Наносистеми, наноматеріали, нанотехнології
Nanosistemi, Nanomateriali, Nanotehnologii
2022, т. 20, № 4, сс. 1037–1045

PACS numbers: 68.37.Hk, 81.16.Be, 82.39.Wj, 87.19.xb, 87.64.Ee, 87.85.Rs

Synthesis and Characterization of 2-(Aminothiazole-4-yl) Coumarin-2-One, and Studying Its Nanoparticles as Antibacterial Activity

Ali Alasmi[1], Joumaa Merza[1,2], Mirna Jabbour[3], and Shaimaa Rabah[4]

[1]*Department of Chemistry,*
Albaath University,
Homs, Syria
[2]*Faculty of Dentist,*
Arab Private University for Science and Technology,
Homs, Syria
[3]*Faculty of Pharmacy,*
Damascus University,
Damascus, Syria
[4]*Middle East University College,*
Baghdad, Iraq

The total synthesis of aminothiazole coumarin derivative (IV) in four steps is reported. The propriety of compound (IV) is studied. To evaluate the biological activity of the Schiff base (IV), the nanoparticles in solution and the nanoparticles carried on cellulose membrane are prepared, and their antibiotic activity is evaluated in two cases in comparing with the antibiotic activity of the ampicillin as a reference antibiotic. The compound (IV) shows an antibacterial activity about 50% in comparing to the ampicillin. The nanoparticles in solution have a higher antibiotic activity at lower concentrations than at high concentrations. The nanoparticles carried on cellulose membrane show a high activity about 50% in comparing to the activity of the ampicillin.

Повідомляється про загальну синтезу похідного кумарину амінотіазолу (IV) у чотири стадії. Властивість сполуки (IV) вивчається. Для оцінки біологічної активности Шиффової основи (IV) готують наночастинки в розчині та наночастинки, що переносяться на целюлозну мембрану, і їхню антибіотичну активність оцінюють у двох випадках у порівнянні з антибіотичною активністю ампіциліну як еталонного антибіотика. Сполука (IV) виявляє антибактеріяльну активність приблизно на 50% у порівнянні з ампіциліном. Наночастинки в розчині мають вищу антибіотичну активність за нижчих концентрацій, аніж за високих концен-

трацій. Наночастинки, нанесені на целюлозну мембрану, демонструють високу активність близько 50% у порівнянні з активністю ампіциліну.

Key words: 1.3-thiazole, Schiff base, nanoparticles, membrane, antibiotics.

Ключові слова: 1.3-тіазол, Шиффова основа, наночастинки, мембрана, антибіотики.

(Received 6 May, 2022; in revised form, 13 June, 2022)

1. INTRODUCTION

The first antibiotic, magic bullet, salvarsan 606, was discovered in 20^{th} century [1, 2], and the utilization of antibiotics in clinical treatment was arguably the greatest medical breakthrough of the 20^{th} century [1] that extended the average human lifespan by more than two decades [3]. The golden age of natural product antibiotic discovery started by the discovery penicillin [4] and peaked in the mid-1950s [1]. Since then, drug resistance in many human pathogens has led to the antibiotic resistance crisis [5] because a gradual decline in antimicrobial discovery and development [1]. The overuse and misuse of antibiotics are the main causes of increased antibiotic resistance [6] in addition to inappropriate waste management and environmental transmission [7]. Synthesis of new antibiotics is one of the most important current trends in pharmaceutical chemistry [8]. However, the synthesis of antibiotic and its study is very long and needs many efforts [9, 10], and the results are not guaranteed [11], and they may face the same fate as their predecessors after a decade of their clinical use [11]. Nanotechnology may be the solution to this crisis. Nanomaterial antibiotic compounds have a more effect than non-nanomaterial antibiotics [12]. The 1.3-thiazole and its derivatives are the interesting building blocks in a variety of synthetic and natural compounds [13]. These compounds and their derivatives have a good antibacterial potential activity [14], and their structure is essential part of many compounds used frequently in pharmaceutical treatment [15]. Generally, this propriety is due to their low-risk for the human body [16, 17].

