Research Article

An Efficient Sonochemical Synthesis of Novel Schiff’s Bases, Thiazolidine, and Pyrazolidine Incorporating 1,8-Naphthyridine Moiety and Their Cytotoxic Activity against HePG2 Cell Lines

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Novel Schiff’s bases 4a–e, 5a, 5b, and 6, thiazolidine 7a–d, and pyrazolidine 8 have been synthesized using the versatile synthon 4-hydroxy-2,7-dimethyl-1,8-naphthyridine 1. Reactions carried out under ultrasound irradiation showed higher rates and yields than those done under silent conditions. The newly 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 doxorubicin as a reference drug (IC50: 0.04). Compounds 4a and 7b showed the highest inhibition activity against the HepG2 cell line (IC50: 0.047 and 0.041 µM, resp.) among all the tested compounds.

1. Introduction

Substituted nitrogen heterocycles are common motifs in biological and pharmaceutical science [1]. For example, 1,8-naphthyridine derivatives have promising medicinal properties, including anti-HIV [2], anticancer [3], anti-inflammatory [4], antimalarial [5], antibacterial [6], antiprotozoal [7], antitubercular [8], and antithrombotic [9] activity. In addition, 1,8-naphthyridine derivatives are found to display cytotoxic activity against the murine P388 leukemia cell line when changes were carried out at the N-1 and C-7 positions [10,11]. Moreover, it was recently found that the 1,8-naphthyridine derivative vosaroxin (formerly SNS-595, AG-7352, ATV-3639, or vorexoxin) is found to have potential anticancer activity. This drug (Figure 1) is believed to exert its action via topoisomerase II inhibition [12]. Topoisomerase II is one of the well-known targets for antitumor agents like doxorubicin, etoposide, ellipticine, and amsaquine [13]. We have reported in a previous article that 1,8-naphthyridine substituted with Mannich bases, N-β-glycosides, and Schiff’s bases showed potent cytotoxic activity against the HepG2 cell line [14].

The application of ultrasound in synthetic organic chemistry became crucial. Sonochemistry is a new trend in organic chemistry, offering a versatile pathway for a wide variety of syntheses. A large number of organic reactions can be carried out under ultrasound irradiation in high yields, short time, and mild conditions [15–20]. We are motivated by the aforementioned findings, our ongoing endeavors in the development of convenient synthetic approaches for the construction of biologically active heterocycles, and the growing interest in sonochemistry [21]. Our strategy is to develop a facile sonochemical synthesis and high yield procedure to prepare some novel 1,8-naphthyridine-4-oxyacetohydrazide Schiff’s bases and 1,8-naphthyridine-4-oxyacetamide incorporated into thiazolidine and pyrazolidine moieties and the investigation of their biological activities in suppressing the growth of HepG2 liver cancer cells.

2. Results and Discussion

2.1. Chemistry. The starting material, namely, 2-(2,7-dimethyl-1,8-naphthyridin-4-yl oxy) acetohydrazide 3, was
synthesized by the reaction of 4-hydroxy-2,7-dimethyl-1,8-naphthyridine 1 [22] with ethyl bromoacetate in the presence of anhydrous potassium carbonate [23] in absolute ethanol under reflux to give the nonisolated ester 2. The ester 2 reacted directly with hydrazine hydrate in refluxing ethanol which afforded the acid hydrazide 3 (Scheme 1). The structure of the acid hydrazide was established on elemental analysis and from spectral data. The IR spectra revealed the two absorption bands at 3338 and 3193 cm\(^{-1}\) which correspond to -NHNH\(_2\) and a band at 1671 cm\(^{-1}\) due to amide carbonyl group. Its \(^1\)H NMR spectrum showed two D\(_2\)O exchangeable signals due to NH\(_2\) and NH protons at \(\delta\) 3.99 and 9.28, respectively. Two singlets due to 2 methyl groups at \(\delta\) 2.44 and 2.61 were observed. A broad singlet is present at \(\delta\) 5.20 for methylene protons in addition to the 3 aromatic protons of naphthyridine at \(\delta\) 6.18, 7.20, and 8.46. The hydrazide obtained 3 was then condensed with different aromatic aldehydes, ketones, and isatin, in absolute ethanol under ultrasound irradiation at 60–65°C, and produced the corresponding Schiff’s bases 4a–e, 5a, 5b, and 6, respectively (Scheme 1).

