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SYNTHESIS OF SOME NEW 1, 8-NAPHTHYRIDINE DERIVATIVES UNDER ULTRASOUND IRRADIATION AND ITS CYTOTOXIC ACTIVITY AGAINST HEPG2 CELL LINES

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Abstract: A versatile synthon 2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy) acetohydrazide**1** have been used to synthesized Novel pyrazole derivatives **3a,b**, **5** incorporated into 1,8-naphthyridine.Derivatives **3a and 3b** was synthesized by heating a mixture of acid hydrazide, acetyl acetone and benzoyl acetone. Derivative **5** were synthesized by heating reaction mixture in steam bath. An improvement in rates of synthesis and yields was observed when the reactions were carried out under ultrasonic irradiation compared with the classical synthesis. The synthesized compounds were evaluated for HepG2 cell growth inhibition. The results obtained revealed that the tested compounds possess inhibitory effect on the growth of HepG2 liver cancer cells. The results were compared to DOX (doxorubicin) as a reference drug (IC_{50}: 0.04 μM).

Keywords: Synthon, Pyrazole, Naphthyridine, DOX , HepG2

Introduction

Naphthyridine derivatives have exceptionally broad spectrum of biological activity.1,8-naphthyridine derivatives have promising medicinal properties, including antibacterial [1], antiprotozoals [2], antimycobacterial [3], antimalarial [4], anti-inflammatory [5], anticancer [6], anti-HIV [7] and antiplatelet[8]. 1,8-naphthyridine derivatives alsoshow their cytotoxic activity against murine P388 leukemiacell line when some changes were done at C-7 and N-1 positions [9, 10]. Vosaroxin was found to have potential anticancer activity. Vosaroxin is believed to exert itsaction via topoisomerase II inhibition [11]. Topoisomerase II is a well-known targets for antitumor agents like doxorubicin, etoposide, ellipticine, and amsacrine [12]. Due to such a broad spectrum biological activity Naphthyridine derivatives received significant attention.

An important class of heterocyclic compounds such as 1,3,4-oxadiazoles [13], 1,2,4-triazole derivative[14], pyrazoles [15, 16], and1,3,4-thiadiazoles [17] showed a remarkable anticancer effect [13–17]. Above observations prompt us to incorporate the 1,8-naphthyridine ring system into the above mentioned heterocyclic systems in one molecule in a trial to obtain a new target and product of dual mode of biological function. Organic chemistry became more and more interesting after application of ultrasound. “Sonochemistry”offers a pathway for a large variety of syntheses. Hence, a large number of organic reactions can be carried out underultrasonic irradiation in high yields, short time, and mildconditions [18–23].

As an extension of our efforts directed towards developmentof convenient synthetic approaches for the synthesisof biologically active heterocyclic compounds and as a part of growinginterest in sonochemistry [24–26], our strategy is to develop a facile sonochemical synthesis of some novel

pyrazole incorporated into 1,8-naphthyridine and to findings of their biological activities in suppressingthe growth of HepG2 liver cancer cells.

Results and Discussion

The starting material, 2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy) acetohydrazide**1** [27], allowed to react with the acetylacetone and benzoyl acetone, under ultrasound irradiation at 65℃ (**Scheme 1**).

The IR spectra of **3a [**2-((2,7-dimethyl-1,8- naphthyridin-4-yl)oxy)-1-(3,5-dimethyl-1*H*-pyrazol-1-yl) ethanone]revealed the disappearance of –$NHNH_2$ bands of hydrazide and showed only one band at 1676 cm^{-1}characteristic for amidic CO group. ^{1}HNMR for compound **3a** showed the appearance of three singlet signals due to 2 methyl groups and CH pyrazole at δ 1.68, 2.00, and 6.47, and disappearance of the broad singlet signals from δ3.99 and 9.28 corresponding to NH_2 and NH protons, respectively, in acid hydrazide **1,** beside theoriginal methyl groups, 3CH—of naphthyridine and the methylene protons. The mass spectrum of this compound showed molecular iopeak *m/z* 310 consistent with itsmolecular formula $C_{17}H_{18}N_4O_2$. Also, reaction of excess ethyl acetoacetate with2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy) acetohydrazide(**1)**,under ultrasound irradiation at 60℃ for 10 min gives only one isolable uncyclized product identified as ethyl-3-(2-(2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy)acetyl)hydrazono)butanoate **4** (Scheme 1).

