Synthesis and biological studies for some heterocyclic compounds derived from 2-Morpholino-1,8-naphthyridine-4-carboxylic acid

*Ala I. Ayoob**

Received 14, June, 2012
Accepted 4, December , 2012

Abstract:

New heterocyclic compounds derived from 2-Morpholino-1,8-naphthyridine-4-carboxylic acid such as oxadiazolo, thiadiazolo – thione and triazolo-thione have been prepared and characterized on the basis of IR and ^{1}H NMR spectra data. The hydrizide compound was utilized as a starting material for preparing of these compounds. The second part of this study involves the biological studies of some of these naphthyridine derivatives by using three different kinds of bacteria namely: *Staphylococcus aureus, Pseudomonas aeruglnosa and Escherichia coli*. The data indicated that some of these compounds have a good activity against the tested bacteria in comparison to antibiotics.

Key words: Synthesis , biological , heterocyclic compounds ,2-Morpholino-1,8-naphthyridine-4-carboxylic acid

Introduction:

1,8-Naphthyridine derivatives have attracted considerable attention because 1,8-naphthyridine skeleton is present in many compounds that have been isolated from natural substances with various biological activities, substituted 1,8-naphthyridine compounds themselves used as anti hypertensive, antiarrhythmics, herbicide safeners, and also immunostimulants [1-3]. It is known that E and Z-O-(diethylamino)ethyl oximes of 1,8-naphthyridine series (A) are potential drugs for logical anesthia [4] and 2,7-difunctionalized–1,8-naphthyridine and novel triethyleneglycol ether–Linked dinaphthyridine are aforesaid potential medicinal activity as well as for their use as important binding units in the molecular design of synthetic receptors [5–8] also 1-(2-Flurobenzyl)-3-(2-tolyl)-1,8-aphthyridine–2(1H)-one is used in treatment of a memory disorders in particular Al Zheimer's disease [9]. 2-Amino-N-hydroxy-1,8-naphthyridine-3-carboxamidine possesses herbicidal properties and used for selective control of weeds in barley. Wheat. Maize. sorghum and rice corops[10]. 1,8-Naphthyridine derivatives [11] also react with adenosine receptors of subtypes A_1 and A_{2A}. Indeed some 3-phenyl [1,8-naphthyridine] were used in designing new drugs for oral administration indeed 3-phenyl [1,8-naphthyridine] which carry piperidyl, piperazinyl or morpholinyl group or an N-diethylnolamine side chain in 2-, 7- and 2,7 position have been reported to show significant activity as inhibitors of human platelets aggregation induced by arachidonate and collagen [12]. In addition, 4-(N-methylenecycloalkyl amino-1,8-naphthyridine derivative substituted in position 2 and 7 were found effective as antihypertensive agent [13]. Chemically the acid derivatives are useful starting materials for the preparation of many other

*Dept. of Chemistry – College of Sciences University of Mosul

heterocyclic compounds such as Thiadiazole, Triazole and Oxadiazole derivatives.

The present work attempts to prepare such compounds from 1,8-naphthyridine-4-carboxylic acid having alicyclic amino residue at 2-position on the naphthyridine ring for the purpose of studying the effect of such residue on the biological properties of these compounds which is our goal in the next work.

Materials and Methods:

Melting points were recorded on electrothermal CIA9300 melting point apparatus and are uncorrected; IR spectra were measured in KBr disk with a Buck 500 Scientific IR spectrophotometer. ^{1}H NMR spectrum was recorded by Bruker AM300 instrument using tetramethylsilane (TMS) as internal standard.

2-Morpholino-1,8-naphthyridine-4-carboxylic acid (1).

A mixture of Morpholine-4-formyl (0.025mol) and ethanol (10 mL) as a solvent was heated at 30°C and amount of 2-aminopyridine (0.025mol) in 5 mL of ethanol was added. The mixture was stirred and heated for (1 *hr*.) at 30°C then pyruvic acid (0.025mol) was added drop by drop with stirring and keeping the temperature below 35°C for (1 *hr*.), the mixture was refluxed for (24 *hr*.). The mixture was left to stand at room temperature for (24 *hr*.). Distilled water (300 mL) was added with stirring to the solution. Brown precipitate was formed and was crystallized from ethanol. The melting point was 136°C dec. with 55% yield. The IR and ^{1}H NMR spectra are listed in Tables 1 and 2.

2-Morpholino-1,8-naphthyridine-4-methyl ester (2).

