USE OF ONE-POT MULTICOMPONENT FOR SYNTHESIS OF SOME 2,3-DIHYDROQUINAZOLIN-4(1H)-ONES DERIVATIVES AND THEIR ANTIMICROBIAL EVALUATION

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ABSTRACT:

The objective of this research is to make a series of new quinazoline derivatives during multi compound reaction in one-pot condensation between isatoic anhydride and sulfadiazine with aromatic aldehydes using the Sodium bisulfate (NaHSO₄) as a catalyst in reflexing Tetrahydrofuran (THF). All of the products characterized using melting point, and monitored by TLC technique and determination of Retardation factor(Rf). The Structure formula of these derivatives were verified by Spectral data infrared (FT-IR) and Nuclear magnetic resonance (¹H-NMR) spectroscopy and can also be compared to the reliable reference. the synthesized compounds were tested versus bacterial and fungi, The majority of the compounds demonstrated good activity.

GRAFICAL ABSTRACT

KEYWORDS: One-pot synthesis; Quinazolinones; Isatoic anhydride; sulfadiazine; biological activity

1. INTRODUCTION

Quinazoline is a fusid bicyclic compound six-membered made-up a benzene ring and a pyrimidine ring, earlier known as benzo-1,3-diazine was first prepared in the laboratory by Gabriel (1) in 1903. Quinazolinone derivatives are extremely important heterocyclic compounds, frequently employed because of their potential biological and pharmaceutical activities. They reveal various medicinal properties such as anti-inflammatory and analgesic activity, as well as antimicrobial activity. These heterocyclic are valuable intermediates in organic synthesis (2-8). 2,3-Dihydroquinazolinones are heterocycles that have attracted much attention because they are reported to possess a wide range of pharmacological properties Many derivatives of this system showed antifungal(9), antibacterial(10), anticancer(11), anti-inflammatory(12), anticonvulsant(13), immunotropic(14), hypolipidemic(15), antiulcer(16), analgesic(17) and antiproliferative(18). One of the most groundbreaking concepts in synthetic organic chemistry is multicomponent reactions (MCRs). A convergent chemical process employing three or more reactants to generate products that maintain all structural and sub structural properties of the starting materials is defined as an multicomponent reactions. MCRs are useful in all areas of synthetic chemistry because they have a short reaction time, a simple manufacturing technique, and a high yield. MCRs produce far fewer chemical wastes than traditional multistep one-pot synthesis, resulting in substantially cleaner syntheses.
importance of MCRs grows as huge libraries of promising pharmacological and agricultural compounds are created (18,22).

2. EXPERIMENTAL

Melting points in open capillary tubes were measured using an SMPLU-K and have been uncorrected. Infrared spectra (FT-IR) were recorded utilizing KBr disk on shimadzu infrared spectrophotometer Fourier Transform FT-IR-8400s spectrophotometer in college of Education of pure Sciences / Anbar University. The 1H NMR spectra is collected on NMR spectrometer 400-130 MHz, Bruker Biosoin GmbH 400 MHz were, Germany at 400 using DMSO-d$_6$ as the solvent and TMS as the internal standard as an internal standard in Iran. The progress of reactions was monitored using thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel. The chemicals were purchased commercially from Merck (Germany), Sigma-Aldrich, and Fluka (Switzerland), They were used without being purified further.

General procedure for the synthesis of 2,3-Dihydroquinazolin-4(1H)-ones derivatives (1-6):

In one-pot three-component of Isatoic anhydride (0.0018mol) aromatic aldehydes (0.0018 mol) and sulfadiazine(0.0018mol) were dissolved in (100 ml) tetrahydrofuran (THF) in the presence of catalytic Sodium bisulfate (NaHSO$_4$) (0.0036 mol) was heated under reflux on a water bath a temperature of (68°C) for 3h. The progress of the reaction is monitored by TLC (eluent: Ethanol:benzene,6:4). After completion of the reaction, the corresponding solid product was obtained through simple filtering, and recrystallized from ethanol to yield the highly pure 2,3-dihydroquinazolin-4(1H)-one derivatives (1-6). The spectral data (IR, $^1$H NMR, $^{13}$C NMR) of known compounds were found to be identical with those reported in the literature. physical and Spectroscopic data for selected examples are shown below.

