Original Article

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEWLY SYNTHESIZED SCHIFF BASE DERIVED QUINAZOLINONE AND CINNAMALDEHYDE

Abbas H. Abdulsada[1], Ammar Abdul Aziz Alibeg[2], Ali N. Wannas[3]

[1]Department of pharmaceutical chemistry, College of pharmacy, University of Babylon, Iraq

[2]Department of pharmaceutical chemistry, College of pharmacy, University of Kufa, Iraq

[3]Department of Pharmaceutics, College of pharmacy, University of Kufa, Iraq

Abstract

The goal of this research is to synthesize novel Schiff base-derived quinazolinone derivatives (4a and 4b) with improved antibacterial activities. Chemical procedures and spectrophotometric (IR and NMR) techniques were used to study and describe the produced compounds. Antibacterial screening tests for the target compounds were implemented against two gram-positive strains (Staphylococcus aureus, Staphylococcus faecalis) and two gram-negative strains (Escherichia coli, salmonella typhi) by scaling the diameter of the zone of bacterial inhibition. The results of these tests indicate that the synthesized Schiff bases exhibit an accepted level of biological activity against these microorganisms.

Keywords: Schiff base, cinnamaldehyde, quinazolinone, antibacterial activity.

INTRODUCTION

Quinazolinones and their derivatives constitute heterocyclic compounds with a wide range of applications. Quinazolin-4(3H)-one nucleus and its derivatives are a class of nitrogen-containing heterocyclic compounds that could be physiologically active. (1,2) Because of their intriguing biological activity, plentiful structural and pharmacological studies were performed to evaluate quinazolinones and their Schiff's bases for a long time.(2,3) they often show beneficial therapeutic and pharmacological properties like antibacterial, antiviral, antifungal, anticancer, antimalarial, diuretic, sedative, antihypertensive, antitubercular, anticonvulsant, anti-inflammatory, antioxidant, hypolipidemic, tranquilizer and also known to act as protein tyrosine-kinase inhibitor.

Cinnamaldehyde, the main component of cinnamon essential oils, can be found in nature in the bark and leaves of cinnamon plants. Antibacterial activities have been demonstrated against a number of Gram-positive and Gram-negative microorganisms. (10-12) When combined with other oils, such as clove oil, it has a synergistic antimicrobial effect. (13)

For tubercle bacillus H37Ra, cinnamonaldehyde has a high inhibitory and killing power. (14) It also inhibits the activation of the aryl hydrocarbon receptor (AHR) and has an antioxidant effect that is blocked by NRF2/HO1 signaling. (15)

It has promise anti-inflammatory, antiviral, antifungal, anti-tumor, and suppresses toxin formation by micro-organisms properties in addition to those key biological functions. (16-19) Cinnamaldehyde-derived Schiff bases have a variety of biological actions, including antibacterial, antifungal, and antimycobacterial properties. (20-25).

Address for correspondence: Abbas H. Abdulsada,
Department of pharmaceutical chemistry, College of pharmacy, University of Babylon, Iraq

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MATERIALS AND METHODS:

Chemistry:

Materials and Equipment: All of the chemicals and solvents used were analytical grade (Merk, Fluka, and Sigma-Aldrich) and were not purified further. The open capillary method was used to assign the melting points (mp) of the intermediates and end products, and the results were uncorrected. Potassium bromide discs were used to score FTIR spectra using a Perkin Elmer FT-IR spectrophotometer. The Bruker i400MHz spectrometer was used to score proton nuclear magnetic resonance (1H NMR) spectra in dimethyl sulphoxide (DMSO-d6) using trimethyl-silane (TMS) as an internal standard.

General Procedure for the Synthesis of 2-phenyl benzoxazin-4(3H)-one (2a,2b)

At room temperature, anthranilic acid (20 mmol) was thawed in 50 mL of anhydrous pyridine. After cooling the solution to about 0 oC a solution of either 2-hydroxybenzoyl chloride or 4-Methylbenzoyl chloride (20 mmol) in anhydrous pyridine (50 ml) was progressively poured to it, stirring constantly for 3 hours. Water was then added to the pasty material to dilute it, followed by the addition of an aqueous sodium bicarbonate solution, which caused effervescence, which stopped when filtration and washing with water yielded a solid product. From dilute ethanol, the crude product was allowed to dry recrystallize.

2-(4-Methylphenyl)-benzoxazin-4(3H)-one (2a)

Yield 67 %, M.p.= 148-150, IR (KBr) cm-1: 1715 (C=O ester), 2867 (CH3 aliphatic), 3041 (C-H aromatic), 1493 (C=C aromatic).

