Asian Journal of Chemistry; Vol. 25, No. 2 (2013), 1039-1042

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.13405

Synthesis of Novel Quinazolinone Derivatives with Methyl (E)-2-(3-methoxy)acrylate Moiety

KUI-KUI DONG[1], HUA-HONG ZHOU[2], A-RONG GUO[1], TIAN CHEN[2] and YU-LIANG WANG[1,*]

[1]Faculty of Chemistry, Sichuan University, Chengdu 610065, P.R. China
[2]Department of Pathogenic Biology, School of Biomedical Science, Chengdu Medical College, Chengdu 610083, P.R. China

*Corresponding author: Tel: +86 153781 95811, E-mail: chemwang2008@163.com; allendkk@163.com

(*Received*: 7 January 2012; *Accepted*: 30 August 2012) AJC-12039

A new series of quinazolinone derivatives with methyl (E)-2-(3-methoxy)acrylate moiety have been designed and synthesized. All target compounds had been identified by ^{1}H NMR spectrum, IR spectrum and HR-MS (high resolution mass spectrum). Three target compounds (**10a**, **10e**, **10h**) were chosen to preliminarily test the antibacterial activities, the results showed that all three target compounds exhibited antibacterial activities against three bacterial strains (*Proteobacteria*, *Salmonella*, *Colibacillus*).

Key Words: Quinazolinone derivatives, Methyl (E)-2-(3-methoxy)acrylate, Synthesis, Identification, Antibacterial activity.

INTRODUCTION

Quinazoline derivatives (Fig. 1) are recognized as a class of important heterocycles for their pharmacological properties, such as antifungal, antibacterial and anticoccidial activities. Fenazaquin(I), was successfully developed by Dow-Elanco company as a kind of high efficient acaricides[1]. Fluquinconazole (**II**), a triazole microbicide with quinazoline structure commercialized by Schering[2], can prevent and cure powdery mildew, apple scab in a concentration of 2.5-15 g/L. Compound(**III**) showed antibacterial activity against *Staphylococcus aureus* in a very low concentration[3], compounds (**IV**)[4], (**V**)[5] and (**VI**)[6] also showed potent antimicrobial activities. In 1967 halofuginone (**VII**) (commercial name Stenorol) was designed and synthesized based on the structure of febrifugine[7]. Halofuginone is a broad-spectrum anticoccidial medicine with low toxicity and no cross-resistance[8]. Compared to other anticoccidial drugs, halofuginone has a higher anticoccidial activity when administered to chickens.

In previous publications, several series of compounds (**VIII**)[9], (**IX**)[10] and (**X**)[11] exhibited anticoccidial activity against *Eimeria tenella* in the chicken's diet with a dose of 9 or 18 mg/Kg. And a series of compounds (**XI**)[12] displayed potent antibacterial activity against *Staphylococcus aureus* ATCC26112 and *Staphylococcus aureus* SC. These studies have encouraged a continuing search for new varieties of compounds with novel modes of bioactivity. In this article, a new series of quinazoline derivatives (**10a-h**) with methyl (*E*)-2-(3-methoxy)acrylate moiety have been used in the synthesis of several agricultural fungicides[13] were designed and prepared.

EXPERIMENTAL

Starting materials were either commercially available or prepared as the method reported in the literature [9,14]. Melting points were determined with XRC-1 melting point apparatus without corrected. Analytical TLC was performed on silica gel GF_{254}, and spots were visualized with ultraviolet (UV) light. IR spectra were recorded on a Perkin-Elemer 16PC-FT spectrometer. Mass spectra (MS) were recorded with Agilent 6210 (DOF-MAS) spectrometer (Agilent Inc., Santa Clara, CA, USA) using the electrospray ionization (ESI) method. ^{1}H NMR spectra were run on a Varian INVOA-400 spectrometer. Chemical shift values (δ) are given in ppm and were downfield from internal tetramethylsilane. The reagents were all analytically or chemically pure. All solvents (except DMSO in the synthesis of compounds **10a-h**) and liquid reagents were used without further purification.