In the \(^1\)H NMR spectra of Schiff’s bases 4a–e, the disappearance of the broad singlet band at \(\delta\) 3.99 which corresponds to NH\(_2\) protons and an additional set of signals assigned to the –N=CH– group in the range \(\delta\) 7.95–8.12 were observed. This observation confirmed the condensation between the amino group of the hydrazide and the carbonyl compounds. The structure of Schiff’s bases derived from aromatic ketones 5a, 5b was established on the basis of its elemental analysis and spectral data. The \(^1\)H NMR spectrum of 5a revealed a new singlet signal for an extra CH\(_3\) group at \(\delta\) 2.17 beside the 3 protons of the thiophene ring at \(\delta\) 7.06, 7.32, and 7.37. Moreover, an interesting observation appeared in the IR spectra of Schiff’s base derived from the isatin 6, where broad absorption bands at 3214–3454 cm\(^{-1}\) were attributed to the contribution of enolic OH and NH groups. This observation is consistent with similar reported compounds containing the isatin moiety [24]. The enolic character in this compound was further confirmed by the \(^1\)H NMR at 600 MHz. Four signals centered in the range of \(\delta\) 10.8 to 12.27 were assigned to amide iminol structures [25] (Scheme 2 and Figure 2).

To find the specific effect of ultrasound on this reaction, all previously mentioned reactions were carried out under the same conditions in the absence of ultrasound irradiation (Table 1). The data cited in Table 1 show that the reaction time increased while the product yields slightly decreased in the absence of ultrasonic irradiation. These results confirm that the ultrasonic irradiation played a crucial role in the enhancement of the rapid synthesis of Schiff’s bases. Based on the above findings, we further extended our study to investigate the reactivity of compounds 4a–e which are considered as suitable precursors for the synthesis of novel [4-((oxyacetamido)thiazolidin-3-yl)2,7-dimethyl-1,8-naphthyridine] derivatives 7a–d and pyrazolidine derivative 8.

Treatment of 4a–d with thioglycolic acid in acetic acid under “silent” conditions resulted in cyclocondensation giving the corresponding thiazolidinone derivatives 7a–d. Upon repeating the reaction using ultrasonic irradiation instead of the classical method, the formation of the desired product in a shorter time (as examined by TLC) without an improvement in yield was observed. However, a catalyzed ultrasound irradiation process using molecular sieve (4 Å) resulted in a good yield from 7a–d in an even shorter time. The structures of the compounds 7a–d were established on the basis of their elemental analysis, IR, \(^1\)H NMR, \(^{13}\)C NMR, and mass spectral data. Compounds 7a–d may be formulated as the oxo-form 7a–d or its tautomeric enol-form 7a\(_\text{enol}\)-d (Scheme 3).

IR spectra of the isolated products revealed the predominance of the enol-form 7a\(_\text{enol}\)-d due to the existence of strong absorption peaks in the region of \(\nu = 3360–3380\) cm\(^{-1}\) which corresponds to cyclic enol, while the amide carbonyl absorption appeared at \(\nu = 1680\) cm\(^{-1}\). The \(^1\)H NMR of compound 7a showed a new singlet signal at \(\delta = 2.07\) due to an acetyl group, two doublet signals at \(\delta = 3.71\) and 3.90 for CH\(_2\)– in thiazolidine, and CH– thiazolidine appeared at \(\delta = 8.29\). The time of the reaction and the product yields are cited in Table 2, which also shows that the catalyzed ultrasound technique reduced the time of the reactions from several hours to minutes and improved the product yields from 40–49% (under conventional conditions) to 89–93%. Treatment of Schiff’s base 4b with bromoacetyl bromide in ethanol and the presence of MgO as a solid base catalyst under ultrasonic irradiation afforded only one isolable product (as examined by TLC) identified as pyrazolidin-3-one core structure 8 in 96% yield within 10 minutes. The same reaction was carried out in the absence of ultrasonic irradiation and gave just 45%
yield, in a much longer reaction time (72 h). The structure of 8 was established on the basis of its elemental analysis and spectral data. For example, its mass spectrum revealed a molecular ion peak at m/z 485 and at 487 for M^+ + 2 and; its 1H NMR revealed two doublet signals due to the pyrazolidine 2–CH at δ 2.99 and 3.32.

