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Research Article

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Synthesis, Method Optimization of 2,3-Disubtitutedquinazolin-4(3H)-One Derivatives

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ABSTRACT

Quinzolinones have various biological activities such as anticancer, antidiabetic, anticonvulsant, antihistaminic, anti-inflammatory, antifungal, anthelmintics and antiviral activites. In this research some of compounds 2,3-disubtitutedquinazolin-4(3H)-one derivatives had been synthesized under microwave irradiation. The compounds were obtained from reaction some of benzoxazine derivatives with hydrazine hydrate using microwave irradiation and the result of reaction we obtained 82-96%. The productshad been tested by IR, ^{1}H-NMR, ^{13}C-NMR and Mass Spectroscopy analysis. The using microwave irradiation was more effective and efficient to produce compounds 2,3-disubtituted quinazolin-4(3*H*)-one derivative because the reaction runs perfectly without any minor products such as compounds *N*-(2-(hydrazinecarbonyl)phenyl)benzamide derivatives.

Keywords: 2,3-disubtituted quinazolin-4(3*H*)-one derivatives; *N*-(2-(hydrazinecarbonyl)phenyl)benzamide derivatives; Microwave irradiation

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INTRODUCTION

GLOBOCAN, International Agency for Research on Cancer (IARC) was reported 14.1 million has been indicated as a new cancer case and 8.2 million have died againts cancer. Breast cancer was indicated as higher new case than another cancer disease [1-3]. There are many chemotherapeutic strategies for the anticancer treatment have been proposed and tested in some cases. The main procedures of cancer treatment are surgery, irradiation, and chemotherapy. Although the chemotherapeutic management has been conducted as major advances for patients, the continuous researching for new anticancer agent remains important [1-7]. In the course of identifying chemical agents are very importans for designing novel agents. One of agents were knowns as lead compound of anticancer drug is quinazolinone [8,9]. Quinazolinone is a fused bicyclic heterocyclic framework was known as benzo-1,3-diazanaphthalene. Numerous compounds of quinazolines have been reported have biological and pharmacological activity such as antimicrobial, antitumor, antimitotic, anticancer and others [5,6]. In previous of the research, the novel quinazolinones was synthesized by Nolvi and Patel in 2013. They have been using refluks as conventional method for this reaction. This reaction was produced 2 isomers includes ring opened and ring closed of quinazolinone [8]. The ring closed as target of synthesis and to obtained by fusing benzoxazinone at high temperature resulting in the synthesis. The method of heating reactants are slowly activated by a conventional external heat source. Heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and the reactants. This is a slow and inefficient method for transferring energy into the reacting system. In this research is using microwave-assisted organic chemistry. Microwave have been used to speed up chemical reactions in the laboratories to investigate the mechanism of microwave dielectric heating and to identify the

advantages of the technique for chemical synthesis [4,9,10]. By using microwave irradiation at high t temperature as methodology of 2,3-disubtituted quinazolin-4(3*H*)-one derivatives are simple, high t purity, improved yields, simplified and improved synthetic procedure and higher energy efficiency.

EXPERIMENTAL SECTION

All chemicals and solvents were purchased from Sigma Aldrich and Merck. Reactions were monitored with TLC using pre-coated aluminum sheets with GF254 silica gel. Eluen for TLC using n-hexane: ethyl acetate (1:1) and the spots were visualized in UV chamber. Melting points of the synthesized compounds were measured with an Electrothermal melting point apparatus. Infrared spectra were obtained using a Perkin Elmer Spectrum One Spectrophotometer using KBr disks. ^{1}H- NMR and ^{13}C-NMR spectra were obtained on JEOL JNM-ECS 400 (1H-NMR: 400 M Hz, 13C-NMR: 100 MHz) instrument from Institute of Tropical Disease Airlangga University, Indonesia. We used DMSO-d6 as solvent for ^{1}H- NMR and ^{13}C-NMR analysis. MS spectra were measured by a JEOL JMS 600 spectrometer by using the ESI methods.

General Synthesisof 2-Phenyl-Benzo [1,3] Oxazine-4-Onederivatives (3a-c)

A mixture of 2-phenyl-benzo [1,3] oxazine-4-one derivatives (2 mmol) and hydrazine hydrate (2 mmol) was dissolved in 2 mL of DMSO. The mixture was heated in microwave irradiation at 600 W for 1 minute. The mixture was cooled and aquadest (20 mL) was added to the mixture. The separated solid was collected by filtration, washed with cooled ethanol, dried, and crystallized by ethanol 96%.