2-[2-(6-Chloro-pyrimidin-4-yloxy)phenyl]-3-methoxy-acrylic acid (5) was prepared according to the literature[14] with little modification. In the synthesis of 2-[2-(6-chloro-pyrimidin -4-yloxy)-phenyl]-3-methoxy-acrylic acid methyl ester (**4**), sodium methoxide was freshly prepared by sodium and methanol, because sodium methoxide placed for a long time would reduce the yield. And **5** was purified by column chromatography.

6,8-Substituted-3*H*-quinazolin-4-one (9a-h) were synthesized according to the literature[9].

Synthesis of 6,8-substituted-3-methoxy-2-{2-[6-(4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}acrylic acid methyl ester (10a-h): A solution of 0.84 g 5 (0.0026 mol) in **5** mL DMSO was added dropwise to a mixture of **9a-h** (0.0031

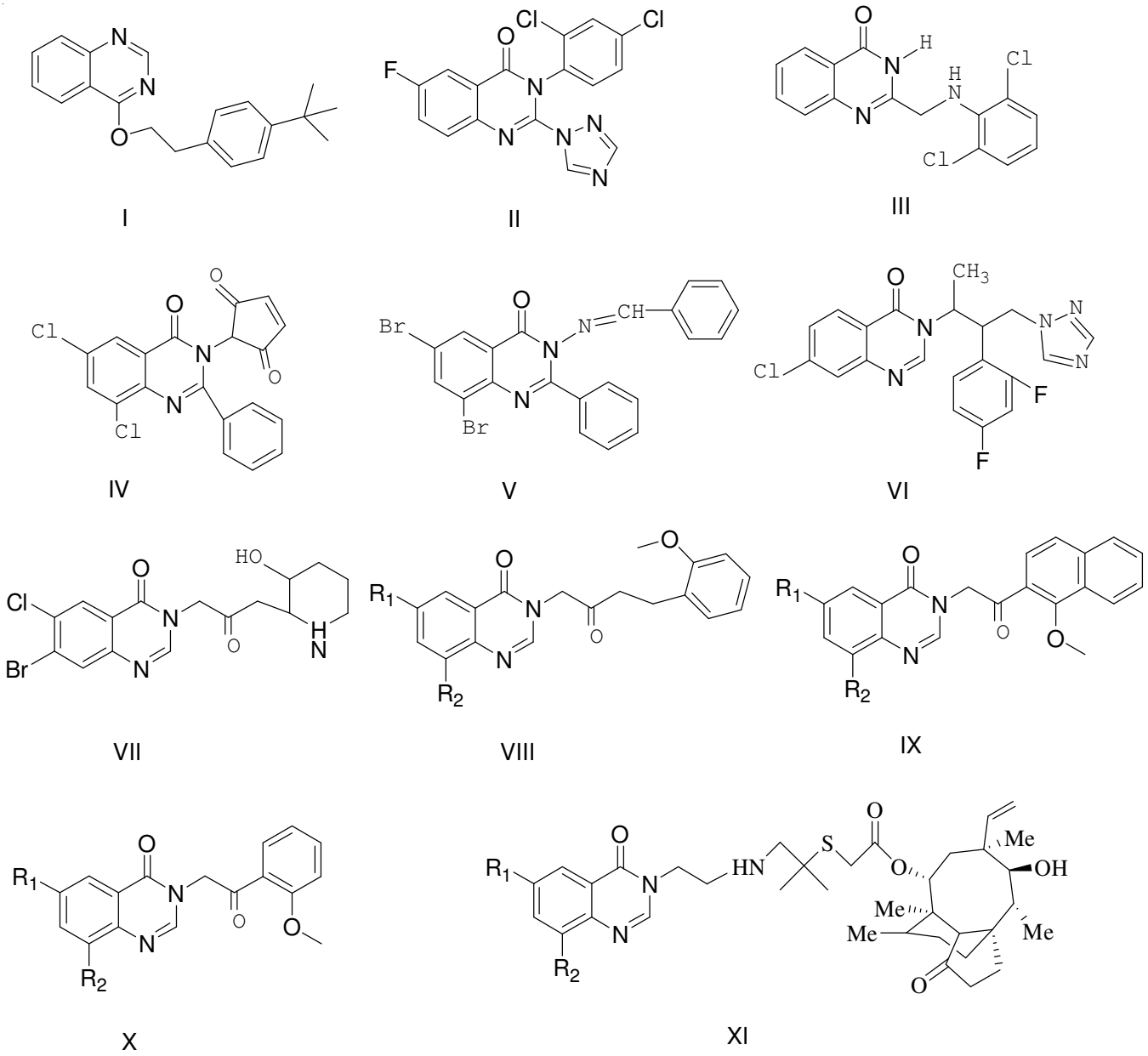


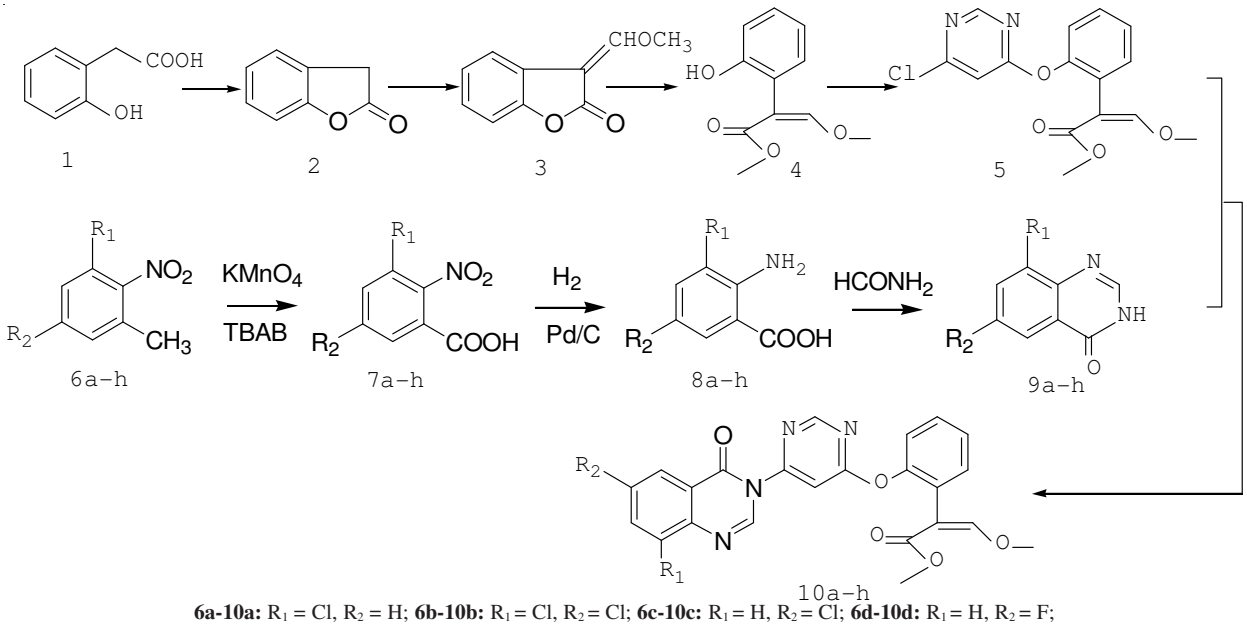
Fig. 1. Quinazolinones derivaties and methyl (E)-2-(3-methoxy)acrylate derivaties

mol), 0.35 g KI, 0.075 g (0.0031 mol) NaH and 15 mL DMSO under stirring at 75 ºC. After 10 h the mixture was cooled to room temperature and then 40 mL water and 20 mL ethyl acetate was added. The organic layer was separated, washed with 40 mL water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a crude product, which was chromatographed on a silica gel column using petroleum ether-ethyl acetate (2:1 v/v) as the mobile phase to give **10a-h (Scheme-I)**.

