# Synthesis and Reactions of New Chiral Linear Carboxamides with an Incorporated Peptide Linkage Using Nalidixic Acid and Amino Acids as Starting Materials

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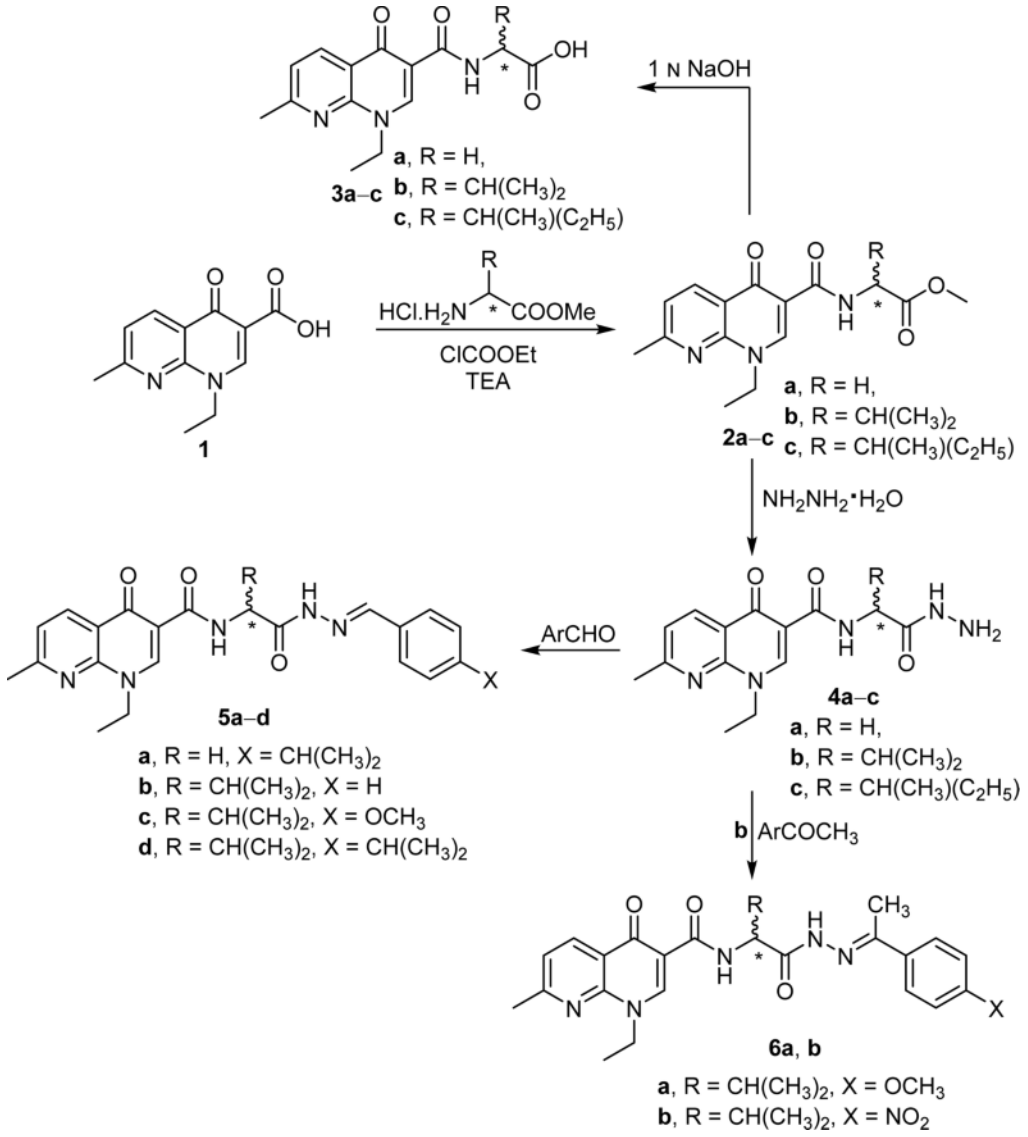
A series of chiral linear carboxamide derivatives (**2** – **15**) with an incorporated peptide linkage have been prepared *via* the coupling of 1-ethyl-1,4-dihydro-7-methyl-4-oxo-quinoline-3-carboxylic acid (nalidixic acid, **1**) with appropriate amino acid methyl esters. Coupling of **1** with amino acid methyl esters gave the corresponding peptide methyl esters **2**, which were hydrolyzed with methanolic sodium hydroxide to the corresponding acids **3**. Hydrazinolysis of esters **2** with hydrazine hydrate afforded the corresponding acid hydrazide derivatives **4**. The latter compounds were coupled with appropriate aldehydes or acetophenone derivatives to afford the corresponding Schiff base derivatives **5** and **6**, respectively. The hydrazide derivative **4b** was reacted with phenyl isothiocyanate or carbonyl derivatives to give the corresponding thiosemicarbazide **7** and compounds **8** – **10**, respectively. Also, **4b** was treated with acid monoanhydrides to give the corresponding imide derivatives **11** – **13**. Finally, **4b** was reacted with tetracarboxylic acid dianhydride derivatives to afford the corresponding diimido carboxamide derivatives **14** and **15**.

*Key words:* 1-Ethyl-1,4-dihydro-7-methyl-4-oxoquinoline-3-carboxylic Acid, Amino Acids, Chiral Derivatives, Schiff Base, Imides

## Introduction

In different areas of supramolecular and macrocyclic chemistry, the synthesis and complexing properties of azacrown compounds have been a subject of intensive exploration [1 – 7]. Synthesis and chemical modifications of existing antibacterial agents in order to generate novel macromolecules with better therapeutic properties are necessary because of the emergence of multidrug-resistant bacteria [8]. Peptides rarely function well as drugs due to their low bioavailability and rapid degradation within cells [9]. The conversion of these active peptides into peptidomimetics has been a successful approach for making new biologically active compounds [10]. In addition, we reported the synthesis of some macrocyclic candidates from dipicolinic acid with amino acids and the screening of their biological activity [11 – 16]. The peptide derivatives have antimicrobial and anti-inflammatory activities [17 – 20] and antitumor properties [21 – 24]. We also demonstrated that some peptido-heterocyclic derivatives exhibit a general ionophoric potency for divalent cations [25] and are useful for assembling novel thiocyanate-selective membrane sensors [26]. Recently, some new heterocyclic derivatives were synthesized which exhibit analgetic, anti-parkinsonian, androgenic anabolic, and anti-inflammatory activities [27 – 32]. On the other hand, semicarbazide, thiosemicarbazide, and imide derivatives show promising biological and pharmacological activities [33]. Recently, some new heterocyclic and macrocyclic pentapeptide derivatives have been studied with respect to anti-HIV [34, 35], anti-inflammatory [36], anticoagulant [37], analgesic and