In general, the improvement induced by ultrasound in the abovementioned reaction is based on the well-established cavitation theory [26]. The formation of Schiff’s bases follows a false sonochemistry type according to the sonochemical reactions classification of Luche [27, 28]. The cavitation effect provides the mechanical energy for all subsequent chemical reactions, including bond scission induced by viscous frictional forces. In the present study, the substantial improvement induced by ultrasound irradiation in the reactions involving the formation of thiazolidine and pyrazolidine was assisted by the presence of solid catalysts. The pronounced enhancement of the ultrasound effect in the presence of solid catalysts is mainly due to cavitation in the liquid-solid system [29, 30]. The cavitation occurred in the liquid near the solid surface of the catalyst, resulting in a cavity collapse that generates high-speed jets of liquid, which hit the surface.
of the catalyst with tremendous force. This process could generate more reaction active sites at the catalyst’s surface, which led to a pronounced increase in the reaction rate and the production of a high percentage yield in short reaction times.

2.2. Pharmacology. Preliminary screening of some selected compounds is given in Table 3. It is clear from the data cited in Table 3 that the tested compounds exhibit a moderate to strong growth inhibition activity on the tested cell line between 0.041 and 0.094 μM concentrations in comparison to the known anticancer drug doxorubicin (DOX.). The cytotoxic activity of the selected derivatives on liver HepG2 cell lines, in comparison to the traditional anticancer drug DOX, revealed that compounds 4a and 7b were the most active and induced a marked growth inhibition against HepG2 when compared to DOX (4a and 7b IC50 equal 0.047 and 0.049 μM, resp., whereas DOX was 0.040 μM).

3. Conclusion

A class of novel Schiff’s bases, thiazolidine and pyrazolidine, incorporated into 1,8-naphthyridine nucleus under both sonication and classical conditions were synthesized successfully. Ultrasound irradiation resulted in pronounced improvements in both rates and yield of reactions. The use of solid catalysts enhances the efficacy of sonication and leads to the formation of high percentage yields in shorter reaction times. The cytotoxicity screening of some selected new compounds revealed that the selected compounds showed reasonable antitumor activity against the HepG2 cancer cell line in

Table 2: Synthesis of 4-oxothiazolidine derivatives (7a–d) under catalyzed ultrasonic irradiation, uncatalyzed ultrasonic irradiation, and using the conventional method.

| Compound | Catalyzed ultrasonic irradiation | Uncatalyzed ultrasonic irradiation | Conventional |
|----------|----------------------------------|-----------------------------------|--------------|
|          | Time (min) | Yield % | Time (min) | Yield % | Time (h) | Yield % |
| a        | 40         | 90      | 100        | 43      | 36        | 40      |
| b        | 60         | 89      | 100        | 51      | 44        | 43      |
| c        | 40         | 93      | 85         | 47      | 48        | 44      |
| d        | 65         | 92      | 90         | 56      | 39        | 49      |

Table 3: Cytotoxic activity of the newly synthesized selected derivatives on the liver HepG2 cancer cell line in comparison to the traditional anticancer drug DOX.

| Compounds | IC50 (μM) |
|-----------|-----------|
| 3         | 0.086     |
| 4a        | 0.047     |
| 4b        | 0.057     |
| 4c        | 0.094     |
| 4d        | 0.053     |
| 7a        | 0.052     |
| 7b        | 0.041     |
| 7c        | 0.053     |
| 7d        | 0.049     |
| DOX       | 0.040     |
comparison to the traditional anticancer drug DOX. Among all the compounds tested, 4a and 7b were found to have the highest inhibitory activity against the HepG2 cell line with IC_{50} values of 0.047 and 0.041 \mu M, respectively.

