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RESEARCH PAPER

Synthesis of Some Novel 1,8-Naphthyridine Chalcones as Antibacterial Agents

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ABSTRACT

Nanomaterials are interesting candidates as heterogeneous catalysts for different organic reactions. In this research SiO_2 nanoparticles was applied for synthesis of some new 2-chloro-1,8-naphthyridine-3-carbaaldehyde (1) through vilsmeier – haack cyclization of N-(pyridine-2-yl)acetamide has been reported and transformation to new chalcones containing morpholine ring from reaction of 2-morpholine-3-formyl-1,8-naphthyridine (2) and 2-aminoacetophenone to produce E-3-(2-morpholino-1,8-naphthyridine-3-yl)-1-(4-aminophenyl) prop-2-en-1-one (3) through Claisen-Schmidt reaction by used (Nano silicon dioxide imidazolidin sulfite propyl silyl trifloroacetate) as catalyst . which on treatment with N-chloroacetyl-4,6-diphenyl pyrimidinyl amine (4) gave compound (5). Compound (3) treated chloro acetyl arylamine (4) in presence of small amount of carbonate in DMF gave compound (6). The structures of the final compounds were confirmed by IR and ^{1}HNMR. These compounds were evaluated for their antibacterial activity against gram positive and gram-negative bacteria using dilution procedure showed activity against the bacteria under study; 1,8-naphthyridine derivatives boost the fluoroquinolone antibiotics' efficiency against multi-resistant bacteria, and therefore appealing prospects for development of treatments against bacterial infections caused by multidrug-resistant strains.

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INTRODUCTION

Nano-catalysts include metals, metal oxide, and non-oxides with nanoscale size and shape. Due to their unique physical and chemical properties, nanomaterials have been found more attention in process based on organic chemistry [1, 2]. The morphology, size and crystalline structures of nanomaterials-based catalysts lead to their catalytic performance, recyclability, and selectivity. The structural and morphological engineering of nanomaterials lead to higher catalytic activity. Till now, various nanostructures have been applied as a heterogeneous catalyst for organic process [3-5].

Heterocyclic compounds are the most important branches of organic chemistry, which are widely distributed in nature and are essential to life fund as potential [5], anticancer agent [6] and antimalarial agent [7]. 1,8-naphthyridine derivates possessing a wide spectrum of biological activities such as antibacterial [8], antibiotic of group is being widely used for the diagnostics and chemotherapy of infection disease of human including aids [9]. Chalcones and pyrimidine derivatives of this group also useful drugs with many biological, pharmaceutical and therapeutically

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activities and used as analgesics, antiviral, anti-inflammatory agent, antibacterial and anti-tuberculosis agent [10-12]. As well as its proposal as a drug against the emerging corona virus, by studying a theory using the Docking program [13]. There are two general methods available for the preparation of 1,8-naphthyridinenamely the Skraup and Friedlander reaction [14] but the vilsmeier – Haack reagent used as a versatile reagent for the preparation of 1,8-naphthyridine [15,16]. Recently, a substance has been used nanomaterial namely nano-[SiO_2@R-Im-SO_3H] [CF_3COO] (NSRISC) Thereafter, the solvent-free production of bis-coumarins (from aryl aldehydes and 4-hydroxycoumarin) was catalysed by NSRISC for condensation reactions[17,18]. Antimicrobial-resistant microorganisms, such as bacteria and fungi, necessitate the continual discovery and development of novel antibacterial agents through the modification and synthesis of new classes of molecule due to the obtained resistance encoded by the resistance issue [19, 20]. There are six distinct isomeric forms of naphthyridines [21]. The 1,8-naphthyridines are the most investigated of them because of their scientifically verified biological actions. Antiparasitic, antibacterial, anti-inflammatory, anti-allergic, and anticancer properties have been demonstrated for these compounds [22]. This study aimed to Synthesis Novel 1,8-Naphthyridine Chalcones derivatives and detect their antibacterial activity against Gram and Negative bacteria

MATERIALS AND METHODS

Electro-thermal (CIA9300) device was used to evaluate the Melting Points of various organic compounds (open capillary tube method). The melting point is the simplest and most significant way to distinguish one substance from another. IR spectra were recorded in KBr powder on tensor 27 , Bruker Co. Germany. The ^1H, ^{13}C NMR spectra were measured in DMSO-d6 solvent on JEOL 400 MHz.

Synthesis of NSRISC

Stirred for 12 hours in reflexed toluene (15 mL) with a mixture of imidazole and (3-chloropropyl) trimethoxysilane (0.99 g, 5 mmol). I was produced by distilling the solvent at 100°C under vacuum. It took 18 hours for me to make II by refluxing nano-SiO_2 in EtOAc (15 mL) for 18 hours. After a 4-hour stirring period, dry CH_2Cl_2 (15 mL) was progressively added to an aqueous solution of $ClSO_3H$ (0.34 mL, 5 mmol) in order to create III. This was followed by stirring III for 9 hours at room temperature and 3 hours under reflux for the last time, giving NSRISC, which was obtained by slowly adding 0.46 mL (six molecular weight) of CF3CO2H solution in dry CH_2Cl_2 (15 mL). It was dried after being cleaned with the solvent and then rinsed