2-{2-[6-(8-Chloro-4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}-3-methoxy-acrylic acid methyl ester (10a): Light yellow solid; yield: 31.03 %; m.p.: 165-167 ºC; ^{1}H NMR (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm): 9.00 (1H, s, Quina-H), 8.78 (1H, s, Py-H), 8.29 (1H, d, *J* = 7.6Hz, Ar-H), 7.91 (1H,d, *J* = 7.6 Hz, Ar-H), 7.66 (1H, s, CH), 7.56 (1H, m, Ar-H), 7.49 (1H, s, Py-H), 7.31-7.43 (4H, m, Ar-H), 3.75 (3H, s, CH_3), 3.63 (3H, s, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3420, 3109, 2960, 2838, 1704, 1627, 1445, 1386, 1260, 1213, 1102, 1044, 900, 850, 806, 768; HR-MS (+ESI): Calcd. for $C_{23}H_{18}N_4O_5Cl$ $[M+H]^+$: 465.0966, Found: 465.0953.

2-{2-[6-(6,8-Dichloro-4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}-3-methoxy-acrylic acid methyl ester (10b): Light yellow solid; yield: 25.78 %; m.p.: 168-170 ºC; ^{1}H NMR (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm): 9.00 (1H, s, Quina-H), 8.78 (1H, s, Py-H), 8.41 (1H, d, *J* = 2Hz, Ar-H), 8.03 (1H, d, *J* = 2.4Hz, Ar-H), 7.63 (1H, s, CH), 7.48 (1H, s, Py-H), 7.23-7.45 (4H, m, Ar-H), 3.76 (3H, s, CH_3), 3.62 (3H, s, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3431, 2961, 2926, 2855, 1699, 1617, 1578, 1455, 1407, 1323, 1260, 1098, 1026, 902, 869, 804, 702; HR-MS (+ESI): Calcd. for $C_{23}H_{17}N_4O_5Cl_2$ $[M+H]^+$: 499.0576, Found: 499.0555.

2-{2-[6-(6-Chloro-4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}-3-methoxy-acrylic acid methyl ester (10c): White solid; yield: 32.59 %; m.p.: 166-168 ºC; ^{1}H NMR (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm): 8.88 (1H, s, Quina-H), 8.78 (1H, s, Py-H), 8.33 (1H, d, *J* = 1.6Hz, Ar-H), 7.76 (1H, dd, J_1



6a-10a: R_1 = Cl, R_2 = H; **6b-10b:** R_1 = Cl, R_2 = Cl; **6c-10c:** R_1 = H, R_2 = Cl; **6d-10d:** R_1 = H, R_2 = F; **6e-10e:** R_1 = Br, R_2 = Br; **6f-10f:** R_1 = H, R_2 = H; **6g-10g:** R_1 = H, R_2 = I; **6h-10h:** R_1 = Cl, R_2 = Br

Scheme-I: Synthetic route of compound **10a-h**

= 8.8 Hz, J_2 = 2 Hz, Ar-H), 7.72 (1H, d, J = 8.4 Hz, Ar-H), 7.65 (1H, s, CH), 7.49 (1H, s, Py-H), 7.24-7.45 (4H, m, Ar-H), 3.76 (3H, s, CH_3), 3.63 (3H, s, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3434, 3068, 2945, 2848, 1697, 1623,1574, 1446,1381, 1251, 1205, 1127, 832, 769; HR-MS (+ESI): Calcd. for $C_{23}H_{18}N_4O_5Cl$ $[M+H]^+$: 465.0966, Found: 465.0955.

2-{2-[6-(6-Fluoro-4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}-3-methoxy-acrylic acid methyl ester (10d): Light yellow solid; yield: 36.60 %; m.p.: 152-154 ºC; ^{1}H NMR (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm): 8.85 (1H, s, Quina-H), 8.78 (1H, s, Py-H), 8.00 (1H, m, Ar-H), 7.79 (1H, dd, J_1 = 8.8 Hz, J_2 = 4.8Hz, Ar-H), 7.66 (1H, s, CH), 7.54 (1H, m, Ar-H), 7.49 (1H, s, Py-H), 7.24-7.45 (4H, m, Ar-H), 3.76 (3H, s, CH_3), 3.63 (3H, s, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3033, 2949, 1699, 1624, 1486, 1444, 1561, 1332, 1258, 1200, 1131, 1103, 1064, 990, 901, 838, 766, 720; HR-MS (+ESI): Calcd. for $C_{23}H_{18}N_4O_5F$ $[M+H]^+$: 449.1261, Found: 449.1256.

