Reactivity of 4H-3,1-benzoxazin-4-ones towards nitrogen and carbon nucleophilic reagents: applications to the synthesis of new heterocycles

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Abstract
6,8-Dibromo-(4H)-3,1-benzoxazinone 1a was synthesized and allowed to react with some nitrogen nucleophiles namely, hydroxylamine hydrochloride, 4-aminoacetophenone, o-phenylenediamine, sulfanilamide, sulfamethoxazole, semicarbazide hydrochloride and ethanolamine to afford 3-substituted-4(3H)-quinazolinones 2-8, 10-12 and triazolo[2,3-c]quinazoline 9. 6-Bromo(4H)-3,1-benzoxazin-4-one 1b was also synthesized and converted into 3-amino-4(3H) quinazolinone 13 by reaction with hydrazine hydrate. The latter product was utilized to construct new heterocyclic systems namely, triazino[2,3-c] quinazoline 14 and the thiazole derivative 16. An interesting heterocyclic transformation occurred on treatment of benzoxazinone 1a with malononitrile in presence of sodium ethoxide to give quinoline derivative 18 which reacted with phenyl isocyanate to yield oxazinoquinoline 19. The reaction of benzoxazinone 1a with Grignard' reagents afforded unexpected products 20 and 21 whereas Friedel-Crafts reaction of the same oxazinone with some aromatic hydrocarbons namely, benzene, ethylbenzene, m- and p-xlenes afforded either two benzophenone derivatives 20 and 22 or 23 and 24 in case of less bulky hydrocarbons i.e., benzene and ethylbenzene or only one product 25 and 26 in case of more bulky m- and p-xlenes. Oxazinone ring cleavage occurred when barbituric and/or thiobarbituric acid reacted with benzoxazinone 1a in refluxing pyridine to give the corresponding 5-arylidene derivatives 27a,b.

Keywords: Benoxazinones, quinazolinones, cyanoquinoline

Introduction

The present work is in conjunction with our ongoing programme on the utilizing of readily obtainable starting materials for the synthesis of heterocyclic systems. 1-7 One of the most important features in (4H)-3,1-benzoxazinones chemistry is their use as key starting materials for
further transformations. They are indeed useful intermediates in organic synthesis affording through reaction with nitrogen nucleophiles 4(3H)quinazolinones. With the aim of extending information on the reactivity of 4H-3,1-benzoxazinones and also synthesizing from them new heterocyclic systems, potentially with biological activity 8-12 and in continuation of our work on the behaviour of stable benzoxazinones 13 towards nitrogen and carbon nucleophiles, other derivatives were obtained via the interaction of acetic anhydride and/or isobutyroyl chloride with anthranilic acid derivatives. The electronically unsaturated character of unstable benzoxazinones which are (4H)-3,1-benzoxazinones bearing saturated substituents such as CH3, CH2COCH3, CH2CN and CH2CH2CO2H at position 2 14-17 renders their synthesis difficult because they are not satisfactorily stable rings. Our contribution to solve this problem includes the construction of bulky substituents involving strong conjugation power to obtain stable benzoxazinones. 13,18 Herein, we report the synthesis of 2-substituted (4H)-3,1-benzoxazinones 1a and b via the reaction of freshly distilled acetic anhydride 19 and/or isobutyroyl chloride in dry pyridine 20 with 3,5-dibromo-, or 3-bromoanthranilic acids respectively.

![Chemical Structure](image)

1a, R1 = Me, R2 = Br; b, R1 = priso, R2 = H

**Results and Discussion**

With the aim of expanding the synthetic potential of the (4H) 3,1-benzoxazinones formed, we have studied the reaction of 1a with hydroxylamine hydrochloride. This is a simple and convenient route to the synthesis of 3-hydroxy-4(3H)-quinazolinone 2 which is a promising intermediate for diverse organic synthesis [Scheme 1]. Thus reactions of the latter compound with acetic anhydride and ethyl chloroacetate afforded 3-acetoxy- and 3-ethoxycarbonylmethoxy-4(3H)-quinazolin-ones 3 and 4 respectively. Aminolysis of benzoxazinone 1a occurred when it was treated with 4-aminoacetophenone to yield 3-(4-acetophenyl)-4(3H)-quinazolinone 5 via heteroring opening followed by ring closure. 21

A variety of 2,3-disubstituted 4(3H)-quinazolinones containing a heterocyclic group in position 3 have been prepared from the reaction of 2-methyl and 2-phenyl-(4H)-3,1-benzoxazinones with different heterocycles containing the amino functionality. 22 Various quinazolinone dyes have been synthesized from coupling diazotized aminooquinazolinone with various coupling components and their dyeing effect on viscose rayon, silk and wool fibers has been assessed. 23 The forementioned findings prompted the author to carry out the reaction of 1a with o-phenylenediamine to obtain 3-(2-aminophenyl)-4(3H)-quinazolinone 6 which could be diazotized and coupled.
Scheme 1. Reagents and reaction conditions: (i) NH₂OH.HCl, pyridine, 115°C; (ii) Ac₂O, 140°C; (iii) ClCH₂CO₂Et, anhydrous K₂CO₃, dry acetone, 56°C; (iv) NH₂.C₆H₄.COMe (1,4), EtOH, 78°C; (v) C₆H₄(NH₂)₂-1,2, AcOH, 116°C; (vi) sulfanilamide, dry pyridine, 115°C; (vii) sulfamethoxazole, dry pyridine, 115°C; (viii) H₂NCONHNH₂.HCl, dry pyridine, 115°C; (ix) H₂NCH₂CH₂OH, 170°C; (x) phthalimide, conc. HCl, fusion; (xi) 2-naphthol, conc. HCl, fusion.
It is of interest to compare the previous result with the cyclocondensation of 2-aryl-(4\(H\))-3,1-benzoxazinones with \(o\)-phenylenediamine to give benzoimidazoquinazolines if the reaction is conducted in orthophosphoric acid at reflux temperature.\(^{24}\) Sulfanilamide and its derivatives have great antibacterial power and are widely used in medicine against "coccic infections". Consequently, we have tried to expand the applicability of sulfanilamides, and herein we report the synthesis of novel heterocycles of anticipated biological activity containing quinazolinone moiety incorporated sulfa drug residue. Thus, treatment of 4\(H\)-3,1-benzoxazinone 1a with sulfanilamide and/or sulfamethoxazole afforded 2,3-disubstituted 4(3\(H\))-quinazolinones 7 and 8 respectively.\(^{13,25}\) Successful attempt to construct a third heterocyclic ring condensed with quinazoline was achieved \textit{via} reaction of 1a with semicarbazide hydrochloride in refluxing dry pyridine to give triazolo[2,3-c]quinazoline 9. Reaction of (4\(H\))-3,1-benzoxazin-4-one 1a with ethanolamine at refluxing temperature resulted in the hydroxyethylquinazolinone 10 which was utilized to alkylate some aromatic systems namely, phthalimide and 2-naphthol in acidic media to afford the respective quinazolinones 11 and 12.