In this paper, the total synthesis of (2-aminothiazole-4-yl) coumarin-2-one (IV) from the salicylaldehyde and beta keto aster in four steps has been described. The preparation of the nanoparticles of the compound (IV) has been studied and described by means of the SEM. The prepared nanoparticles of (IV) loaded with cellulose membrane.

The activity antibacterial against two types of bacteria has been

studied: *A. aurus* and *E. coli* (in comparing with ampicillin). The antibiotic effects of nanoparticles of compound (IV) has been studied and compared to the activity of ampicillin as antibiotic reference.

2. EXPERIMENTAL

2.1. Chemical Materials and Apparatus

All the used chemicals (salicylic aldehyde, ethyl acetoacetate, furfural, iodine, thiourea, ethanol, chloroform DMF, and DMSO) were purchased from Aldrich. The IR spectrum of the compounds was recorded with JASCO M400 instrument in KBr disk. ^{1}H-NMR spectrum of the compounds was recorded on a Bruker 400 MHz spectrometer.

I. Synthesis of 3-acetyl coumarin-2-one. Salicylic aldehyde 50 mmol and ethyl acetoacetate 50 mmol and ethanol 250 ml are placed in a flask and heated under reflux for three hours. The reaction mixture is cooled. Yellow precipitate is formed and isolated by filtering, washed with cold ethanol and recrystallized in ethanol.

II. Synthesis of 3-(2-iodoacetyl)-coumarin-2-one. 30 mmol of acetylcoumarin is dissolved in 20 ml of ethanol, gently heated with several drops of acetic acid; then, 30 mmol of iodine is added in 10 ml of chloroform. The reaction mixture is heated under reflux for five hours. The reaction mixture is cooled, and yellow precipitate is formed and isolated by filtering and washed with cold ethanol. It is recrystallized in ethanol.

III. Synthesis of 2-(aminothiazole-4-yl) coumarin-2-one. 2-iodoacetyl coumarin 25 mmol is dissolved in 15 ml of ethanol with heating, and 20 mmol of thiourea is added in 10 ml of ethanol. The reaction mixture is heated under reflux for 6 hours; the reaction mixture is cooled, a precipitate is formed and isolated by filtration, washed with cold ethanol and recrystallized in ethanol.

IV. Synthesis of Schiff base. 2-(3-aminothiazole 4-yl) coumarin 20 mmol and furfural 20 mmol are dissolved in 10 ml ethanol and heated under reflux distillation for 5 hours. The reaction mixture is cooled, and a precipitate is formed and isolated by filtering, washed with cold ethanol and recrystallized in ethanol. Preparation of nanoparticles loaded with cellulose membrane: 10, 25, 50, 100 mg of Schiff base (IV) dissolved in 100 ml of dimethylformamide. Cellulose membrane was soaking within the solution in an ultrasonic bath for 1 hour at 50°C. The membrane is transferred to an aqueous solution in an ultrasonic bath for 30 minutes, then, washed with distilled water and cold alcohol.

The process is repeated several times. Then, the resulting film is dried.

2.2. Antibiotic Performance

Two bacteria (*S. aureus*, *E. coli*) were selected to evaluate the antimicrobial activity of compound (IV) in two forms: its nanoparticles in solution and nanoparticles carried on the cellulose membrane.

a. The nanoparticles of compound (IV) in solution. The measuring of the inhibition zone was used for evaluating the antibacterial activity of nanoparticles in solution using the agar well diffusion method [18]. A plate containing agar medium was inoculated with a microbial strain to ensure its growth. Then, 6 mm diameter hole was punched aseptically at five different positions and followed by introduction of extract (about 20 μL) into each well and a reference drug (ampicillin) at the central hole. Each group of plate was placed and cultured at 37°C for 16 h. The diameter of the inhibition zone was measured.

b. The nanoparticles carried on cellulose membrane [19]. The composite membrane was cut into discs with a diameter of 6 mm, and the antimicrobial activity was evaluated by measuring the inhibition zone surrounding each disc. The cellulose membrane without compound (IV) was included as a control. 100 μL of the microbiome cells were transferred to an agar plate; each group of composite membrane sample was placed in, and cultured at 37°C for 16 h. The diameter of the inhibition zone was measured.