2-(2-hydroxyphenyl)-benzoxazin-4(3H)-one (2b)

Yield 72 %, M.p.= 162-165, IR (KBr) cm-1: 1733 (C=O ester), 3426 (OH phenol), 3057 (C-H aromatic), 1513 (C=C aromatic).

General Procedure for the Synthesis of 3-amino-2-phenyl-quinazolin-4(3H)-one (3a,3b)

Dropwise with continual stirring, add a solution of hydrazine hydrate (20 mmol) in anhydrous pyridine (30 ml) to a cold solution of 2-(2-hydroxyphenyl)-benzoxazine or 2-(4-methylphenyl)-benzoxazine (10 mmol) in anhydrous pyridine (30 ml). Following the addition, the mixture was busily agitated for 30 minutes at lab temperature before being reflux-heated for 6-9 hours in anhydrous circumstances. Allow the reaction mixture to cool to ambient temperature after that before being decanted into dilute hydrochloric acid in ice-cold water. Precipitation occurred after about 1 hour, with the solid product settling down. The reaction medium was filtered out, multiple times cleaned with water, dried, and then recrystallized from dilute ethanol.

3-Amino-2-(4-methylphenyl)- quinazolin- 4(3H)-one (3a)

Yield 63 %, M.p.= 156-159, IR (KBr) cm-1: 3368 (N-H), 2894 (C-H aliphatic), 3047 (C-H aromatic), 1741 (C=O), 1459 (C=C aromatic).

3-Amino-2-(2-hydroxyphenyl)- quinazolin- 4(3H)-one (3b)

Yield 65 %, M.p.= 168-172, IR (KBr) cm-1: 3383 (N-H), 3472 (OH phenol), 3016 (C-H aromatic), 1726 (C=O), 1474 (C=C aromatic).

Synthesis of Quinazolinone Fused Schiff Bases (4a,4b): A General Procedure

The ethanolic solution of cinnamaldehyde (12 mmol) added slowly to the ethanolic solution of either 3-amino-2-(2-hydroxyphenyl)-quinazolin-4(3H)-one or 3-amino-2-(4-methylphenyl)-quinazolin-4(3H)-one (10 mmol). Using glacial acetic acid to render the reaction mixture of acidic pH (pH was adjusted to 4.0-4.5) and refluxed for 6 h. Then cooling the solution and decanting it into ice-cold water. The resulting product was filtrated, washed with dried ethanol and recrystallized from ethanol.

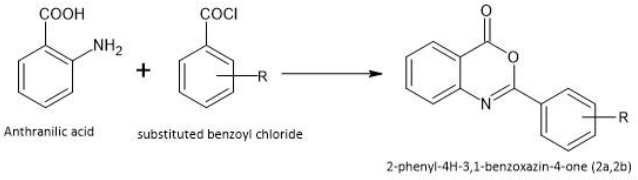
Schiff base (4a)

Yield 74 %, M.p.= 174-177, IR (KBr) cm-1: 2917 (C-H aliphatic), 3043 (C-H aromatic), 1748 (C=O), 1615 (C=N imine), 1467 (C=C aromatic). 1H NMR (400MHz, DMSO-d6): δ 7.38-7.46 (m, 6H, Ar-H), δ 8.09-8.23 (m, 3H, Ar-H), δ 7.71-7.80 (m, 4H, Ar-H), δ 8.62 (d, 1H, H-C=N), δ 2.61 (s, 3H, CH3).

Schiff base (4b)

Yield 77 %, M.p.= 193-195, IR (KBr) cm-1: 3465 (O-H phenol), 3026 (C-H aromatic), 1739 (C=O), 1623 (C=N imine), 1446 (C=C aromatic). 1H NMR (400MHz, DMSO-d6): δ 7.23-7.38 (m, 6H, Ar-H), δ 8.13-8.27 (m, 3H, Ar-H), δ 7.73-7.81 (m, 4H, Ar-H), δ 8.67 (d, 1H, H-C=N), δ 5.08 (s, 1H, -OH).