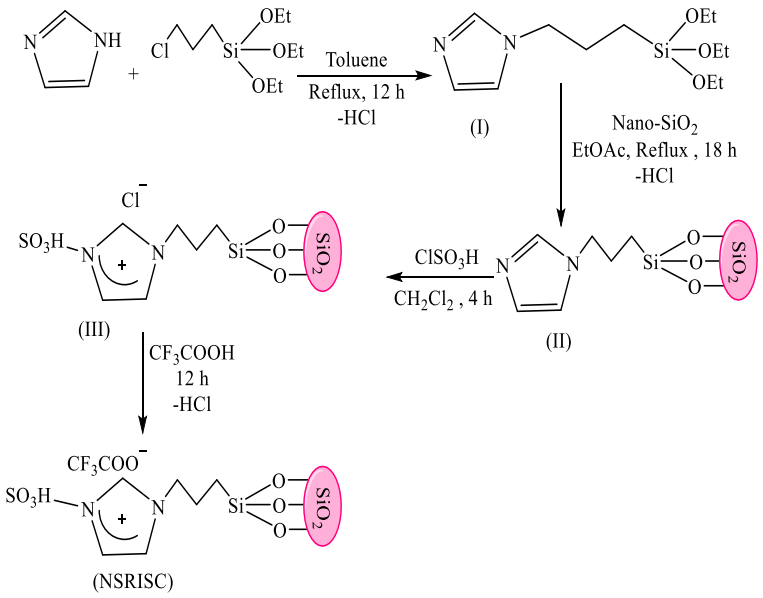

Fig. 1. Synthesis of NSRISC.

(Fig. 1).

Synthesis of 2-chloro-1,8-naphthyridine-3-carboaldehyde (1)[23,24]

N-(pyridine -2- yl) acetamide (1 mol) equivalent was taken in around bottom flask (250 ml) to this add (3 mol) equivalent of dimethyl formamide (DMF) the round bottom flask in then equipped with a dropping funnel filled with (7 mol) equivalent $POCl_3$ (phosphoryl chloride), the whole assembly was placed on an ice bath and (0-5 °C) temperature was maintained. then drop wise adding of $POCl_3$ was done with continuous stirring after the drop-wise addition, dropping funnel was removed and immediately the contents of reaction mixture in round bottom flask were equipped with a reflux condenser and then the mixture was stirred at (80-90 °C) for (15 hrs) then the reaction mixture was immediately poured in ice cold water and stirred for half an hour. the reaction mixture was filtered on Buchner funnel; the crystals obtained were washed with cold water and dried. the recrystallization was done by ethanol (Fig. 2).

The melting point was found to be 165-167 °C , The % Yield obtained was 65% , Color pale yellow. F.T. IR (KBr. ν , cm^{-1}) 3055(Ar-H), 2780 (C-H), 1685 (C=O), 1565 (C=N), 775 (C-Cl), ^{1}H NMR spectra (400 MKz, DMSO-d6, δ , ppm) 8.39-8.41 (d, 1H, C-7), 7.26-7.29(d, 1H, C-6), 7.48-7.50(d, 1H, C-5), 7.91(s, 1H, C-4), 10.45(s, 1H, CHO).

Synthesis of 2-morpholeno-1,8-naphthyridine-3-carboaldehyde (2)[25]

Morpholine (0.01 mol) and 2-chloro-3-formyl-1,8-napthyridine(1) (0.01 mol) in DMF (10 ml) were stirred at 35 °C for 6 hrs. the PH was controlled using sodium bicarbonate . after cooling, the precipate was washed with cold water. the recrystallization was done by ethanol to obtained above compound(2) . yield 55% as yellow , m.p. 187-189 °C . F.T. IR (KBr. ν , cm^{-1}) 3055(Ar-H), 1685 (C=O), 1577 (C=N), 1045 (C-O-C), 760 (C-Cl), ^{1}H NMR spectra (400 MKz, DMSO-d6, δ , ppm) 3.82-3.75 (t, 4H, CH_2), 3.98-3.88 (t, 4H, CH_2), 8.63-8.62 (d, 1H, C-7), 7.02-7.04 (d, 1H, C-6), 7.95-7.93 (d, 1H, C-5), 6.57-6.65 (s, 1H, C-4), 10.19 (s, 1H, CHO).

Synthesis of E-3-(2-morpholino-1,8-naphthyridine-3-yl)-1-(4-aminophenyl)prop-2-en-1-one(3)[26]

A mixture of 2-morpholino-3-formyl-1,8-naphthyridine (0.01 mol) and p-aminoacetophenone (0.01mol) and NSRISC (0.04 g) were stirred by a rod at 100ºC. TLC revealed the end point reaction, the mixture was cooled, EtOAc (30 mL) was added, and stirred followed by refluxing for 5 minutes, the precipitate was produced, washed with cold water, dried, and recrystallized from ethanol; yield 70%, yellow solid m.p. 135-137 °C ; F.T. IR (KBr. ν, cm^{-1}) 3342 (N-H), 1655 (C=O), 19595 (C=C), 1565 (C=N), 1055 (C-O-C), ^{1}H NMR spectra (400 MKz, DMSO-d6, δ , ppm) 3.92 (s, 2H, NH_2), 3.78-3.75 (t, 4H, CH_2), 3.88-3.86 (t, 4H, CH_2), 7.18-7.21 (d, 1H, CHα), 7.96-7.94 (d, 1H, CHβ), 8.65-8.64 (d, 1H, C-7), 7.68-7.67 (d, 1H, C-6), 6.69-6.67 (d, 1H, C-5), 7.16 (s, 1H, C-4), 7.13-9.91 (m, 4H, Ar-H).

Synthesis of 1,3-diphenyl prop-2-en-1-one[27]

Acetophenone (10 m.mol) was mixed with benzaldehydes (10 m.mol) and desolved in 50 ml of ethanol. The mixture was then stirred at room temperature for half an hour. after that drop wise addition of (4 ml) of (40%) aqueous sodium hydroxide (NaOH), stirred continuously for two hours and then kept at 0 °C for 24 hours. The precipitate was washed with cold water. The recrystallization was done by ethanol (scheme-5-).

