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بسم اللّه الرحمن الرحيم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

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Faculty of Science
Chemistry Department

Nitrogen and oxygen containing compounds as building blocks in synthesis of some heterocyclic compounds

A Thesis submitted for the Degree of Master in Science
(Organic Chemistry)

Presented by

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Utilization of 2-substituted 3, 1-benzoxazin-4-ones in synthesis of some quinazoline annulated derivatives

Asmaa M. Abd-Alaziz, Hanan A. Sallam, Ahmed S. A. Youssef & Abeer M. El-Naggar

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Utilization of 2-substituted 3, 1-benzoxazin-4-ones in synthesis of some quinazoline annulated derivatives

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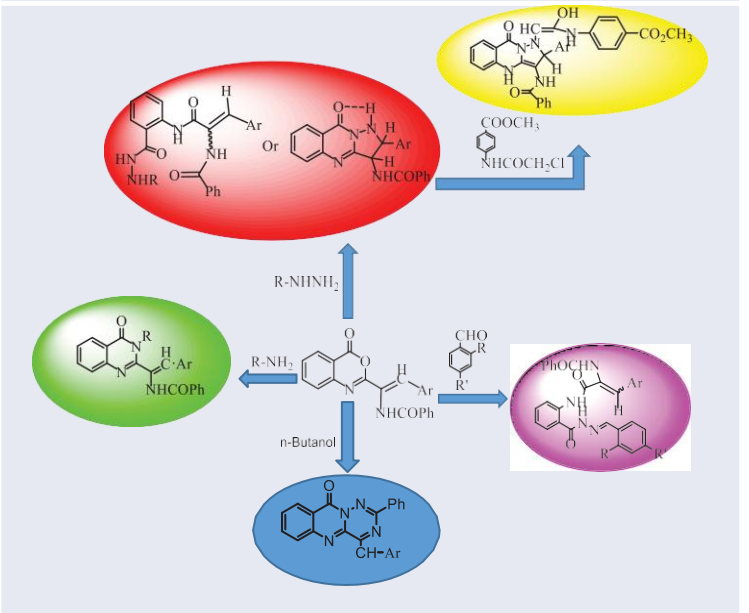
ABSTRACT

In this study, a new series of quinazoline and their annulated derivatives have been synthesized. A number of quiazolinone derivatives substituted at position-3 were prepared from 3, 1-benzoxazinone by the treatment of 3,1-benzoxazinone with different nitrogen nucleophiles such as, hydrazine hydrate, phenylhydrazine, ethanolamine, and cyano acetohydrazide afforded the quinazolinone derivatives **7–11**. The reaction of hydrazide derivative **5** with aromatic aldehydes gave the Schiff's bases derivative **16a–c**. Some of the synthesized compounds were tested against the breast cancer cell line (MCF-7). The structures of all the newly synthesized compounds were established based on IR, ^{1}H, ^{13}C NMR, mass spectral data, and elemental analyses.

GRAPHICAL ABSTRACT



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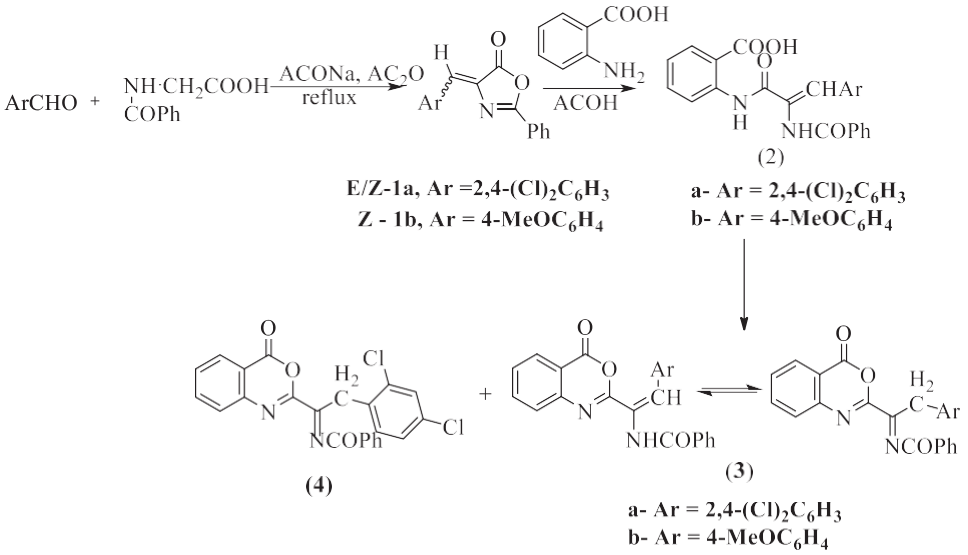
Introduction