According to our previous works, the reaction of hydrazine hydrate with 2-substituted 4\(H\)-3,1-benzoxazinones results in the formation of 3-aminoquinazolinone derivatives when the substituent at position-2 is bulky\(^{13}\) or when the reaction is carried out in presence of anhydrous zinc chloride.\(^{6}\) Thus, when 4\(H\)-3,1-benzoxazinone 1b was allowed to react with hydrazine hydrate in boiling ethanol, it yielded the respective 3-amino-4(3\(H\))-quinazolinone 13 and this agreed well with our reported finding [cf. Scheme 2]. 3-Aminoquinazolinone 13 could be used as versatile building blocks in the synthesis of new heterocyclic systems. Thus, the amino functionality of 3-amino-4(3\(H\))-quinazolinone reacts with carbon electrophiles namely, chloroacetamide and aromatic aldehydes \textit{viz} benzaldehye, 4-methoxy-benzaldehyde and 4-chlorobenzaldehyde to afford triazino[2,3-c]quinazoline 14 and 3-arylideneamino-4(3\(H\))-quinazolinones 15a-c respectively. The former compound was formed through 3-carbamoylmethylamino-4(3\(H\))-quinazolinone intermediate followed by ring closure, whereas the latter was formed by nucleophilic attack of the amino group on the electronically deficient carbonyl carbon atom of the aldehyde followed by dehydration, a process in which the driving force of removing the bad leaving hydroxyl group is the conjugation with the aromatic nucleus in the more thermodynamically stable compound 15a-c. It is of interest to investigate the behaviour of azomethines 15a-c which contain an activated C=N bond towards aliphatic and aromatic mercaptans. Cyclocondensation of 15c with 2-mercaptoacetic acid in the presence of few drops of piperidine gave the thiazolidin-4-one derivative 16.\(^{26}\)

The reaction proceeded \textit{via} nucleophilic addition of sulfur to C=N followed by cyclization and a thiazole nucleus attached to N3 of quinazolinone derivative 16 was obtained. On the other hand, when azomethine 15c was allowed to react with thiophenol in the presence of piperidine as a basic catalyst, the adduct 17 was isolated.\(^{27}\)
It has been reported that 2-phenyl-(4H)-3,1-benzoxazin-4-one underwent base-catalyzed ring opening with active methylene containing compounds e.g., ethyl acetoacetate, diethylmalonate and ethyl cyanoacetate in refluxing pyridine to afford ethyl o-benzamidobenzoylacetate. In the present work, it has been found that hitherto unknown reaction of malononitrile with benzoxazinone 1a in presence of ethanolic sodium ethoxide resulted in 4-hydroxy-3-cyanoquinoline derivative 18 [cf. Scheme 3]. The o-hydroxynitrile 18 could be versatile in the synthesis of fused heterocycles utilizing its bifunctionality. Thus, when compound 18 reacted with phenyl isocyanate in the presence of triethylamine in refluxing benzene, it gave the oxazino[5,6-c] quinoline 19. On the other hand, it has been reported that 2-substituted (4H)-3,1-benzoxazin-4-ones reacted with Grignard reagents affording either tertiary carbinols through addition of two molecules of the reagent on the carbonyl carbon with the cleavage of oxazinone moiety or 4,4-disubstituted benzoxazines through dehydration of the first formed carbinol. Thus, reaction of oxazinone 1a with ethereal solution of phenylmagnesium bromide and/or benzylmagnesium bromide yielded the unexpected carbinols 20 and 21 respectively.
Scheme 3. Reagents and reaction conditions: (i) CH₂(CN)₂, EtONa, steam bath; (ii) PhNCO, Et₃N, fusion; (iii) PhMgBr, Et₂O, 25°C; (iv) PhCH₂MgBr, Et₂O, 25°C; (v) dry benzene, anhydrous AlCl₃, steam bath; (vi) C₆H₅Et, anhydrous AlCl₃, steam bath; (vii) dry m-xylene, anhydrous AlCl₃, steam bath; (viii) dry p-xylene, anhydrous AlCl₃, steam bath; (ix) barbituric acid and/or thiobarbituric acid, pyridine, 115°C.
The reaction proceeded through attack of the Grignard's reagent on the carbonyl group of the oxazinone nucleus to give the \( o \)-acetamidobenzophenone or \( o \)-acetamidoacetophenone intermediate which was attacked by another molecule of the reagent to afford the corresponding carbinol. The isolation of one and the same product from two different routes; reaction of benzoxazinone \( 1a \) with phenylmagnesium bromide and/or dry benzene in presence of anhydrous aluminium chloride led us to assume that the addition of the second Grignard's molecule occurred at the carbonyl functionality adjacent to N-Mg bond [cf. Scheme 4].