4. Experimental

4.1. Chemistry

4.1.1. General. All melting points were measured on a Mel-Temp apparatus and were uncorrected. Thin layer chromatography (TLC) was performed on aluminum silica gel 60 F_{254} (E-Merk). The spots were detected by iodine and UV light absorption. IR spectra were recorded on a FTIR, Perkin Elmer SP 100 spectrometer. \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectra were recorded on Burker WM 350 and 600 MHz spectrometers using TMS (0.00 ppm) or the signal of the deuterated solvent was used as an internal standard. Chemical shift (\delta) is given in ppm relative to the signal for TMS as standard and the coupling constant in Hz. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.v. Sonication was performed by Daihan (Wiseclean, D-40 kHz). Microanalysis was performed using a Perkin Elmer elemental analyzer at the Faculty of Science, King Abdul Aziz University. Biological activity tests were performed at the National Cancer Institute, Cairo, Egypt.

4.1.2. Typical Procedure for the Reactions

4.1.2.1. Synthesis of Acid Hydrazide Derivative 3. A mixture of 1 \textsuperscript{[22]} (5 gm, 0.03 mL), ethyl bromoacetate (3.33 mL, 0.03 mL), and (5 gm) anhydrous potassium carbonate in abs.
2-(2,7-Dimethyl-1,8-naphthyridin-4-yloxy)-N^′-(4-methoxybenzylidene) Acetohydrazide (4b). Off-white crystals; m.p. 256–258°C. FTIR: 1245 (−OCH_3); 1605 (C=C); 1640 (C=N); 1679 (C=O amicid); 3100 (−NH). ^1H NMR (600 MHz, CDCl_3; DMSO-d_6) δ_H: 2.15; 2.46 (6H, 2s, 2CH_2); 3.85 (3H, s, −OCH_3); 5.77 (2H, brs, −OCH_3CO); 6.19 (1H, s, C_6–H); 6.95; 7.65 (4H, 2d, p-disubstituted benzene J = 9.0 Hz); 7.20 (1H, d, C_6–H, J = 7.8 Hz); 8.00 (1H, s, −N=CH); 8.40 (1H, d, C_6–H, J = 7.8 Hz); 11.40 (1H, s, NH, D_2O exchangeable). ^13C NMR (CDCl_3) δ_C: 21.45, 25.13, 45.90, 55.46, 71.24, 114.41, 116.36, 118.52, 122.81, 123.54, 135.80, 152.00, 153.77, 157.11, 178.04; MS (m/z): 364 M^+ (found: C, 66.03; H, 5.33; N, 15.46. C_20H_20N_4O_3 requires C, 65.92; H, 5.53; N, 15.38).

N^′-(Benz煙[1.3]dioxol-5-yl methylene)-2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy) Acetohydrazide (4d). Yellow crystals; m.p. 256–258°C. FTIR: 1247 (ether linkage); 1604 (C=C); 1640 (C=N), 1676 (C=O amicid), 3102 (NH); ^1H NMR (600 MHz, CDCl_3; DMSO-d_6) δ_H: 2.16; 2.48 (6H, 2s, 2CH_2); 5.76 (2H, brs, −OCH_3CO); 6.02 (2H, dd, −OCH_3CO, J = 12.6 Hz); 6.85, 7.34, 7.58 (3H, trisubstituted benzene); 7.95 (1H, s, −CH=N−); 11.43 (1H, s, −NH, D_2O exchangeable). ^13C NMR (CDCl_3) δ_C: 21.45, 25.43, 45.89, 101, 105.48, 106.62, 108.4, 125.23, 148.33, 150.32, 112.48, 116.37, 119.81, 123.87, 128.78, 144.31, 152.11, 161.12, 178.00, 207.04; MS (m/z): 378 M^+ (found: C, 63.12; H, 5.43; N, 14.61. C_20H_18N_4O_4 requires C, 63.48; H, 4.79; N, 14.81).