Benzoxazinone derivatives are considered important in chemical syntheses of various physiologically and pharmaceutically important compounds. They have a kind of biological effects including antitubercular,[1] antifungal,[2–5] antimalarial, anticancer, anti-HIV,[3,6] antiviral, and antibacterial activities.[4,7,8] 3H-Quinazolin-4-ones and their derivatives have been described to have a significant activity as antihypertensive,[9] antifibrillatory, choler- etic, antiphlogistic,[10] antimitotic anticancer,[11] antifungal,[12,13] and anticonvulsant agents.[14] They have also been successfully tested as central nervous system depressants,[15] muscle relaxants[16] and for their antineoplastic activity.[17] In continuation of our previous work on quinazolinone molecular system by incorporating different substituted amines as cyanoacetamide, thiazolidinone, thiazolidinthione, azet-2-thione, azet-2-one, thiadiazole, and pyrazolone on third position of quinazolinone[18–20] and fused annulated pyrazolo, imidazole, and tetrazinoquinazolinone[21] and studies of their antimicrobial activities, we have tried in this investigation to synthesize a new series of N-3-substituted-quinazoline- 4(3*H*)-one derivatives incorporating *N* and *O* heterocyclic derivatives.

Results and discussion

Hippuric acid reacted with 2,4-dichloro- and 4-methoxybenzaldehydes in acetic anhyd- ride in the presence of fused sodium acetate as a base to give 4-arylideneoxazolone derivatives 1a, b. The IR spectra of compounds 1a, b exhibited bands for CO, C N, and C C groups. Further support for their assigned structures was gained from their ^{1}H NMR spectra, which revealed two singlet signals for the olefinic proton of compound 1a at *d* 7.57, 8.19 ppm that suggested its existence as a mixture of *E*/*Z* stereoisomers. However, one singlet signal was observed for the olefinic proton of 1b at *d* 7.33 ppm, which was in accordance with its existence as the Z-configurated isomer. Moorkoth et al.[22] prepared the other isomer but they did not mention its configur- ation, thus according to its *J* value for the olefinic proton (*J* ¼ 6.91 Hz) must have the *E*-configuration. The higher *d* value for the olefinic proton of the *Z*-isomer as compared to that of the *E*-counterpart may be due to its existence in the deshielding regions of the aryl and oxazolone carbonyl. The integration values for olefinic proton of com- pound 1a showed that the *E/Z* mixture exist in ratio of 3:2. The high percentage of the *E*-isomer may be due to the extension of conjugation because of coplanarity of the aryl group with oxazolone ring. Heating of the oxazolones 1a, b with anthranilic acid in acetic acid afforded the open chain adducts 2a, b. Their spectral data were in accord-ance with the proposed structure (cf. Experimental). Refluxing the benzoic acid deriva- tives 2a, b with acetic anhydride yielded mixtures of the benzoxazinone derivatives 3, b as equilibrium mixtures in the ratios of 79:21 and 31: 69, respectively, as well as com- pound 4 in case of compound 2b (Scheme 1). The structures of compounds 3 and 4 were evidenced by studying their spectral data. Their IR spectra exhibited bands corre- sponding to NH and CO groups. Inspection of the ^{1}HNMR spectra of compounds 3a, b revealed the existence of one singlet signal in the upfield region for protons of CH_2 group as well as two singlet signals in the downfield region, one for the olefinic proton and the other for NH proton which was exchanged upon shaking with D_2O. This suggested that they are existing as mixtures of enamine–imine tautomers in the