Scheme 4
The behavior of 2-methyl-(4H)-3,1-benzoxazin-4-one 1a towards aromatic hydrocarbons namely, benzene, ethylbenzene, m- and p-xylene under Friedel-Crafts reaction conditions was also studied. The present study revealed that the less bulky hydrocarbons viz benzene and ethylbenzene afforded two simultaneous products. The first is obtained due to attack of the acylating agent upon one molecule of the substrate hydrocarbon to give the respective benzophenone derivative 22 and 23 and the second resulted from the reaction of the acylating agent with two molecules of the hydrocarbon to afford the carbinols 20 and 24 respectively. When the reaction is carried out with more bulky hydrocarbons viz m- and p-xylene, a sole product was isolated which was identified as the 2-acetamidobenzophenone derivatives 25 and 26. According to our speculation, the formation of one product in case of more bulk hydrocarbons is due to the bulk of the substrate hydrocarbon. Finally, when (4H)-3,1-benzoxazin-4-one 1a, was allowed to react with barbituric and/or thiobarbituric acids in refluxing pyridine, 5-arylidene-barbituric and thiobarbituric acids 27a and b were obtained through fission of oxazinone nucleus. The product 27 was obtained from heteroring opening of the oxazinone nucleus followed by enolization. This seems to be reasonable owing to compound 27 is being thermodynamically stable via cinnamoyl resonance and hydrogen-bonding as well, while the keto form of compound 27 stabilizes by benzoyl resonance (stabilization by cinnamoyl resonance is higher than benzoyl resonance).

**Experimental Section**

**General Procedures.** All melting points reported are uncorrected and were determined on a Stuart electric melting point apparatus. The IR spectra were measured on a Unicam 1200 Spectrophotometer using potassium bromide Wafer technique. Mass spectra were measured on Shimadzu GC-MS-QP 1000 EX instrument operating at 70 eV. The values of m/z of the fragments are written followed by (I, / %) percentage of relative intensity. The 1H- and 13C-NMR spectra were recorded in CDCl3 or DMSO-d6 solutions on Varian Gemini 200 MHz instrument34,35 TMS was used as internal standard with chemical shifts δ from downfield to upfield. TLC were performed on ready-to-use silica gel plates Merck 60. Satisfactory results were obtained for elemental analysis in Institut für Organische Chemie, Tubingen University, Tubingen, Germany: C ± 0.41%, H ± 0.29%, N ± 0.32%. Physical characteristics of the
synthesized compounds are given in Table 1. $^{13}$C-NMR spectra of some synthesized compounds are listed in Table 2.

### Table 1. Physical characteristics of synthesized compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>mp/°C</th>
<th>Solvent</th>
<th>Yield %</th>
<th>Colour</th>
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<tbody>
<tr>
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<td>250-252</td>
<td>B $^a$</td>
<td>75</td>
<td>White</td>
</tr>
<tr>
<td>3</td>
<td>190</td>
<td>LP$_3$</td>
<td>58</td>
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<td>4</td>
<td>160</td>
<td>LP$_3$</td>
<td>85</td>
<td>White</td>
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<tr>
<td>5</td>
<td>190-192</td>
<td>B</td>
<td>72</td>
<td>Pale Yellow</td>
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<tr>
<td>6</td>
<td>230-232</td>
<td>E</td>
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<td>7</td>
<td>&gt;320</td>
<td>T</td>
<td>89</td>
<td>Beige</td>
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<tr>
<td>8</td>
<td>244-246</td>
<td>E</td>
<td>83</td>
<td>Beige</td>
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<tr>
<td>9</td>
<td>227-229</td>
<td>T</td>
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<td>10</td>
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<td>B</td>
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<tr>
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<td>18</td>
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<td>68</td>
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</tr>
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</tr>
<tr>
<td>27b</td>
<td>290-292</td>
<td>A</td>
<td>59</td>
<td>Beige</td>
</tr>
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</table>

$^a$ B = benzene; LP$_1$ = light petroleum 40-60°C; LP$_2$ = light petroleum 60-80°C; LP$_3$ = light petroleum 80-100°C; E = ethanol; T = toluene; M = methanol; A = acetic acid.
Table 2. $^{13}$C-NMR of some synthesized compounds

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<tr>
<th>Structural Formula and Compound No.</th>
<th>δ (ppm) Carbon Atom No.</th>
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<td><img src="image2.png" alt="Formula 2" /></td>
<td>163.2 (C-1), 162.3 (C-2), 131.1 (C-3), 130.7 (C-4), 123.5 (C-5), 139.4 (C-6), 118.7 (C-7), 149.8 (C-8), 11.1 (C-9)</td>
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<tr>
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<td>163.6 (C-1), 158.3 (C-2), 135.0 (C-3), 132.4 (C-4), 123.8 (C-5), 138.3 (C-6), 118.5 (C-7), 151.7 (C-8), 12.6 (C-9), 161.4 (C-10).</td>
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<td><img src="image13.png" alt="Formula 13" /></td>
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Table 2. Continued

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6,8-Dibromo-3-hydroxy-2-methyl-4(3H)-quinazolinone (2). An equimolar mixture of benzoazinone 1a (3.19 g; 10 mmol) and hydroxylamine hydrochloride (0.69 g; 10 mmol) in 30 mL of dry pyridine was heated under reflux for 6 h, left to cool and then poured into cold water with constant stirring. The solid product that separated out was filtered off, thoroughly washed with water, dried and then recrystallized from the appropriate solvent to give
quinazolinone 2. Elemental analysis for C₉H₆Br₂N₂O₂ (M. wt. 334); Found: C, 31.98; H, 1.63; N, 8.25; Calcd: C, 32.34; H, 1.80; N, 8.38. IR spectrum, \( \tilde{\nu} / \text{cm}^{-1} \): 1671 (CO), 3073 (C-H arom), 2980 (C-H aliph), 3358 (OH, hydrogen bonded and 3465 (OH, free). \(^1\)H NMR (CDCl₃), \( \delta \): 8.39 (d, 1H, J = 2.16 Hz, C₅-H), 8.16 (d, 1H, J = 2.05 Hz, C₇-H), 6.61 (s, 1H, OH) and 2.48 (s, 3H, -N=C-CH₃).

3-Acetoxy-6,8-dibromo-2-methyl-4(3\(H\))-quinazolinone (3). 10 mmol of compound 2 (3.34 g) was heated under reflux in 20 mL of freshly distilled acetic anhydride for 2 h. The reaction solution was left to cool and the solid that deposited was filtered off, washed several times with light petroleum, dried and recrystallized from proper solvent to afford the desired product 3. Elemental analysis for C₁₁H₈Br₂N₂O₃ (M. wt. 376); Found: C, 35.30; H, 2.24; N, 7.77; Calcd: C, 35.11; H, 2.13; N, 7.45. IR spectrum, \( \tilde{\nu} / \text{cm}^{-1} \): 1674 (CO quinazolinone), 1756 (CO ester), 2927 (C-H aliph) and 3071 (CH arom) with the lack of \( \tilde{\nu} \text{OH} \). \(^1\)H NMR spectrum (CDCl₃), \( \delta \): 8.43 (d, 1H, J = 2.25 Hz, C₅-H), 8.21 (d, 1H, J = 2.25 Hz, C₇-H) and 2.51 (s, 6H, 2CH₃).