1. 4-(2-(4-nitrophenyl)-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide : (C$_{24}$H$_{18}$N$_{6}$O$_{5}$S) (brown solid), Yield: 76%, m.p 92-94°C. (R$_f$ = 0.72), IR (KBr): 3325cm$^{-1}$ (N-H), 1665cm$^{-1}$ (C=O lactam), 2941 cm$^{-1}$ (C-H) Aliphatic, 3173 cm$^{-1}$ (C-H) aromatic, 1264 cm$^{-1}$ (C-N) $^1$H NMR (DMSO-d$_6$, δ ppm): 6.79 (s, 1H, =C-NH), 6.97 - 8.49 (m, 15H, Ar-H), 6.73 (s, 1H, N-CH-Aryl), 11.78 (s, 1H, -SO$_2$-NH) $^{13}$C NMR (100MHz,CDCl3): 69.36, 112.84, 115.49, 118.89, 141.03, 145.34, 148.40, 156.88, 163.99

2. 4-(2-(4-hydroxyphenyl)-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide : (C$_{25}$H$_{19}$N$_{5}$O$_{4}$S) (yellow solid), Yield: 72%, m.p 93-96°C. (R$_f$ = 0.75). IR (KBr): 3322 cm$^{-1}$ (N-H), 1650 cm$^{-1}$ (C=O lactam), 2938 cm$^{-1}$ (C-H) Aliphatic, 3165 cm$^{-1}$ (C-H) aromatic, 1165 cm$^{-1}$ (C-N) and 3479 cm$^{-1}$ (OH) $^1$H NMR (DMSO-d$_6$, δ ppm): 6.86 (s, 1H, =C-NH), 6.80 - 8.49 (m, 15H, Ar-H), 6.53 (s, 1H, N-CH-Aryl), 11.67 (s, 1H, -SO$_2$-NH), 9.5 (s, 1H, Aryl-OH) $^{13}$C NMR (100 MHz,CDCl3): 69.45, 112.09, 115.50, 119.07, 122.64, 123.22, 127.27, 131.11, 141.00, 145.34, 156.84, 157.76, 163.96

3. 4-(4-oxo-2-phenyl-1,4-dihydroquinazolin-3(2H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide : (C$_{24}$H$_{18}$N$_{5}$O$_{3}$S) (Light brown solid), Yield: 74%, m.p 91-95°C. (R$_f$ = 0.74). IR (KBr): 3375 cm$^{-1}$ (N-H), 1695cm$^{-1}$ (C=O lactam), 2937 cm$^{-1}$ (C-H) Aliphatic, 3181 cm$^{-1}$ (C-H) aromatic, 1152 cm$^{-1}$ (C-N): $^1$H NMR (DMSO-d$_6$, δ ppm): 6.45 (s, 1H, =C-NH), 6.80 - 8.48 (m, 15H, Ar-H), 6.5 (s, 1H, N-CH-Aryl), 11.37 (s, 1H, -SO$_2$-NH), $^{13}$C NMR (100 MHz, CDCl3): 69.38, 112.94, 116.35, 119.07, 122.64, 131.11, 138.92, 141.00, 145.34, 156.30, 164.09

4. 4-(2-(4-chlorophenyl)-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide: (C$_{24}$H$_{18}$Cl$_{2}$N$_{5}$O$_{3}$S) (Light brown solid), Yield: 70%, m.p 96-99°C, (R$_f$ = 0.63). IR (KBr): 3308 cm$^{-1}$ (N-H), 1665cm$^{-1}$ (C=O lactam), 2938 cm$^{-1}$ (C-H) Aliphatic, 3172 cm$^{-1}$ (C-H) aromatic, 1260cm$^{-1}$ (C-N): $^1$H NMR (DMSO-d$_6$, δ ppm): 6.32 (s, 1H, =C-NH), 6.74 - 8.46 (m, 15H, Ar-H), 6.8 (s, 1H, N-CH-Aryl), 11.36 (s, 1H, -SO$_2$-NH), $^{13}$C NMR (100 MHz, CDCl3): 69.03, 112.90, 115.48, 119.07, 122.65, 127.27, 137.78, 141.00, 145.34, 156.88, 163.96.