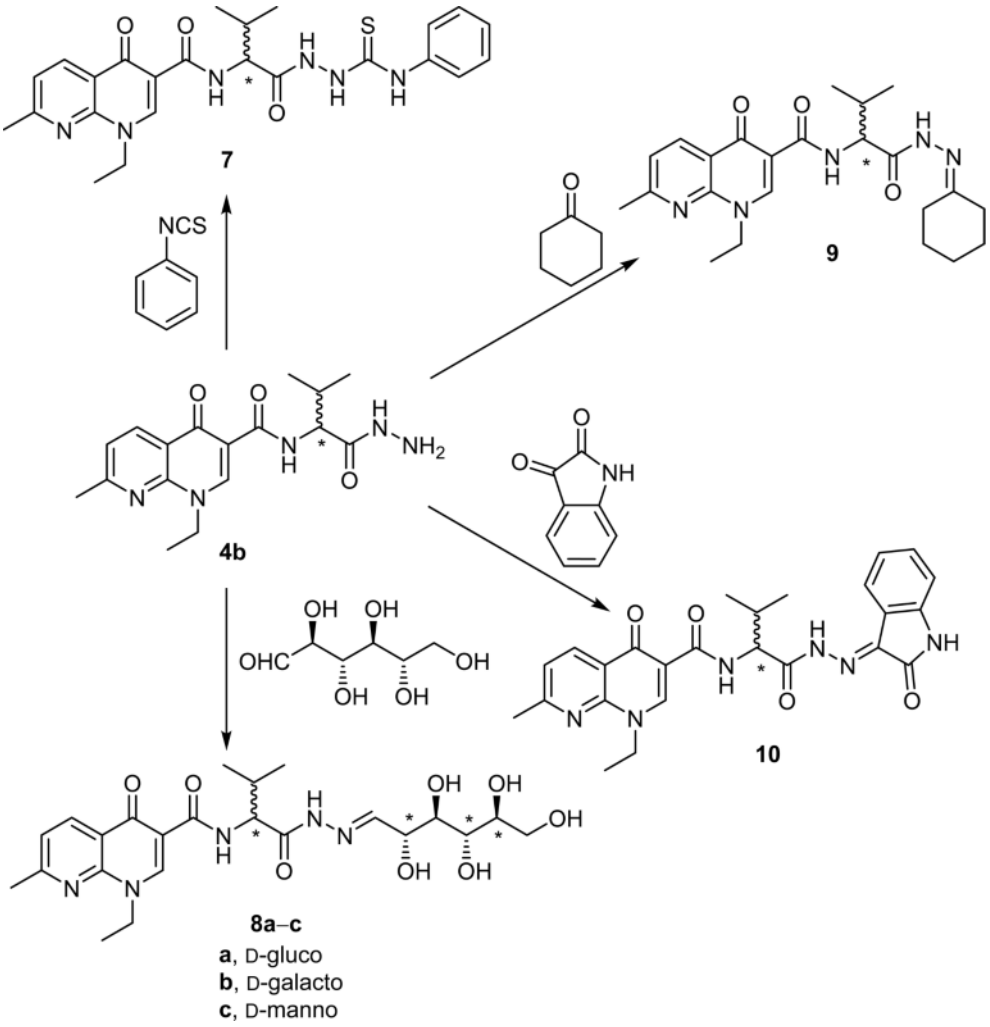

Scheme 1. Synthetic routes for compounds **2** – **6**.

anticonvulsant [38], anticancer [39], and antimicrobial activities [40 – 42]. In view of these observations and as a continuation of our previous works in heterocyclic chemistry, we have carried out the study presented in this report.

## Results and Discussion

Coupling of **1** (nalidixic acid) with amino acid methyl esters gave the corresponding peptide methyl esters **2**, which were hydrolyzed with methanolic sodium hydroxide to the corresponding acids **3**. Hydrazinolysis of esters **2** with hydrazine hydrate afforded the corresponding acid hydrazide derivatives **4**. The latter compounds were coupled with appropriate aldehyde and acetophenone derivatives to afford the corresponding Schiff bases **5** and **6**, respectively (Scheme 1).

The hydrazide derivative **4b** was reacted with phenyl isothiocyanate to give the corresponding



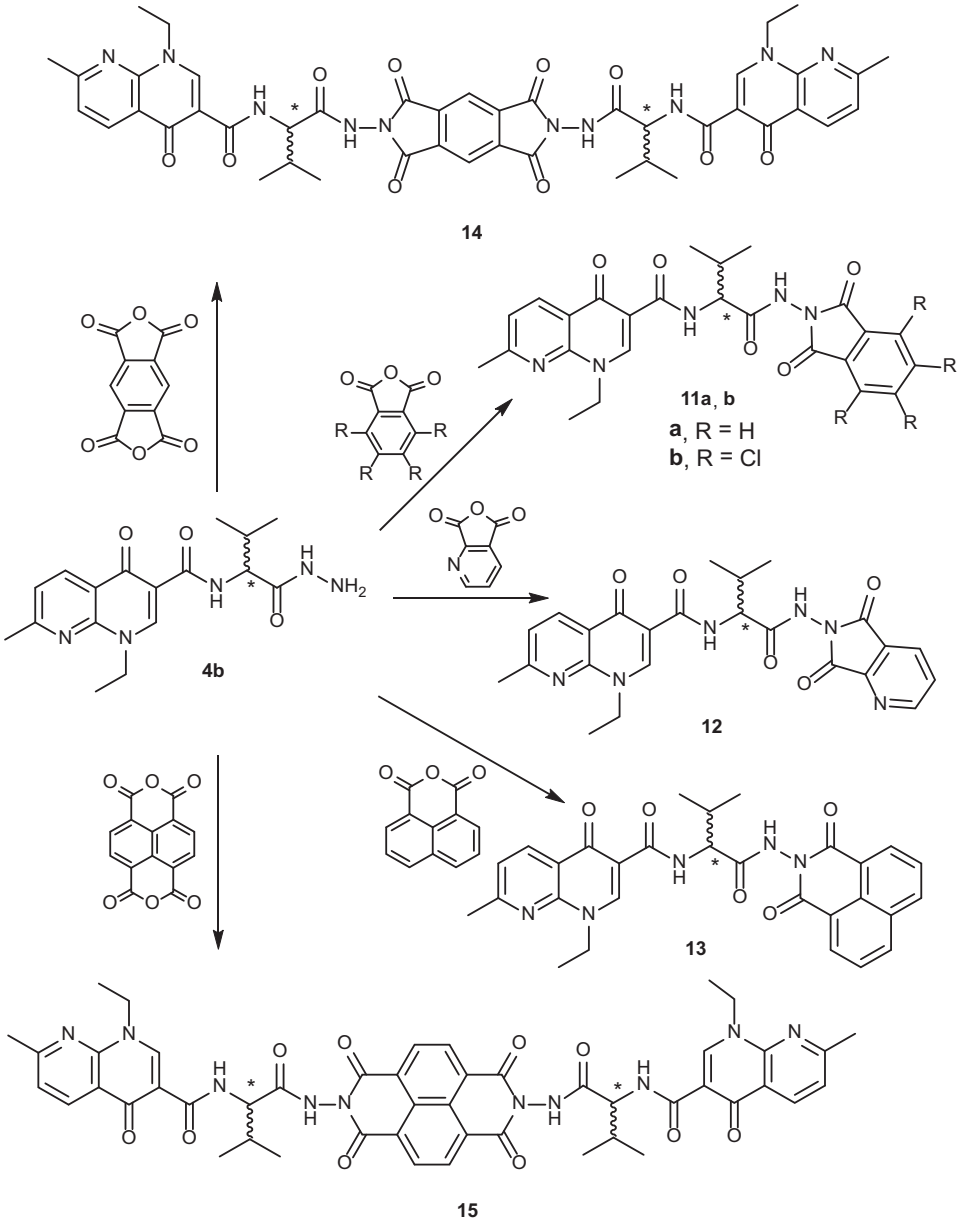

Scheme 2. Synthetic routes for compounds **7** – **10**.

thiosemicarbazide derivative **7**. In addition, **4b** was condensed with carbonyl derivatives, namely, hexoses, cyclohexanone or indoline-2,3-dione, in refluxing glacial acetic acid to give the corresponding condensed products **8** – **10**, respectively (Scheme 2).