6,8-Dibromo-3-ethoxycarbonylmethoxy-2-methyl-4(3\(H\))-quinazolinone (4). To a solution of 3-hydroxyquinonazolinone 2 (3.34 g; 10 mmol) in 50 mL of dry acetone were added ethyl chloroacetate (4.92 g; 40 mmol) and anhydrous potassium carbonate (5.52 g; 40 mmol). The reaction mixture was heated under reflux for 24 h. The excess acetone was removed by distillation and the residue was poured into cold water with stirring. The solid that separated out was filtered by suction, washed with cold water, dried and purified by recrystallization from suitable solvent to afford product 4. Elemental analysis for C₁₃H₁₂Br₂N₂O₄ (M. wt. 420); Found: C, 36.90; H, 2.59; N, 6.43; Calcd: C, 37.14; H, 2.86; N, 6.67. IR spectrum, \( \tilde{\nu} / \text{cm}^{-1} \): 1672 (CO quinazolinone), 1734 (CO ester), 2987 (CH aliph) and 3066 (CH arom) and disappearance of \( \tilde{\nu} \text{OH} \). \(^1\)H NMR (DMSO-d₆), \( \delta \): 8.28 (d, 1H, J = 2.20 Hz, C₅-H), 8.09 (d, 1H, J = 2.20 Hz, C₇-H), 4.83 (s, 2H, OCH₂CO), 4.23 (q, 2H, J = 7.26 Hz, CH₂CH₃), 2.57 (s, 3H, N=C-CH₃) and 1.29 (t, 3H, J = 7.04, CH₂CH₃).

3-(4-Acetophenyl)-6,8-dibromo-2-methyl-4(3\(H\))-quinazolinone (5). To a solution of benzoazinone 1a (3.19 g; 10 mmol) in ethyl alcohol (30 mL) 4-aminoacetophenone (1.35 g; 10 mmol) was added and the reaction mixture was heated under reflux for 6 h and left to cool after distilling off the excess solvent. The solid product which deposited was filtered off, dried and recrystallized from suitable solvent to yield compound 5. Elemental analysis for C₁₇H₁₂Br₂N₂O₂ (M. wt. 436); Found: C, 46.57; H, 2.46; N, 6.23; Calcd: C, 46.79; H, 2.75; N, 6.42. IR spectrum, \( \tilde{\nu} / \text{cm}^{-1} \): 1667 (CO quinazolinone), 1702 (CO acetyl), 2945 (CH aliph), and 3072 (CH arom). \(^1\)H NMR (DMSO-d₆), \( \delta \): 8.92-8.11 (m, 6H, ArH), 2.48 (s, 3H, N=C-CH₃) and 2.22 (s, 3H, COCH₃).

3-(2-Aminophenyl)-6,8-dibromo-2-methyl-4(3\(H\))-quinazolinone (6). An equimolar mixture of benzoazinone 1a (3.19 g; 10 mmol) and o-phenylenediamine (1.08 g; 10 mmol) in 30 mL of ethyl alcohol was heated under reflux for 8 h. The excess alcohol was distilled off and the reaction solution was left to cool. The solid so obtained was filtered off, dried and recrystallized from proper solvent to afford 6. Elemental analysis for C₁₅H₁₁Br₂N₃O (M. wt. 409); Found: C, 43.62; H, 2.45; N, 9.98; Calcd: C, 44.01; H, 2.69; N, 10.27. IR spectrum, \( \tilde{\nu} / \text{cm}^{-1} \): 1677 (CO
quinazolinone), 3359 and 3468 (NH₂). ¹H NMR (DMSO-d₆), δ: 8.85-7.67 (m, 6H, ArH), 3.17 (s, 2H, NH₂) and 2.39 (s, 3H, CH₃).

6,8-Dibromo-2-methyl-3-(4-sulfonamidophenyl)/[4-N-(5-methyl-3-isoxazolyl)-sulfonamidophenyl]-4(3H)-quinazolinones 7 and 8. A mixture of benzoxazinone 1a (3.19 g, 10 mmol) and 10 mmol of sulfanilamide (1.72 g) and/or sulfamethoxazole (2.53 g) was heated under reflux in 50 mL of dry pyridine for 8h. The excess solvent was removed by distillation and the reaction solution was left to cool, then poured into crushed ice with stirring to obtain the crude products which were filtered off, thoroughly washed with cold water, dried and recrystallized from the proper solvent to afford products 7 and 8 respectively.

**Compound 7.** Elemental analysis for C₁₅H₁₁Br₂N₃O₃S (M. wt. 473); Found: C, 38.35; H, 2.52; N, 9.09; Calcd: C, 38.05; H, 2.33; N, 8.88. IR spectrum, ν/cm⁻¹: 1687 (CO), 2922 (CH aliph), 3067 and 3107 (CH arom), 3222 and 3316 (NH₂). ¹H NMR (DMSO-d₆), δ: 8.42 (d, 1H, J = 1.36 Hz, C₅-H), 8.18 (d, 1H, J = 1.36 Hz, C₇-H), 8.05-7.70 (m, 4H, ArH), 7.58 (s, 2H, NH₂) and 2.18 (s, 3H, CH₃).

**Compound 8.** Elemental analysis for C₁₉H₁₄Br₂N₄O₄S (M. wt. 554); Found: C, 41.44; H, 2.79; N, 10.34; Calcd: C, 41.16; H, 2.53; N, 10.11. IR spectrum, ν/cm⁻¹: 1661 (CO), 2923 (CH aliph), 3071 (CH arom), 3386 (NH). ¹H NMR (DMSO-d₆), δ: 8.42 (d, 1H, J = 2.20 Hz, C₅-H), 8.16 (d, 1H, J = 2.18 Hz, C₇-H), 8.10-7.75 (m, 4H, ArH), 7.38 (s, 1H, proton of isoxazole nucleus), 6.24 (s, 1H, exchangable, NH), 2.35 (s, 3H, CH₃ of isoxazole nucleus) and 2.14 (s, 3H, CH₃ of quinazolinone nucleus).

