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Synthesis and antimicrobial activities of some newly 2,4,6-tri-substituted pyridine derivatives

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Abstract A series of novel 2-(2-(substituted benzylidene)hydrazinyl)-*N*′-(substituted benzylidene)-6-chloropyridine-4-carbohydrazide (**5a–e**), 2-(2-cycloalkylidenehydrazinyl)-6-chloro-*N*'-cyclo-alkylidenepyridine-4-carbohydrazide (**6a,b**), 2-(2-(1-(4-substituted phenyl)ethylidene)hydrazinyl)-6-chloro-*N*′-(1-(4-substituted phenyl)ethylidene)pyridine-4-carbohydrazide (**7a,b**) and 2-(2-(1-(pyridinyl)ethylidene)hydrazinyl)-6-chloro-N′-(1-(pyridinyl) ethylidene)pyridine-4-carbo-hydrazide (**8a–c**) derivatives have been synthesized by treating treating 2-chloro-6-hydrazinoisonicotinic acid hydrazide **4** with selected active reagents. Their structures were confirmed by spectral and analytical data. The synthesized compounds were investigated for antimicrobial activities. The antimicrobial screening showed that many of these obtained compounds have good activities comparable to Streptomycin and Fusidic acid as reference drugs.

Keywords Citrazinic acid · Hydrazide · Hydrazones · Antimicrobial activities

Introduction

Several publications have reported isonicotinic acid hydrazide and its derivatives as antitubercular [1–3], virucide and bactericide [4] agents. In our previous work, we

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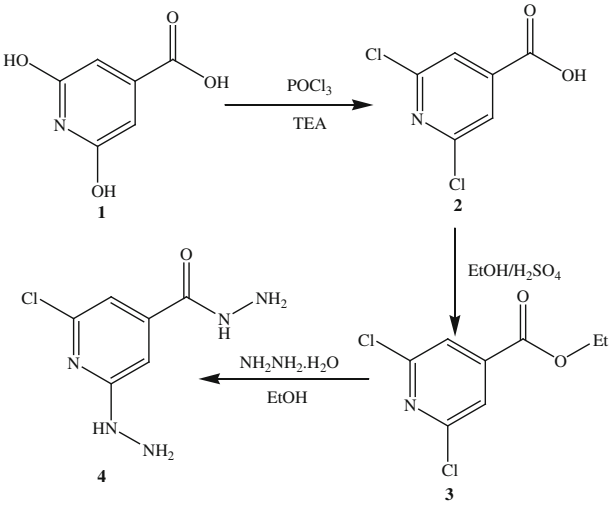
reported the synthesis, characterization, and preliminary biological activity of some series of substituted pyridine derivatives as antimicrobial agents [5–9]. Also, we found that certain substituted pyridine and their amide derivatives show analgesic and anticonvulsant [10], antimicrobial [11, 12] and antitumor activities [13, 14]. In addition, the biological and analgesic activities of many heterocyclic compounds containing a sulfur atom have been reviewed [15–17]. On the other hand, some of the nitrogenous candidates have promising biological [18, 19] and anticancer activities [20, 21]. Recently, some new Schiff's base derivatives have been synthesized and tested as antimicrobial agents [22–24]. In continuation of our previous work aiming at the synthesis of heterocyclic systems with remarkable biological importance [5–13], we report here on the synthesis of some new pyridine derivatives with different substituted at positions-2,4,6 and their antimicrobial activities.