Treatment of **4b** with acid mono acid anhydrides, namely, phthalic, tetrachlorophthalic-, 2,3-pyridine- or 1,8-naphthalenedicarboxylic acid anhydride, gave the corresponding imide derivatives **11** – **13**, respectively. **4b** was also reacted with tetracarboxylic acid dianhydride derivatives, namely, benzene- or naphthalenetetracarboxylic acid dianhydride, to afford the corresponding diimido carboxamide derivatives **14** and **15**, respectively (Scheme 3).

## Experimental

Melting points were determined in open glass capillary tubes with an Electro Thermal Digital apparatus, (model: IA9100) and are uncorrected. Elemental microanalyses for carbon, hydrogen and nitrogen (Microanalytical Unit, NRC) were found within the acceptable limits of the calculated values. Infrared spectra (KBr) were recorded on a Nexus 670 FTIR Nicolet Fourier transform infrared spectrometer. Proton nuclear magnetic resonance ($^1$H NMR) spectra were run in ([$D_6$]DMSO) on a Jeol 500 MHz instrument. Mass spectra were obtained on a MAT Finnigan SSQ 7000 spectrometer, using the electron impact technique (EI). Analytical thin layer chromatography (TLC) was performed on silica gel aluminum sheets, 60 $F_{254}$ (E. Merck). Specific op-




Scheme 3. Synthetic routes for compounds **11** – **15**.

tical rotations were measured with a A. Krawss, Optronic, P8000 polarimeter, in a 1 dm length observation tube, at the indicated conditions, and evaluated according to the equation: $[\alpha]_{\mathrm{D}}^{\mathrm{T}} = 100\alpha/(cl)$, where: $\alpha$ = observed rotation angle, D = sodium line ($\lambda = 589$ nm), $c$ = concentration (g per 100 mL), $l$ = path length in dm and $T$ = experimental temperature (°C).

*Synthesis of carboxamides **2a** – **c***

To a cold and stirred dry dichloromethane solution (25 mL, −20 °C) of nalidixic acid **1** (1 mmol), ethyl chloroformate (1 mmol) and triethylamine (1 mmol) were successively added. Ten minutes later, a cold methylene chloride solution (10 mL, −20 °C) of an amino acid methyl es-

ter, namely glycine methyl ester, L-valine methyl ester and isoleucine methyl ester (1 mmol), was added. Stirring of the cold reaction mixture (−20 °C) was continued for 3 h and at room temperature overnight. The solution was then washed with water, 1 N hydrochloric acid, 1 N sodium bicarbonate, and finally with water (250 mL). The dried solution (anhydrous $CaCl_2$) was evaporated, and the obtained oily residue was solidified by trituration with dry ether, filtered off, dried under vacuum, and recrystallized to afford the esters **2a – c**.

*Methyl {[(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)carbonyl]amino}acetate (**2a**)*

Yield 73 %; m. p. 134 – 135 °C (MeOH). – IR (KBr): $\nu$ = 3391 (NH), 1745 (C=O, ester), 1719 (C=O), 1665, 1534, 1255 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta$ = 0.99 (t, 3H, $CH_3$), 2.48 (s, 3H, $CH_3$), 3.12 (q, 2H, $CH_2$), 3.86 (s, 3H, $OCH_3$), 4.09 (s, 2H, $CH_2$), 6.90 (d, 1H, Ar-H), 7.81 (d, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 9.85 (s, 1H, NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta$ = 13.23, 24.94, 41.25, 50.12, 52.31, 113.28, 114.56, 118.87, 138.12, 149.11, 155.62, 160.35, 163.10, 170.02, 177.81 ppm. – MS (EI, 70 eV): $m/z(\%)$ = 303 (22) $[M]^+$. – $C_{15}H_{17}N_3O_4$ (303.31): calcd. C 59.40, H 5.65, N 13.85; found C 59.35, H 5.60, N 13.80.

*Methyl 2-{[(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)carbonyl]amino}-3-methylbutanoate (**2b**)*

Yield 67 %; m. p. 122 – 123 °C (MeOH). – $[\alpha]_D^{25}$ = −105.3 ($c$ = 0.5, MeOH). – IR (KBr): $\nu$ = 3375 (NH), 1741 (C=O, ester), 1722 (C=O), 1662, 1530, 1252 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta$ = 1.01 (t, 3H, $CH_3$), 1.03 (d, 6H, 2 $CH_3$), 2.40 (s, 3H, $CH_3$), 3.04 (q, 2H, $CH_2$), 2.86 (m, 1H, CH), 3.89 (s, 3H, $OCH_3$), 4.58 (d, 1H, CH), 6.68 (d, 1H, Ar-H), 7.65 (d, 1H, Ar-H), 8.01 (s, 1H, Ar-H), 9.54 (s, 1H, NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta$ = 13.08, 17.62, 24.78, 33.37, 49.80, 52.26, 56.74, 113.93, 114.29, 118.66, 138.13, 148.42, 155.68, 160.18, 163.12, 172.03, 178.24 ppm. – MS (EI, 70 eV): $m/z(\%)$ = 345 (34) $[M]^+$. – $C_{18}H_{23}N_3O_4$ (345.39): calcd. C 62.59, H 6.71, N 12.17; found C 62.54, H 6.65, N 12.12.

*Methyl 2-{[(1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)carbonyl]amino}-3-ethylbutanoate (**2c**)*

Yield 70 %; m. p. 140 – 141 °C (MeOH). – $[\alpha]_D^{25}$ = −76.45 ($c$ = 0.5, MeOH). – IR (KBr): $\nu$ = 3371 (NH), 1735 (C=O, ester), 1715 (C=O), 1662, 1536, 1254 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta$ = 0.98 (t, 3H, $CH_3$), 1.05 (t, 3H, $CH_3$), 1.14 (d, 3H, $CH_3$), 1.35 (m, 2H, $CH_2$), 2.45 (s, 3H, $CH_3$), 2.89 (m, 1H, CH), 3.14 (q, 2H, $CH_2$), 3.80 (s, 3H, $OCH_3$), 4.59 (s, 1H, CH), 6.72 (d, 1H, Ar-H), 7.86 (d, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 10.12 (s, 1H, NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta$ = 11.71, 12.96, 14.87, 24.57, 25.43, 37.25, 49.81, 52.38, 54.02, 113.51, 114.32, 118.84, 138.38, 148.34, 155.78, 160.20, 162.80, 172.18, 178.35 ppm. – MS (EI, 70 eV): $m/z(\%)$ = 359 (22) $[M]^+$. – $C_{19}H_{25}N_3O_4$ (359.42): calcd. C 63.49, H 7.01, N 11.69; found C 63.44, H 6.95, N 11.64.

*Synthesis of acid derivatives **3a – c***

Sodium hydroxide (1 N, 25 mL) was added dropwise to a cold and stirred ethanolic solution (1 mmol, −5 °C) of an ester **2a – c**. Stirring was continued at that temperature for 2 h and then for 12 h at room temperature followed by evaporation of the solvent. The cold reaction mixture was acidified with 1 N hydrochloric acid to pH ≈ 3, and the obtained solid was filtered off, washed with cold water, dried, and recrystallized to afford the title acid derivatives **3a – c**, respectively.