Synthesis of 2-amino-4,6-diphenyl-1,3,4-dihdropyrimidine [28,29]

Around bottom flask with two necked (250 ml) equipped with a dropping funnel which charged with a solution of sodium hydroxide (0.4 gm in 5 ml of water). A mixture of 1,3-diphenyl prop-2-en-1-one (0.0048 mol) and quinidine hydrochloride (0.0048 mol) in 20 ml of ethanol was refluxed while the solution of sodium hydroxide was added drop by drop with stirring during 2 hrs. Then mixture was reflux for 10 hrs. let the mixture at (25 °C) then dilute with water and left overnight, precipitate

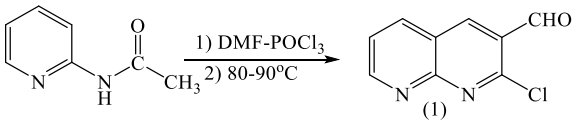

Fig. 2. Synthesis of 2-Chloro-3-formyl-1.8-naphthyridine

was formed washed with 20 ml of mixture of water / ethanol (1:1 v/v) then recrystallized frombenzene.

Synthesis of 2-chloro-N-(4,6-diphenylpyrimidin-2-yl)acetamide(4)

A chloroacetylchlorid (0.03 mol, 3.38 gm , 2.4 ml) and three drops of acetic acid was stirred at (60 °C) for 20 min. 2-amino-4,6-diphenyl-3,4-dihydropyrimidine (0.03 mol) in 5 ml ethanol was added drop wise and the mixture was refluxed for 5 hrs. Then the white solid crystals were filtered and washed with (10 ml) benzene, dried and recrystallized from ethanol to give compound(4).

Synthesis of (E)-N-(4,6-diphenylpyrimidine-2-yl)-2-((4-(3-(2-morpholino-1,8-naphthyridin-3-yl)allyl) amino)acetamide (5)[30]

A mixture of compound (3) (10 m.mol) andcompound (4) (10 m.mol) in (15 ml) dimethyl formamide. small quantity of sodium bicarbonate was added heated at 90 °C for 10 hrs and then the reaction mixture was immediatcly poured in ice cold water and stirred continuously for half an hrs , the reaction mixture was filtered on buchner funnel , the crystals obtained were washed with ethanol and dried. The recrystallization was done by acrylonitrile ; yield 60% as brown solid, m.p. 196-199 °C; F.T. IR (KBr. ν, cm^{-1}): 3325 (N-H), 1665,1680 (C=O), 1565 (C=C), 1623 (C=N), 1123 (C-O-C), ^{1}H NMR spectra (400 MKz, DMSO-d6, δ , ppm) 3.42-3.44 (t, 4H, CH_2), 3.82-3.85 (t, 4H, CH_2), 3.89 (s, 2H, CH_2), 6.34 (s, 1H, NH), 9.90 (s, 1H, NH), 7.12-7.15 (m, 14H, Ar-H), 7.06-7.08 (d, 1H, CHα), 7.98-7.99 (d, 1H, CHβ), 6.96 (s, 1H, CH), 8.32-8.35(d, 1H, H-7), 6.64-6.66 (t, 1H, H-6), 6.64-6.66 (d, 1H, H-5), 6.94 (s, 1H, H-4).

Preparation of N-chloroacetylaniline [31]

A Chloroacetylchloride (0.03 mol) and 2-3 drops of acetic acid at (60 °C) for 15 min. a solution of aniline (0.02 mol) was added drop wise and reflux for 3 hrs. Then white precipitate was formed washed with benzene and recrystallized from ethanol.

Preparation of (E)-2-((4-(3-(2-morpholine-1,8-naphthyridine-3-yl)acryloyl)phenyl)amino)-N-

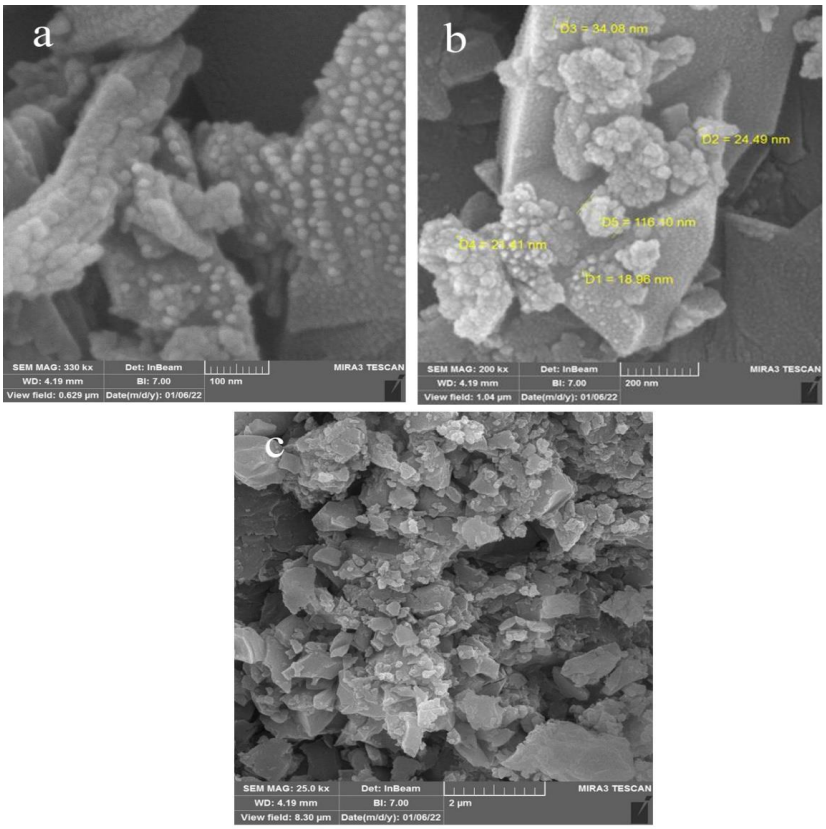

Fig. 3. SEM images pf applied SiO_2 nanoparticles

phenylacetamide(6)