2-(2,7-Dimethyl-1,8-naphthyridin-4-yloxy)-N^′-(4-(trifluoromethyl)benzylidene)-acetohydrazide (4a). Off-white crystals; m.p. 262–284°C. FTIR: 3200 (−NH), 1675 (C=O amicid), 1640 (C=N), 1605 (C=C); ^1H NMR (600 MHz, CDCl_3; DMSO-d_6) δ_H: 1.84; 2.48 (6H, 2s, 2CH_2); 5.78 (2H, brs, −CH_2); 6.22 (1H, s, C_6–H); 7.20 (1H, d, C_6–H, J = 7.8 Hz), 7.68, 7.88 (4H, 2d, disubstituted benzene, J = 8.4 Hz), 8.12 (1H, s, −N=CH); 8.49 (1H, d, C_6–H, J = 7.8 Hz), 11.87 (1H, s, NH, D_2O exchangeable). ^13C NMR (CDCl_3) δ_C: 22.70, 25.13, 45.86, 112.53, 118.53, 119.89, 125.79, 127.49, 128.84, 142.9, 150.32, 161.15, 116.36, 135.92, 151.58, 169.17, 178.12, 207.06; MS (m/z): 402 M^+ (found: C, 59.90; H, 4.32; N, 13.62%. C_20H_17F_3N_4O_2 requires C, 59.70; H, 4.26; N, 13.92).
4.1.2.3. Synthesis of 2-(2,7-Dimethyl-1,8-naphthyridin-4-yloxy) Acetohydrazide—Aromatic Ketones Schiff’s Bases (5a, 5b)

4.1.2.3.1. Method A: Silent Reactions. An equimolar mixture of (3) (0.004 mol) and the appropriate aromatic heterocyclic ketones, namely, 2-acetyliophene and 2-acetylfuran (0.004 mol) in 20 mL absolute ethanol, were stirred under reflux for 6 h. The reaction mixture was concentrated and cooled and the formed precipitate was recrystallized from ethanol/petroleum ether to give the title product 5a, 5b.

4.1.2.2. Method B: Sonicated Reactions. To a solution of 2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy) acetohydrazide 3 (0.004 mol) in ethanol (20 mL) in a 100 mL Erlenmeyer flask, an appropriate aromatic heterocyclic ketone (0.004 mol) was added. The mixture was subjected to ultrasound irradiation for 10 minutes. The reaction was kept at a temperature of 60–65°C which was attained by addition or removal of water in the ultrasonic bath (the temperature inside the reaction vessel was 60°C). The filtered precipitate was washed thoroughly with ether and recrystallized from dilute ethanol to produce the corresponding Schiff’s bases 6 as brown crystals; m.p. 298–301°C. FTIR: 3154, 3214 (NH, OH); 1685 (C=O amide); 1H NMR (600 MHz, CDCl3) δH: 2.37, 2.42 (6H, 2s, 2CH3), 5.80 (2H, brs, –OCH2CO), 6.15–8.35 (7H, m., aromatic CH), 10.88 (1H, brs, –NH of isatin), 11.3 (1H, brs, NH amide) and 11.62, 12.72 (2H, brs, enolic OH); 13C NMR (CDCl3-δC): 20.80, 24.80, 45.36, 111.26, 115.17, 117.92, 119.77, 122.7, 126.30, 131.96, 135.23, 142.70, 143.94, 149.96, 153.00, 161.45, 164.45, 169.78, 176.25, 207.00; MS (m/z): 375 M+ (found: C, 64.12; H, 4.23; N, 18.32. C20H18N4O3 requires C, 63.99; H, 4.56; N, 18.66).

4.1.2.4. Synthesis of N-Acetyl-2-(2,7-dimethyl-1,8-naphthyridin-4-yloxy)-(4-oxo-2-aryl)-thiazolidin-3-yl) Acetamide (7a-d)

4.1.2.4.1. Method A: Silent Reaction. A mixture of Schiff’s bases 4a–d (0.001 mol) and (0.4 mL, 0.001 mol) thiglyolic acid in 8 mL glacial acetic acid was refluxed for 36–48 h (until disappearance of the starting materials as examined by TLC) (cf. Table 2). The reaction mixture was cooled at r.t., neutralized with ammonia and the precipitate formed was collected, filtered, and crystallized from ethanol.