*{[(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)carbonyl]amino}acetic acid (**3a**)*

Yield 61 %; m. p. 201 – 202 °C (EtOH-ether). – IR (KBr): $\nu$ = 3473, 3375 (NH, OH), 1724 (C=O, acid), 1718 (C=O), 1666, 1537, 1256 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta$ = 0.98 (t, 3H, $CH_3$), 2.43 (s, 3H, $CH_3$), 3.16 (q, 2H, $CH_2$), 4.12 (s, 2H, $CH_2$), 6.60 (d, 1H, Ar-H), 7.74 (d, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 9.31, 10.61 (2s, 2H, NH, OH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta$ = 14.16, 23.89, 44.13, 50.32, 113.64, 114.78, 118.41, 137.95, 149.11, 154.83, 160.14, 163.25, 173.50, 179.21 ppm. – MS (EI, 70 eV): $m/z(\%)$ = 289 [$M^+$, 26]. $C_{14}H_{15}N_3O_4$ (289.29): calcd. C 58.13; H 5.23; N 14.53; found C 58.07; H 5.18; N 14.47.

*2-{[(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)carbonyl]amino}-3-methyl-butanoic acid (**3b**)*

Yield 67 %; m. p. 180 – 182 °C (EtOH-ether). – $[\alpha]_D^{25}$ = −112.1 ($c$ = 0.5, MeOH). – IR (KBr): $\nu$ = 3482, 3370 (NH, OH), 1723 (C=O, acid), 1716 (C=O), 1662, 1535, 1254 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta$ = 1.00 (t, 3H, $CH_3$), 1.04 (d, 6H, 2 $CH_3$), 2.49 (s, 3H, $CH_3$), 2.81 (m, 1H, CH), 3.16 (q, 2H, $CH_2$), 4.47 (d, 1H, CH), 6.65 (d, 1H, Ar-H), 7.78 (d, 1H, Ar-H), 8.01 (s, 1H, Ar-H), 9.54, 10.52 (2s, 2H, NH, OH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta$ = 13.45, 18.53, 23.94, 31.86, 49.26, 59.12, 114.33, 115.49, 118.24, 138.65, 149.06, 156.11, 160.22, 163.18, 175.25, 178.98 ppm. – MS (EI, 70 eV): $m/z(\%)$ = 331 (18) $[M]^+$. – $C_{17}H_{21}N_3O_4$ (331.37): calcd. C 61.62, H 6.39, N 12.68; found C 61.56, H 6.33, N 12.63.

*2-{[(1-Ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridin-3-yl)carbonyl]amino}-3-ethyl-butanoic acid (**3c**)*

Yield 63 %; m. p. 192 – 194 °C (EtOH-ether). – $[\alpha]_D^{25} = -96.5$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3486$, 3378 (NH, OH), 1728 (C=O, acid), 1722 (C=O), 1664, 1532, 1251 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta = 0.98$ (t, 3H, $CH_3$), 1.06 (t, 3H, $CH_3$), 1.12 (d, 3H, $CH_3$), 1.34 (m, 2H, $CH_2$), 2.48 (s, 3H, $CH_3$), 2.76 (m, 1H, CH), 3.17 (q, 2H, $CH_2$), 4.31 (s, 1H, CH), 6.79 (d, 1H, Ar-H), 7.86 (d, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 9.62, 10.49 (2s, 2H, NH, OH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta = 11.75$, 13.29, 15.36, 25.16, 25.64, 36.57, 49.55, 56.19, 113.79, 114.69, 118.85, 138.74, 148.96, 155.81, 160.38, 162.78, 175.49, 177.61 ppm. – MS (EI, 70 eV): $m/z(\%) = 345$ (15) $[M]^+$. – $C_{18}H_{23}N_3O_4$ (345.39): calcd. C 62.59, H 6.71, N 12.17; found C 62.54, H 6.65, N 12.12.

*Synthesis of hydrazide derivatives **4a – c***

Hydrazine hydrate (0.8 mL, 16 mmol) was added to a methanolic solution (10 mL) of **3** (1 mmol). The reaction mixture was refluxed for 10 h, after which the solvent was evaporated under reduced pressure. The obtained residue was triturated with ether, filtered off, and recrystallized to afford the corresponding hydrazides **4a – c**.

*1-Ethyl-N-(2-hydrazinyl-2-oxoethyl)-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**4a**)*

Yield 68 %; m. p. 243 – 245 °C (MeOH). – IR (KBr): $\nu = 3510 - 3376$ (NH, $NH_2$), 1718 (C=O), 1665, 1535, 1252 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta = 1.00$ (t, 3H, $CH_3$), 2.40 (s, 3H, $CH_3$), 3.11 (q, 2H, $CH_2$), 4.05 (s, 2H, $CH_2$), 4.28 (s, 2H, $NH_2$, exchangeable with $D_2O$), 6.58 (d, 1H, Ar-H), 7.80 (d, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 8.34, 9.67 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta = 13.24$, 24.61, 44.93, 50.45, 113.49, 114.71, 118.56, 138.04, 149.26, 155.10, 169.97, 162.85, 170.43, 178.50 ppm. – MS (EI, 70 eV): $m/z(\%) = 303$ (12) $[M]^+$. – $C_{14}H_{17}N_5O_3$ (303.32): calcd. C 55.44, H 5.65, N 23.09; found C 55.40, H 5.60, N 23.00.

*1-Ethyl-N-(1-hydrazinyl-3-methyl-1-oxobutan-2-yl)-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**4b**)*

Yield 60 %; m. p. 258 – 260 °C (MeOH). – $[\alpha]_D^{25} = -146.6$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3486 - 3319$ (NH, $NH_2$), 1716 (C=O), 1660, 1534, 1256 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta = 1.00$ (t, 3H, $CH_3$), 1.06 (d, 6H, 2 $CH_3$), 2.47 (s, 3H, $CH_3$), 2.84 (m, 1H, CH), 3.13 (q, 2H, $CH_2$), 4.36 (s, 2H, $NH_2$, exchangeable with $D_2O$), 4.45 (d, 1H, CH), 6.70 (d, 1H, Ar-H), 7.84 (d, 1H, Ar-H), 7.88 (s, 1H, Ar-H), 8.17, 9.71 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta = 13.34$, 18.42, 24.06, 31.53, 49.18, 59.73, 113.92, 114.85, 118.79, 138.44, 148.90, 155.81, 159.78, 163.20, 170.65, 178.01 ppm. – MS (EI, 70 eV): $m/z(\%) = 345$ (44) $[M]^+$. – $C_{17}H_{23}N_5O_3$ (345.40): calcd. C 59.12, H 6.71, N 20.28; found C 59.06, H 6.65, N 20.22.