To a stirred solution of compound (1) (0.259 g, 1.0 mmol) in 20 mL methanol was slowly added 2 mL of Sulfuric acid at 0°C and the reaction mixture was stirred overnight at 80°C, the contents of the flask were allowed to cool to room temperature, poured onto crushed ice and neutralized with 20% Sodium carbonate solution. The mixture was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, filtered off and evaporated under reduced pressure to give compound (4). The melting point was (143-145°C) with 45% yield. The IR and ^{1}H NMR spectra of compound (2) are listed in Tables 1 and 2.

2-Morpholino-1,8-naphthyridine-4-hydrazide (3).

To a solution of (2) (0.273, 1.0 mmol) in ethanol, Hydrazine hydrate (6.5 mL) was added and the reaction mixture was stirred overnight temperature below 100°C. The precipitate which separated on cooling and collected by filtration then crystallized from chloroform-methanol to afford compound (3). The melting point was (162-164°C) with (60%) yield. The IR and ^{1}H NMR spectra of compound (3) are listed in Tables 1 and 2.

2-Morpholino-1,8-naphthyridine-4-thiosemicarbazide (4).

To ethanolic solution of compound (3) (0.273 g, 1.0 mmol), ammonium thiocyanate (0.03 mol), and concentrated hydrochloric acid (4 mL) was added and stirred for (8 *hr*.) at temperature below 100°C. The solvent was evaporated under reduced pressure. The residue was added to water (50 mL) and extracted with chloroform. The solvent was evaporated to dryness to get the desired compound (4). The melting point was (201-203°C) with 65% yield. The IR and ^{1}H NMR spectra of compound (4) are listed in Tables 1 and 2.

2-Morpholino-4-[5¯(1¯,2¯,4¯ -triazolo-3-thione]- 1,8-naphthyridine (5)

To Ethanolic solution of compound (4) (0.332 g, 1.0 mmol), sodium hydroxide (0.056 g, 1.0 mmol) in 5 mL water was added and stirred for 5 *hr*. at 90°C. The solution was filtered; the solution was then neutralized with diluted hydrochloric acid. The crystalline material was filtered off and crystallized from ethanol. The melting point was (215°C) with 55% yield. The IR and ^{1}H NMR spectra of compound (5) are listed in Tables 1 and 2.

2-Morpholino-4-[5¯(1¯,3¯,4¯-oxadiazolo-2-thione]-1,8-naphthyridine(6)

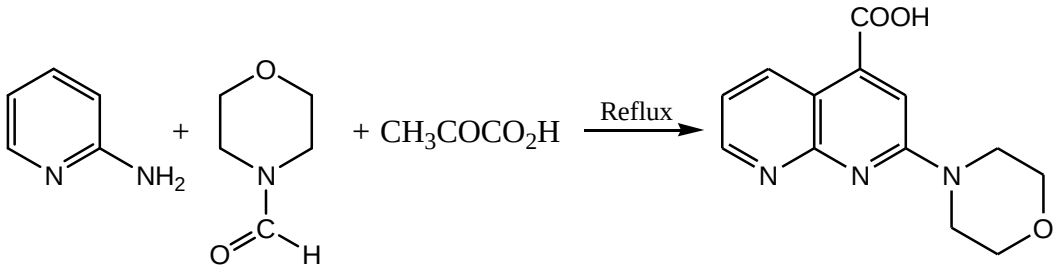
To Ethanolic solution of compound (3) (0.273 g, 1.0 mmol), Potassium hydroxide (0.056 g, 1.0 mmol) and carbon disulfide (2 mmol) was added. The mixture was heated under reflux until the hydrogen sulfide evolution ceased under reduced pressure. The solvent was then removed; water added and the solution was filtered off. The filtrate was acidified with diluted hydrochloric acid. The precipitate formed was collected, washed with water and crystallized from chloroform. The melting point was (211°C) with 50% yield. The IR and ^{1}H NMR spectra of compound (6) are listed in Tables 1 and 2.

2-Morpholino-4-[5¯(2-amino-1¯,3¯,4¯-thiadiazolo]-1,8-naphthyridine(7)

To a stirred solution of compound (4) (0.332 g, 1.0 mmol) in (50 mL) ethanol, concentrated sulfuric acid (6 mL) was added and refluxed for 6*hr*. at 90°C. The solution was poured onto ice water, ammonia was added until basic, a precipitate was obtained which was filtered and crystallizes from chloroform. The melting point was (196-198°C) with 50% yield. The IR and ^{1}H NMR spectra of compound (7) are listed in Tables 1 and 2.