Results and discussion

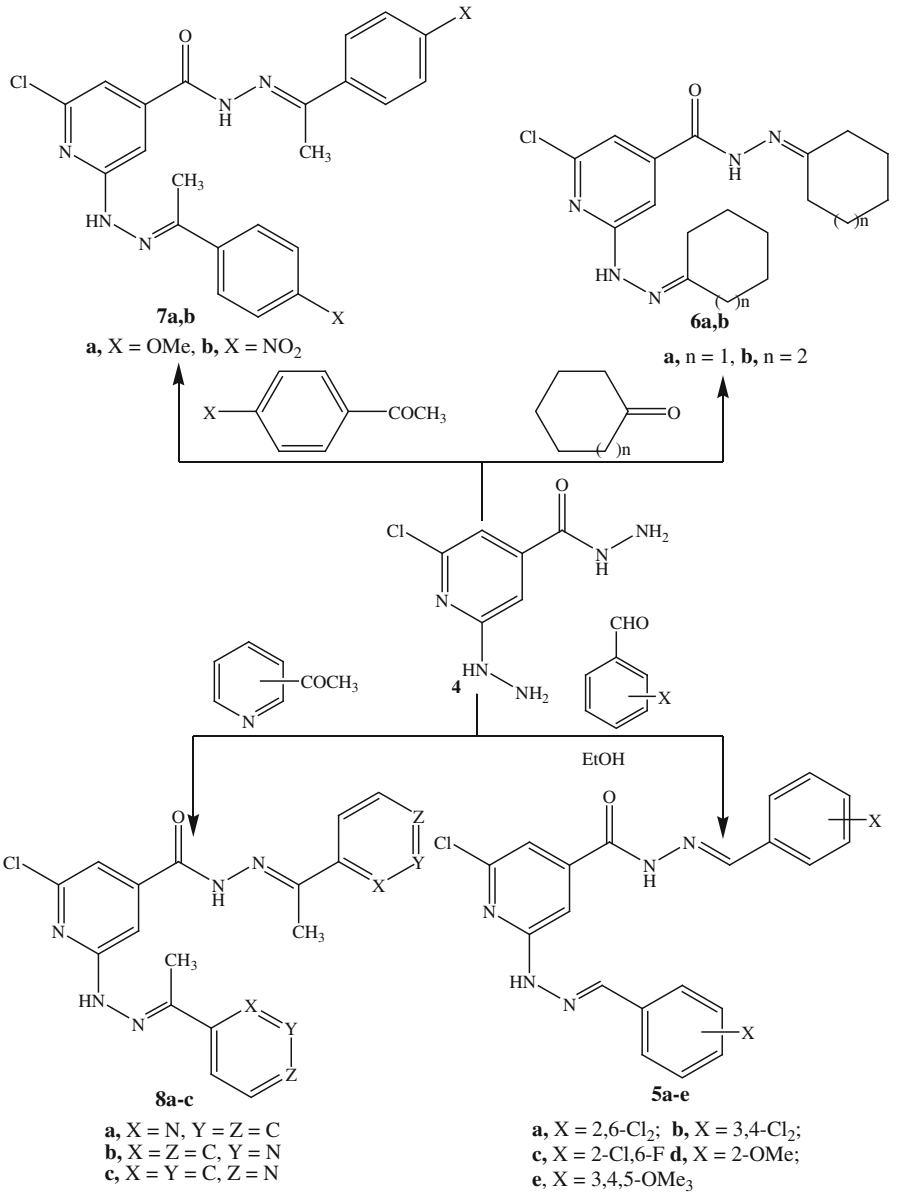
2-Chloro-6-hydrazinoisonicotinic acid hydrazide (**4**) was synthesized using as starting material according to the reported procedure [6, 25]. Chlorination of 2,6-dihydroxyisonicotinic acid (citrazinic acid) (**1**) with phosphorus oxychloride in the presence of TEA afforded the corresponding 2,6-dichloroisonicotinic acid (**2**), which was esterified with absolute ethanol in the presence of concentrated sulfuric acid to afford ethyl 2,6-dichloro-isonicotinate (**3**). The ester **3** was treated with hydrazine hydrate in refluxing ethanol to afford 2-chloro-6-hydrazino isonicotinic acid hydrazide (**4**) in pure form and good yield (Scheme 1).

