 and 10 showed signals at $\delta$ 2.23 ppm for three protons corresponding to $CH_3$–$C=O$, 1.25–1.34 (t, $J=6.5$ Hz, 3H, $CH_3$–$CH_2$–), 4.14–4.27 (q, $J=6.6$ Hz, 2H, $-OCH_2CH_3$), which indicated the presence of the acetyl group in compound 9 and the ester group in compound 10, respectively. Treatment of compound 2 with hydrazoic acid (sodium azid in acetic acid) gave a mixture of the tetrazole derivative 11 and the benzimidazolone derivative 12, respectively (Chart 2).
Formation of compounds 11 and 12 could be visualized as shown in Charts 3 and 4.

An interesting result was obtained when compound 2 was boiled with maleic anhydride in xylene, which afforded the Diels–Alder adduct 13, which was hydrolyzed with alcoholic NaOH to give the diacid 14. The investigation was further extended to explore the reactivity of the benzoxazin-4-one 2 towards aromatic hydrocarbons under Friedel–Crafts reaction conditions. Thus, when compound 2 was reacted with benzene, toluene and/or cumene in the presence of anhydrous AlCl₃, aromatic ketones 15a–c were obtained, respectively (Chart 5). The reaction proceeded via ring opening and the structures of the formed compounds were elucidated from their spectral data. Finally, the reaction of 2 with compounds containing an active methylene group was also investigated. Thus, treatment of compound 2 with diethyl malonate and/or ethyl acetoacetate in refluxing pyridine produced the ethyl acetate derivatives 16 as a sole product in both cases (Chart 5). The reaction took place via heterocyclic ring opening as a result of attack of the carbanion from the active methylene compounds. The proposed structure was indicated by its ¹H-NMR spectrum which displayed signals at δ 1.23–1.32 (t, J=6.5 Hz, 3H, CH₃–CH₂–), 3.75 (s, 2H, CH₂–C=O), 4.24–4.35 (q, J=6.6 Hz, 2H, –OCH₂CH₃), which indicated the presence of the COCH₂COOC₂H₅ group. Also, the IR spectrum showed a peak at 1715 cm⁻¹ corresponding to νC=O of the ester group, analytical and spectral data for compounds 15 and 16 confirmed their chemical structures.

**Biological Activity**

**Antimicrobial Activity**

All of the new synthesized compounds were screened for in vitro antibacterial and antifungal activities. The microorganisms used were Serratia marcescens, Proteus meralbites (Gram-negative bacteria), Staphylococcus aureus, Bacillus cereus (Gram-negative bacteria), Aspergillus ochraceus Wilhlem and Penicillium chrysogenum Thom (fungi). The standard drugs used were ampicillin and mycostatine, following the agar diffusion technique.³¹ The antimicrobial activity results are shown in Table 1. The antimicrobial activity results revealed that most of the tested compounds have moderate to
high activity. Minimum inhibitory concentration (MIC) of the most potent compounds are listed in Table 2.

Carrageenan-induced rat paw edema (Anti-inflammatory) Carrageenan-induced edema is a nonspecific inflammation resulting from a complex of diverse mediators. Since edemas of this type are highly sensitive to non-steroidal anti-inflammatory drugs (NSAIDs), carrageenan has been accepted as a useful agent for studying new anti-inflammatory drugs. This model reliably predicts anti-inflammatory efficacy of the NSAIDs, and during the second phase it detects compounds which are anti-inflammatory agents as a result of inhibition of prostaglandin amplification. The method developed by Winter et al.\textsuperscript{32} was employed. Values, which are listed in Table 3, were expressed as the mean ± standard error (S.E.). Comparisons between means were carried out using one way ANOVA followed by Tukey multiple comparisons test. The results, listed in Table 3, revealed that some of the tested compounds have higher efficacy than indomethacin.

### Table 1. Antimicrobial Activity of the Synthesized Compounds

<table>
<thead>
<tr>
<th>Compd. no.</th>
<th>Antibacterial activity</th>
<th>Antifungal activity</th>
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<tbody>
<tr>
<td></td>
<td>Gram-positive</td>
<td>Gram-negative</td>
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<tr>
<td></td>
<td>Staphylococcus aureus</td>
<td>Bacillus cereus</td>
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<td>2</td>
<td>24</td>
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<tr>
<td>3a</td>
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<td>3b</td>
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<td>3c</td>
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<td>3d</td>
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<td>16</td>
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<td>9</td>
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<tr>
<td>Ampicillin</td>
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<td>33</td>
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<tr>
<td>Mycostatine</td>
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The width of the zone of inhibition indicates the potency of antibacterial activity; (0) no antimicrobial activity; the diameter of zones equal to 2–5 mm, weak reactivity; 6–14 mm, moderate activity; 15–30 mm, high activity and very high activity with the diameter of the zones (more than 30 mm).