The structureof compound **4** was confirmed on the basis ofits elemental and spectral data. The IR spectrum for **4** showed str. absorption band at 3198 cm^{-1} characteristic for NH and strong absorption band at 1721 $cm^{-1}$for CO of ester.^{1}HNMR of the compound **4** revealed one D_2O exchangeable signal at δ 9.05 due to NH, triplet and quartet signals at δ 1.31 and 4.23 for ethyl group, and two singletsignals at δ 2.15 and 3.40 for new methyl and methylene groups, respectively. The cyclized product, 1-(2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy)acetyl)-3-methyl-1*H*-pyrazol-5(4H)-one **5** ,was obtained on increasing the time of the foregoing reaction to 25min under the same conditions (Scheme 1).

The structure of the new pyrazolone**5** was confirmed on the basis of its elemental analysis and IR, ^{1}HNMR,^{13}CNMR, and mass spectral data, and its ^{1}HNMR revealed the disappearance of the two singlet signals from δ 3.99 and 9.28 corresponding to $NH_2$and NH protons and new two singletsignals at δ 2.17 and 3.39 for methyl group and CH_2-pyrazole,respectively.To find the effect of ultrasound on this reaction, all previously mentioned reactions were carried out under the same conditions in absence of ultrasound irradiations (Table 1). The data cited in Table 1 showed that the reaction time increased and the yields of the products decreased in absence of ultrasonic irradiation. Thus, the ultrasound irradiationwas found to have useful effect on the synthesis of the pyrazole derivatives.

Table 1: Synthesis of pyrazole derivatives 3a-b, 4, and 5 under both ultrasonic irradiation and conventional method.

Compound	Ultrasonic irradiation		Conventional	
	Time (min.)	Yield %	Time (min.)	Yield %
3a	10	96	60	94
3b	10	98	60	90
4	10	92	60	88
5	25	95	180	85