Step 1



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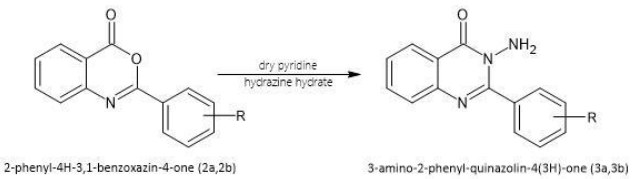
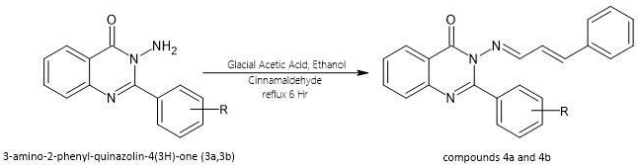


Step 3:



Compound 4a: R = 4-CH3

Compound 4b: R = 2-OH

Antimicrobial activity

The antibacterial activity of compounds 4a and 4b against certain types of bacterial strains was tested using the filter paper disc plate method. The bacteria were grown on Muller Hinton agar plates (37°C, 24 hours). Table 1 summarizes the antibacterial activity test results and compares them to the standard medication ciprofloxacin. Compound i4a had modest activity against all of the microorganisms tested, whereas compound 4b had less action against Escherichia coli.

Compounds	Zone of Inhibition (mm) 100 μg mL^{-1}			
	E. coli	*S. typhi*	*S. aureus*	*S. fecalis*
Compound 4a	19	15	18	20
Compound 4b	13	19	16	17
Ciprofloxacin	33	27	28	30

Results and discussions:

In this research, attempts were undertaken to construct novel quinazoline 4(3H)-one Schiff bases, and the synthetic approach used to make the target compounds is given in Scheme 1. Spectral analysis was used to describe two novel quinazolinone Schiff base compounds that were produced.

Benzoxazinones (2a,2b) are created by treating anthranilic acid with various substituted benzoyl chlorides, while 3-Amino-2-phenyl-quinazolinones are produced by treating Benzoxazinones with hydrazine hydrate in anhydrous pyridine (3a,3b). By ethanolic solution of cinnamaldehyde in acidic medium, final target compounds (4a,4b) were produced from 3-amino-2-phenylquinazolinones (3a,3b). R and NMR spectrum analyses were used to confirm the structures of the newly synthesized compounds, followed by the assessment of their physicochemical properties.

FTIR spectra

Traditional methodologies for determining the structure of simple molecules include infrared spectroscopy. Because of its vulnerability to the chemical structure and design of molecules, it holds this position [15]. The intermediate and final chemicals were analyzed using infrared spectroscopy. Under each molecule, characteristic IR bands of the final ligands as well as intermediates are provided. The absence of the wide band in the 2500–3100 cm-1 range suggests that the carboxylic acid groups included in the lactone generation n benzoxazinones (2a and 2b). The phenolic O-H and aliphatic C-H stretching vibrations n compounds 4b and 4a, respectively, are responsible for the occurrence of a robust band at 3450 cm-1 and a medium band at 2900 cm-1 n the R spectrum of the ligands. The ligands' IR spectra revealed the privation of bands at (3360 and 3380 cm-1) due to v(NH2) stretching vibrations, and the appearance of a novel band at 1620 cm-1 attributed to azomethine v(HC=N). This indicated that the quinazolinone and cinnamaldehyde amino and aldehyde moieties have been transformed to the Schiff bases. In the spectra, there was no C=O stretching vibration about 1870 cm-1. It means there were no contaminants, such as an aldehyde, present. For intermediates and final compounds, all of the absorption bands for all other important groups were detected.

H1 Nuclear magnetic resonance

nuclear magnetic resonance (NMR) spectroscopy, is one of the advanced and worthy techniques for determining the structure of a chemical. It differentiates the carbon-hydrogen skeleton of an organic molecules. Using this technology alone or with other techniques as infrared and mass spectrometry, scientists can now elucidate the structure of a whole molecule (26). The final ligands' 1H-NMR spectra were published in dimethylsulfoxide DMSO.d6 with chemical shifts in ppm and tetramethylsilane TMS used as an internal standard. Furthermore, the 1H NMR spectra, which give analytic instruments for the site clarification of the protons, provided confirmation for the formation of the Schiff base derivative. The signal assignments are made according to the chemical shifts and intensity patterns. Schiff bases' 1H NMR spectra revealed aromatic, methyl, phenolic, olefinic, and azomethine (-N=CH-) proton peaks. Both Schiff base compounds had sharp doublets at 8.67 and 8.62 ppm n their 1H NMR spectra, confirming the occurrence of an azomethine (-CH=N-) proton. The -CH3 group linked to the aromatic ring in 4a ligand was identified by the strong singlet signal at 2.61 ppm. The phenolic O-H in the 4b ligand was responsible for the strong singlet signal of 5.08 ppm.

Conclusion

Two novel Schiff base derivatives of quinazolinone with cinnamaldehyde were synthesized and their structures validated using infrared spectroscopy (FT-IR spectra) and NMR spectra, as indicated in the scheme.

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