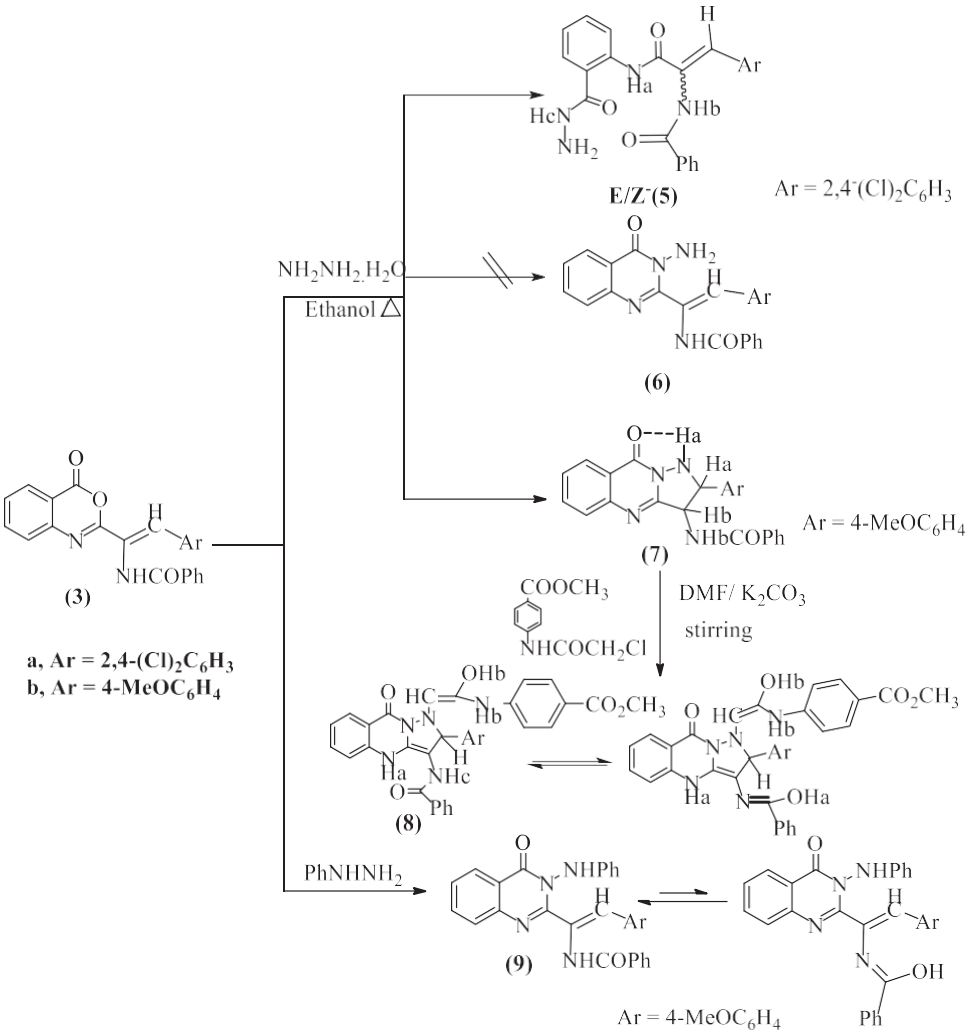


Scheme 1. Synthesis of compounds 1–4.

ratios 80:20 and 31:69, respectively. However, the ^{1}HNMR spectrum of 4 exhibited a singlet signal for methylene protons and was devoid of any signals for the olefinic and NH protons. The EIMS spectra of compounds 3a, b and 4 supported their structures as they showed their molecular ion peaks.

The aim of the work is to utilize 4 *H*-3, 1-benzoxazin-4-one derivatives 3a, 3b for the synthesis of 3-aminoquinazolin-4(3*H*)-one derivatives which are promising intermedi- ates for diverse organic synthesis. Thus, hydrazinolysis of 3a using hydrazine hydrate in boiling ethanol afforded the open chain hydrazide 5 instead of the 3-amino quinazoli- none derivative 6 (Scheme 2). The structure of the hydrazide 5 was substantiated from its analytical and spectral data. Thus, its IR spectrum exhibited bands for NH and CO groups. The appearance of two singlet signals for the olefinic proton as well as extra exchangeable broad singlet signals for NH protons in the down field region of its ^{1}HNMR spectrum is in accordance with its existence as a mixture of *E*/*Z* stereoisomers in the ratio of 54:46. The higher *d* value for the signal of the olefinic proton of the *Z*-isomer as compared with that of the *E*-counterpart may be due to its existence in the deshielding regions of dichlorophenyl and the carbonyl groups.

However, hydrazinolysis of 3b with hydrazine hydrate afforded the pyrazoloquinazoli- none derivative 7. IR spectrum of compound 7 showed bands for NH and CO groups. Further support for the proposed structure of 7 was gained from its ^{1}HNMR spectrum that revealed the coupling pattern between protons of CHb–CHa–NHa moiety. Proton Ha appeared as doublet–doublet signals at *d* 4.97 ppm with *J* ¼ 11.2, 11.6 Hz due to cou- pling with CHb and NHa protons. The reason for coupling with NHa proton may be due to chelation with C¼O group. Proton Hb appeared as triplet signal at *d* 4.48 ppm with *J* ¼ 11.2, 11.6 Hz, also proton NHa appeared as doublet signal at *d* 5.33 ppm with *J* ¼ 11.2 Hz which was exchanged upon shaking with D_2O. Reaction of 7 with methyl 4- (2-chloroacetamido) benzoate afforded compound 8. The structure of 8 was evidenced by studying its spectral data. Its IR spectrum showed bands characteristic for NH and



Scheme 2. Synthesis of compounds 5, 7–9.

CO groups. The ^{1}HNMR spectrum of compound 8 revealed the existence of extra broad singlet signals in the down field region; this suggests its existence as an equilibrium mixture of lactam–lactim tautomers in a ratio of 1:1. Heating an alcoholic solution of 3b with phenylhydrazine yielded the quinazolinone derivative 9. Its IR spectrum exhib- ited bands for C¼O and NH groups. Furthermore, the ^{1}HNMR spectrum supported its structure as it showed signals for protons of OCH_3, NH and aromatic groups as well as a broad singlet signal in the down field region at *d* 11.84 ppm corresponding to proton of OH group. This suggests the existence of compound 9 as an equilibrium mixture of lactam–lactim tautomers in the ratio 72:28.

Reactions of compound 3b with ethanolamine and cyano acetohydrized gave the benzoxazinone derivatives 10 and 11, respectively. However, its reaction with semi- carbazide hydrochloride yielded the open chain semicarbazide derivative 12. The IR spectra of compounds 10–12 showed bands for NH and CO groups as well as a