General Synthesisof 3-Amino-2-Phenylquinazolin-4(3*H*)-One Derivatives (4d-f)

A mixture of 2-phenyl-benzo [1,3] oxazine-4-one derivatives (2 mmol) and hydrazine hydrate (2 mmol) was dissolved in 2 mL of DMSO. The mixture was heated in microwave irradiation at 600 W for 7 minutes. The mixture was cooled and aquadest (20 mL) was added to the mixture. The separated solid was collected by filtration, washed with cooled ethanol, dried, and crystallized by ethanol 96%.

RESULTS AND DISCUSSION

Reactionhydrazine hydrate with some of 2-phenyl-benzo[1,3]oxazine-4-one derivatives such as 2-phenyl-4H-benzo[d][1,3]oxazin-4-one; 2-(3,4-dichlorophenyl)-4H-benz[1,3]oxazin-4-one; 2-(2,4-dichlorophenyl)-4H-benzo[1,3]oxazin-4-onewas dissolved in 2 mL of DMSO and it was heated in microwave irradiation at 600 W for 1 minute. We evaluated reaction by TLC using n-hexane: ethyl acetate (1:1) as mobile phase, we got single spot (Rf=0.26) under UV chamber. The mixture was cooled and aquadest (20 mL) was added to the mixture. The separated solid was collected by filtration, washed with cooled ethanol, dried, and crystallized by ethanol 96%. We obtained compounds N-(2-(hydrazinecarbonyl)phenyl)benzamide derivatives. The mechanism of the reaction shown in Figure 1.

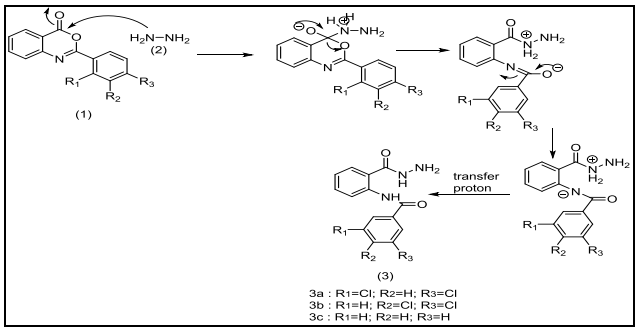

Figure 1: Hydrazine hydrate attack on carbonyl on benzoxazine ring

The reaction mechanism between (1) and hydrazine hydrate was dissolved in DMSO, we obtained a product (3a-c) or (4a-c) depending on the duration of the reaction time and the strength of the given wave irradiation. The lack of microwave irradiated power and a relatively short reaction time leads to compounds (3a-c). Their mechanism shown in Figure 1.The nucleophile attack of hydrazine hydrate on C carbonyl lactone ring causes opening of lactone ring and forms amide groups to obtain N-(2-(hydrazinecarbonyl)phenyl)benzamide derivatives.

Detailed physicochemical and spectral data of the obtained compounds N-(2-(hydrazinecarbonyl)phenyl)benzamide derivatives are as follows.

Compound 2,4-Dichloro-*N*-(2-(Hydrazinecarbonyl)Phenyl)Benzamide (3a)

Obtained in white powders; yield 96%; mp: 119-120°C. FT-IR (KBr) cm^{-1}: 3263 (N-H); 3052 and 675 (=C-H aromatic); 1650 (C=O amide); 1628 (C-N); 1596 and 1465 (C=C aromatic); 1311 (C-N) and 756 (C-Cl). ^{1}H-NMR (DMSO-d6, δ, ppm): δ 11.88 (1H, s); δ 10.07 (1H, s); δ 8.46 (1H, d, J=8.4 Hz); δ 8.75 (1H, d; J=8.4 Hz); δ 7.71-7.67 (2H, m); δ 7.56-7.50 (2H,m); δ 7.17 (1H, t, J=7.6);); δ 4.54 (2H, s). ^{13}C-NMR (DMSO-d6, δ, ppm): δ 169.4; δ 162.6; δ 150.8; δ 139.3; δ 135.7; δ 135.4; δ 132.6; δ 132.4; δ 131.8; δ 129.7; δ 128.2; δ 127.5; δ 123.9; δ 121.1. ESI/MS m/z values (Rel. abundance): $[M+Na]^{+}$=346 (100%); $[M^{+2}+Na]^{+}$=348 (65%); $[M^{+4}+Na]^{+}$=350 (10%) (Figure 2).