Additionally, bis-Schiff base derivatives **5a–e** were synthesized via simple condensation of the hydrazide **4** with appropriate substituted aromatic aldehydes,



Scheme 1 Synthetic route for starting material **4**

namely, 2,6-dichlorobenzaldehyde, 3,4-dichlorobenzaldehyde, 2-chloro-6-flouro-benzaldehyde, 2-methoxybenzaldehyde, or 3,4,5-trimethoxy-benzaldehyde in refluxing absolute ethanol. Also, condensation of hydrazide **4** with selected active ketones, namely, cycloalkanone (cyclohexanone or cycloheptanone), substituted acetophenone or acetyl pyridine derivatives in refluxing ethanol in the presence a



Scheme 2 Synthetic route for the target compounds **5–8**

few drops of glacial acetic acid afforded the corresponding condensed derivatives **6a,b, 7a,b** and **8a–c**, respectively (Scheme 2).

Antimicrobial activity

The newly synthesized compounds (**5–8**) have been tested for their preliminary antimicrobial activity against *Bacillus subtilis* (NRRL B-543) and *Staphylococcus aureus* (NRRL B-313) (as Gram-positive bacteria), and *Esherishia coli* (NRRL B-558) (as Gram-negative bacteria), while *Candida albicans* (NRRL Y-477) and *Aspergillus niger* (NRRL Y-3) (as fungi). The antimicrobial activity was measured at 50 μ/mL of the tested compounds using the bioassay sensitivity technique of antibiotics specified in the United States Pharmacopoeia [26]. The degree of inhibition is measured in comparison with that of Streptomycin and Fusidic acid taken as standards at the same concentration. The results are summarized in Table 1.

Experimental

Melting points were uncorrected and determined in open glass capillaries using in Electrothermal IA 9000 Series digital melting point apparatus (Electrothermal, Essex, UK.). Elemental analyses were performed with all final compounds with an Elementar Vario EL (Microanalytical Unit, Cairo University, Cairo, Egypt), and

Table 1 Antimicrobial activity of the new synthesized compounds **5–8**

Comp. no.	Inhibition zone diameter (mm)				
	Gram-positive bacteria		Gram-negative bacteria	Fungi	
	B. subtilis	*S. aureus*	*E. coli*	*C. albicans*	*A. niger*
5a	15	14	21	11	15
5b	20	15	20	16	18
5c	12	13	13	19	18
5d	11	12	14	10	15
5e	19	10	22	17	15
6a	20	18	18	12	12
6b	10	15	10	14	14
7a	14	21	16	10	10
7b	13	22	11	15	16
8a	14	22	12	11	15
8b	16	15	15	18	19
8c	15	22	14	15	16
Streptomycin	21	22	21	–	–
Fusidic acid	–	–	–	17	18

were in good agreement (±0.4 %) with the calculated values. The IR spectra (KBr) were recorded on an FT IR-8201 PC spectrophotometer (Schimadzu, Japan). The NMR spectra were measured with a Jeol 270 MHz spectrometer (FTGNM-EX 270; Japan) in DMSO-d_6 as solvent. The chemical shifts were recorded relative to TMS. The mass spectra (EI) were run at 70 eV with a Finnegan SSQ 7000 spectrometer (Thermoinstrument System, USA), *m/z* values are indicated in Dalton. TLC (Silica gel, aluminum sheets 60 F_{254}; Merck, Darmstadt, Germany) was used for tracing the reactions. Antimicrobial screening was carried out in Department of Microbial Chemistry, National Research Center, Cairo, Egypt.

Synthesis of 2-(2-(substituted benzylidene)hydrazinyl)-*N*′-(substituted benzylidene)-6-chloropyridine-4-carbohydrazide (**5a–e**)

A mixture of the hydrazide derivative **4** (0.554 g, 1 mmol) and the appropriate aldehydes, namely, 2,6-dichloro-, 3,4-dichloro-, 2-chloro-6-flouro-, 2-methoxy- or 3,4,5-trimethoxybenzaldehydes (2 mmol) in absolute ethanol (50 mL) was heated under reflux for 6 h. The reaction mixture was poured onto ice-water, the obtained solid was collected by filtration, washed with water and crystallized from a proper solvent to afford the corresponding Schiff base derivatives **5a–e**, respectively.