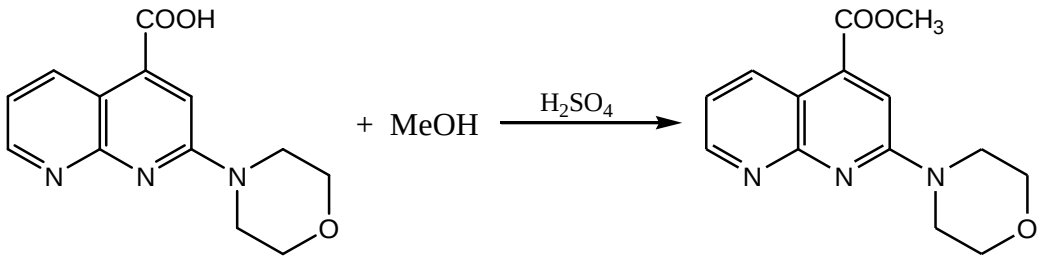
Results and Discussion:

2-Morpholino-1,8-naphthyridine-4-carboxylic acid (1) was synthesized from the condensation of 2-aminopyridine, Morpholin-4-formyl and pyruvic acid following a reported procedure [13] (Equation 1).



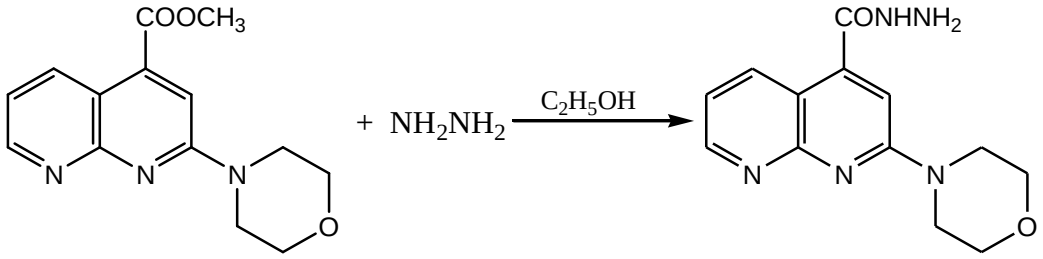
(1)

The ester of this acid was synthesized according to the similar procedure described in the literature [14] (Equation 2).



(2)

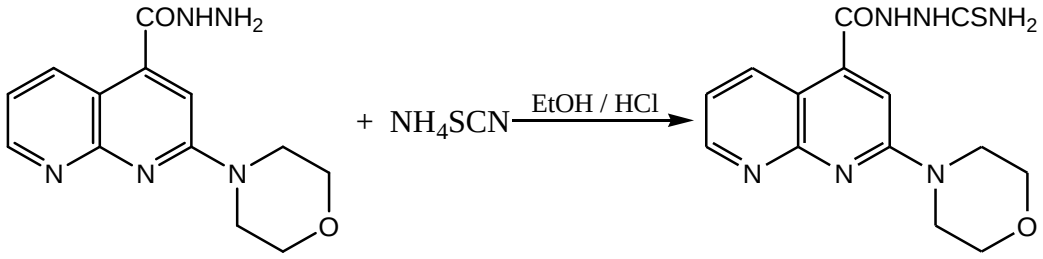
Compound (2) was reacted with Hydrazine hydrate to give the corresponding hydrazide (3) (Equation 3).



(3)

In the next step of the reaction, compound (3) was treated with ammonium thiocyanate to give the thiosemicarbazide derivative (4), (Equation 4).

^{1}H NMR of compound (3) showed low filed broad signal at (10.79 ppm) for the NH proton and a high flied singlet at (3.5 ppm) for the NH_2 proton.