3. RESULTS AND DISCUSSION

3.1. Characterization

I. 3-acetyl coumarin-2-one: yellow powder ($y = 75\%$), m.p. 120°C, FT/IR: 3050 cm^{-1}(C_{sp^2}–H), 2980 cm^{-1} (C_{sp^3}–H), 1715 cm^{-1} (C=O), and 1285 cm^{-1} (C–O).
II. 3-(2-iodoacetyl)-coumarin-2-one: yellow powder ($y = 84\%$), m.p. 160°C, FT/IR: 3020 cm^{-1} (C_{sp^2}–H), 2965 cm^{-1} (C_{sp^3}–H), 1685 cm^{-1} (C=O), 1315 cm^{-1} (C–O), and 720 cm^{-1} (C–I). ^{1}H-NMR ($CDCl_3$): 3.43 ppm (*s*, 2H), 10.39 ppm (*m*, 1H), 10.59 ppm (*d*, 1H, $j = 8.7$), 10.62 ppm (*m*, 1H), 10.72 ppm (*m*, 1H), and 11.7 ppm (*s*, 1H).
III. (2-(aminothiazole-4-yl) coumarin-2-one: light green powder ($y = 55\%$), m.p. 185°C, FT/IR: 3360–3455 cm^{-1} (–NH_2), 3045 cm^{-1} (C_{sp^2}–H), and 1680 cm^{-1} (C=O). ^{1}H-NMR (DMSO-d_6): 6.72 ppm (*s*, 2H, NH_2), 7.16 ppm (*s*, 1H), 7.51 ppm (*d*, 1H, j = 6.9), 7.62 ppm (*d*, 1H, $j = 10.2$), 7,96 ppm (*s*, 1H), 8.26 ppm (*d*, 1H, $j = 6.6$), 8.35 ppm (*d*, 1H, $j = 9.1$).
IV. (2-((furan-2-ylmethylene)amino) thiazole-4-yl) coumarin-2-one): yellow powder ($y = 68\%$), m.p. 195°C, FT/IR: 3023 cm^{-1} (C_{sp^2}–H), 2966 cm^{-1} (C_{sp^3}–H), and 1624 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6): 6.99

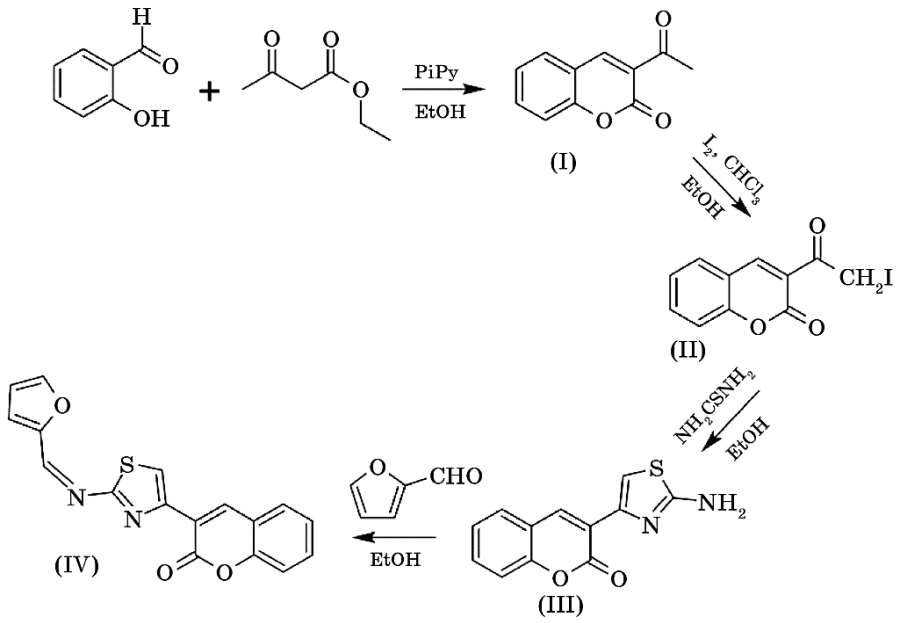

Fig. 1. Steps of the synthesis of compound (IV).

ppm (*m*, 1H), 7.71 ppm (*d*, 2H, $j = 11.1$), 8.3 ppm (*m*, 2H), 8.38 ppm (*d*, 1H, $j = 8.8$), 8.95 ppm (*s*, 1H, Imine), 11.12 ppm (*s*, 1H), 12.44 ppm (*s*, 1H).