Scheme-1

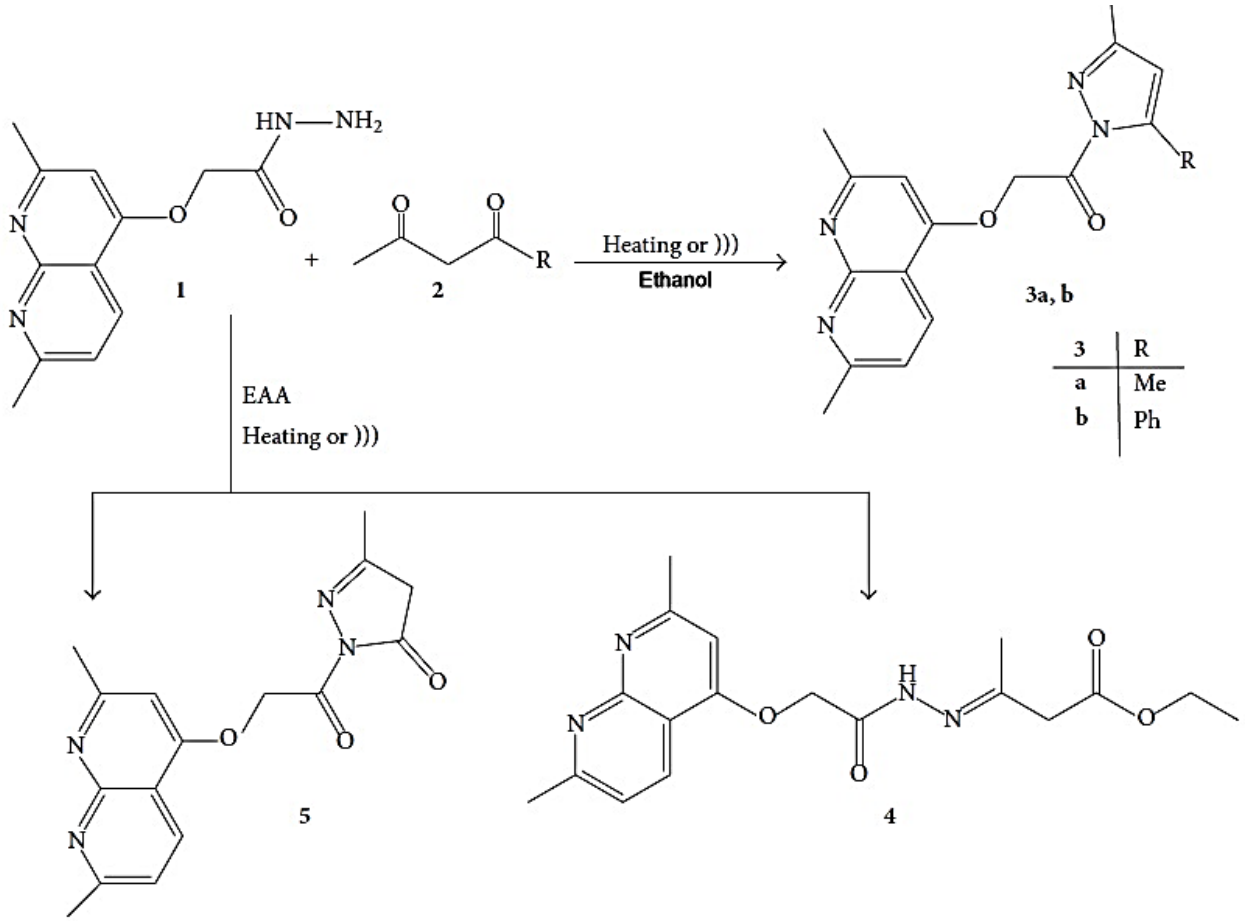

Table-2: "IC_{50}(μM) of new compounds against liver cancer cell line HepG2.

Compound	IC_{50}(μM)
DOX	0.04
3a	0.071
3b	0.064
5	0.091

Pharmacology

Preliminary screening showed that all selected compounds exhibited a moderate to strong growth inhibition activity on the tested cell line (IC_{50}: 0.048– 0.091 μM) concentrations in comparison to the traditional anticancer drug doxorubicin (DOX). It can be deduced from the results cited in Table 2.The pronounced activity of newly synthesized compound might be due to the presenceof N-aminophenyl triazole attached to (2,7-dimethyl-1,8-naphthyridine-4-yloxy) methyl moiety [28].

Conclusion

We have synthesized a class of novel substituted pyrazoles, incorporated into 1, 8-naphthyridine nucleus under both sonication and classical conditions. In general, improvements in rates and yield of the reactions are observed when reactions were carried out under sonication compared with classical condition.

Experimental

Melting points were taken in open glass capillary tube and are uncorrected. Thin layer chromatography (TLC) was performed on aluminum silica gel 60 F254 (E-Merk). The spots were detected by iodine and UV light absorption. IR spectra were recorded on a FTIR, Perkin Elmer SP 100 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker WM 350 and 600MHzspectrometers using TMS (0.00 ppm). Chemical shift (δ) is given in ppm. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.v. Sonication was performed byDaihan (Wiseclean,D-40 kHz).

Synthesis of 2-((2,7-Dimethyl-1,8-naphthyridin-4-yl)oxy)-1(3,5-substituted-1H-pyrazol-1 yl)ethanone (3a,b)

Method A:

Silent Reactions.Acid hydrazide **1** (15 mmol), acetylacetone and benzoylacetone (64mmol) mixture in absolute ethanol (10mL), was heated at 100℃ in a steam for a suitable time. Then Cooled and treated with pet. ether. The precipitate formed was collected by filtration, washed with pet. ether, and dried. On recrystallization, fromethanol, compounds **3a,b**were produced.

Method B:

Sonicated Reactions. In a 50mL Erlenmeyer flask, Acid hydrazide **1** (15mmol),acetylacetone and benzoylacetone (64mmol) mixture in absolute ethanol (10 mL), was subjected to ultrasound

irradiation for suitable time (***cf.* Table 1**) until the starting material was no longer detectable by TLC. All the reactions were kept at temperature 60–65℃ (the temperature inside reaction vessel was 60℃). The precipitate formed was filtered off and washed with pet. ether . On recrystallization from ethanol compounds **3a,b**were produced.

Physical data of the synthesized compounds (3a,b):

2-((2,7-Dimethyl-1,8 naphthyridin-4-yl)oxy)-1-(3,5-dimethyl-1H-pyrazol-1-yl)ethanone (3a).