*1-Ethyl-N-(1-hydrazinyl-3-ethyl-1-oxobutan-2-yl)-7-methyl-4-oxo-1,4-dihydro-1,8-naphth-yridine-3-carboxamide (**4c**)*

Yield 64 %; m. p. 221 – 223 °C (MeOH). – $[\alpha]_D^{25} = -89.5$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3594 - 3349$ (NH, $NH_2$), 1721 (C=O), 1668, 1537, 1255 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta = 0.95$ (t, 3H, $CH_3$), 1.02 (t, 3H, $CH_3$), 1.14 (d, 3H, $CH_3$), 1.32 (m, 2H, $CH_2$), 2.43 (s, 3H, $CH_3$), 2.86 (m, 1H, CH), 3.19 (q, 2H, $CH_2$), 4.30 (s, 2H, $NH_2$, exchangeable with $D_2O$), 4.49 (s, 1H, CH), 6.60 (d, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 8.28, 9.64 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta = 11.64$, 13.22, 15.29, 25.11, 25.54, 36.74, 49.68, 56.21, 113.60, 114.72, 118.93, 138.68, 149.03, 155.75, 160.43, 162.82, 170.66, 177.65 ppm. – MS (EI, 70 eV): $m/z(\%) = 359$ (8) $[M]^+$. – $C_{18}H_{25}N_5O_3$ (359.42): calcd. C 60.15, H 7.01, N 19.48; found C 60.10, H 6.95, N 19.43.

*Synthesis of hydrazone derivatives **5a – d** and **6a, b***

A stirred solution of hydrazide **4** (1 mmol) and active carbonyl derivatives, namely 4-isopropylbenzaldehyde, benzaldehyde, 4-methoxybenzaldehyde, 4-methoxyacetophenone, or 4-nitroacetophenone (1 mmol), in acetic acid (30 mL) was refluxed for 2 – 4 h. The reaction mixture was allowed to cool and the obtained solid product was filtered off, dried, and recrystallized to give the corresponding hydrazones **5a – d**, respectively.

*N-{2-[2-(4-Isopropylbenzylidene)hydrazinyl]-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**5a**)*

Yield 68 %; m. p. 201 – 203 °C (AcOH). – IR (KBr): $\nu = 3370$, 3229 (2 NH), 1715 (C=O), 1662, 1534, 1250 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [$D_6$]DMSO): $\delta = 1.00$ (t, 3H, $CH_3$), 1.32 (d, 6H, 2 $CH_3$), 2.45 (s, 3H, $CH_3$), 3.16 (q, 2H, $CH_2$), 3.27 (m, 1H, CH), 4.10 (s, 2H, $CH_2$), 6.76 –8.11 (m, 8H, Ar-H + CH=N), 8.42, 9.71 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [$D_6$]DMSO): $\delta = 13.19$, 23.86, 24.74, 36.49, 45.70, 49.23, 113.43, 114.55, 118.48, 126.56, 129.24, 131.19, 138.15, 142.94, 149.09, 151.14, 155.57, 160.00,

162.79, 173.50, 177.63 ppm. – MS (EI, 70 eV): $m/z(\%) =$ 433 (32) $[M]^+$. – $C_{24}H_{27}N_5O_3$ (433.50): calcd. C 66.49, H 6.28, N 16.16; found C 66.44, H 6.23, N 16.11.

*N-{2-[2-Benzylidenehydrazinyl]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**5b**)*

Yield 70 %; m. p. 213 – 215 °C (AcOH). – $[\alpha]_D^{25} = -58.7$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3364$, 3210 (2 NH), 1721 (C=O), 1656, 1538, 1254 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.02$ (t, 3H, $CH_3$), 1.10 (d, 6H, 2 $CH_3$), 2.40 (s, 3H, $CH_3$), 2.80 (m, 1H, CH), 3.16 (q, 2H, $CH_2$), 4.47 (d, 1H, CH), 6.75 −8.13 (m, 9H, Ar-H + CH=N), 8.37, 9.68 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.25$, 17.98, 24.86, 31.42, 49.23, 60.81, 113.75, 114.46, 118.69, 129.19, 129.57, 131.28, 134.15, 138.39, 143.50, 148.86, 155.92, 160.01, 163.35, 176.95, 177.91 ppm. – MS (EI, 70 eV): $m/z(\%) = 433$ (12) $[M]^+$. – $C_{24}H_{27}N_5O_3$ (433.50): calcd. C 66.49, H 6.28, N 16.16; found C 66.43, H 6.22, N 16.12.

*N-{2-[2-(4-Methoxybenzylidene)hydrazinyl]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**5c**)*

Yield 72 %; m. p. 278 – 280 °C (AcOH). – $[\alpha]_D^{25} = -38.3$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3469$, 3219 (2 NH), 1718 (C=O), 1664, 1537, 1248 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.00$ (t, 3H, $CH_3$), 1.08 (d, 6H, 2 $CH_3$), 2.45 (s, 3H, $CH_3$), 2.83 (m, 1H, CH), 3.12 (q, 2H, $CH_2$), 3.86 (s, 3H, $OCH_3$), 4.55 (d, 1H, CH), 6.68 – 8.09 (m, 8H, Ar-H + CH=N), 8.22, 9.78 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.21$, 18.10, 24.71, 31.56, 49.41, 56.14, 61.23, 113.83, 114.26, 114.52, 118.64, 126.27, 130.34, 138.32, 143.56, 148.89, 155.71, 159.87, 162.77, 163.25, 177.06, 177.84 ppm. – MS (EI, 70 eV): $m/z(\%) =$ 463 (10) $[M]^+$. – $C_{25}H_{29}N_5O_4$ (463.53): calcd. C 64.78, H 6.31, N 15.11; found C 64.72, H 6.25, N 15.05.

*N-{2-[2-(4-Isopropylbenzylidene)hydrazinyl]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**5d**)*

Yield 53 %; m. p. 238 – 240 °C (AcOH). – $[\alpha]_D^{25} = -140.8$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3369$, 3225 (2 NH), 1716 (C=O), 1660, 1540, 1249 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.99$ (t, 3H, $CH_3$), 1.04 (d, 6H, 2 $CH_3$), 1.23 (d, 6H, 2 $CH_3$), 2.44 (s, 3H, $CH_3$), 2.95 (m, 1H, CH), 3.12 (q, 2H, $CH_2$), 3.21 (m, 1H, CH), 4.43 (d, 1H, CH), 6.72 – 8.10 (m, 8H, Ar-H + CH=N), 8.41, 9.73 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.20$, 18.14, 23.55, 24.83, 31.51, 36.49, 49.15, 60.92, 113.70, 114.42, 118.71, 126.42, 129.35, 131.26, 138.37, 143.59, 148.86, 151.14, 155.81, 160.11, 163.26, 177.19, 177.89 ppm. – MS (EI, 70 eV): $m/z(\%) = 476$ (24) $[M]^+$. – $C_{27}H_{33}N_5O_3$ (475.58): calcd. C 68.19, H 6.99, N 14.73; found C 68.14, H 6.93, N 14.68.

*N-(2-{2-[1-(4-Methoxyphenyl)ethylidene]hydrazinyl}-1-isopropyl-2-oxoethyl)-4-oxo-1-ethyl-7-methyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**6a**)*

Yield 51 %; m. p. 154 – 156 °C (AcOH). – $[\alpha]_D^{25} = -27.4$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3393$, 3212 (2 NH), 1718 (C=O), 1658, 1536, 1251 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.99$ (t, 3H, $CH_3$), 1.15 (d, 6H, 2 $CH_3$), 2.23 (s, 3H, $CH_3$), 2.44 (s, 3H, $CH_3$), 2.76 (m, 1H, CH), 3.11 (q, 2H, $CH_2$), 3.81 (s, 3H, $OCH_3$), 4.46 (d, 1H, CH), 6.72 – 7.90 (m, 7H, Ar-H), 8.35, 9.64 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.17$, 18.22, 23.11, 24.95, 31.43, 49.50, 56.23, 61.14, 113.64, 114.20, 114.57, 118.71, 126.39, 130.31, 138.29, 148.81, 155.74, 159.83, 162.79, 163.19, 169.05, 177.14, 177.80 ppm. – MS (EI, 70 eV): $m/z(\%) = 478$ (6) $[M]^+$. – $C_{26}H_{31}N_5O_4$ (477.56): calcd. C 65.39, H 6.54, N 14.66; found C 65.34, H 6.50, N 14.60.