3.2. SEM of Nanoparticles

A. nanoparticles. The morphology of nanoparticles is studied by scanning electron microscope images. The image gives information about the size and shape of the particles and their surface morphology. Figure 2 shows a SEM image of compound (IV) nanoparticles. The particles seem to be spherical, irregular in size, and aggregate together to form clusters; their size ranges between 40 and 150 nm, and their average size is 85 nm. They have a rough surface that appears to be composed of a cluster of tiny 15 nm size particles.

B. nanoparticles on cellulose membrane. Figure 3 shows an electron microscope image of nanoparticles loaded on cellulose fibres. The cellulose fibres appear to have an ordered, slightly tortuous surface, with a diameter of about 15 μm. Nanoparticles cover most of the surface of the fibre, forming a thin film that surrounds it, and sometimes, clusters are formed on the surface of the fibre. The size of the particles in the clusters is of about 85 nm. The particles appear to have a rough surface made up of smaller particles (about

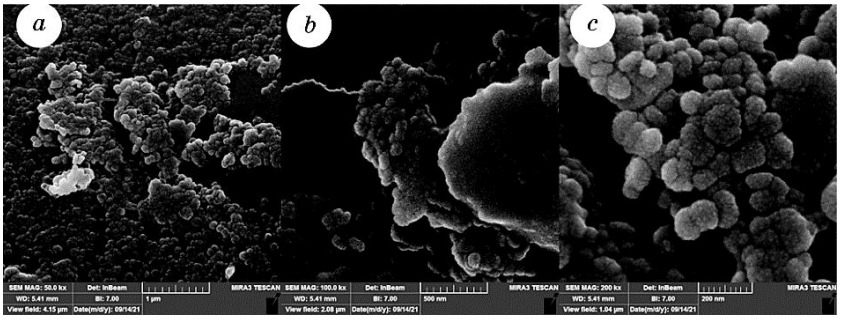

Fig. 2. SEM images of Schiff base (IV) nanoparticles.

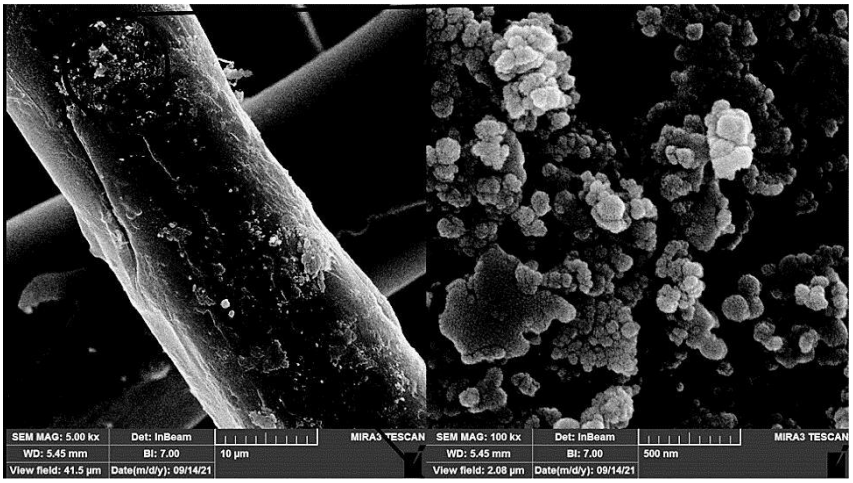

Fig. 3. SEM images of nanoparticles carried on cellulose membrane of compound (IV).

10 nm). These tiny particles also cover the surface of the fibre.

Schiff base solution in DMSO was used as an antibacterial substance on two species of bacteria (*E. coli* (gram-negative) and *S. aureus* (gram-positive)) at concentrations of 50, 100, 200, and 500 ppm. It was shown the inhibition *vs*. Schiff base (IV) in different concentrations. It was found that the inhibition increases with increasing the concentration until the concentration of 200 ppm becomes almost constant. The activity of the compound (IV) used in this study is equivalent to 50% of that to the reference substance (ampicillin). The relatively good activity of the substance (IV) is due probably to the presence of the thiazole ring, which is at the forefront of antibiotics.