(4)

The ^{1}H NMR of compound (4) showed two characteristic singlet for the CSNH and CONH at (9.50 ppm) and (10.75 ppm) respectively. The IR spectrum supported this result and showed the presence of four bands characteristic for (–N–C=S) mixed band due to (NH) bending, C–N stretching and C=S stretching appeared at (1585-1600 cm^{-1}), (1325-1355 cm^{-1}), (1005-1015 cm^{-1}) and (870-885 cm^{-1}). Compound (4) was then boiled in aqueous sodium hydroxide to give the corresponding 1,2,4-Triazolo-3-thione (5). The ^{1}H NMR of (5) is characterized by the disappearance of the thiosemicarbazide singlet proton. The SH proton also is absent in the spectrum. This result was also confirmed by the presence of absorption band at (1005-1015 cm^{-1}) of the IR spectrum for compound (5) which is attributed to C=S stretching

vibration [15]. 2-Amino-1,3,4-thiadiazolo (7) was prepared from cyclization of the corresponding thiosemicarbazide by concentrated sulfuric acid. ^{1}H NMR of compound (7) shows the existence of two singles signals at (3.40 ppm) for the NH_2, while the two bands of the corresponding thiosemicarbazide proton has disappeared, (Scheme 1).The reaction of compound (3) with carbon disulfide in the presence of alcoholic potassium hydroxide affords the oxadiazolo-2-thione (6). (Scheme 2

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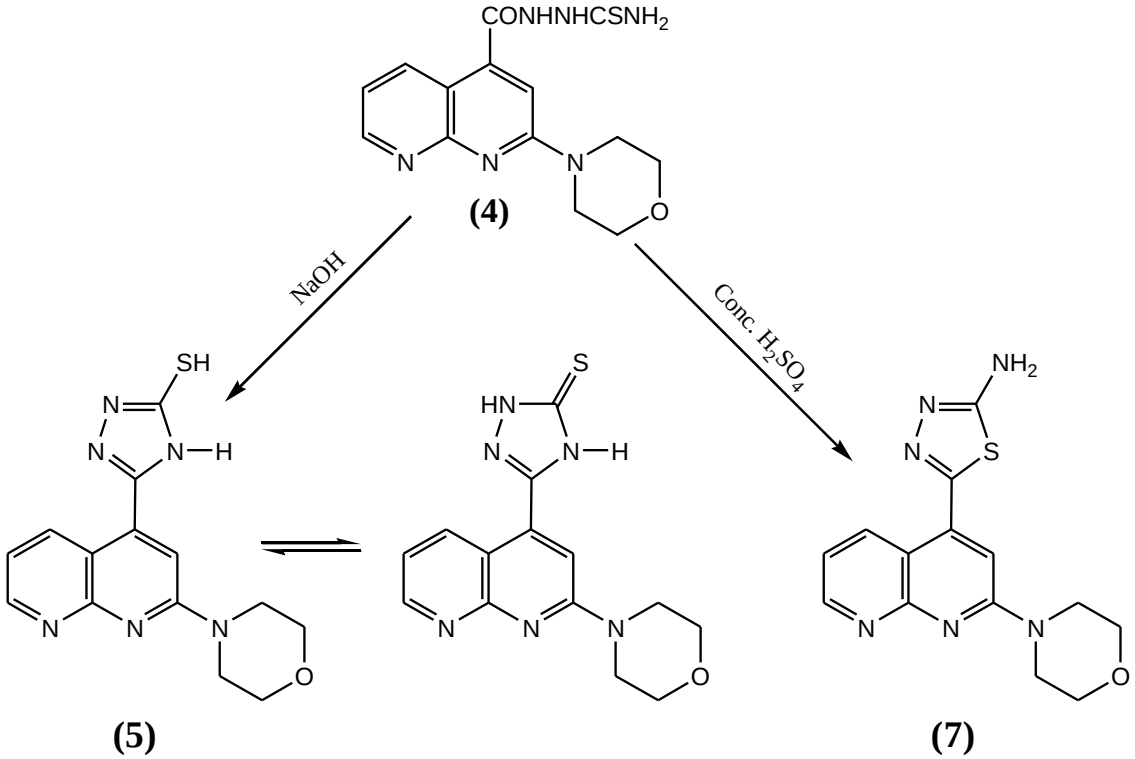
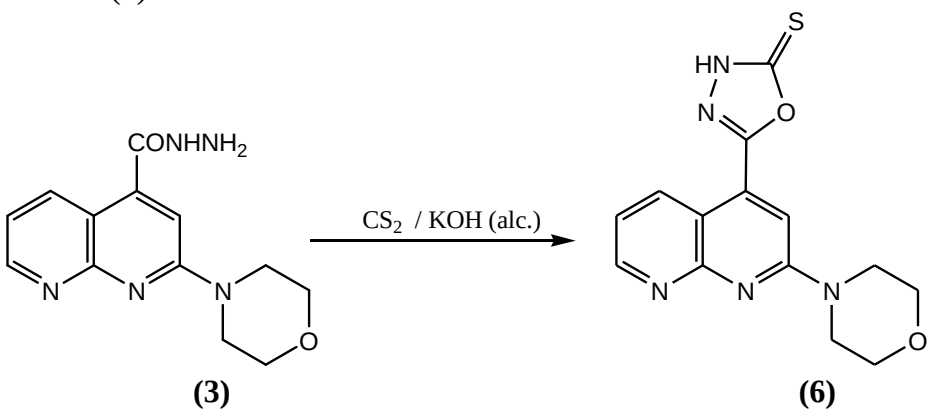