*N-(2-{2-[1-(4-Nitrophenyl)ethylidene]hydrazinyl}-1-isopropyl-2-oxoethyl)-4-oxo-1-ethyl-7-methyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**6b**)*

Yield 53 %; m. p. 196 – 198 °C (AcOH). – $[\alpha]_D^{25} = -66.2$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3380$, 3329 (2 NH), 1720 (C=O), 1654, 1532, 1250 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.00$ (t, 3H, $CH_3$), 1.10 (d, 6H, 2 $CH_3$), 2.41 (s, 3H, $CH_3$), 2.46 (s, 3H, $CH_3$), 2.99 (m, 1H, CH), 3.16 (q, 2H, $CH_2$), 4.56 (d, 1H, CH), 6.70 – 8.0 (m, 7H, Ar-H), 8.41, 9.76 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.22$, 18.20, 23.24, 24.89, 31.47, 49.58, 60.91, 113.59, 114.26, 118.69, 121.42, 130.38, 138.31, 141.12, 148.78, 151.03, 155.79, 159.66, 162.75, 168.90, 177.24, 177.63 ppm. – MS (EI, 70 eV): $m/z(\%) = 492$ (10) $[M]^+$. – $C_{25}H_{28}N_6O_5$ (492.53): calcd. C 60.96, H 5.73, N 17.06; found C 60.90, H 5.65, N 17.00.

*N-{2-Oxo-1-isopropyl-2-[2-(phenylcarbamothioyl)hydrazinyl]ethyl}-1,4-dihydro-1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxamide (**7**)*

Equimolar quantities of the acid hydrazide **4** (20 mmol) and phenyl isothiocyanate (20 mmol) were dissolved in absolute ethanol (50 mL) and the solution refluxed for 3 h and then allowed to cool to room temperature. Fine crystals of

the thiosemicarbazide **8** were separated out, filtered off, and recrystallized from methanol to afford the compound in 81 % yield; m. p. 131 – 133 °C. – $[\alpha]_D^{25} = -64.6$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3375 - 3211$ (2 NH), 1719 (C=O), 1656, 1535, 1251 (C=O, amide I, II and III), 1198 (C=S) $cm^{-1}$. – $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.01$ (t, 3H, $CH_3$), 1.10 (d, 6H, 2 $CH_3$), 2.51 (s, 3H, $CH_3$), 2.85 (m, 1H, CH), 3.17 (q, 2H, $CH_2$), 4.41 (d, 1H, CH), 6.53 – 7.96 (m, 8H, Ar-H), 8.53, 9.74, 10.34 (br s, 3H, 3 NH, exchangeable with $D_2O$) ppm. – $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.28$, 18.23, 24.86, 31.47, 49.25, 61.17, 113.89, 114.36, 118.82, 125.12, 126.78, 128.94, 137.21, 138.34, 148.86, 155.79, 160.14, 162.72, 170.55, 177.68, 181.60 ppm. – MS (EI, 70 eV): $m/z(\%) = 480$ (7) $[M]^+$. – $C_{24}H_{28}N_6O_3S$ (480.58): calcd. C 59.98, H 5.87, N 17.49, S 6.67; found C 59.92, H 5.81, N 17.44, S 6.62.

*Synthesis of N'-(glycosyl)acetohydrazide derivatives **8a – c***

A mixture of **4** (10 mmol), D-glucose, D-galactose or D-mannose (10 mmol), and a catalytic amount of acetic acid was heated at reflux in ethanol (50 mL) for 2 – 4 h, the reaction mixture was allowed to cool to room temperature, the precipitate was filtered off, washed with ethanol, dried and recrystallized from methanol to afford compounds **8a – c**.

*N-{2-(D-Glucomethylene)hydrazinyl]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**8a**)*

Yield 45 %; m. p. 223 – 225 °C (MeOH). – $[\alpha]_D^{25} = -18.4$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3546 - 3319$ (OH, NH), 1719 (C=O), 1660, 1538, 1258 (C=O, amide I, II and III) $cm^{-1}$. – $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.00$ (t, 3H, $CH_3$), 1.14 (d, 6H, 2 $CH_3$), 2.40 (s, 3H, $CH_3$), 2.84 (m, 1H, CH), 3.18(q, 2H, $CH_2$), 3.25 – 3.61 (m, 4H, 6′H, 6″H, 5′H, 4′H), 3.96 (t, 1H, 6′OH), 4.37 (m, 2H, 5′OH, 4′OH), 4.53 (d, 1H, CH), 5.26 (m, 3H, 2′H, 3′H, 3′OH), 5.57 (d, 1H, 2′OH), 6.90 (d, 1H, Ar-H), 7.13 (d, 1H, 1′H), 7.81 (d, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 8.31, 9.84 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.18$, 18.24, 24.68, 31.52, 49.45, 60.89, 63.96, 67.11, 71.32, 72.15, 73.50, 113.52, 114.33, 118.54, 138.36, 148.82, 153.64, 155.75, 159.60, 162.78, 177.17, 177.59 ppm. – MS (EI, 70 eV): $m/z(\%) = 507$ (22) $[M]^+$. – $C_{23}H_{33}N_5O_8$ (507.54): calcd. C 54.43, H 6.55, N 13.80; found C 54.38, H 6.50, N 13.75.

*N-{2-[2-(D-Galactomethylene)hydrazinyl]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**8b**)*

Yield 43 %; m. p. 202 – 204 °C (MeOH). – $[\alpha]_D^{25} = -38.5$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3540 - 3328$ (OH, NH), 1715 (C=O), 1660, 1540, 1247 (C=O, amide I, II and III) $cm^{-1}$. – $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.01$ (t, 3H, $CH_3$), 1.11 (d, 6H, 2 $CH_3$), 2.43 (s, 3H, $CH_3$), 2.78 (m, 1H, CH), 3.16 (q, 2H, $CH_2$), 3.24 – 3.38 (m, 2H, 6′-H, 6″-H), 3.54 (m, 2H, 5′-H, 4′-H), 3.81 (t, 1H, 6′-OH, exchangeable with $D_2O$), 4.16 (m, 2H, 5′-OH, 4′-OH, exchangeable with $D_2O$), 4.45 (m, 3H, 2′-H, 3′-H, 3′-OH, exchangeable with $D_2O$), 4.55 (d, 1H, CH), 4.76 (d, 1H, 2′-OH, exchangeable with $D_2O$), 6.95 (t, 1H, Ar-H), 7.23 (d, 1H, 1′-H), 7.90 (t, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 8.42, 9.75 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.12$, 18.32, 24.74, 31.62, 49.40, 60.93, 63.01, 68.16, 72.28, 73.24, 74.55, 113.63, 114.45, 118.49, 138.41, 148.78, 153.72, 155.69, 159.56, 162.80, 177.21, 177.65 ppm. – MS (EI, 70 eV): $m/z(\%) = 507$ (30) $[M]^+$. – $C_{23}H_{33}N_5O_8$ (507.54): calcd. C 54.43, H 6.55, N 13.80; found C 54.35, H 6.50, N 13.75.