2-(2-(2,6-Dichlorobenzylidene)hydrazinyl)-N'-(2,6-dichlorobenzylidene)-6-chloropyridine-4-carbohydrazide ***(5a)***

Yield 82 %, mp 184-186 °C (AcOH/H_2O). IR (KBr, cm^{-1}): 3233 (NH), 1665 (C=O); ^{1}H NMR (DMSO-d_6, ppm): δ = 6.86–7.40 (m, 6H, Ar–H), 8.10–8.32 (m, 4H, pyr-H + 2CH = N), 8.75, 10.45 (2 s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): δ = 108.05, 112.08, 146.98, 149.35, 153.86 (5C, pyr-C), 126.42, 129.56, 132.48, 134.15 (12C, Ar–C), 142.68 (2CH=N), 162.70 (CO); MS, *m/z* (%): 515 [M^+, 12] and 186 (100). Anal. Calcd. for $C_{20}H_{12}Cl_5N_5O$ (515.61): C, 46.59; H, 2.35; N, 13.58; Cl, 34.38. Found: C, 46.52; H, 2.30; N, 13.50; Cl, 34.32.

2-(2-(3,4-Dichlorobenzylidene)hydrazinyl)-N'-(2,6-dichlorobenzylidene)-6-chloropyridine-4-carbohydrazide ***(5b)***

Yield 68 %, mp 200-204 °C (EtOH). IR (KBr, cm^{-1}): 3352 (NH), 1660 (C=O); ^{1}H NMR (DMSO-d_6, ppm): δ = 6.92–7.55 (m, 4H, Ar–H), 7.72 (s, 2H, Ar–H), 8.08–8.36 (m, 4H, pyr-H + 2CH=N), 8.82, 10.36 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): δ = 108.15, 112.22, 147.05, 149.42, 154.02 (5C, pyr-C), 126.86, 129.35, 129.56, 132.62, 132.70, 134.65 (12C, Ar–C), 143.55 (2CH=N), 171.80 (CO); MS, *m/z* (%): 515 [M^+, 18] and 215 (100). Anal. Calcd. for $C_{20}H_{12}Cl_5N_5O$ (515.61): C, 46.59; H, 2.35; N, 13.58; Cl, 34.38. Found: C, 46.53; H, 2.28; N, 13.52; Cl, 34.34.

2-(2-(2-Chloro-6-flourobenzylidene)hydrazinyl)-N′-(2,6-dichlorobenzylidene)-6-chloropyridine-4-carbohydrazide ***(5c)***

Yield 75 %, mp 175–177 °C (AcOH/H_2O). IR (KBr, cm^{-1}): 3348 (NH), and 1665 (C=O); ^{1}H NMR (DMSO-d_6, ppm): δ = 6.88–7.55 (m, 6H, Ar–H), 8.14–8.35 (m, 4H, pyr-H + 2CH=N), 8.78, 10.32 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): δ = 107.98, 112.04, 147.14, 149.40, 153.88 (5C, pyr-C), 113.65, 117.82, 124.80, 133.50, 134.52, 161.00 (12C, Ar–C), 143.64 (2CH=N), 171.86 (CO); MS, *m/z* (%): 483 [M^++1, 6] and 199 (100). Anal. Calcd. for $C_{20}H_{12}Cl_3F_2N_5O$ (482.70): C, 49.76; H, 2.51; N, 14.51; Cl, 22.03. Found: C, 49.70; H, 2.46; N, 14.44; Cl, 21.96.

2-(2-(2-Methoxybenzylidene)hydrazinyl)-N′-(2,6-dichlorobenzylidene)-6-chloropyridine-4-carbohydrazide ***(5d)***

Yield 92 %, mp 222–224 °C (MeOH). IR (KBr, cm^{-1}): 3332 (NH) and 1664 (C=O); ^{1}H NMR (DMSO-d_6, ppm): δ = 3.72 (s, 6H, $2OCH_3$), 6.84-7.45 (m, 8H, Ar–H), 8.02-8.40 (m, 4H, pyr-H + 2CH=N), 8.76, 10.28 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): δ = 55.14 ($2OCH_3$), 107.86, 112.05, 147.14, 149.32, 154.10 (5C, pyr-C), 112.66, 115.82, 120.90, 130.98, 132.02, 157.10 (12C, Ar–C), 144.04 (2CH=N), 172.12 (CO); MS, *m/z* (%): 438 [M^+, 6] and 107 (100). Anal. Calcd. for $C_{22}H_{20}ClN_5O_3$ (437.88): C, 60.34; H, 4.60; N, 15.99; Cl, 8.10. Found: C, 60.30; H, 4.55; N, 15.93; Cl, 8.00.