### Table 2. Minimum Inhibitory Concentration (MIC) of the Most Potent Compounds

<table>
<thead>
<tr>
<th>Compd. no.</th>
<th>MIC (µg/mL)</th>
<th>Staphylococcus aureus</th>
<th>Bacillus cereus</th>
<th>Serratia marcescens</th>
<th>Proteus mirabilis</th>
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Experimental

Chemistry Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded in KBr disks on a PerkinElmer, Inc. System 2000 Fourier transform (FT)-IR spectrophotometer (ν in cm\(^{-1}\)) and \(^1\)H-NMR spectra on a DPX 300 MHz Bruker FT-NMR spectrophotometer. The chemical shifts were reported as parts per million (δ ppm) and coupling constant (J) values are given in Hz using tetramethyl silane (TMS) as internal standard and CDCl\(_3\) or DMSO-\(_d_6\) as solvents. Elemental analysis was performed on a Perkin-Elmer 2400 C, H, N analyzer. Elemental analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%). The progress of reactions and the purity of compounds were monitored by TLC analytical silica gel plates (Merck 60F 254) (3 × 8 cm) and spots were located by Ultraviolet chamber. All the chemicals were obtained from Aldrich; all the solvents used were of commercial grade only. The antibacterial and anti-inflammatory were evaluated in Biochemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt.

Synthesis of 2-(2-Benzamido-3-phenylacrylamido)-3,5-dibromobenzoic Acid (1) A mixture of 3,5-dibromoanthranilic acid (0.01 mol, 2.95 g) and 4-benzylidene-2-phenyl-oxazolidine-5-one (0.01 mol, 2.49 g) in pyridine (30 mL) was stirred for one hour at room temperature. The precipitated solid was filtered off, washed with water, dried and crystallized from ethanol to give compound 1. Yellow solid, mp: 176–178°C, yield: 4.52 g (83%); IR, ν cm\(^{-1}\): 3432, 3314 (br) (NH, OH),
Edema inhibition

was refluxed for one hour. The excess acetic anhydride was

8.34 (2s, 2H, Ar-H), 10.49 (br s, 2H, NH, D2O exchangeable),

1H, CH

51.11; H, 3.26; N, 5.44.

(M

3421, 3303 (NH), 1749, 1676 (C

1696, 128.8, 129.2, 131.2, 132.3, 134.3, 141.7 (aromatic+sp2-C), 162.3, 166.1, 169.3

(CO); MS: m/z: 544 M+ (4.2%), 546 (9.6%), 548 (5.1%), 500

(M–CO2 43%), 502 (73.4) and 504 (36.3%). Anal. Calcd for

C2-H7Br2N2O4 (544): C, 50.74; H, 2.94; N, 5.15. Found: C, 51.11; H, 3.26; N, 5.44.

Synthesis of N-(1-(6-Dibromo-4-oxo-4H-benzo[d][1,3]-oxazin-2-yl)-2-phenylvinyl)benzamide (2) A solution of 1 (0.01 mol, 5.44g) in a freshly distilled acetic anhydride (30mL) was refluxed for one hour. The excess acetic anhydride was removed in a rotary evaporator. The solid obtained was washed with cold dilute sodium carbonate solution (20%, 3x50mL) then with water (3x50mL). The solid was collected by filtration, dried and recrystallized to furnish compound 2. Pale yellow solid, mp: 124–126°C (from Light petroleum (L.P.), bp 100–120°C), yield: 3.11 g (59%); IR, ν cm–1: 3421, 3303 (NH), 1749, 1676 (C=O), 1590 (C=N); 1H-NMR (DMSO-d6) δ ppm: 6.71 (s, 1H, CH=), 7.28–7.77 (m, 10, Ar-H two phenyl groups), 8.20, 8.37 (2s, 2H, Ar-H benzoazinone), 10.22 (brs, 1H, NH, D2O exchangeable). 13C-NMR (DMSO-d6) δ ppm: 118.2, 120.6, 121.7, 123.1, 125.3, 126.6, 127.3, 128.8, 132.6, 134.3, 141.7 (aromatic+sp2-C), 162.3, 166.1, 169.3 (CO); MS: m/z: 544 M+ (4.2%), 546 (9.6%), 548 (5.1%), 500 (M–CO2 43%), 502 (73.4) and 504 (36.3%). Anal. Calcd for C2H7Br2N2O4 (544): C, 50.74; H, 2.94; N, 5.15. Found: C, 51.11; H, 3.26; N, 5.44.