*N-{2-[2-(D-Mannomethylene)hydrazinyl]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**8c**)*

Yield 50 %; m. p. 191 – 193 °C (MeOH). – $[\alpha]_D^{25} = -46.3$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3560 - 3347$ (OH, NH), 1722 (C=O), 1660, 1536, 1254 (C=O, amide I, II and III) $cm^{-1}$. – $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.98$ (t, 3H, $CH_3$), 1.10 (d, 6H, 2 $CH_3$), 2.52 (s, 3H, $CH_3$), 2.72 (m, 1H, CH), 3.16 (q, 2H, $CH_2$), 3.21 – 3.38 (m, 2H, 6′-H, 6″-H), 3.46 – 3.57 (m, 3H, 5′-H, 4′-H, 6′-OH, exchangeable with $D_2O$), 4.19 (d, 1H, 5′-OH, exchangeable with $D_2O$), 4.29 (d, 1H, 4′-OH, exchangeable with $D_2O$), 4.45 (m, 3H, 2′-H, 3′-H, 3′-OH, exchangeable with $D_2O$), 4.53 (d, 1H, CH), 4.78 (d, 1H, 2′-OH, exchangeable with $D_2O$), 6.90 (d, 1H, Ar-H), 7.70 (d, 1H, 1′-H), 7.86 (d, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 8.39, 9.76 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.15$, 18.19, 24.71, 31.47, 49.51, 60.93, 63.89, 67.23, 71.27, 72.31, 73.63, 113.49, 114.33, 118.59, 138.33, 148.89, 153.75, 155.83, 159.77, 162.85, 177.23, 177.61 ppm. – MS (EI, 70 eV): $m/z(\%) = 507$ (18) $[M]^+$. – $C_{23}H_{33}N_5O_8$ (507.54): calcd. C 54.43, H 6.55, N 13.80; found C 54.36, H 6.50, N 13.74.

*Synthesis of acetohydrazone derivatives **9** and **10***

A stirred glacial acetic acid suspension (20 mL) of hydrazide **4** (10 mmol) and ketonic derivatives, namely cyclohexanone or isatin (10 mmol), was refluxed for 3 h and then allowed to cool to room temperature. The separated solid was collected by filtration, dried, and recrystallized to yield the corresponding acetohydrazide derivatives **9** and **10**, respectively.

*N-[2-(2-Cyclohexylidenehydrazinyl)-1-isopropyl-2-oxoethyl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**9**)*

Yield 66 %; m. p. 131 – 133 °C (AcOH). – $[\alpha]_D^{25} = -78.2$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3347, 3319$ (2 NH), 1718 (C=O), 1658, 1540, 1254 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.99$ (t, 3H, $CH_3$), 1.08 (d, 6H, 2 $CH_3$), 1.25 – 1.37 (m, 10H, $CH_2$), 2.45 (s, 3H, $CH_3$), 2.85 (m, 1H, CH), 3.12 (q, 2H, $CH_2$), 4.56 (d, 1H, CH), 6.73 (d, 1H, Ar-H), 7.79 (d, 1H, Ar-H), 8.02 (s, 1H, Ar-H), 8.43, 9.84 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.22$, 18.20, 24.78, 24.96, 27.13, 28.36, 31.44, 34.25, 49.31, 60.98, 113.75, 114.29, 118.71, 138.28, 148.80, 155.72, 159.67, 161.85, 162.78, 177.15, 179.59 ppm. – MS (EI, 70 eV): $m/z(\%) = 425$ (14) $[M]^+$. – $C_{23}H_{31}N_5O_3$ (425.52): calcd. C 64.92, H 7.34, N 16.46; found C 64.85, H 7.30, N 16.40.

*4-Oxo-N-{2-oxo-1-isopropyl-2-[(2E)-2-(2-oxo-1,2-dihydro-3H-indol-3-ylidene)hydrazinyl]-ethyl}-1-ethyl-7-methyl-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**10**)*

Yield 77 %; m. p. 160 – 162 °C (AcOH). – $[\alpha]_D^{25} = -86.4$ ($c = 0.5$, MeOH). – IR (KBr): $\nu = 3429 – 3365$ (3NH), 1720 (C=O), 1655, 1542, 1254 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.02$ (t, 3H, $CH_3$), 1.12 (d, 6H, 2 $CH_3$), 2.40 (s, 3H, $CH_3$), 2.69 (m, 1H, CH), 3.16 (q, 2H, $CH_2$), 4.43 (d, 1H, CH), 6.67 – 8.11 (m, 7H, Ar-H), 8.38, 9.79, 10.57 (3s, 3H, 3 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.19$, 17.95, 24.73, 31.51, 49.26, 60.90, 113.82, 114.17, 117.92, 118.65, 121.83, 124.55, 129.63, 131.56, 133.05, 138.21, 146.74, 148.65, 155.79, 159.77, 162.70, 167.60, 177.10, 177.55 ppm. – MS (EI, 70 eV): $m/z(\%) = 474$ (16) $[M]^+$. – $C_{25}H_{26}N_6O_4$ (474.51): calcd. C 63.28, H 5.52, N 17.71; found C 63.22, H 5.46, N 17.65.

*Synthesis of imide derivatives **11 – 13***

A stirred glacial acetic acid suspension (30 mL) of hydrazide **4** (1 mmol) and an acid anhydride derivative, namely phthalic anhydride, 1,2,4,5-tetrachlorophthalic anhydride, naphthalene-1,8-dicarboxylic acid anhydride or quinolinic anhydride (1 mmol), was heated (80 °C) for 1 – 3 h. The reaction mixture was concentrated under reduced pressure, cooled, and the separated solid was collected by filtration, dried, and recrystallized to yield the corresponding imide derivatives **11a**, **b**, **12** and **13**, respectively.

*N-{2-[(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**11a**)*

Yield 78 %; m. p. 126 – 128 °C (AcOH-ether). – $[\alpha]_D^{25} = -106.4$ ($c = 0.5$, DMF). – IR (KBr): $\nu = 3371, 3324$ (2 NH), 1719 (C=O), 1654, 1534, 1250 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.01$ (t, 3H, $CH_3$), 1.06 (d, 6H, 2 $CH_3$), 2.48 (s, 3H, $CH_3$), 2.74 (m, 1H, CH), 3.14 (q, 2H, $CH_2$), 4.41 (d, 1H, CH), 6.65 – 8.15 (m, 7H, Ar-H), 8.79, 9.34 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.16$, 18.25, 24.81, 31.40, 49.27, 60.73, 113.62, 114.34, 118.78, 127.66, 131.94, 132.46, 138.37, 148.75, 155.68, 159.70, 162.69, 165.09, 172.55, 177.62 ppm. – MS (EI, 70 eV): $m/z(\%) = 475$ (15) $[M]^+$. – $C_{25}H_{25}N_5O_5$ (475.50): calcd. C 63.15, H 5.30, N 14.73; found C 63.10, H 5.25, N 14.67.