7,9-Dibromo-5-methyl-2-oxo-1,2,4-triazolo[2,3-c]quinazoline (9). To a solution of benzoxazinone 1a (3.19 g; 10 mmol) in 30 mL of pyridine semicarbazide hydrochloride (3.36 g; 10 mmol) was added and the reaction mixture was heated under reflux for 6 h, left to cool, poured into cold water with stirring. The solid crude product that separated out was filtered off by suction, washed with cold water, dried and recrystallized from the appropriate solvent to give compound 9. Elemental analysis for C₁₀H₆Br₂N₄O (M. wt. 358); Found: C, 33.88; H, 1.78; N, 15.95; Calcd: C, 33.52; H, 1.68; N, 15.64. IR spectrum, ν/cm⁻¹: 1677 (CO), 2933 (CH aliph), 3071 (CH arom), 3206 and 3314 (NH hydrogen-bonded and free). ¹H NMR (DMSO-d₆), δ: 8.16 (d, 1H, J = 2.18 Hz, C₁₀-H), 8.07 (d, 1H, J = 2.18 Hz, C₈-H), 5.78 (s, 1H, NH) and 2.28 (s, 3H, CH₃).

6,8-Dibromo-3-(2-hydroxyethyl)-2-methyl-4(3H)-quinazolinone (10). A solution of benzoxazinone 1a (3.19 g; 10 mmol) in ethanolamine (20 mL) was refluxed for 3 h. Most of the solvent was removed, the solid that formed was collected, washed with light petroleum, dried and recrystallized from appropriate solvent to afford compound 10. Elemental analysis for C₁₁H₁₀Br₂N₂O₂ (M. wt. 362); Found: C, 36.87; H, 2.97; N, 7.90; Calcd: C, 36.46; H, 2.76; N, 7.73. IR spectrum, ν/cm⁻¹: 1677 (CO), 2931 (CH aliph), 3070 (CH arom) and 3452 (OH). ¹H NMR (CDCl₃), δ: 8.20 (d, 1H, J = 2.00 Hz, C₅-H), 8.07 (d, 1H, J = 1.86 Hz, C₇-H), 4.79 (s, 1H, OH exchangable), 4.29 (t, 2H, J = 5.02 Hz, -CH₂OH), 4.03 (t, 2H, J = 4.96 Hz, -CH₂-N) and 2.72 (s, 3H, CH₃).
6,8-Dibromo-3-(N-phthalimidoethyl)/[(2-hydroxy-1-naphthyl)ethyl]-2-methyl-4(3H)-quinazolinones 11 and 12. A mixture of compound 10 (3.58 g; 10 mmol) and 10 mmol of phthalimide (1.47 g) and/or 2-naphthol (1.44 g) was heated without solvent and 110-120°C in presence of few drops of concentrated hydrochloric acid for 3 h. The solid was triturated with warm light petroleum. The solid separated was filtered, dried and crystallized to afford 11 and 12 respectively.

**Compound 11.** Elemental analysis for C_{10}H_{13}Br_{2}N_{3}O_{3} (M. wt. 491); Found: C, 46.21; H, 2.51; N, 8.30; Calcd: C, 46.44; H, 2.65; N, 8.55. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1720 and 1680 (CO of phthalimide and quinazolinone), 2927 and 2977 (CH aliph) and 3072 (CH arom) with the disappearance of $\tilde{\nu}$ OH. $^1$H NMR (CDCl$_3$), $\delta$: 8.83-7.72 (m, 6H, ArH), 4.23 (t, 2H, J = 5.16 Hz, CH$_2$N(CO)$_2$), 3.97 (t, 2H, J = 5.16 Hz, CH$_2$-NCO) and 2.49 (s, 3H, CH$_3$).

**Compound 12.** Elemental analysis for C$_{21}$H$_{16}$Br$_2$N$_2$O$_2$ (M. wt. 488); Found: C, 51.43; H, 3.03; N, 5.57; Calcd: C, 51.64; H, 3.28; N, 5.74. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1674 (CO), 2972 (CH aliph), 3100 (CH arom) and 3294 (OH). $^1$H NMR (CDCl$_3$), $\delta$: 8.77 (d, 2H, J = 6.70 Hz, ArH of phenolic nucleus), 8.31 (d, 1H, J = 2.11 Hz, C$_7$-H), 8.13 (d, 1H, J = 2.09 Hz, C$_5$-H), 7.01 (s, 1H, OH), 6.92-6.14 (m, 4H, ArH of benzene nucleus), 4.35 (t, 2H, J = 5.24 Hz, CH$_2$-NCO), 4.14 (t, 2H, J = 5.24 Hz, CH$_2$-C=) and 2.55 (s, 3H, CH$_3$).

6-Bromo-2-isopropyl-3-amino-4(3H)-quinazolinone (13). To a solution of benzoxazinone 1b (2.48 g; 10 mmol) in 50 mL of ethyl alcohol, hydrazine monohydrate 98% (0.75 g, 15 mmol) was added and the solution was heated under reflux for 3 h. The solid that deposited on cooling after distilling off most of the solvent was filtered off and recrystallized from appropriate solvent to yield 13. Elemental analysis for C$_{11}$H$_{12}$BrN$_3$O (M. wt. 282); Found: C, 46.50; H, 4.19; N, 14.71; Calcd: C, 46.81; H, 4.26; N, 14.89. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1645 (C=N), 1684 (C=O), 3350 and 3447 (NH$_2$). $^1$H NMR (DMSO-d$_6$), $\delta$: 4.38 (s, 2H, NH$_2$), 8.42-7.51 (m, 3H, ArH), 3.66 (septet, 1H, methine proton of isopropyl group) and 1.32 (d, 6H, J = 6.25 Hz, 2 Me of isopropyl group). MS, m/z (I,%): 282 ([M$^+$], 100), 283 (M+1, 82), 266 (8.8), 253 (41.5), 239 (7.5), 224 (6.1), 184 (5.4), 159 (4.8), 144 (3.4), 116 (2.7) and 76 (4.8).