A mixture of compound (3) (10 m.mol) and N-chloroacetylaniline (10 m.mol) in (25ml DMF) in the presence of small quantity of sodium bicarbonate was heated at 90-100 °C for 10 hrs. then the result was immediately poured in ice cold water and stirred continuously for half an hour. then brown parcipate was formed, washed with water and recrystallized from ethanol to give compound(6). Yield 55% as brown , m.p. 226-228 °C; stirred for F.T. IR (KBr. ν, cm^{-1}): 3355 (N-H), 1645,1680 (C=O), 1595 (C=C), 1125 (C-O-C), ^{1}H NMR spectra (400 MKz, DMSO-d6, δ , ppm) 3.46-3.42 (t, 4H, CH_2), 3.91-3.88 (t, 4H, CH_2), 3.98 (s, 2H, CH_2), 5.99 (s, 1H, NH), 8.73-6.63 (m, 5H, Ar-H), 6.94-6.99 (t, 1H, H-6), 7.14-7.12 (d, 1H, H-5), 7.73-7.75 (d, 1H, CHα), 8.57-8.45(d, 1H, CHβ), 7.91-7.92 (s, 1H, H-4), 7.58-7.63 (m, 14H, Ar-H), 8.84-8.85 (d, 1H, H-7) , 10.08 (s, 1H, N-H).

Antibacterial activity of synthesized compounds

The newly synthesized compounds (5,6) were screened for their antibacterial activity against [32,33] two-gram positive organism Staphylococcus aurous and Staphylococcus epidermises and two-gram negative such as Escherichia coli and Proteus vagaries at three concentration 500, 250 and 100 mg using disc diffusion methods [34-36]. Ampicillin was used as standard for comparison by measuring the diameter of inhibition zone at the end of 24 hrs. at 37 °C. the newly synthesized compounds were screened for them for antibacterial activity against two gram positive and two gram negative with these three concentrations.

RESULTS AND DISCUSSION

Fig. 3 shows the SEM image of applied SiO_2 nanoparticles. As well as seen, the homogenous spherical SiO_2 nanoparticles with average particle size of 28 nm was provided.

In this work, 2-chloro-1,8-naphthyridine-3-carboaldehyde (1) was prepared from reaction of N-(pyridine-2-yl) acetamide and Vilsmeier reagent, the Vilsmeier cyclization was done by adding $POCl_3$ to the substrate in dimethyl formamide at 0-5 °C then heating to 90 °C for 1 hrs. (Fig. 4)

The IR in this compound (1) showed C=O stretch peak at 1685 cm^{-1}, C=N stretch in ring shows peak at 1565 cm^{-1} and C-Cl group at 775 cm^{-1}. The ^{1}H NMR spectra for this compound in DMSO showed a significant peak at 10.45 ppm for aldehydic

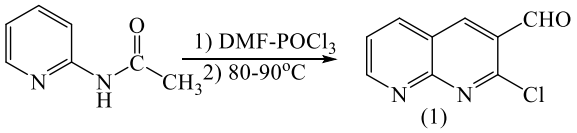

Fig. 4. Synthesis of 2-Chloro-3-formyl-1.8-naphthyridine

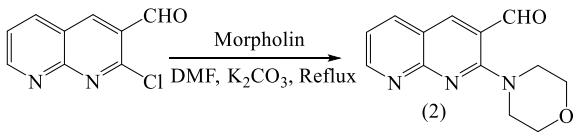

Fig. 5. Synthesis of morpholino-3-formyl-1,8-naphthyridine

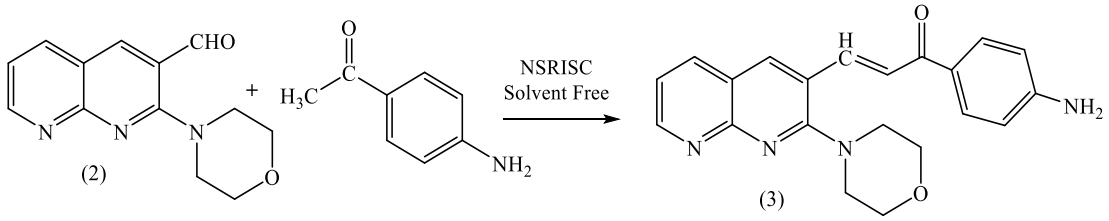

Fig. 6. Synthesis of E-3-(2-morpholino-1,8-naphthyridine-3-yl)-1-(4-aminophenyl)prop-2-en-1-one