Scheme (1)



Scheme (2)

The second part of this investigation involves the biological studies of these derivatives against three kinds of bacteria namely *Staphylococcus aureus*, *Pseudomonas aeruglnosa and Escherichia coli.*The results indicate that the triazolo and oxadiazolo compounds have a good activity against the tested bacteria in comparison to antibiotics. Thiadiazolo, thiosemicarbazide and hydrazide have a moderated activity, and we found that all compounds have very little local anesthetic activity.

Table(1): ^{1}H NMR data of compounds (1-7)

Compound No.	^{1}H NMR (ppm) – DMSO-d_6
1	2.95 [t.N(CH_2)$_2$], 3.65 [t,O(CH_2)$_2$], 7.20-8.10 [m, Ar-H], 11.0 [s, OH].
2	3.00 [t.N(CH_2)$_2$], 3.68 [t,O(CH_2)$_2$], 4.05 [s, CH_3], 7.20-8.20 [m, Ar-H].
3	3.00 [t.N(CH_2)$_2$], 3.51[s, NH_2], 3.68 [t, O(CH_2)$_2$], 7.22-8.15 [m, Ar-H], 10.79 [s, NH].
4	3.00 [t.N(CH_2)$_2$], 3.70 [t,O(CH_2)$_2$], 5.15 [s, NH_2], 7.10-8.30 [m, Ar-H], 9.50 [s, NHCS], 10.75 [s, CONH].
5	3.10 [t.N(CH_2)$_2$], 3.75 [t,O(CH_2)$_2$], 7.20-8.20 [m, Ar-H].
6	3.10 [t.N(CH_2)$_2$], 3.73 [t,O(CH_2)$_2$], 7.12-8.20 [m, Ar-H].
7	3.05 [t.N(CH_2)$_2$], 3.4 [s, NH_2], 3.75 [s, O(CH_2)$_2$], 7.20-8.10 [m, Ar-H].

Table (2): Physical and IR spectral data of compounds (1-7)

Comp. No.	m.p °C	% Yield	Formula	IR data				
				NH	C=O	C=S	C-O-C	OH
1	136 d	55	$C_{13}H_{13}N_3O_3$	---	1700	---	1160-1270	2700-3300
2	143-145	45	$C_{14}H_{15}N_3O_3$	---	1720	---	1160-1270	---
3	162-164	60	$C_{13}H_{15}N_5O_2$	3250	1650	---	1160-1270	---
4	201-203	65	$C_{14}H_{16}N_6O_2S$	3200	1670	1005-1015	1160-1270	---
5	215 d	55	$C_{14}H_{14}N_6OS$	3350	---	1005-1015	1160-1270	---
6	211 d	50	$C_{14}H_{13}N_5O_2S$	3225	---	1080-1045	1160-1270	---
7	196-198	50	$C_{14}H_{14}N_6OS$	3225	---	---	1160-1270	---

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تشييد ودراسة بايولوجية لبعض المركبات الحلقية غير المتجانسة المشتقة من حامض 2-مورفولينو-4-كاربوكسي-8,1-نفثايردين

علاء إسماعيل أيوب *

* قسم الكيمياء – كلية العلوم جامعة الموصل

الخلاصة:

يتضمن البحث تحضير عدد من مشتقات حوامض النفثايريدين المحتوية على الثايدايزولو و اوكسادايازولو - ثايون وترايازولو - ثايون. شخصت المركبات المحضرة باستخدام الأشعة تحت الحمراء (IR) واستخدام طيف الرنين النووي المغناطيسي (^{1}H NMR)، حيث يعتبر الهايدرازيد المقابل هو المادة البنائية في التحضير. تم دراسة تأثير بعض المركبات المحضرة على ثلاثة أنواع من البكتريا هي *Ps. Aeruginosa. E.Coli Stap. aureus* و وجد أن قسم منها لها فعالية جيدة ضد بعض هذه الأنواع من البكتريا مقارنة بالمضادات الحيوية.