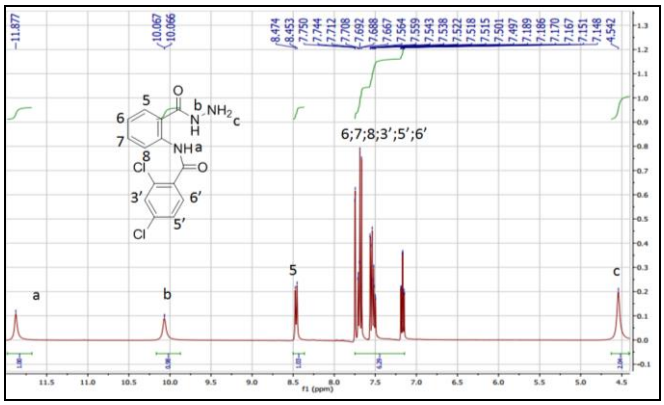

Figure 2: ^{1}H-NMR spectrum of compound 3a in (400 M Hz, DMSO-d6)

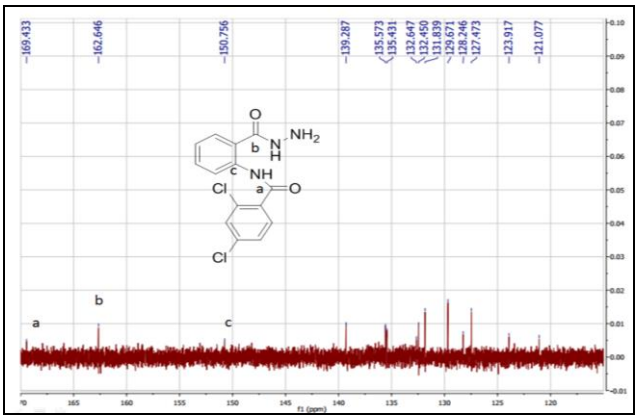

Figure 3:13C-NMR spectrum of a compound 3a in (100 M Hz, DMSO-d6)

Compound3,4-Dichloro-*N*-(2-(Hydrazinecarbonyl)Phenyl)Benzamide (3b)

Obtained in white powders; yield 90%; mp: 116-118°C.FT-IR (KBr) cm^{-1}: 3384 (N-H); 3061 and 675 (=C-H aromatic); 1628 (C-N); 1666 (C=O amide); 1592 and 1450 (C=C aromatic); 1342 (C-N) and 748 (C-Cl). ^{1}H-NMR (DMSO-d6, δ, ppm): δ 11.88 (1H, s); δ 10.07 (1H, s); δ 8.52 (1H, dd, J=8.4 Hz; 1.2 Hz); δ 8.07 (1H, t); δ 7.85 (2H, d, J=1.2 Hz,); δ 7.75 (1H, dd, J=7.6; J=1.2 Hz,); δ 7.54-7.50 (1H, m); δ 7.16 (1H, dt, J=7.6; J=1.2 Hz); δ 4.56 (2H, s). ^{13}C-NMR (DMSO-d6, δ, ppm): δ 169.4; δ 162.6; δ 150.8; δ 139.3; δ 135.7; δ 135.4; δ 132.6; δ 132.4; δ 131.8; δ 129.7; δ 128.2; δ 127.5; δ 123.9; δ 121.1. ESI/MS m/z values (Rel. abundance): $[M+Na]^{+}$=346 (100%); $[M^{+2}+Na]$+=348 (65%); $[M^{+4}+Na]$=350 (10%) (Figure 3).

Compound*n*-(2-(Hydrazinecarbonyl)Phenyl)Benzamide (3c)

Obtained in white powders; yield 82%; mp: 115-117°C. FT-IR (KBr) cm^{-1}: 3445 (N-H); 3061 and 672 (=C-H aromatic); 1660 (C=O amide); 1628 (C-N); 1592 and 1450 (C=C aromatic) and 1340 (C-N). ^{1}H-NMR (DMSO-d6, δ, ppm): δ 12.40 (1H, s); δ 10.31 (1H, s); δ 8.56 (1H, d, J=8.2 Hz); δ 8.19 (1H, s); δ 7.92 (2 H, d, J=7.2 Hz,); δ 7.70

(1H,d, J=8 Hz); δ 7.58 (1H, d, J=7.2 Hz); δ 7.53(2 H, t, J=7.6 Hz); δ 7.51-7.48 (1H, m); δ 4.57 (2 H, s).^{13}C-NMR (DMSO-d6, δ, ppm): δ 168.0; δ 165.0; δ 139.5; δ 134.9; δ 132.3; δ 129.5 (2C); δ 128.2; δ 127.4 (2C); δ 123.6; δ 120.8; δ 119.8. ESI/MS m/z values (Rel. abundance): $[M^{+}+Na]^{+}$=278 (100%); $[M^{+2}+Na]^{+}$=280 (65%); $[M^{+4}+Na]^{+}$=392 (10%).