C. nanoparticles. To evaluate the biorepelling efficiency of nano-

particles, a suspension of compound Schiff base (IV) has been prepared in water, and the particles have been used with concentrations of 50, 100, 200 and 500 ppm by SEM. The images show the diameter of the inhibitory potentiometer *versus* the concentration. It was noted that the diameter of the damping increased to a bone value and then decreased. The reason for the low efficacy may be due to the agglomeration of nanoparticles at high concentrations. At lower concentrations, the nanoparticles were more active than the solution at the same concentration. Whereas, the activity of nanoparticles was lower at higher concentrations.

D. Nanoparticles carried on cellulose membrane. Efficacy of cellulose film grafted with Schiff base (IV) was used as an antibiotic in the form of tablets, and its activity was estimated depending on the diameter of the inhibiting aura. Figure 4 shows the diameter of the damping halo against the amount of Schiff base (IV) in the disc. Efficiency increases and then stabilizes at a certain value.

When comparing the activity of the three studied cases, it has

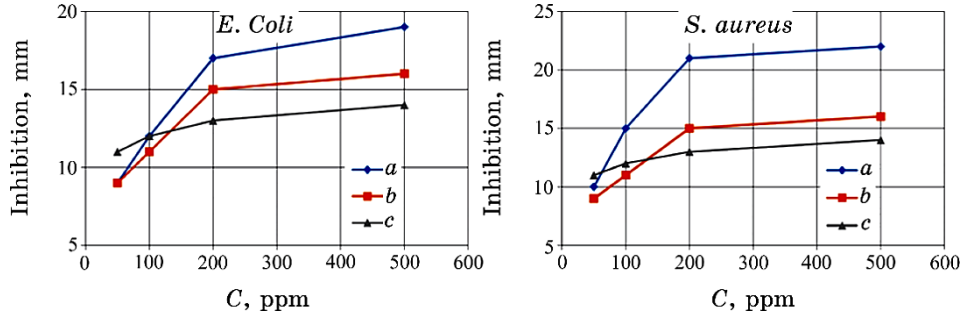

Fig. 4. *A. aureus* and *E. coli* inhibition *vs.* Schiff base concentration: *a*) ampicillin; *b*) solution; *c*) nanoparticles.

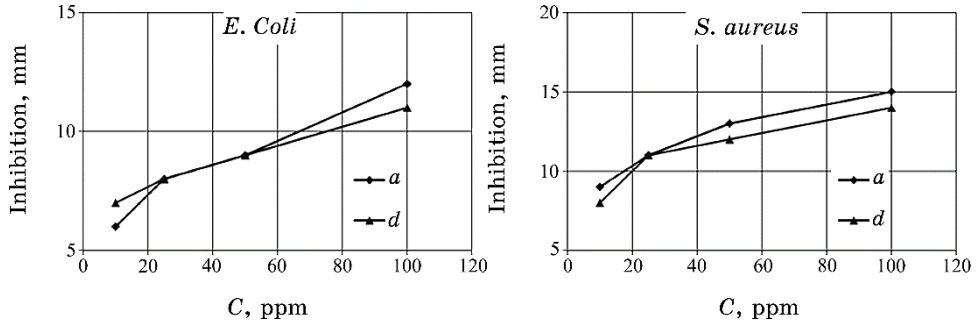

Fig. 5. *A. aureus* and *E. coli* inhibition *vs.* Schiff base (IV) concentration: *a*) ampicillin; *d*) membrane.

been noticed that a smaller amount of Schiff base (IV) carried on the cellulose membrane gives a higher efficiency than the suspension solution of compound (IV).

4. CONCLUSIONS

The Schiff base (IV) containing the thiazole ring have been synthesized and described using IR and H-NMR from salicylic aldehyde in four steps. The nanoparticles were prepared from the compound (IV) by the phase inversion method, and a cellulose membrane grafted with nanoparticles has been prepared in the same way. The size of the nanoparticles was of 85 nm. The Schiff base (IV) has antibacterial activity, but the nanoparticles carried on cellulose membrane are more active than the nanoparticles in solution.

5. HIGHLIGHTS

Synthesis of the Schiff base (IV) that contains heterogeneous rings has an antibiotic activity.