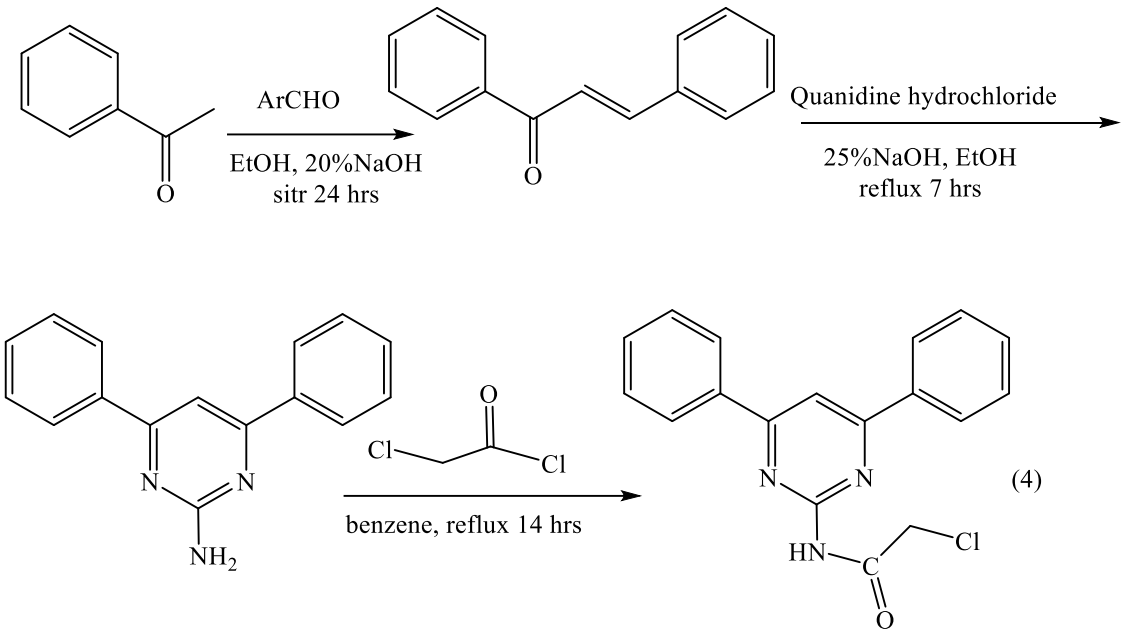

Fig. 7. Synthesis of 2-chloro-n-(4,6-diphenylpyrimidine-2-yl)acetamide

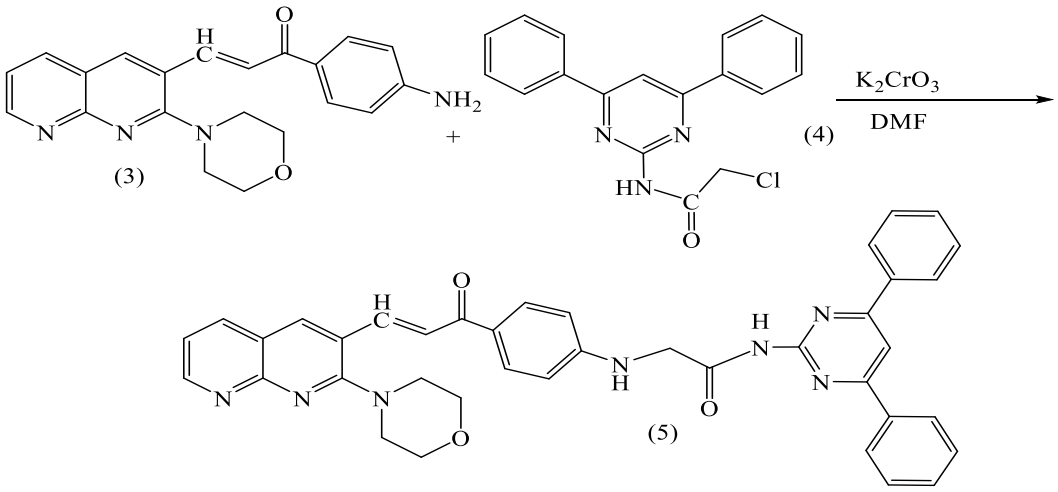

Fig. 8. Synthesis of (E)-N-(4,6-diphenylpyrimidin-2-yl)-2-((4-(3-(2-morpholino-1,8-naphthyridin-3-yl)acryloyl)phenyl)amino) acetamide

proton. The chlorine group of 1,8-naphthyridine (1) is difficult to displace by N-nucleophiles (such as amine under various condition). However, the reaction morpholine with compound (1) at 90-100 °C result compound (2) (Fig. 5).

The IR in this compound (2) showed C=O stretch peak at 1685 cm^{-1} and C-O-C group appeared at 1045 cm^{-1}. The ^1H NMR spectra of compound (2) showed two triplets at 3.42-3.46 ppm and at 3.96-4.00 ppm for morpholine proton. Compound (3) has been prepared via condensation in nano catalyst / solvent free of compound (2) with 4-aminoacetophenone (Fig. 6).

The IR in this compound (3) showed C=O stretch peak at 1655 cm^{-1}, NH_2 group showed at 3342 cm^{-1} , C=N stretch in ring shows peak at 1565 cm^{-1},