2-{2-[6-(6,8-Dibromo-4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}-3-methoxy-acrylic acid methyl ester (10e): Light yellow solid; yield: 29.92 %; m.p.: 182-184 ºC; ^{1}H NMR (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm): 9.00 (1H, s, Quina-H), 8.77 (1H, s, Py-H), 8.46 (1H, d, J = 2 Hz, Ar-H), 8.20 (1H, d, J = 2 Hz, Ar-H), 7.62 (1H, s, CH), 7.48 (1H, s, Py-H), 7.23-7.44 (4H, m, Ar-H), 3.75(3H, s, CH_3), 3.63 (3H, s, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3438, 3068, 2924, 2852, 1702, 1629, 1563, 1444, 1381, 1258, 1208, 1129, 902, 802, 665, 465; HR-MS (+ESI): Calcd for $C_{23}H_{17}N_4O_5Br_2$ $[M+H]^+$: 586.9566, 588.9545, 590.9525 (isotope:), Found: 586.9554, 588.9537, 590.9520 (isotope).

3-Methoxy-2-{2-[6-(4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}acrylic acid methyl ester (10f): Light yellow solid; yield: 33.95 %; m.p.: 112-114 ºC; ^{1}H NMR (400 MHz; d_1-$CDCl_3$; TMS): δ (p.p.m.): 8.95 (1H, s, Quina-H), 8.77 (1H, s, Py-H), 8.37 (1H, d, J = 8 Hz, Ar-H), 7.83 (1H, m, Ar-H), 7.78 (1H, d, J = 7.2Hz, Ar-H), 7.67 (1H, s, CH), 7.57 (1H, m, Ar-H), 7.49 (1H, s, Py-H), 7.24-7.45 (4H, m, Ar-H), 3.75 (3H, s, CH_3), 3.63 (3H, s, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3433, 2960, 2924, 2852, 1699, 1628, 1562, 1449, 1391, 1325, 1260, 1211, 1131, 1056, 900, 859, 781, 699; HR-MS (+ESI): Calcd. for $C_{23}H_{19}N_4O_5$ $[M+H]^+$: 431.1355, Found: 431.1341.

2-{2-[6-(6-Iodo-4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}-3-methoxy-acrylic acid methyl ester (10g): Light yellow solid; yield: 34.25 %; m.p.: 181-183 ºC; ^{1}H NMR (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm): 8.89 (1H, s, Quina-H), 8.77 (1H, s, Py-H), 8.70 (1H, d, J = 2 Hz, Ar-H), 8.08 (1H, dd, J_1 = 8.8 Hz, J_2 = 2 Hz, Ar-H), 7.63 (1H, s, CH), 7.51(1H, s, Py-H), 7.48 (1H, d, J = 5.2 Hz, Ar-H), 7.23-7.44 (4H, m, Ar-H), 3.75 (3H, s, CH_3), 3.62 (3H, s, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3431, 2961, 2923, 2852, 1700, 1629, 1565, 1453, 1383, 1294, 1259, 1204, 1100, 1026, 902, 803, 728; HR-MS (+ESI): Calcd. for $C_{23}H_{18}N_4O_5I$ $[M+H]^+$: 557.0322, Found: 557.0301.