10-Bromo-6-isopropyl-2-oxo-3H,4H,1,2,4-triazino[2,3-c] quinazoline (14). A mixture of quinazolinone 13 (2.82 g; 10 mmol) and chloroacetamide (0.94 g; 10 mmol) was heated without solvent on an oil bath at 130-140°C for 6 h. The reaction solid mixture was left to cool, triturated with water and the solid which separated out, was filtered off, washed with water, dried and recrystallized from proper solvent to afford 14. Elemental analysis for C$_{13}$H$_{13}$BrN$_4$O (M. wt. 321); Found: C, 48.92; H, 4.30; N, 17.58; Calcd: C, 48.60; H, 4.05; N, 17.45. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1632 (C=N), 1675 (C=O) and 3320 (NH). $^1$H NMR (CDCl$_3$), $\delta$: 8.86-8.21 (m, 3H, ArH), 5.62 (s, 1H, NH), 5.25 (s, 2H, -COCH$_2$-N), 3.70 (septet, 1H, methine proton of isopropyl group) and 1.36 (d, 6H, J = 6.18 Hz, 2 Me of isopropyl group).

3-Arylidenoamino-6-bromo-2-isopropyl-4(3H)-quinazolinones 15a-c. A mixture of 3-amino-4(3H)-quinazolinone 13 (2.82 g; 10 mmol) and the appropriate aldehyde (10 mmol) in ethyl alcohol (50 mL) was heated under reflux for 4 h in presence of catalytic amount of piperidine.
The excess alcohol was distilled off and the reaction solution was left to cool to obtain the crude product which was recrystallized from suitable solvents to give 15a-c.

**Compound 15a.** Elemental analysis for C_{18}H_{16}BrN_{3}O (M. wt. 370); Found: C, 58.55; H, 4.51; N, 11.62; Calcd: C, 58.38; H, 4.32; N, 11.35. IR spectrum, $\tilde{\nu}$ / cm$^{-1}$: 1625-1620 (C=N), 1678-1685 (CO), 2875-2985 (CH aliph), and 3080-3098 (CH arom).

**Compound 15b.** Elemental analysis for C_{19}H_{18}BrN_{3}O_{2} (M. wt. 400); Found: C, 56.81; H, 4.38; N, 10.36; Calcd: C, 57.00; H, 4.50; N, 10.50. $^1$H NMR (DMSO-d$_6$) for 15b, $\delta$: 8.92 (s, 1H, N=CH), 8.76-8.11 (m, 7H, ArH), 3.684 (septet, 1H, methine proton of isopropyl), 3.67 (s, 3H, OMe) and 1.41 (d, 6H, $J = 6.22$ Hz, 2 Me of isopropyl).

**Compound 15c.** Elemental analysis for C_{18}H_{15}BrClN_{3}O (M. wt. 404.5); Found: C, 53.03; H, 3.48; N, 10.08; Calcd: C, 53.40; H, 3.71; N, 10.38.

**6-Bromo-3-[2-(4-chlorophenyl)-4-oxo-1,3-thiazol-3-yl]-2-isopropyl-4(3H)-quinazolinone (16).** A mixture of 15c (4.00 g; 10 mmol) of 15c and 2-mercaptoacetic acid (0.92 g; 10 mmol) was stirred in dry benzene (50 mL) and then refluxed for 3 h. The yellow solution was distilled to get rid of the excess solvent and the residue was recrystallized from suitable solvent to afford 16. Elemental analysis for C_{20}H_{17}BrClN_{3}O_{2}S (M. wt. 478.5); Found: C, 50.39; H, 3.81; N, 9.06; Calcd: C, 50.16; H, 3.55; N, 8.78. IR spectrum, $\tilde{\nu}$ / cm$^{-1}$: 692 (C-S), 1670 and 1697 (two C=O groups) with the lacking of any N-H bond. $^1$H NMR (CDCl$_3$), $\delta$: 8.87-8.18 (m, 7H, ArH), 5.62 (s, 1H, benzylic proton), 4.81 (s, 2H, COCH$_2$S), 3.71 (septet, 1H, methine proton) and 1.38 (d, 6H, $J = 6.20$ Hz, 2Me of isopropyl).

**6-Bromo-3-[(4-chlorophenylthio-phenyl)methylamino]-2-isopropyl-4(3H) quinazolinone (17).** To a mixture of 15c (4.00 g; 10 mmol) and thiophenol (1.10 g, 10 mmol) in dry benzene (40 mL) was added few drops of piperidine and the reaction mixture is then heated under reflux for 2 h. Distilling off the excess solvent and cooling gave a crude solid which was filtered off, washed with light petroleum (2 x 10 mL) and recrystallized to afford product 17. Elemental analysis for C_{24}H_{21}BrClN_{3}O_{2}S (M. wt. 514.5); Found: C, 56.15; H, 4.17; N, 8.35; Calcd: C, 55.98; H, 4.08; N, 8.16. IR spectrum, $\tilde{\nu}$ / cm$^{-1}$: 684 (C-S), 1677 (C=O) and 3400 (NH). $^1$H NMR (CDCl$_3$), $\delta$: 8.80 (s, 1H, NH), 8.10-6.90 (m, 12H, ArH), 4.00 (s, 1H, CH-S), 3.68 (septet, 1H, methine proton) and 1.30 (d, 6H, $J = 6.78$ Hz, 2 Me of isopropyl group).