2-(2-(3,4,5-Trimethoxybenzylidene)hydrazinyl)-N′-(2,6-dichlorobenzylidene)-6-chloropyridine-4-carbohydrazide ***(5e)***

Yield 78 %, mp 215–217 °C (DMF/EtOH). IR (KBr, cm^{-1}): 3238 (NH), 1662 (C=O); ^{1}H NMR (DMSO-d_6, ppm): δ = 3.72 (s, 18H, $6OCH_3$), 7.38 (s, 4H, Ar–H), 7.88–8.25 (m, 4H, pyr-H + 2CH=N), 8.76, 10.40 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): δ = 55.12 (4C, $4OCH_3$), 58.74 (2C, $2OCH_3$), 108.00, 112.02, 146.96, 149.32, 153.88 (5C, pyr-C), 105.10, 127.32, 140.66, 152.78 (12C, Ar–C), 142.78 (2CH=N), 163.22 (CO); MS, *m/z* (%): 558 [M^+, 38] and 235 (100). Anal. Calcd. for $C_{26}H_{28}ClN_5O_7$ (557.98): C, 55.97; H, 5.06; N, 12.55; Cl, 6.35. Found: C, 55.92; H, 5.00; N, 12.50; Cl, 6.30.

Synthesis of 2-(2-cycloalkylidenehydrazinyl)-6-chloro-*N′*-cycloalkylidenepyridine-4-carbo-hydrazide (**6a,b**)

To a solution of cyclohexanone or cycloheptanone (2 mmol) in absolute ethanol (50 mL) in the presence of few drops glacial acetic acid, compound **4** (0.34 g, 1 mmol) was added with stirring. The reaction mixture was heated under reflux for 6 h, and evaporated under reduced pressure to dryness. The obtained residue was solidified with *n*-hexane, and the solid formed was filtered off, dried and crystallized from the proper solvent to give the corresponding title compounds **6a,b**, respectively.

2-(2-Cyclohexylidenehydrazinyl)-6-chloro-N′-cyclohexylidenepyridine-4-carbohydrazide ***(6a)***

Yield 65 %, mp 156–158 °C (EtOH). IR (KBr, cm^{-1}): 3345 (NH), 2934 (CH-aliphatic), 1665 (C=O); ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.58–1.65$ (m, 12H, $6CH_2$, hexyl rings), 2.15–2.28 (m, 8H, $4CH_2$, hexyl ring), 7.98, 8.10 (2s, 2H, pyr-H), 8.86, 10.46 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 23.85$, 26.45, 35.10, 161.45 (12C, hexane ring), 106.05, 111.32, 146.50, 148.90, 153.04 (5C, pyr-C), 163.14 (CO); MS, *m/z* (%): 361 [M^+, 14] and 154 (100). Anal. Calcd. for $C_{18}H_{24}ClN_5O$ (361.86): C, 59.74; H, 6.68; N, 19.35; Cl, 9.80. Found: C, 59.70; H, 6.62; N, 19.29; Cl, 9.74.

2-(2-Cycloheptylidenehydrazinyl)-6-chloro-N'-cycloheptylidenepyridine-4-carbohydrazide ***(6b)***

Yield 72 %, mp. 205-207 °C (EtOH/ether). IR (KBr, cm^{-1}): 3356 (NH), 2945 (CH-aliphatic), 1662 (C=O); ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.62–1.72$ (m, 16H, $8CH_2$, heptyl ring), 2.10-2.32 (m, 8H, $4CH_2$, heptyl ring), 8.05, 8.12 (2s, 2H, pyr-H), 8.94, 10.56 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 23.78$, 28.40, 33.18, 175.55 (14C, heptane rings), 106.12, 110.96, 146.32, 149.06, 153.12 (5C, pyr-C), 162.96 (CO); MS, *m/z* (%):390 [M^+, 10] and 250 (100). Anal. Calcd. for $C_{20}H_{28}ClN_5O$ (389.92): C, 61.61; H, 7.24; N, 17.96; Cl, 9.09. Found: C, 61.54; H, 7.20; N, 17.88; Cl, 9.02.