2-{2-[6-(6-Bromo-8-chloro-4-oxo-4*H*-quinazolin-3-yl)-pyrimidin-4-yloxy]phenyl}-3-methoxy-acrylic acid methyl ester (10h): Gray solid; yield: 33.21 %; m.p.: 228-230 ºC; ^{1}H NMR (400 MHz; d_1-$CDCl_3$; TMS): δ (ppm): 8.98 (1H, s, Quina-H), 8.78 (1H, s, Py-H), 8.25 (1H, d, J = 2.4 Hz, Ar-H), 7.88 (1H, d, J = 2.4 Hz, Ar-H), 7.63 (1H, s, CH), 7.49 (1H, s, Py-H), 7.23-7.45 (4H, m, Ar-H), 3.76 (3H, s, CH_3), 3.62 (3H, s, CH_3); IR (KBr, ν_{max}, cm^{-1}): 3435, 2926, 2855, 1703, 1628, 1565, 1462, 1379, 1260, 1098, 1027, 865, 804, 721; HR-MS (+ESI): Calcd for $C_{23}H_{17}N_4O_5BrCl$ $[M+H]^+$: 543.0071, 545.0050 (isotope:), Found: 543.0061, 545.0037 (isotope).

Biological assay: The antibacterial activities of three target compounds were tested via agar-well diffusion method *in vitro*. Target compounds (1000 μg) were dissolved with ethanol (1 mL) and diluted to 20 μg/mL with ethanol, A 50 μL solution of each compound was injected into the corresponding well in the Luria Bertani (LB) culture medium, which was covered with bacteria suspension in advance, and the plates were incubated at 37 ºC for 24 h. The results of average diameters of the bacteriostatic circle were listed in Table-1.

TABLE-1
In vitro ANTIBACTERIAL ACTIVITY OF **10a, 10e** AND 10 h AT THE CONCENTRATION 20.0 μg/mL

Compound	Diameter of inhibition zone (mm)		
	Proteobacteria	*Salmonella*	*Colibacillus*
10a	11	10	11
10e	13	14	9
10h	14	9	10
Ethanol[a]	7	7	7

[a]Negative control: ethanol; diameter of the well in each plate: 6 mm

RESULTS AND DISCUSSION

In the synthesis of intermediate **4**, the temperature and the quality of sodium methoxide influenced the yeild significantly. The mixture of intermediate **3** in THF should be added dropwise to a mixture of sodium methoxide and methanol while the temperature was lower than 5 ºC. Additionally, the sodium methoxide should be freshly prepared by sodium and methanol.

In the synthesis of intermediate **9a-h**, methanamide was used as both solvent and reactant. Through screening, the optimum ratio of **8a-h** :methanamide was 1:5.

The acidity of intermediate **9a-h** is so weak that K_2CO_3 and NaOH could not work to form the related sodium salt. Finally, NaH was chosen because hydrogen, the only by-product of this reaction, could escaped and the reaction system became simple. According to the literature[16], the methyl-(*E*)-2-(3-methoxy)-acrylate group was unstable in alkaline environment, so the alkalinity of reaction system should be maintained at a low level. Intermediate **5** was added afer intermediate **9a-h** and NaH had been stirred together for 2 h, this could ensure intermediate **9a-h** and NaH had been adequately reacted and provided a low alkalinity.

The amount of intermediate **5** was excessive to improve the yeild. The optimum ratio of intermediate **9a-h**: NaH: intermediate **5** was set at 1:1.25:1.25.

Temperature was another important influencing factor. The synthetic reaction of **10a-h** ran slowly at room temperature. An increase in temperature could speed up the process, 75-78 ºC was identified as the best condition.

Among the commonly polar aprotic solvents, DMSO was the best solvent. When DMF was used as solvent, NaH reacted slowly with DMF at 75-78 ºC, which consumed the NaH, thus decreased the yield, anhydrous DMSO could meet the reaction condition well.