**3-Cyano-6,8-dibromo-4-hydroxy-2-methylquinoline (18).** To 40 mL of absolute ethanol containing 0.23 g (10 mmol) of sodium metal was added 0.66 g of malonitrile (10 mmol). After few minutes 3.19 g of benzoxazinone 1a (10 mmol) was added. The reaction mixture was heated under reflux with stirring for 20 h. Most of the solvent was distilled off and the reaction solution was acidified with hydrochloric acid to give a crude product which was filtered off, washed several times with cold water, dried, and recrystallized to yield quinoline-3-carbonitrile 18. Elemental analysis for C_{11}H_{6}Br$_2$N$_2$O (M. wt. 342); Found: C, 38.86; H, 1.83; N, 8.37; Calcd: C, 38.60; H, 1.75; N, 8.19. IR spectrum, $\tilde{\nu}$ / cm$^{-1}$: 1645 (C=N), 2220 (C=N), 2926 and 2996 (CH aliph), 3082 (CH arom) and 3320 and 3384 (OH H-bonded and free respectively). $^1$H NMR (DMSO-d$_6$), $\delta$: 10.34 (s, 1H, phenolic OH), 8.82 (d, 1H, $J = 2.18$ Hz, C$_7$-H), 8.60 (d, 1H, $J = 2.18$ Hz, C$_8$-H), 8.50 (d, 1H, $J = 2.18$ Hz, C$_9$-H).
Hz, C5-H) and 2.38 (s, 3H, Me). MS, m/z (I, %): 345 (51), 344 (17.8), 343 (100), 342 (7.6), 341 (38), 278 (16), 277 (11), 276 (13), 155 (13), 128 (10), 63 (11) 62 (17), and 61 (13).

7,9-Dibromo-2-oxo-3-phenyl-4-[phenylaminocarbonyl]jimino-1,3-oxazino [5,6-c]quinoline (19). A mixture of 18 (3.4 g; 10 mmol) and phenyl isocyanate (2.38 g; 20 mmol) in 50 mL of benzene was heated under reflux in presence of catalytic amount of triethylamine for 12 h. Removal of excess benzene afforded a crude solid after cooling. The crude solid was filtered off, dried and recrystallized to yield compound 19. Elemental analysis for C25H16Br2N4O3 (M. wt. 580); Found: C, 52.09; H, 2.96; N, 9.81; Calcd: C, 51.72; H, 2.76; N, 9.66. IR spectrum, ν/cm⁻¹: 1667 (CO amide), 1704 (CO oxazinone), 2922 (CH aliph), 3072 (CH arom) and 3263 (NH). 1H NMR (CDCl₃), δ: 8.80-7.69 (m, 12 H, ArH), 5.79 (s, 1H, NH), 2.15 (s, 3H, Me).

3,5-Dibromo-2-(1-hydroxy-1-phenyl)ethylaminobenzophenone 20 and benzyl 3,5-dibromo-2-(1-hydroxy-1-benzyl)ethyl-aminophenyl ketone (21). To a solution of benzoxazinone 1a (3.19 g; 10 mmol) in dry ether (20 mL) was added portionwise an ethereal solution of Grignard's reagent namely, phenylmagnesium bromide and/or benzylmagnesium bromide (30 mmol). The reaction mixture was heated under reflux on a steam bath for 4 h, left at room temperature overnight, decomposed with saturated ammonium chloride solution and finally extracted by ether. The ether extract was dried over anhydrous magnesium sulfate and the ether was removed to yield a crude solid which was recrystallized from suitable solvent to afford 20 and 21 respectively.

Compound 20. Elemental analysis for C21H17Br2NO2 (M. wt. 475); Found: C, 52.87; H, 3.33; N, 2.83; Calcd: C, 53.05; H, 3.58; N, 2.95. IR spectrum, ν/cm⁻¹: 1675 (CO), 2990 (CH aliph), 3083 (CH arom), 3251 (NH) and 3380 (OH). 1H NMR (CDCl₃), δ: 7.78 (d, 1H, J = 2.22 Hz, C₄-H), 7.74 (d, 1H, J = 2.27 Hz, C₆-H), 7.36-6.82 (m, 10H, ArH), 4.08 (s, 1H, NH exchangeable), 1.62 (s, 1H, OH exchangeable) and 1.54 (s, 3H, Me).

Compound 21. Elemental analysis for C23H21Br2NO2 (M. wt. 503); Found: C, 55.08; H, 4.28; N, 3.02; Calcd: C, 54.87; H, 4.17; N, 2.78. IR spectrum, ν/cm⁻¹: 1664 (CO), 2930 and 2989 (CH aliph), 3065 (CH arom), 3257 (NH) and 3416 and 3618 (OH H-bonded and free). 1H NMR (CDCl₃), δ: 7.69 (d, 1H, J = 2.20 Hz, C₄-H), 7.37 (d, 1H, J = 2.28 Hz, C₆-H), 7.27-7.06 (m, 10H, ArH), 3.25 and 3.14 (dd, 4H, J = 13.96 Hz and 13.72 Hz, two CH₂Ph), 2.72 (s, 1H, NH exchangeable), 2.05 (s, 3H, Me), and 1.78 (s, 1H, OH exchangeable).

20. 2-Acetylamino-3,5-dibromobenzophenone 22, 2-acetylamino-3,5-dibromo-4'-ethylbenzophenone 23, 3,5-dirbomo-2-[1-(4-ethylphenyl)-1-hydroxy]ethylbenzophene 24 and 2-acetylamino-3,5-dibromo-2',4',5'-dimethylbenzophenone (25 and 26). To a vigorously stirred suspension of benzoxazinone 1a (3.19 g; 10 mmol) in dry aromatic hydrocarbon namely, benzene, ethylbenzene, m- and/or p-xylene (100 mL) was added anhydrous aluminium chloride (4.0 g; 30 mmol) portionwise then the reaction mixture was heated on steam bath for 6 h, allowed to stand at room temperature overnight, then it was added with continuous stirring to ice-hydrochloric acid (50 mL). The organic layer was separated, washed with cold water (3 x 30 mL) and the excess hydrocarbon was removed by steam distillation. The organic material was extracted with ether, dried over anhydrous magnesium
sulfate, then ether was distilled off to obtain the crude product which was recrystallized or fractionally crystallized to afford the product(s).

**Compound 22.** Elemental analysis for C15H11Br2NO2 (M. wt. 397); Found: C, 45.65; H, 2.82; N, 3.68; Calcd: C, 45.34; H, 2.77; N, 3.53. IR spectrum, $\tilde{\nu}/$cm$^{-1}$: 1692 (CO ketone), 1646 (CO of NHCOMe), 2925 and 2974 (CH aliph), 3061 (CH arom) and 3270 (NH). $^1$H NMR (CDCl$_3$), $\delta$: 8.78 (d, 1H, J = 2.18 Hz, C4-H), 8.49 (d, 1H, J = 2.1 Hz, C6-H), 7.43-6.96 (m, 5H, ArH), 4.73 (s, 1H, NH) and 2.46 (s, 3H, Me).