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5. 4-(2-(4-methoxyphenyl)-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide: (C_{28}H_{21}N_{6}O_{5}S) 
(yellow solid), Yield: 64%, m.p 100-103°C, (R_f = 0.73). IR (KBr) ν: 3296 cm⁻¹ (N-H), 1676 cm⁻¹ (C=O lactam), 2910 cm⁻¹ (C-H) Aliphatic, 3160 cm⁻¹ (C-H) aromatic, 1168 cm⁻¹ (C-N). H NMR (DMSO-d₆, δ ppm): 6.66 (s, 1H, =C-NH), 6.80 - 8.14 (m, 15H, Ar-H), 6.43 (s, 1H, N-CH-Aryl), 11.37 (s, 1H, -SO₂-NH), 3.89 (s, 3H, Ar-OCH₃), 13C NMR (100 MHz, CDCl₃): 55.34, 69.33, 112.90, 113.09, 115.49, 119.07, 127.27, 141.04, 156.84, 159.24, 163.96.

6. 4-(2-(4-(dimethylamino)phenyl)-4-oxo-1,4-dihydroquinazolin-3(2H)-yl)-N-(pyrimidin-2-yl)benzenesulfonamide: (C_{32}H_{26}N_{6}O_{5}S) 
(red solid), Yield: 79%, m.p 90-92°C, (R_f = 0.56). IR (KBr) ν: 3242 cm⁻¹ (N-H), 1653 cm⁻¹ (C=O lactam), 2939 cm⁻¹ (C-H) Aliphatic, 3068 cm⁻¹ (C-H) aromatic, 1261 cm⁻¹ (C-N). H NMR (DMSO-d₆, δ ppm): 6.65 (s, 1H, =C-NH), 6.79 - 8.48 (m, 15H, Ar-H), 6.29 (s, 1H, N-CH-Aryl), 11.30 (s, 1H, -SO₂-NH), 3.6 (s, 6H, Ar-N(CH₃)₂), 13C NMR (100 MHz, CDCl₃): 40.27, 68.55, 111.53, 118.89, 122.74, 128.89, 130.09, 141.03, 145.34, 151.31, 157.67, 163.99.

3. RESULT AND DISCUSSION

In present work involves the Multi-component reactions method have been used as they are useful method for carbon-carbon and heterogeneous bond formation and for the synthesis of important organic molecules with multiple degrees of structural diversity. High yields, ease of work up procedure, use of cheap and commercially available starting materials, convenient manipulation, and mild reaction conditions are the advantages of this new method. The isatoic anhydride, sulfadiazine, and aromatic aldehyde, were treated with catalytic amounts of Sodium bisulfate (NaHSO₄) in tetrahydrofuran under reflux, the condensation products 2,3-Dihydroquinazolin-4(1H)-ones , were obtained in good yields. A possible mechanism for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones was proposed. Initially, condensation of isatoic anhydride with sulfadiazine followed by decarboxylation to yield the corresponding anthranilamide. Then condensation of the aromatic aldehyde with the amino group of anthranilamide gives imine which undergoes cyclization to give the 2,3-dihydroquinazolin-4(1H)-ones (Scheme 1).

\[ \text{Cat}\rightarrow\text{H-Shift} \]
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\[ \text{SO}_3 \]

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Table 1: shows the antimicrobial and antifungal activity of synthetic compounds (1-5)

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<th>Gram positive</th>
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REFERENCES