2-(2-(1-(4-Substituted phenyl)ethylidene)hydrazinyl)-6-chloro-*N′*-(1-(4-substituted phenyl) ethylidene)pyridine-4-carbohydrazide (**7a,b**)

A mixture of **4** (0.34 g, 1 mmol) and substituted acetophenone derivatives, namely, *p*-methoxy- or *p*-nitroacetophenenone (2 mmol) in absolute ethanol (100 mL), was refluxed for 6 h in the presence of glacial acetic acid (2 mL). The reaction mixture was concentrated under reduced pressure, and the solid formed was collected by filtration, dried and purified by crystallization from the proper solvent to give the corresponding title compounds **7a,b**, respectively.

2-(2-(1-(4-Methoxyphenyl)ethylidene)hydrazinyl)-6-chloro-N′-(1-(4-methoxyphenyl)ethylidene) pyridine-4-carbohydrazide ***(7a)***

Yield 55 %, mp 234–236 °C (DMF/H_2O). IR (KBr, cm^{-1}): 3376 (NH), 2952 (CH-aliphatic), 1665 (C=O); ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.72$ (s, 6H, $2CH_3$), 3.65 (s, 6H, $2OCH_3$), 6.95-7.72 (m, 8H, Ar–H), 7.96, 8.08 (2s, 2H, pyr-H), 9.10, 10.76 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 17.60$ ($2CH_3$), 56.76 ($2OCH_3$), 114.08, 126.25, 129.64, 162.75 (12C, Ar–C), 168.55 (2C=N), 105.98, 112.05, 146.18, 148.76, 152.98 (5C, pyr-C), 163.35 (CO); MS, *m/z* (%): 466 [M^+, 10] and 191 (100). Anal. Calcd. for $C_{24}H_{24}ClN_5O_3$ (465.93): C, 61.87; H, 5.19; N, 15.03; Cl, 7.61. Found: C, 61.80; H, 5.15; N, 14.96; Cl, 7.55.

2-(2-(1-(4-Nitrophenyl)ethylidene)hydrazinyl)-6-chloro-N′-(1-(4-nitrophenyl)ethylidene) pyridine-4-carbohydrazide ***(7b)***

Yield 62 %, mp 245-247 °C (DMF/H_2O). IR (KBr, cm^{-1}): 3366 (NH), 2968 (CH-aliphatic), 1668 (C=O); ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.68$ (s, 6H, $2CH_3$), 6.98-7.88 (m, 8H, Ar–H), 8.02, 8.12 (2s, 2H, pyr-H), 9.15, 10.84 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 17.42$ ($2CH_3$), 119.10, 129.28, 138.86, 149.72 (12C, Ar–C), 169.25 (2C=N), 105.85, 112.14, 146.08, 148.66, 153.92 (5C, pyr-C), 164.15 (CO); MS, *m/z* (%): 496 [M^+, 24] and 196 (100). Anal. Calcd. for $C_{22}H_{18}ClN_7O_5$ (495.87): C, 53.29; H, 3.66; N, 19.77; Cl, 7.15. Found: C, 53.24; H, 3.60; N, 19.70; Cl, 7.07.

(2-(2-(1-(Pyridinyl)ethylidene)hydrazinyl)-6-chloro-*N′*-(1-(pyridinyl)ethylidene)-pyridine-4-carbohydrazide (**8a–c**)

To a hot solution of acetylpyridine, namely, 2-acetyl-, 3-acetyl- or 4-acetylpyridine derivatives (2 mmol) in absolute ethanol (100 mL), hydrazide of **4** (0.34 g, 1 mmol) was added with stirring. The reaction mixture was refluxed for 5 h, and, after cooling, the reaction mixture was poured into ice-water. The obtained solid was separated by filtration, washed with water, dried and crystallized from the proper solvent to give the corresponding title compounds **8a–c**, respectively.