**Compound 23.** Elemental analysis for C17H15Br2NO2 (M. wt. 425); Found: C, 48.19; H, 3.80; N, 3.40; Calcd: C, 48.00; H, 3.53; N, 3.29. IR spectrum, $\tilde{\nu}/$cm$^{-1}$: 1698 (CO of diaryl ketone), 1646 (CO of NHCOMe), 2927 and 2960 (CH aliph), 3065 (CH arom) and 3247 (NH). $^1$H NMR (DMSO-d$_6$), $\delta$: 9.90 (s, 1H, NH exchangable), 8.21 (d, 1H, J = 2.14 Hz, C4-H), 7.94 (d, 1H, J = 2.24 Hz, C6-H), 7.69-7.25 (m, 4H, ArH), 2.75 (q, 2H, J = 7.38 Hz, CH$_2$CH$_3$), 1.76 (s, 3H, COCH$_3$), and 1.26 (t, 3H, J = 7.50 Hz, CH$_2$CH$_3$).

**Compound 24.** Elemental analysis for C25H25Br2NO2 (M. wt. 531); Found: C, 56.65; H, 4.89; N, 2.87; Calcd: C, 56.50; H, 4.1; N, 2.64. IR spectrum, $\tilde{\nu}/$cm$^{-1}$: 1676 (CO), 2930 and 2972 (CH aliph), 3064 (CH arom), 3315 (NH) and 3460 (OH). $^1$H NMR (DMSO-d$_6$), $\delta$: 9.92 (s, 1H, NH exchangable), 8.62 (d, 1H, J = 2.11 Hz, C4-H), 8.27 (d, 1H, J = 2.18 Hz, C6-H), 8.12-7.74 (m, 8H, ArH), 5.36 (s, 1H, OH exchangable), 2.69 (q, 4H, J = 7.44 Hz, two CH$_2$CH$_3$), 1.52 (s, 3H, NHC-Me), and 1.22 (t, 6H, J = 7.44 Hz, two CH$_2$CH$_3$).

**Compound 25.** Elemental analysis for C17H15Br2NO2 (M. wt. 425); Found: C, 48.33; H, 3.75; N, 3.45; Calcd: C, 48.00; H, 3.53; N, 3.29. IR spectrum, $\tilde{\nu}/$cm$^{-1}$: 1645 (CO of COMe), 1670 (CO of Ar$_2$CO), 2980 (CH aliph), 3063 (CH arom) and 3227 (NH). $^1$H NMR (CDCl$_3$), $\delta$: 8.28 (s, 1H, NH), 7.69 (d, 1H, J = 2.11 Hz, C4-H), 7.31 (d, 1H, J = 2.08 Hz, C6-H), 7.40 (d, 1H, J$_{ortho}$ = 7.78 Hz, Ar-H), 7.02 (s, 1H, Ar-H), 7.02 (d, 1H, J$_{ortho}$ = 7.74 Hz, 1H, Ar-H), 2.49 (s, 3H, Ar-Me), 2.26 (s, 3H, Ar-Me) and 2.11 (s, 3H, COMe).

**Compound 26.** Elemental analysis for C17H15Br2NO2 (M. wt. 425); Found: C, 48.27; H, 3.68; N, 3.60; Calcd: C, 48.00; H, 3.53; N, 3.29. IR spectrum: $\tilde{\nu}/$cm$^{-1}$: 1640 (CO of COMe), 1673 (CO of Ar$_2$CO), 2922 and 2957 (CH aliph), 3100 (CH arom) and 3221 (NH). $^1$H NMR (CDCl$_3$), $\delta$: 8.33 (s, 1H, NH), 7.75 (d, 1H, J = 2.14 Hz, C4-H), 7.36 (d, 1H, J = 2.09 Hz, C6-H), 7.45 (d, 1H, J$_{ortho}$ = 7.88 Hz, Ar-H), 7.02 (s, 1H, Ar-H), 7.03 (d, 1H, J$_{ortho}$ = 2.94 Hz, Ar-H), 2.53 (s, 3H, Ar-Me), 2.37 (s, 3H, Ar-Me) and 2.07 (s, 3H, COMe).

**1-Hydroxy-1-(2-acetylamino-3,5-dibromophenyl)methylidene barbituric and thiobarbituric acids (27a,b).** An equimolar mixture of benzoxazine 1a (3.19 g; 10 mmol) and barbituric acid (1.28 g; 10 mmol) or 2-thiobarbituric acid (1.44 g, 10 mmol) was heated under reflux in pyridine (30 mL) for 7 h. The reaction solution was left to cool, poured into ice/hydrochloric acid with stirring. The solid that separated out was filtered off, washed with cold water, dried and crystallized from suitable solvent to afford 27a and 27b.

**Compound 27a.** Elemental analysis for C13H8Br2N3O5 (M. wt. 447); Found: C, 35.14; H, 2.12; N, 9.53; Calcd: C, 34.90; H, 2.01; N, 9.40. IR spectrum, $\tilde{\nu}/$cm$^{-1}$: 1730 (CO of CONH), 1690 (CO of COMe), 2920 (CH aliph), 3034 (CH arom), 3261 (NH) and 3500 (OH). $^1$H NMR
(DMSO-d$_6$), δ: 13.62 (s, 1H, NH of acetyl, exchangeable), 10.97 (s, 1H, NH, exchangeable), 10.66 (s, 1H, NH, exchangeable), 9.98 (s, 1H, OH, exchangeable), 8.35 (d, 1H, J = 2.20 Hz, C$_4$-H), 8.08 (d, 1H, J = 2.20 Hz, C$_6$-H) and 2.30 (s, 3H, COMe).

**Compound 27b.** Elemental analysis for C$_{13}$H$_9$Br$_2$N$_3$O$_4$S (M. wt. 463); Found: C, 33.81; H, 2.07; N, 9.29; Calcd: C, 33.69; H, 1.94; N, 9.07. IR spectrum, $\tilde{\nu}$/cm$^{-1}$: 1742 (CO of CONH), 1675 (CO of NHCOMe), 2876 (CH aliph), 3064 (CH arom), 3317 (NH) and 3450 (OH).

**References**