Schiff nanoparticles in an easy way and preparing a film inlaid with Schiff nanoparticles.

Study and comparison the activity of the prepared materials.

6. ACKNOWLEDGEMENTS

The authors express their thanks to Central Laboratory in the Department of Chemistry, Al Baath University, Faculty of Sciences for their help during the work, and we extend our thanks and gratitude to Dr. Waed Abodaboos for support this work.

REFERENCES

1. H. Matt, T. Andrew, and W. Barrie, *Current Opinion in Microbiology*, **51**, No. 1: 72 (2019); https://doi.org/ 10.1016/j.mib.2019.10.00
2. K. A. Sepkowitz, *New England Journal of Medicine*, **365**, No. 4: 291 (2011); https://doi.org/10.1056/nejmp1105345
3. E. M. Crimmins, *Lifespan and Healthspan: Past, Present, and Promise. The Gerontologist*, **1**, No. 1: 130 (2015); https://doi.org/10.1093/geront/gnv130
4. R. Gaynes, *Emerging Infectious Diseases*, **23**, No. 5: 849 (2017); http://dx.doi.org/10.3201/eid2305.161556
5. F. Prestinaci, P. Pezzotti, and A. Pantosti, *Pathogens and Global Health*, **2**, No. 1: 1 (2015); https://doi.org/10.1179/2047773215Y.0000000030
6. M. Miethke, M. Pieroni, T. Weber, and M. Brönstrup, *Nature Reviews Chemistry*, **3**, No. 2: 726 (2021); https://doi.org/10.1038/s41570-021-

00313-1
7. R. Laxminarayan, A. Duse, and C. Wattal, *The Lancet Infectious Diseases*, **13**, No. 12: 1057 (2013); https://doi.org/10.1016/S1473-3099(13)70318-9
8. P. M. Wright, I. B. Seiple, and A. G. Myers, *Angewandte Chemie International Edition*, **53**, No. 34: 8840 (2014); https://doi.org/10.1002/anie.201310843
9. M. M. Usman, A. Usman, and M. S. Sajal, *International Journal of Nanomedicine*, **15**, No. 1: 7329 (2020); https://doi.org/10.2147/ijn.s265934
10. H. Diarmaid and K. Anders, *Upsala Journal of Medical Sciences*, **119**, No. 2: 162 (2014); https://doi.org/10.3109/03009734.2014.896437
11. S. Leekha, C. L. Terrell, and R. S. Edson, *General Principles of Antimicrobial Therapy*, **86**, No. 2: 156 (2011); https://doi.org/10.4065/mcp.2010.0639
12. N. Y. Lee, W. C. Ko, and P. R. Hsueh, *Pharmacol.*, **10**, No. 10: 1 (2019); https://doi.org/ 10.3389/fphar.2019.01153
13. B. Sadek, M. M. Al-Tabakha, and K. M. Fahelelbom, *Molecules*, **16**, No. 12: 9386 (2011); https://doi.org/10.3390/molecules16119386
14. F. Lemilemu, M. Bitew, T. B. Demissie et al., *BMC Chemistry*, **5**, No. 10: 726 (2021); https://doi.org/10.1186/s13065-021-00791-w
15. A. Petrou, M. Fesatidou, and A. Geronikaki, *Molecules*, **26**, No. 11: 3166 (2021); https://doi.org/10.3390/molecules26113166
16. G. Jin, Y. Mi Kim, A. Lee, and J. Choi, *Bioorganic and Medicinal Chemistry*, **28**, No. 23: 1 (2020); https://doi.org/10.1016/j.bmc.2020.115797
17. Joumaa Merza, *Chemistry and Materials Research*, **10**, No. 2: 16 (2018); http://iiste.org/Journals/index.php/CMR/article/view/40944
18. M. Zahid, S. Akram, A. Rashid, Z. A. Rehan, T. Javed, R. Shabbir, M. M. Hessien, and M. E. El-Sayed, *Membranes*, **11**, No. 7: 510 (2021); https://doi.org/10.3390/membranes11070510
19. X. Sun, L. Yin, H. Zhu, J. Zhu, J. Hu, X. Luo, H. Huang, and Y. Fu, *Membranes*, **12**, No. 2: 239 (2022); https://doi.org/10.3390/membranes12020239