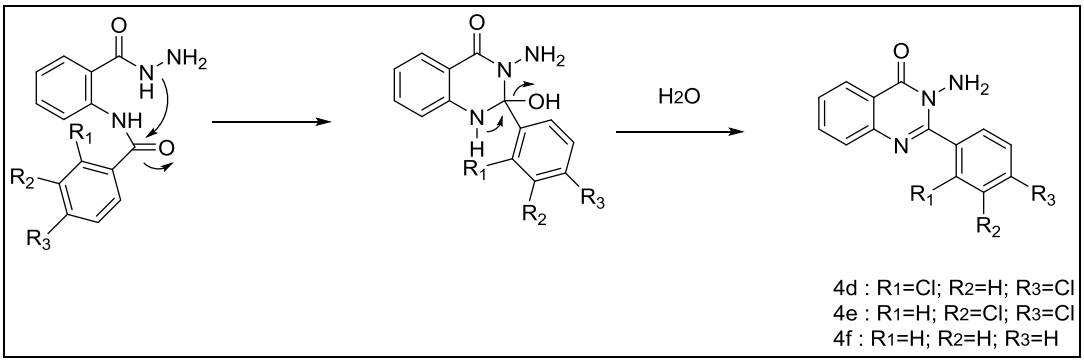

Figure 4: The nucleophile -NH attack causes the cyclicization of the quinazolinone ring

Reaction on hydrazine hydrate with some of 2-phenyl-benzo [1,3] oxazine-4-one derivatives was dissolved in 2 mL of DMSO and it was heated in microwave irradiation at 600 W for 7 minutes. We evaluated reaction by TLC using n-hexane: ethyl acetate (1:1) as mobile phase, we got single spot (R_f=0.69) under UV chamber. The mixture was cooled and aquadest (20 mL) was added to the mixture. The separated solid was collected by filtration, washed with cooled ethanol, dried, and crystallized by ethanol 96%. We obtained compound3-amino-2-phenylquinazolin-4(3*H*)-one derivatives. The mechanism of the reaction if it was heated in microwave irradiation at 600 W for 7 minutes shown in Figure 4.

Excessive microwave irradiation and relatively long reaction time resulted in intramolecular attack -NH at C=O amide followed by H_2O release. The nucleophile -NH attack causes the cyclicization of the quinazolinone ring and the result of compounds 3-amino-2-phenylquinazolin-4(3*H*)-one derivatives. Their mechanism shown in Figure 4.

Detailed physicochemical and spectral data of the obtained compounds N-(2-(hydrazinecarbonyl)phenyl)benzamide derivatives are as follows.

Compound3-Amino-2-(2,4-Dichlorophenyl)Quinazolin-4(3H)-One (4d)

Obtained in white powders; yield 92%; mp: 174-175°C FT-IR (KBr) cm^{-1}: 3128 (N-H primer); 3025 dan 691 (=C-H aromatic); 1685 (C=O lactam); 1628 (C=N); 1622 and 1473 (C=C aromatic); 1324 (C-N); 1034 (C-O-C) and 775 (C-Cl). ^{1}H-NMR (DMSO, δ, ppm): δ 8.19-8.17(1H, dd, J=8.0 Hz; 0.4 Hz); δ 7.86-7.81 (1H, m); δ 7.73 (1H, dd, J=2.0 Hz; 0.4 Hz); δ 7.86(1H, dd, J=8.0 Hz; 1.2 Hz); δ 7.59-7.51(3H, m); δ 5.52(2H, s).^{13}C-NMR (DMSO, δ, ppm): δ 161.5; δ 155.4; δ 147.1; δ 135.1; δ 134.9; δ 134.4; δ 133.2; δ 131.9; δ 128.9; δ 128.0; δ 127.9; δ 127.7; δ 126.6; δ 121.2.MS m/z values (Rel. abundance): $[M^{+}+Na]^{+}$=305 (100%): $[M^{+2}+Na]^{+}$==307 (65%); $[M^{+4}+Na]^{+}$=309. (10%) (Figure 5).