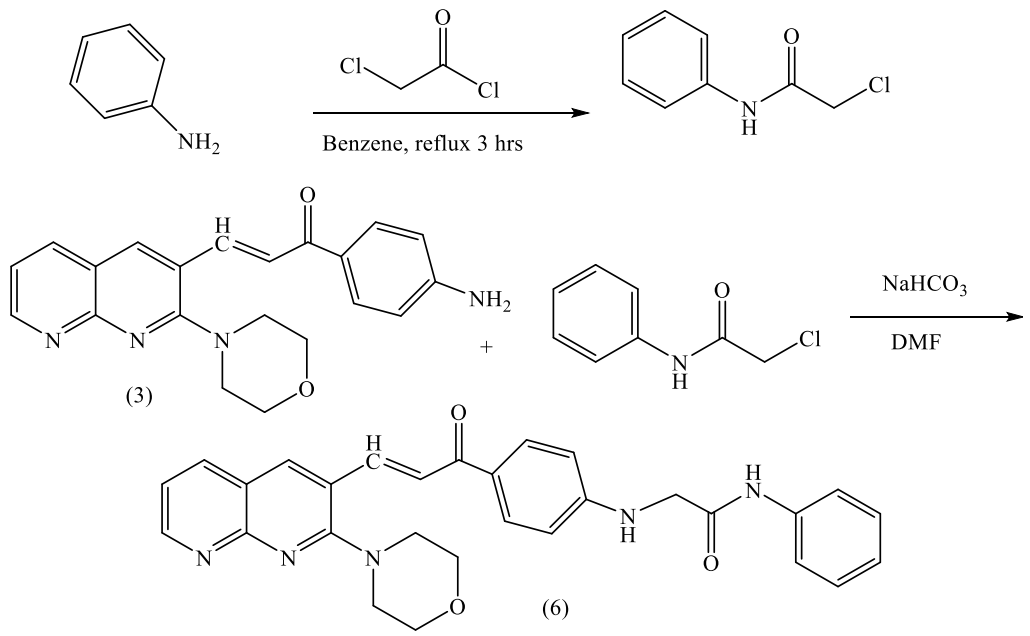

Fig. 9. Synthesis of (E)-2-((4-(3-(2-morpholino-1,8-naphthyridin-3-yl)acryloyl)phenyl)amino)-N-phenylacetamid

C=C stretch appeared at 1595 cm^{-1}. The ^1H NMR spectra of compounds (3) showed a significant peak as the following singlet at 4.16 ppm for NH_2 group and two doublets at 7.18 ppm and 7.75 ppm for Hα and Hβ for unsaturated carbonyl group and two triplet at 3.45 and 3.99 ppm for morpholine proton. The treatment of compound (4) which was synthesized according to literature [37-39] with compound (3) in the presence of small quantity potassium carbonate in dimethyl formamide gave compound (5) (Fig. 7 and Fig. 8).

The IR in this compound(5) gave a peak at 3325 cm^{-1} for NH and at 1565 cm^{-1} for C=C and two absorption for C=O group at 1665 cm^{-1} and 1680 cm^{-1} and at 1623 cm^{-1} for C=N. the ^1H NMR spectra of this compound gave two singlet at 6.03 ppm and at 9.62 ppm for NH group and two doublet at 7.42-7.44 ppm and at 8.11-8.15 ppm for Hα and Hβ for unsaturated carbonyl group . Compound (3) on treatment with N-chloroacetylaniline in the presence of sodium bicarbonate in DMF give compound (6) (Fig. 9)

The IR in this compound(6) showed a peak at 3355 cm^{-1} for NH and two absorption for C=O group at 1680 cm^{-1} and 1645 cm^{-1} and at 1123 cm^{-1} for C-O-C. the ^1H NMR spectra of compound (6) showed two singlet signal at 5.95 ppm and 9.64 ppm for NH group and two triplet at 3.60-3.63 and 3.83-3.86 ppm for CH_2 for morpholine ring and singlet at 4.08 ppm for CH_2 and two doublet at 7.44-7.46 and at 8.06-8.08 ppm for Hα and Hβ.

Antibacterial Activity

Antibiotic resistance in bacteria isolated from diverse environments is the most important public health problem [40], So, new antibacterial drugs have become necessary due to the rapid spread of antibiotic resistance [41]. in this study the two compounds (5,6) were found show excellent activity against gram positive bacteria and good activity against gram negative bacteria as shown in the table 1. A study found that 1,5-naphthyridinone derivatives kill germs by inhibiting bacterial topoisomerase [42]. E. coli and Staphylococcus

Table 1. Antibacterial activity data for compounds (5,6)

Compounds No.	Compounds zone of inhibition in mm			
	Staphylococcus aurous	*Staphylococcus epidermises*	*E.coli*	*Proteus vagaries*
Ampicillin	18	18	15	15
Compound 5	16	17	10	9
Compound 6	14	18	16	14

aureus strains have been shown to be resistant to naphthyridinone-based antibacterials, according to another study [43]. Additionally, Gençer et al. [44] used in silico research to show that 1,8-naphthyridine derivatives block DNA gyrase (topoisomerase), such as fluoroquinolones, and they acquired a strong antibacterial impact against Gram-positive and Gram-negative microorganisms through in vitro investigations.

CONCLUSION

Naphthyridine compounds are considered heterocyclic organics of great importance. In this work, we were able to prepare new substituted compounds (5,6) that showed high activity to some types of bacteria, compared with the known antibiotics (ampicillin) Therefore, we infer that 1,8-naphthyridine derivatives enhance the effectiveness of fluoroquinolone antibiotics against multi-resistant bacterial strains, and thus intriguing candidates for the development of medications against bacterial illnesses caused by multidrug-resistant strains. And the molecular structure of the prepared compounds was diagnosed through NMR spectroscopy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