Products **10a-h** were all new compounds and their structrures were deduced from spectral datas. The ^{1}H NMR spectrum of compounds **10a-h** all displayed two singlets at 3.62-3.76 ppm for two CH_3 groups and a multiplet at 7.23-7.45 ppm for 4 H protons on benzene ring, two singlets at about 7.49 and 8.48 ppm for 2 H protons on pyrimidine ring, a singlet at about 7.63 ppm from a C=CH proton and a singlet at about 9.00 ppm from a N=CH proton. The difference was present in benzene ring of quinazolinone: when **10a-h** was substituted at position 6 (example **10c**), a signal was observed at 7.76 ppm (dd, J_1 = 8.8 Hz, J_2 = 2 Hz) assigned to a C-H proton from position 7, another two doublets or two multiplets were observed at 7.42-8.70 ppm assigned to C-H protons from position 5 and position 8, when **10a-h** was substituted at position 8 (example **10a**), a multiplet and two doublets were observed at 7.56-8.29 ppm, when **10a-h** was substituted at both position 6 and position 8, two doublets were observed at 8.03-8.46 ppm, when there was no substitution (**10f**), two doublets and two multiplets were observed at 7.57-8.37 ppm. The structural assignments of compounds **10a-h** were also supported by its IR spectrum, Example for **10c**, the C-Cl exhibited strong absorption at 1127 cm^{-1}, and the C=CH group exhibited absorption at 3068 cm^{-1}, other groups aslo had the corresponding absorption peaks. The high resolution mass spectrometer of compounds **10a-h** showed that all the errors between the calculated value and measured value of molecular mass were less than 0.0021.

Biological activity: The results of antibacterial activities showed that all three target compounds (**10a, 10e, 10h**) exhibited antibacterial activities against three bacterial strains (*Proteobacteria, Salmonella, Colibacillus*) at the concentration 20.0 μg/mL.

Conclusion

In summary, a series of novel quinazolinone derivatives with a methyl-(*E*)-2-(3-methoxy)acrylate group had been designed and synthesized and characterized by spectroscopy. Three target compounds were chosen to simply test the antibacterial activities, the results showed that all three target compounds (**10a, 10e, 10h**) exhibited antibacterial activities against three bacterial strains (*Proteobacteria, Salmonella, Colibacillus*) at the concentration 20.0 μg/mL.

ACKNOWLEDGEMENTS

The author appreciated the financial support from the National Science Foundation of China (No. 21072135) and Chengdu Medical College for the antibacterial activity test (cx 20100037).

REFERENCES

1. J.M. Huang, *Chem. J. Chin. Univ.*, **8**, 1216 (2000).
2. P.R. Russell, *Pesticides*, **27**, 33 (1988).
3. S. Jantova, S. Stankovsk and K. Spirakova, *Biologica Bratislava,* **59**, 741 (2004).
4. Y. Zhou, D. Murphy, Z. Sun and V. Greogr, *Tetrahedron Lett.*, **45**, 8049 (2004).
5. P. Panneerselvam, B.A. Rather, D.R.S. Reddy and N.R. Kumar, *Eur. J. Med. Chem.*, **44**, 2328 (2009).
6. P.M. Chandrika, T. Yakaiah, A.R.R. Rao, B. Narsaiah, N. Chakra Reddy, V. Sridhar and J.V. Rao, *Eur. J. Med. Chem.*, **43**, 846 (2008).
7. W.P. Emanuel, U.S. Patent 3320124 (1967).
8. C.C. Norton and D.R. Wise, *The Veter. Rec.*, **109**, 554 (1981).
9. J.H. You, C.W. Ye, Y.B. Weng, X.H. Mo and Y.L. Wang, *Arkivoc*, 1 (2008).
10. Y.Y. Zhang and G.M. Chen, *Lett. Drug Design Discov.*, **7**, 471 (2010).
11. C.W. Ye and J.H. You, *Pesticide Biochem. Physiol.*, **97**, 194 (2010).
12. Y.-P. Yao and F.-Y. Dai, *J. Chem. Res.*, 4 (2011).
13. W.A. Battaglin, M.W. Sandstrom, K.M. Kuivila, D.W. Kolpin and M.T. Meyer, *Water Air Soil Pollut.*, **218**, 307 (2011).
14. J. Dong, D.-H. Liao, J.-S. Lou and H.-J. Pi, *Fine Chem. Intermed.*, Vol. **37**, No. 2.