Off-white crystals; m.p 213℃.FTIR: 1676 (C=O), 1618 (C=N), 1607 (C=C); ^{1}H NMR (350MHz, DMSO-d_6): δ_H = 1.68, 2.00 (6H, 2s, 2$CH_3$of pyrazole), 2.47, 2.52 (6H, 2s, 2$CH_3$of naphthyridine), 5.56 (2H, br.s, CH_2), 6.09 (1H, s, C_3-H, naphthyridine), 6.75 (1H, s, C_4-H, pyrazole); 7.25 (1H, d, C_6-H, *J* = 7.8Hz); 8.31 (1H, d, C_7-H, *J* = 7.8 Hz); ^{13}C NMR (150MHz, $CDCl_3$): δ_C = 16.23, 21.44, 25.13, 26.99, 46.56, 91.88, 112.31, 118.41, 119.77, 135.84, 150.37, 151.69, 156.13, 161.73, 166.59, 178, 207.05; MS (*m/z*): 310 M+.. (Found:C, 65.83;H, 5.56; N, 17.98. $C_{17}H_{18}N_4O_2$requires C, 65.78; H, 5.86; N, 18.04.)

2-((2,7-Dimethyl-1,8-naphthyridin-4-yl)oxy)-1-(5-methyl-3- phenyl-1H-pyrazol-1-yl)ethanone (3b).

Pale yellow crystals;m.p. 221–223℃. FTIR: 1676 (C=O); 1608 (C=N); ^{1}H NMR (350MHz, DMSO-d_6): δ_H = 2.08 (3H, s, C_5-CH_3), 2.41 (3H, s, C_7-CH_3), 2.56 (3H, s, C_2-CH_3), 5.63 (2H, br.s, CH_2), 6.02 (1H, s, C3-H) and 6.91 (1H, s, C_4-H of pyrazole), 7.14–7.29 (6H, m, C_6-H and ArH,s), 8.28 (1H, d, C_5-H); ^{13}CNMR(150MHz, $CDCl_3$): δ_C = 16.13, 21.46, 25.11, 46.68, 112.27, 118.46, 119.74, 123.81, 127.01, 128.61, 132.30, 135.82, 142.86, 150.31, 151.57, 155.91, 161.55, 166.32, 178.04, 207.04; MS (*m/z*): 372 M+..

(Found: C, 71.23; H, 5.62; N, 15.33 $C_{22}H_{20}N_4O_2$requires C, 70.91; H, 5.42; N, 15.05.)

Ethyl-3-(2-(2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy) acetyl) hydrazono)butanoate (4)

Method A:

Silent Reaction.A mixture of acid hydrazide **1** (15 mmol) with ethylacetoacetate (64mmol)was heated at 100℃ in steam bath for 1 h. After cooling, the residue obtained was treated with pet. ether and the solid product obtained was filtered off and recrystallized from ethanol; it gives the title compound (**4).**

Method B:

Sonicated Reaction.A mixture of acid hydrazide **1** (15mmol) and ethylacetoacetate (64mmol) in 50mL Erlenmeyerflask was subjected to ultrasound irradiation forsuitable time (***cf.* Table 1**) until the starting material wasno longer detectable by TLC. All the reactions were keptat temperature 60–65℃ (the temperature inside reactionvessel was 60℃).The precipitate formed was filtered off andwashed with pet. ether and finally recrystallized fromethanolto afford the corresponding ethyl-3-(2-(2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy)acetyl)hydrazano)butanoate **4**), m.p. 178–180.5℃. FTIR: 3198 (N–H); 1721 (C=O of ester); 1624 cm^{-1}(C=O amidic); ^{1}H NMR (350MHz, $CDCl_3$): δ_H = 1.31 (3H, q, –CH_2CH_3, *J* = 7.2Hz), 2.14 (3H, s, –N=C– CH_3), 2.41, 2.57 (6H, 2s for C_2-CH_3, C_7-CH_3), 3.40 (2H, s, –N=C–CH_2–CO), 4.23 (2H, q, –CH_2CH_3, *J* = 7.2Hz), 5.65 (2H, s, –OCH_2CO), 6.24 (1H, s, C_3-H), 7.14 (1H, d, C_6-H, *J* = 7.8Hz), 8.55 (1H, d, C5-H, *J* = 7.8Hz), 9.05 (1H, s, – NH, D_2O exchangeable); 13C NMR (150MHz, $CDCl_3$): δ_C = 14.21, 21.42,

25.06, 30.92, 44.48, 46.05, 59.47, 61.81, 112.49, 118.42, 119.97, 135.84, 150.08, 151.17, 161.95, 168.49, 178.12, 207.08;MS (*m/z*): 358M+.. (Found:C, 60.04;H, 6.41; N, 15.38$C_{18}H_{22}N_4O_4$requires C, 60.34; H, 6.17; N, 15.62.)