1. Chng LL, Erathodiyil N, Ying JY. Nanostructured Catalysts for Organic Transformations. Acc Chem Res. 2013;46(8):1825-1837.
2. Khodabakhshi MR, Kiamehr M, Karimian R. Efficient One-Pot Synthesis of 1,4-Dihydropyridine and Polyhydroquinoline Derivatives Using Sulfanilic Acid-Functionalized Boehmite Nano-Particles as an Organic-Inorganic Hybrid Catalyst. Polycyclic Aromatic Compounds. 2021:1-15.
3. Sadeghi B, Mousavi SA. Preparation and Characterization of Nano-coc-OSO_3H as a Novel Nanocatalyst for the One-Pot Synthesis of Spirooxindoles. Polycyclic Aromatic Compounds. 2020;42(2):424-436.
4. Patel G, Patel AR, Maity G, Das S, Patel SP, Banerjee S. Fabrication of self-assembled Co_3O_4 nano-flake for one-pot synthesis of tetrahydrobenzo[b]pyran and 1,3-benzothazole derivatives. Current Research in Green and Sustainable Chemistry. 2022;5:100258.
5. Banoon SR, Ghasemian A. The Characters of Graphene Oxide Nanoparticles and Doxorubicin Against HCT-116 Colorectal Cancer Cells In Vitro. J Gastrointest Cancer. 2021;53(2):410-414.
6. Dominguez JN, Charris JE, Lobo G, de Dominguez NG, Moreno MM, Riggione F, et al. ChemInform Abstract: Synthesis of Quinolinyl Chalcones and Evaluation of Their Antimalarial Activity. ChemInform. 2010;33(1):no-no.
7. Dominguez J, Basante W, Charris J, Riggione F. ChemInform Abstract: Synthesis and Activity of Some Quinolone Derivatives Against Plasmodium falciparum in vitro. ChemInform. 2010;27(45):no-no.
8. Matsumoto J, Miyamoto T, Minamida A, Nishimura Y, Egawa H, Nishimura H. 1,4-Dihydro-4-oxopyridinecarboxylic acids as antibacterial agents. 2. Synthesis and structure-activity relationships of 1,6,7-trisubstituted 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids, including enoxacin, a new antibacterial agent. J Med Chem. 1984;27(3):292-301.
9. Chen K, Kuo S-C, Hsieh M-C, Mauger A, Lin CM, Hamel E, et al. Antitumor Agents. 178. Synthesis and Biological Evaluation of Substituted 2-Aryl-1,8-naphthyridin-4(1H)-ones as Antitumor Agents That Inhibit Tubulin Polymerization. J Med Chem. 1997;40(19):3049-3056.
10. Kuroda T, Suzuki F, Tamura T, Ohmori K, Hosoe H. A novel synthesis and potent antiinflammatory activity of 4-hydroxy-2(1H)-oxo-1-phenyl-1,8-naphthyridine-3-carboxamides. J Med Chem. 1992;35(6):1130-1136.
11. Ferrarini PL, Mori C, Badawneh M, Calderone V, Calzolari L, Loffredo T, et al. Synthesis of 1,8-naphthyridine derivatives: Potential antihypertensive agents — Part VII. Eur J Med Chem. 1998;33(5):383-397.
12. Nadaraj V, Thamarai Selvi S, Mohan S. Microwave-induced synthesis and anti-microbial activities of 7,10,11,12-tetrahydrobenzo[c]acridin-8(9H)-one derivatives. European Journal of Medicinal Chemistry. 2009;44(3):976-980.
13. Naik TRR, Naik HSB, Raghavendra M, Naik SGK. Synthesis of thieno[2,3-b]benzo[1,8]naphthyridine-2-carboxylic acids under microwave irradiation and interaction with DNA studies. Arkivoc. 2006;2006(15):84-94.
14. San Y, Sun J, Wang H, Jin Z-H, Gao H-J. Synthesis of 1,8-Naphthyridines by the Ionic Liquid-Catalyzed Friedlander Reaction and Application in Corrosion Inhibition. ACS Omega. 2021;6(42):28063-28071.
15. Sampathkumar N, Ramalingam ST, Rajendran SP. A Facile Synthesis of 1-Hydroxy-5-chloro-benzo[f][2,7] naphthyridines. ChemInform. 2006;37(15).
16. Bouraiou A, Debache A, Rhouati S, Belfaitah A, Benali-Cherif N, Carboni B. Synthesis of Some New 3-Pyrrolidinylquinoline Derivatives via 1,3-Dipolar Cycloaddition of Stabilized Azomethine Ylides to Quinolinyl α , β - Unsaturated Ketones. The Open Organic Chemistry Journal. 2010;4(1):1-7.
17. Harichandran G, Amalraj SD, Shanmugam P. Boric acid catalyzed efficient synthesis of symmetrical N,N'-alkylidene bisamides. Journal of the Iranian Chemical Society. 2011;8(1):298-305.
18. C Reygaert W. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiology. 2018;4(3):482-501.
19. Vilsmeier A, Haack A. Über die Einwirkung von Halogenphosphor auf Alkyl-formanilide. Eine neue Methode zur Darstellung sekundärer und tertiärer p-Alkylamino-benzaldehyde. Berichte der deutschen chemischen Gesellschaft (A and B Series). 1927;60(1):119-