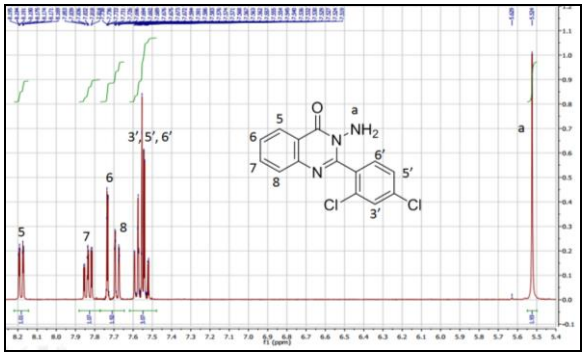

Figure 5: ^{1}H-NMR spectrum of compound 4a in (400 M Hz, DMSO-d6)

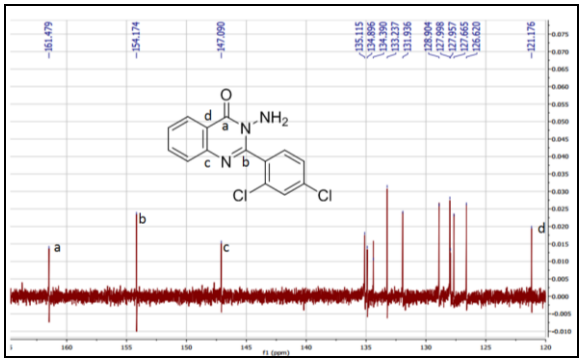

Figure 6: 13C-NMR spectrum of a compound 4a in (100 M Hz, DMSO-d6)

Compound3-Amino-2-(3,4-Dichlorophenyl)Quinazolin-4(3*H*)-One (4e)

Obtained in white powders; yield 85%; mp: 180-182°C; FT-IR (KBr) cm^{-1}: 3025 and 691 (=C-H aromatis); 1685 (C=O lactam); 1628 (C=N); 1622 and 1473 (C=C aromatis); 1324 (C-N); 3128 (N-H primer) and 775 (C-Cl). ^{1}H-NMR (DMSO, δ, ppm): δ 8.52 (1H, dd, J=8.4 Hz; 1.2 Hz); δ 8.07 (1 H, t); δ 7.86 (2 H, d, J=1.2 Hz); δ 7.76(1H, dd, J=7.6; J=1.2 Hz); δ 7.55-7.50 (1H, m, Atom H); δ 7.17 (1H, dt, J=7.6; J=1.2 Hz); δ 4.56 (1H, s). ^{13}C-NMR (DMSO, δ, ppm): δ 159.0; δ 155.0; δ 146.4; δ 137.5; δ 135.9; δ 132.5; δ 132.0; δ 131.3; δ 129.7; δ 129.6; δ 128.7; δ 128.3; δ 127.63; δ 117.6. MS m/z values (Rel. abundance): $[M^{+}+Na]^{+}$=305 (100%): $[M^{+2}+Na]^{+}$=307 (65%); $[M^{+4}+Na]$=309 (10%) (Figure 6).

Compound Amino-2-(2,4-Dichlorophenyl)Quinazolin-4(3*H*)-One (4F)

Obtained in white powders; yield 91%; mp: 170-172°C; FT-IR (KBr) cm^{-1}: 3128 (N-H primer); 3025 dan 691 (=C-H aromatis); 1688 (C=O laktam); 1628 (C=N); 1622 and 1473 (C=C aromatis); 1324 (C-N). ^{1}H-NMR (DMSO, δ, ppm): δ 8.56 (1H, d, J=8.2 Hz); δ 8.19 (1H, s); δ 7.92 (2H, d, J=7.2 Hz,); δ 7.70 (1H,d, J=8.0 Hz); δ 7.58 (1H, d, J=7.2 Hz); δ 7.53(2H, t, J=7.6 Hz); δ 7.51-7.48 (1H, m); δ 4.57 (2H, s). ^{13}C-NMR (DMSO, δ, ppm): δ 165.0; δ 155.1; δ 139.5; δ 134.9; δ 132.3; δ 129.5 (2C); δ 128.2; δ 127.4 (2C); δ 123.6; δ 120.8; δ 119.8. MS m/z values (Rel. abundance): $[M^{++}+Na]^{+}$=237 (100%): $[M^{+2+}+Na]^{+}$=239 (65%); $[M^{+4+}+Na]^{+}$=241 (10%).

CONCLUSION

The using microwave irradiation was more effective and efficient to produce compounds 2,3-disubtitutedquinazolin-4(3*H*)-one derivatives and very good yield 82-96%.

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