4.1.2.4.2. Sonicated Reaction. A solution of Schiff’s bases 4a–d (0.001 mol) in 8 mL glacial acetic acid and (0.4 mL, 0.001 mol) thiglyolic acid in a 50 mL Erlenmeyer flask was subjected to ultrasound irradiation for a suitable time (cf. Table 2) until the starting material was no longer detectable by TLC. The reaction was kept at 70–75°C which was attained by addition or removal of water in the ultrasonic bath (the temperature inside the reaction vessel was 70°C). The reaction mixture was cooled to r.t. and neutralized with ammonia and the precipitate formed was collected, filtered, and crystallized from ethanol.

4.1.2.4.3. Catalyzed Sonicated Reaction. To a solution of Schiff’s bases 4a–d (0.001 mol) in 8 mL glacial acetic acid and thiglyolic acid (0.4 mL and 0.001 mol) in a 50 mL Erlenmeyer flask, a molecular sieve (1 g, 4 Å) was added. The mixture was subjected to ultrasound irradiation for a suitable time (cf. Table 2) until the starting material was no longer detectable by TLC. The reactants were kept at 70–75°C which was attained by addition or removal of water in the ultrasonic bath (the temperature inside the reaction vessel was 70°C). The reaction mixture was decanted, cooled, and neutralized.
with ammonia. The formed precipitate was collected, filtered, and crystallized from ethanol.

The synthesized compounds (7a–d) with their physical data are listed below.

**N-Acetyl-2-(2,7-dimethyl-1,8-naphthyridin-4-yl)-N-(4-oxo-2-(4-(trifluoromethyl)phenyl)thiazolidin-3-yl) Acetamide (7a)**: Yellow crystals; mp 306–308°C. FTIR: 1608 (C=C), 1620 (C=N); 1678 (C=O amidic), 3366 (–OH enolic). 

**N-Acetyl-2-(2,7-dimethyl-1,8-naphthyridin-4-yl)-N-(4-oxo-2-(4-(trifluoromethyl)phenyl)thiazolidin-3-yl) Acetamide (7b)**: Yellow crystals; mp 293–295°C. FTIR: 1425 (ether linkage); 1680 (C=O amidic); 3361 (–OH enolic). 

**N-Acetyl-2-(2,7-dimethyl-1,8-naphthyridin-4-yl)-N-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl) Acetamide (7c)**: Off-white crystals; mp 241–243°C. FTIR: 1631 (C=N), 1681 (C=O amidic), 3460 (–OH enolic). 

**N-Acetyl-2-(2,7-dimethyl-1,8-naphthyridin-4-yl)-N-(2-(benzo[d][1,3]dioxol-5-yl)-4-oxothiazolidin-3-yl) Acetamide (7d)**: Yellow crystals; mp 296–298°C. FTIR: 1603 (C=N), 1680 (C=O amidic), 3480 (–OH).
wall of the plate. Different concentrations of the compound under test (5, 12.5, 25, and 50 μg/mL) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 °C and in an atmosphere of 5% CO₂. Cultures were fixed with trichloroacetic acid and stained for 30 min with 0.4% (wt/vol.) sulforhodamine B (SRB) dissolved in 1% acetic acid. Unbound dye was removed by four washes with 1% acetic acid, and protein-bound dye was extracted with 10 μM unbuffered tris base [tris(hydroxymethyl)aminomethane] for determination of optical density in a computer-interfaced, 96-well microtiter plate reader. The SRB assay results were linear with the number of cells and with values for cellular protein measured by both the Lowry and Bradford assays at densities ranging from sparse subconfluence to multilayered supraconfluence. The signal-to-noise ratio at 564 nm was approximately 1.5 with 1,000 cells per well. The relation between the surviving fraction and drug concentration is plotted to get the survival curve of both cancer cell lines after treatment with the specified compound.

Conflict of Interests

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

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