*N-{2-[(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)amino]-1-isopropyl-2-oxo-ethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**11b**)*

Yield 86 %; m. p. 166 – 168 °C (AcOH-ether). – $[\alpha]_D^{25} = -102.6$ ($c = 0.5$, DMF). – IR (KBr): $\nu = 3394, 3370$ (2 NH), 1728 (C=O), 1650, 1536, 1252 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.00$ (t, 3H, $CH_3$), 1.04 (d, 6H, 2 $CH_3$), 2.40 (s, 3H, $CH_3$), 2.65 (m, 1H, CH), 3.12 (q, 2H, $CH_2$), 4.46 (d, 1H, CH), 6.62 (d, 1H, Ar-H), 7.83 (d, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 8.89, 9.17 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.21$, 18.20, 24.79, 31.46, 49.30, 60.82, 113.58, 114.39, 118.83, 128.89, 133.64, 138.28, 138.45, 148.67, 155.70, 159.76, 162.78, 165.12, 172.49, 177.56 ppm. – MS (EI, 70 eV): $m/z(\%) = 613$ (7) $[M]^+$. – $C_{25}H_{21}Cl_4N_5O_5$ (613.28): calcd. C 48.96, H 3.45, Cl 23.12, N 11.42; found C 48.90, H 3.40, Cl 23.08, N 11.35.

*N-{2-[(5,7-Dioxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyridin-6-yl)amino]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**12**)*

Yield 69 %; m. p. 129 – 131 °C (AcOH-ether). – $[\alpha]_D^{25} = -103.5$ ($c = 0.5$, DMF). – IR (KBr): $\nu = 3412, 3351$ (2 NH), 1722 (C=O), 1648, 1532, 1250 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.99$ (t, 3H, $CH_3$), 1.03(d, 6H, 2 $CH_3$), 2.47 (s, 3H, $CH_3$), 2.78 (m, 1H, CH), 3.14 (q, 2H, $CH_2$), 4.45 (d, 1H, CH), 6.65 – 8.97 (m, 6H, Ar-H), 8.90, 9.36 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.18$, 18.35, 24.85, 31.43, 49.25, 60.84, 113.48, 114.49, 118.83, 127.96, 128.51, 138.31, 138.55, 146.28, 148.68, 152.72, 155.67, 159.60, 162.71, 164.93, 165.41, 171.59, 177.61 ppm. – MS (EI, 70 eV): $m/z(\%) = 476$ (6) $[M]^+$. – $C_{24}H_{24}N_6O_5$ (476.48): calcd. C 60.50, H 5.08, N 17.64; found C 60.44, H 5.02, N 17.60.

*N-{2-[(1,3-Dioxo-3a,6-dihydro-1H-benzo[de]isoquinolin-2(3H)-yl)amino]-1-isopropyl-2-oxoethyl}-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (**13**)*

Yield 74 %; m. p. 147 – 149 °C (AcOH-ether). – $[\alpha]_D^{25} = -98.8$ ($c = 0.5$, DMF). – IR (KBr): $\nu = 3389$, 3341 (2 NH), 1726 (C=O), 1652, 1536, 1249 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.99$ (t, 3H, $CH_3$), 1.02 (d, 6H, 2 $CH_3$), 2.43 (s, 3H, $CH_3$), 2.76 (m, 1H, CH), 3.12(q, 2H, $CH_2$), 4.42 (d, 1H, CH), 6.60 – 8.11 (m, 9H, Ar-H), 8.95, 9.22 (2s, 2H, 2 NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.23$, 18.29, 24.75, 31.41, 49.33, 60.80, 113.61, 114.42, 118.78, 123.81, 125.76, 128.53, 130.79, 137.84, 138.19, 138.36, 148.64, 155.76, 159.14, 159.82, 162.73, 172.68, 177.50 ppm. – MS (EI, 70 eV): $m/z(\%) = 525$ (26) $[M]^+$. – $C_{29}H_{27}N_5O_5$ (525.56): calcd. C 66.27, H 5.18, N 13.33; found C 66.20, H 5.12, N 13.28.

*Synthesis of bis-imide derivatives **14** and **15***

The same procedure as for compounds **11** – **13** was employed except for using 1,2,4,5-benzenetetracarboxylic dianhydride or 1,4,5,8-naphthylenetracarboxylic dianhydride (2 mmol) in refluxing glacial acetic acid.

*2,6-Bis{1-ethyl-7-methyl-N-[3-methyl-1-(methylamino)-1-oxobutan-2-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido}pyrrolo[3,4-f]isoindole-1,3,5,7(2H,6H)-tetrone (**14**)*

Yield 69 %; m. p. 124 – 126 °C (AcOH-ether). – $[\alpha]_D^{25} = -165.2$ ($c = 0.5$, DMF). – IR (KBr): $\nu = 3510 - 3325$ (4 NH), 1722 – 1680 (10 C=O), 1645, 1538, 1256 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 1.00$ (t, 6H, 2 $CH_3$), 1.06 (d, 12H, 4 $CH_3$), 2.45 (s, 6H, 2 $CH_3$), 2.68 (m, 2H, 2CH), 3.14 (q, 4H, 2 $CH_2$), 4.41 (d, 2H, 2CH), 6.60 – 8.99 (m, 8H, Ar-H), 8.86, 9.43 (2s, 4H, 4NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.12$, 18.27, 24.62, 31.38, 49.31, 60.79, 113.68, 114.23, 118.69, 125.35, 135.66, 138.27, 148.57, 155.72, 159.56, 162.69, 164.77, 172.53, 177.67 ppm. – MS (EI, 70 eV): $m/z(\%) = 872$ (8) $[M]^+$. – $C_{44}H_{44}N_{10}O_{10}$ (872.88): calcd. C 60.54, H 5.08, N 16.05; found C 60.50, H 5.00, N 16.00.

*2,8-Bis{1-ethyl-7-methyl-N-[3-methyl-1-(methylamino)-1-oxobutan-2-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamido}benzo[de]isoquinolin-1,3,6,8(2H,7H)-yl) tetraone (**15**)*

Yield 52 %; m. p. 251 – 253 °C (AcOH-ether). – $[\alpha]_D^{25} = -158.1$ ($c = 0.5$, DMF). – IR (KBr): $\nu = 3534 - 3315$ (4 NH), 1726 – 1665 (10 C=O), 1649, 1540, 1248 (C=O, amide I, II and III) $cm^{-1}$. – $^1H$ NMR (500 MHz, [D$_6$]DMSO): $\delta = 0.99$ (t, 6H, 2 $CH_3$), 1.05(d, 12H, 4 $CH_3$), 2.49 (s, 6H, 2 $CH_3$), 2.77 (m, 2H, 2CH), 3.12 (q, 4H, 2 $CH_2$), 4.43 (d, 2H, 2CH), 6.65 – 8.31 (m, 10 H, Ar-H), 8.79, 9.34 (2s, 4H, 4NH, exchangeable with $D_2O$) ppm. – $^{13}C$ NMR (125 MHz, [D$_6$]DMSO): $\delta = 13.15$, 18.24, 24.53, 31.42, 49.25, 60.62, 113.74, 114.18, 118.65, 120.78, 135.27, 138.19, 140.02, 148.68, 155.69, 158.95, 159.51, 162.73, 172.47, 177.55 ppm. – MS (EI, 70 eV): $m/z(\%) = 923$ (4) $[M]^+$. – $C_{48}H_{46}N_{10}O_{10}$ (922.94): calcd. C 62.46, H 5.02, N 15.18; found C 62.40, H 4.96, N 15.13.

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