122.
20. Saleh MY, Ayoub AI. Synthesis of new derivatives of 2-chloro-3-formyl-1,8-naphthyridine. European Journal of Chemistry. 2014;5(3):475-480.
21. Kharb R, Kaur H. THERAPEUTIC SIGNIFICANCE OF QUINOLINE DERIVATIVES AS ANTIMICROBIAL AGENTS. International Research Journal of Pharmacy. 2013;4(3):63-69.
22. Al-Thakafy N, Al-Enizzi M, Saleh M. Synthesis of new Organic reagent by Vilsmeier – Haack reaction and estimation of pharmaceutical compounds (Mesalazine) containing aromatic amine groups. Egyptian Journal of Chemistry. 2021;0(0):0-0.
23. Saleh M, Ayoub A, Hammady A. Synthesis biological studies of some new heterocyclic compound derived from 2-chloro-3-formyl quinoline and 4-(benzyl sulfonyl) acetophenone. Egyptian Journal of Chemistry. 2020;0(0):0-0.
24. Goudarziafshar H, Moosavi-Zare AR, Hosseinabadi F, Jalilian Z. Nano-[Mn-PSMP]Cl2 as a new Schiff base complex and catalyst for the synthesis of N,N'-alkylidene bisamides. Research on Chemical Intermediates. 2022;48(4):1423-1437.
25. Ayoob A, Yahya O, Saleh M, Chemistry C. Synthesis and biological activity of 2-chloro-3-formyl-1,8-naphthyridine chalcone derivative. Egyptian Journal of Chemistry. 2022;DOI: 10.21608/ejchem.2022.134661.5925.
26. Chikhalia KH, Patel MJ, Vashi DB. Design, synthesis and evaluation of novel quinolinyl chalcones as antibacterial agents. Arkivoc. 2008;2008(13):189-197.
27. Hamdoon A, Al-Iraqi M, Saleh M. Synthesis of Some Multi-cyclic Sulfhydryl Donor Compounds Containing 1,2-dithiol-3-thione moiety. Egyptian Journal of Chemistry. 2021;0(0):0-0.
28. Saeed Z, Saleh M, sadeek g. Synthesis and Biological Evolution of Novel Substituted 1,2,4-triazine from Sulfanilic Acid. Egyptian Journal of Chemistry. 2022;0(0):0-0.
29. Abbas A, Mohammed Taib A, Saeed N. Synthesis and Characterization of Linear Thermally Stable polyester contain Schiff Bases. Egyptian Journal of Chemistry. 2020;0(0):0-0.
30. Krein EB, Aizenshtat Z. Phase-transfer-catalyzed reactions between polysulfide anions and .alpha.,.beta.-unsaturated carbonyl compounds. The Journal of Organic Chemistry. 1993;58(22):6103-6108.
31. T Sadeek G, S Al-Ajely M, H Saleem N. Synthesis of Some Oxazine Compounds Derived from TDI and Schiff Bases. Acta Scientific Medical Sciences. 2020;4(9):120-128.
32. Saleh M. Synthesis and Antibacterial Evaluation of 2-(chloro / ethyl thio / seleno)-1,8-naphthyridine-3-azetidine Derivatives. Diyala Journal For Pure Science. 2017;13(3):104-115.
33. sdeek g, Mauf R, Saleh M. Synthesis and Identification of some new Derivatives Oxazole, Thiazole and Imidazol from Acetyl Cysteine. Egyptian Journal of Chemistry. 2021;0(0):0-0.
34. Saleh A, Saleh M, Chemistry C. Synthesis of heterocyclic compounds by cyclization of Schiff bases prepared from capric acid hydrazide and study of biological activity. Egyptian Journal of Chemistry. 2022;0(0):0-0.
35. Aldujaili NH, Banoon SR. ANTIBACTERIAL CHARACTERIZATION OF TITANIUM NANOPARTICLES NANOSYNTHESIZED BY STREPTOCOCCUS THERMOPHILUS. Periódico Tchê Química. 2020;17(34):311-320.
36. Sharma N, Kumar J, Thakur S, Sharma S, Shrivastava V. Antibacterial study of silver doped zinc oxide nanoparticles against Staphylococcus aureus and Bacillus subtilis. Drug Invention Today. 2013;5(1):50-54.
37. Hassan BA, Lawi ZKK, Banoon SR. DETECTING THE ACTIVITY OF SILVER NANOPARTICLES, PSEUDOMONAS FLUORESCENS AND BACILLUS CIRCULANS ON INHIBITION OF ASPERGILLUS NIGER GROWTH ISOLATED FROM MOLDY ORANGE FRUITS. Periódico Tchê Química. 2020;17(35):678-690.
38. Banoon S, Ali Z, Salih T. Antibiotic resistance profile of local thermophilic Bacillus licheniformis isolated from Maysan province soil. Comunicata Scientiae. 2020;11:e3921.
39. Araújo-Neto JBd, Silva MMCd, Oliveira-Tintino CDdM, Begnini IM, Rebelo RA, Silva LEd, et al. Enhancement of Antibiotic Activity by 1,8-Naphthyridine Derivatives against Multi-Resistant Bacterial Strains. Molecules. 2021;26(23):7400.
40. Singh SB, Kaelin DE, Wu J, Miesel L, Tan CM, Black T, et al. Tricyclic 1,5-naphthyridinone oxabicyclooctane-linked novel bacterial topoisomerase inhibitors as broad-spectrum antibacterial agents-SAR of left-hand-side moiety (Part-2). Bioorganic & Medicinal Chemistry Letters. 2015;25(9):1831-1835.
41. Sampson PB, Picard C, Handerson S, McGrath TE, Domagala M, Leeson A, et al. Spiro-naphthyridinone piperidines as inhibitors of S. aureus and E. coli enoyl-ACP reductase (FabI). Bioorganic & Medicinal Chemistry Letters. 2009;19(18):5355-5358.
42. Gençer HK, Levent S, Acar Çevik U, Özkay Y, Ilgın S. New 1,4-dihydro[1,8]naphthyridine derivatives as DNA gyrase inhibitors. Bioorganic & Medicinal Chemistry Letters. 2017;27(5):1162-1168.
43. Madaan A, Verma R, Kumar V, Singh AT, Jain SK, Jaggi M. 1,8-Naphthyridine Derivatives: A Review of Multiple Biological Activities. Arch Pharm. . 2015;348(12):837-860.
44. Belete TM. Novel targets to develop new antibacterial agents and novel alternatives to antibacterial agents. Human Microbiome Journal. 2019;11:100052.