2-(2-(1-(Pyridin-2-yl)ethylidene)hydrazinyl)-6-chloro-N′-(1-(pyridin-2-yl)ethylidene)pyridine-4-carbohydrazide ***(8a)***

Yield 72 %, mp 215-217 °C (AcOH/H_2O). IR (KBr, cm^{-1}): 3360 (NH), 2958 (CH-aliphatic), 1665 (C=O); ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.74$ (s, 6H, $2CH_3$), 7.76-8.65 (m, 10H, pyr-H), 9.25, 10.75 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 17.12$ ($2CH_3$), 146.12 (2C = N), 107.12, 111.75, 122.65, 125.88, 129.15, 145.54, 147.85, 149.07, 152.76, 153.68 (15C, pyr-C), 163.95 (CO); MS, *m/z* (%):407 [M^+, 16] and 162 (100). Anal. Calcd. for $C_{20}H_{18}ClN_7O$ (407.85): C, 58.90; H, 4.45; N, 24.04; Cl, 8.69. Found: C, 58.84; H, 4.40; N, 23.97; Cl, 8.62.

2-(2-(1-(Pyridin-3-yl)ethylidene)hydrazinyl)-6-chloro-N'-(1-(pyridin-3-yl)ethylidene)pyridine-4-carbohydrazide ***(8b)***

Yield 58 %, mp 196–198 °C (AcOH). IR (KBr, cm^{-1}): 3334 (NH), 2963 (CH-aliphatic), 1664 (C=O); ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.68$ (s, 6H, $2CH_3$), 7.66–8.72 (m, 8H, pyri-H), 9.10 (s, 2H, pyr-H), 9.55, 10.84 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 16.98$ ($2CH_3$), 166.05 (2C=N), 106.24, 112.34, 122.60, 125.82, 129.25, 145.50, 147.82, 149.00, 153.15, 153.78 (15C, pyr-C), 163.98 (CO); MS, *m/z* (%):407 [M^+, 16] and 273 (100). Anal. Calcd. for $C_{20}H_{18}ClN_7O$ (407.85): C, 58.90; H, 4.45; N, 24.04; Cl, 8.69. Found: C, 58.83; H, 4.37; N, 23.98; Cl, 8.63.

2-(2-(1-(Pyridin-4-yl)ethylidene)hydrazinyl)-6-chloro-N′-(1-(pyridin-4-yl)ethylidene)pyridine-4-carbohydrazide ***(8c)***

Yield 64 %, mp 184–186 °C (DMF/H_2O). IR (KBr, cm^{-1}): 3344 (NH), 2974 (CH-aliphatic), 1666 (C=O); ^{1}H NMR (DMSO-d_6, ppm): $\delta = 1.65$ (s, 6H, $2CH_3$), 7.86-8.72 (m, 10H, pyr-H), 9.76, 10.80 (2s, 2H, 2NH, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6, ppm): $\delta = 16.98$ ($2CH_3$), 166.56 (2C=N), 106.15, 110.85, 123.65, 137.86, 146.22, 148.45, 149.16, 153.30 (15C, pyr-C), 164.02 (CO); MS, *m/z* (%):407 [M^+, 8] and 169 (100). Anal. Calcd. for $C_{20}H_{18}ClN_7O$ (407.85): C, 58.90; H, 4.45; N, 24.04; Cl, 8.69. Found: C, 58.86; H, 4.40; N, 24.00; Cl, 8.65.