1-(2-(2,7-Dimethyl-1,8-naphthyridin-4-yloxy)acetyl)-3- methyl-1H-pyrazol-5(4H)-one (5)

Method A:

Silent Reaction. A mixture of acid hydrazide **1** (15mmol) with ethylacetoacetate (64mmol) was heated insteam bath for 3h; themixture was left to cool to room temperature.The yellow precipitate so formed was collected byfiltration,washed with pet. ether, and dried. On recrystallization,from ethanol, titled compound **5**were formed.

Method B:

Sonicated Reaction. A mixture of acid hydrazide **1** (15 mmol) and ethylacetoacetate (64mmol) in 50mL Erlenmeyer flask was subjected to ultrasound irradiation for suitable time (***cf.* Table 1**) until the starting material was no longer detectable by TLC. All the reactionswere kept at temperature 60–65℃. The yellow precipitate so formed was filtered off and washed with pet. ether and finally recrystallized from ethanol to afford the corresponding 1-(2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy)acetyl)-3-methyl-1*H*-pyrazol-5(4*H*)-one (**5)**, m.p. 194–196.2℃. FTIR: 1602 (C=C); 1622 (C=N); 1623 (C=O amidic);^{1}H NMR (600MHz, $CDCl_3$): δ_H = 2.16, 2.42, 2.61 (9H, 3s, $3CH_3$), 3.38 (2H, s, $CH_2$of pyrazole), 5.62 (2H,br.s, – OCH_2CO), 6.25 (1H, s, C_3-H), 7.13 (1H, d, C_6-H, *J* = 7.8Hz), 8.54 (1H, d,C_5-H, *J* =7.8Hz); ^{13}CNMR(150MHz,$CDCl_3$): δ_C= 12.92, 21.34, 25.11, 29.72, 45.92, 112.28, 118.41, 119.85, 135.81,150.08, 151.17, 161.87, 161.93, 168.49, 178.12, 207.08; MS (*m/z*): 312M+.. (Found: C, 61.57; H, 5.06; N, 17.62 $C_{16}H_{16}N_4O_3$ requires C, 61.53; H, 5.17; N, 17.93.)

Cytotoxicity

Measurement of Potential Cytotoxicity by SRB Assay. The selected 1,8-naphthyridine derivatives, compounds (**3a**, **3b**, **5**) were subjected to a screening system for evaluation of their antitumor activity against liver HepG2 cancer cell line in comparison to the known anticancer drugs, doxorubicin (DOX). The selected 1,8-naphthyridine derivatives was tested for their **cytotoxic effect**using the method of Skehan et al. [29] as follows: cells were plated in 96- multiwell plate (104 cells/well) for 24 h before treatment with compounds to allow attachment of cell to the wall of the plate. To the cell monolayer, the different concentrations of the compound under test (5, 12.5, 25, and 50 µg/mL) were added.

Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37℃ and in atmosphere of 5% CO_2. Cultures were fixed with trichloroacetic acid and stained for 30min with 0.4% (wt/vol) sulphorhodamine B (SRB) dissolved in 1% acetic acid. The dye which was not bound was removed by four washes with 1% acetic acid. For determination of optical density in a computer-interfaced, 96-well microtiter plate reader, a protein-bound dye was extracted with 10 µM unbuffered Tris base [tris(hydroxymethyl) aminomethane]. The results of SRB assay were linear with values for cellular protein and with the number of cells

measured by both the Lowry and Bradford assays at densities ranging from sparse subconfluence to multilayeredsupraconfluence. The signal-to-noise ratio at 563 nm was approximately 1.6 with 1,000 cells per well. The relation between drug concentration and surviving fraction is plotted to get the survival curve of both cancer cell lines after thespecified compound.

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