oxo-1-phenylprop-1-en-2-yl)benzamide (3d) In 30mL of ethyl alcohol, a mixture of 2 (0.01 mol, 5.26g) and amines (0.01 mol), namely aniline, t-butyl amine, benzyl amine and/or phenyl hydrazine, was refluxed for 3h. The solid precipitated upon cooling was filtered off and recrystallized from suitable solvent to afford compounds 3a–d, respectively.

Compound 3a

Yellow solid, mp: 196–198°C (from ethanol), yield: 4.7g (76%); IR, ν cm–1: 3385–3230 (NH), 1674, 1659, 1645 (C=O); 1H-NMR (DMSO-d6) δ ppm: 6.68 (s, 1H, CH=), 7.22–7.71 (m, 15, Ar-H three phenyl groups), 8.16, 8.33 (2s, 2H, Ar-H, C4, C6), 9.28 (s, 1H, NH, D2O exchangeable), 10.66 (brs, 2H, NH, D2O exchangeable), 13C-NMR (DMSO-d6) δ ppm: 118.4, 119.2, 120.3, 121.2, 121.3, 123.4, 125.3, 126.2, 127.3, 127.9, 128.8, 129.2, 131.2, 132.3, 134.5, 135.6, 138.4, 139.5, 140.3 (aromatic+sp2-C), 163.3, 164.6, 166.6 (CO); MS: m/z: 619 M+ (7.8%), 621 (16.1%), 623 (8.4%), M–CONHPh 499 (18.8%), 501(34.5%) and 503 (16.9%). Anal. Calcd for C2H7Br2N2O4 (619): C, 56.22; H, 3.39; N, 6.78. Found: C, 56.56; H, 3.61; N, 6.43.

Compound 3b

Yellow solid, mp: 184–186°C (from ethanol), yield: 4.7g (76%); IR, ν cm–1: 3372–3214 (NH), 1671, 1655, 1640 (C=O); 1H-NMR (DMSO-d6) δ ppm: 1.32 (s, 9H, t-Bu), 6.59 (s, 1H, CH=), 7.29–7.81 (brm, 10, Ar-H), 8.14, 8.34 (2s, 2H, Ar-H, C4, C6), 9.06 (s, 1H, NH, D2O exchangeable), 10.61 (brs, 2H, NH, D2O exchangeable). Anal. Calcd for C2H7Br2N2O4 (599): C, 54.09; H, 4.17; N, 7.01. Found: C, 54.42; H, 4.44; N, 6.74.

Compound 3c

mp: 135–137°C (from benzene), yield: 4.49 g (71%); IR, ν cm–1: 3334–3202 (NH), 1672, 1658, 1643 (C=O); 1H-NMR (DMSO-d6) δ ppm: 4.83 (d, 2H, CH3), 6.62 (s, 1H, CH=), 7.26–7.76 (brm, 15, Ar-H), 8.18, 8.35 (2s, 2H, Ar-H, C4, C6),
8.94 (s, 1H, NH, D₂O exchangeable), 10.69 (brs, 2H, NH, D₂O exchangeable). Anal. Caled for C₉H₇Br₂N₂O₂: C, 56.87; H, 3.63; N, 6.64. Found: C, 57.13; H, 3.88; N, 6.92.

N-(3-(2,4-Dibromo-6-(2-phenylhydrazidencarbonylphenoxyamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (3d)

mp: 182–184°C (from acetic acid), yield: 4.69 g (74%); IR, ν cm⁻¹: 3350–3242 (NH), 1677, 1660, 1646 (C=O); H-NMR (DMSO-d₆) δ ppm: 6.71 (s, 1H, CH=), 7.30–7.80 (m, 15, Ar-H), 8.16, 8.34 (2s, 2H, Ar-H, C3, C5), 9.12 (s, 1H, NH, D₂O exchangeable). Anal. Caled for C₂₉H₂₂Br₂N₄O₃: C, 54.55; H, 3.31; N, 8.56.