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References

1. A. Tostmann, M.J. Boeree, R.E. Aarnoutse, W.C.M. de Lange, A.J.M. van der Ven, R. Dekhuijzen, J. Gastroenterol. Hepatol. **23**, 192 (2008)
2. F.E. Anderson, G.F. Grail, F. Leonard, L.E. Tenenbaum, J.J. Hart, F.A. Barkley, J. Am. Pharm. Assoc. **45**, 348 (1956)
3. T.C. Sarich, T. Zhou, S.P. Adams, A.I. Bain, R.A. Wall, J.M. Wright, A model of isoniazid-induced hepatotoxicity in rabbits. J. Pharmacol. Toxicol. Methods **34**, 109 (1995)
4. J.R. Vishnu, D.A. Vidyohama, J. Vlietinck, J. Heterocycl. Chem. **24**, 1435 (1987)
5. A. Attia, O.I. Abdel-Salam, M.H. Abo-Ghalia, A.E. Amr, Egypt. J. Chem. **38**, 543 (1995)
6. A. Attia, O.I. Abdel-Salam, A.E. Amr, Egypt. J. Chem. **40**, 317 (1997)
7. A.E. Amr, O.I. Abdel-Salam, A. Attia, I. Stibor, Collect. Czech. Chem. Commun. **64**, 288 (1999)
8. A. Attia, O.I. Abdel-Salam, A.E. Amr, I. Stibor, M. Budesinsky, Egypt. J. Chem. **43**, 187 (2000)
9. A. Attia, O.I. Abdel-Salam, A.E. Amr, Egypt. J. Chem. **43**, 297 (2000)
10. M.A. Al-Omar, A.E. Amr, R.A. Al-Salahi, Arch. Pharm. Chem. Life Sci. **343**, 648 (2010)
11. A.E. Amr, A.M. Mohamed, A.A. Ibrahim, Z. Naturforsch **58b**, 861 (2003)
12. S.F. Mohamed, M.M. Youssef, A.E. Amr, E.R. Kotb, Sci. Pharm. **76**, 279 (2008)
13. A.E. Amr, M.H. Abo-Ghalia, M.M. Abdalah, Z. Naturforsch **61b**, 1335 (2006)
14. C. Kurumurthy, R.P. Sambasiva, S.B. Veera, K.G. Santhosh, R.P. Shanthan, B. Narsaiah, L.R. Velatooru, R. Pamanji, R.J. Venkateswara, Eur. J. Med. Chem. **46**, 3462 (2011)
15. J.K. Chakrabarti, L. Horsman, T.M. Hotten, I.A. Pullar, D.E. Tupper, F.C. Wright, J. Med. Chem. **23**, 878 (1980)
16. D.S. Lorrain, H. Schaffhauser, U.C. Campbell, C.S. Baccei, L.D. Correa, B. Rowe, D.E. Rodriguez, J.J. Anderson, M.A. Varney, A.B. Pinkerton, J.M. Vernier, L. Bristow, J. Neuropsychopharmacol **28**, 1622 (2003)
17. H.H. Fahmy, W. El-Eraky, Arch. Pharm. Res. **24**, 171 (2001)
18. E. De Clercq, Anticancer Res. **6**, 549 (1986)
19. J. Coetzee, S. Cronje, L. Dobrzańska, H.G. Raubenheimer, G. Jooné, M.J. Nell, H.C. Hoppe, Dalton Trans. **40**, 1471 (2011)
20. A.E. Amr, A.M. Mohamed, S.F. Mohamed, N.A. Abdel-Hafez, A.G. Hammam, Bioorg. Med. Chem. **14**, 5481 (2006)
21. A.G. Hammam, A.F.M. Fahmy, A.E. Amr, A.M. Mohamed, Indian J. Chem., Sect B **42B**, 1985 (2003)
22. J. Wang, H. Wang, Int. J. Biol. Macromol. **48**, 523 (2011)
23. M.A. Al-Omar, A.E. Amr, Molecules **15**, 4711 (2010)
24. R.A. Al-Salahi, M.A. Al-Omar, A.E. Amr, Molecules **15**, 6588 (2010)
25. A. Tgolsen, G.H. Rofland, O.G. Berge, K. Hole, J. Pharmacol. Methods **25**, 241 (1991)
26. A.A. Abou-Zeid, Y.M. Shehata, Indian J. Pharmacy **31**, 72 (1969)