Synthesis of Benzamide Derivatives (4a, b) Compound 2 (0.01 mol, 5.26 g) was refluxed in 50 mL of ethanol with piperidine and/or morpholine (0.01 mol) for 3 h. The excess alcohol was removed in a rotatory evaporator. The solid obtained was recrystallized from a suitable solvent to give compounds 4a and 4b.

N-(3-(2,4-Dibromo-6-(morpholine-4-carbonylphenoxyamino)-3-oxo-1-phenylprop-1-en-2-yl)benzamide (4a)

mp: 159–161°C (from ethanol), yield: 3.80 g (61%); IR, ν cm⁻¹: 3321, 3179 (NH), 1675, 1658, 1641 (C=O); H-NMR (CDCl₃) δ ppm: 1.06 (t, 3H, CH₃), 3.46 (br, 4H), 6.44 (s, 1H, CH=), 7.27–7.82 (m, 10, Ar-H), 8.21, 8.41 (2s, 2H, Ar-H, C3, C5), 9.88 (brs, 2H, NH, D₂O exchangeable). Anal. Caled for C₂₉H₂₂Br₂N₄O₃ (634): C, 54.89; H, 3.47; N, 8.83. Found: C, 54.55; H, 3.31; N, 8.56.

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1733, 1659 (C=O); 1H-NMR (DMSO-d6) δ ppm: 1.25–1.34

(13) Maleic anhydride (0.01 mol, 0.98g) and compound 2 (0.01 mol, 5.26g) were dissolved in 50 mL dry xylene and the reaction mixture was refluxed for 4h and left to cool. The solid deposited was collected by filtration, dried and crystallized from suitable solvent to give compounds 15a–c, respectively.

N-(3-(2-Benzoyl-4,6-dibromophenylamino)-3-oxo-phenylprop-1-yl)benzamide (15a)

mp: 192–194°C (from benzene), yield: 5.01g (83%); IR, ν cm⁻¹: 3404, 3333 (NH), 1688, 1668, 1644 (C=O). Anal. Calcd for C₃₂H₂₂Br₂N₂O₅ (624): C, 50.47; H, 2.80; N, 4.36. Found: C, 50.11; H, 3.09; N, 4.00.

N-(3-(2-Benzoyl-4,6-dibromophenylamino)-3-oxo-1-phenylprop-1-yl)benzamide (15b)

mp: 221–223°C (from benzene), yield: 5.13g (83%); IR, ν cm⁻¹: 3421, 3318 (NH), 1691, 1665, 1642 (C=O); 1H-NMR (DMSO-d6) δ ppm: 1.77 (s, 3H, CH3), 6.56 (s, 1H, CH=), 7.29–7.73 (m, 14, Ar-H), 8.13, 8.27 (2s, 2H, Ar-H, quinazolone), 9.89 (brs, 2H, 2NH, D,O exchangeable). 13C-NMR (DMSO-d6) δ ppm: 22.3 (sp²-C), 119.5, 120.6, 122.6, 123.1, 124.2, 125.3, 126.6, 127.3, 128.8, 129.2, 131.4, 132.3, 135.7, 134.2, 141.7, 142.1, 142.5 (aromatic+sp²-C), 161.3, 163.4 (CO); MS: m/z: 618 M⁺ (4.8%), 620 (10.3%) and 622 (3.7%). Anal. Calcd for C₃₀H₂₁Br₂N₂O₅ (618): C, 58.25; H, 3.56; N, 4.53. Found: C, 58.01; H, 3.33; N, 4.31.

N-(3-(2,4-Dibromobenzoyl)phenylamino)-3-oxo-1-phenylprop-1-yl)benzamide (15c)

mp: 212–214°C (from benzene), yield: 4.91g (76%); IR, ν cm⁻¹: 3412, 3309 (NH), 1668, 1663, 1645 (C=O); 1H-NMR (DMSO-d6) δ ppm: 1.18 (d, 6H, 2CH₃), 4.13–4.27 (m, 1H,
Acitivitity

The authors declare no conflict of interest.

References