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Synthesis and Biological Activity of Cycloocta[b]pyridine Derivatives

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ABSTRACT

Cyclooctanone reacts with arylidene malononitrile to afford cycloocta[b]pyridine-3-carbonitrile derivatives 2a-b. 2-Amino-4-(4-chlorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carbonitrile 2a reacts with benzoyl chloride and acetic anhydride to afford compounds 3 and 4 respectively. N-(4-(4-Chlorophenyl)-3-cyano-5,6,7,8,9,10-hexahydrocycloocta[b]pyridin-2-yl)benzamide 3 and N-(4-(4-Chlorophenyl)-3-cyano-5,6,7,8,9,10-hexahydrocycloocta[b]pyridin-2-yl)acetamide 4 reacts with hydrazine hydrate to afford compounds 5a,b. 5-(4-Chlorophenyl)-4-imino-2-phenyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-amine 5a and 5-(4-Chlorophenyl)-4-imino-2-methyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-amine 5b reacts with D-glucose and D-ribose to produce compounds 6a-d. Compounds 6a,b react with acetic anhydride to afford acetylated derivative 7a,b. Anticancer profile of the prepared compounds were tested against three cell lines namely A-549, CaCo-2, and HT-29.

Keywords: Cycloacta[b]pyridine; cycloocta[5,6]pyrido[2,3-d]pyrimidine; synthesis

INTRODUCTION

Pyridine derivatives have attracted many researchers due to its biological importance. They have antimicrobial profileagainst gram negative bacteria, gram positive bacteria, and Escherichia Coli [1]. Pyridine derivatives have herbicidal activity against against T. procumbens, E. indica, C. argentia, E. hirta, E. crusgalli, C. rotundus, and C. dactylon [1]. Also, pyridine derivatives has antifungal activity, antiviral activity, antioxidant activity, antidiabetic and anticancer activity. In addition, pyridine derivatives have antimalarial, analgesic activity, antiamoebic activity. Pyridine derivatives containing benzimidazole moiety have gastric H^+/K^+-ATPase inhibitory activity [1]. Imidazo[1,2-a]pyridine derivatives 1-6 inhibit acyl-COA (cholesterol acyltransferase) [1] (Figure 1).

Cycloocta[b]pyridine derivatives have many applications. The 4-arylcycloocta [b]pyridine is the main skeleton of antipsychotic drug blonanserin which is used in the treatment of schizophrenia [2].

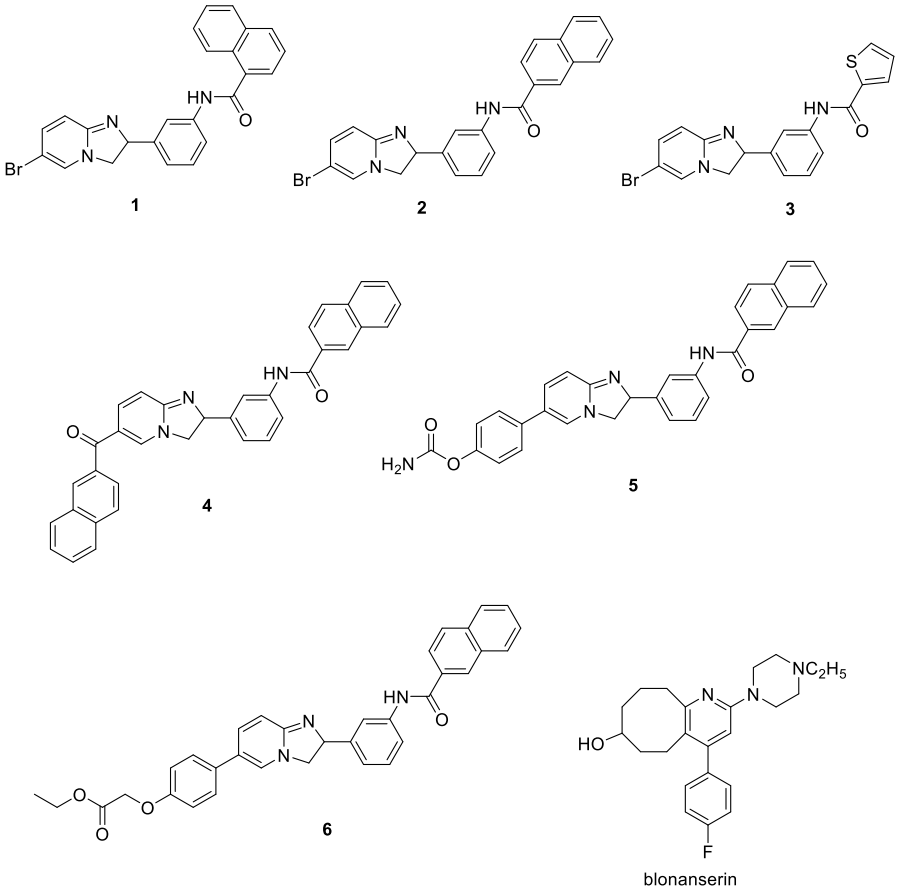

Figure 1: Imidazo[1,2-a]pyridine derivatives 1-6 inhibit acyl-COA (cholesterol acyltransferase)

All the above mentioned information and as a continuation of our previous work [3-19] directed us to synthesize novel cycloocta [b]pyridine derivatives for biological evaluation.

RESULTS AND DISCUSSION

Chemistry

Cyclooctanone reacts with arylidene malononitrile to afford cycloocta[b]pyridine-3-carbonitrile derivatives **2a-b**. Compound **2b** was prepared according to different method than reported [20, 21]. Spectral data (mass, IR, ^{1}H NMR) are in agreement with the proposed structures. Compound **2a** shows appearance of absorption band for CN and NH_2 group at 2235, and 3320 respectively in the IR spectrum. Compound **2a** shows disappearance of absorption band for carbonyl group in the IR spectrum. The ^{1}H NMR of compound **2a** show chemical shifts at 7.40 and 7.60. corresponding to aromatic protons.

Compound **2a** reacts with benzoyl chloride and acetic anhydride to afford compounds **3** and **4** respectively. The structures of compounds **3**, and **4** were elucidated from IR, mass, ^{1}H NMR spectral data. The IR of compounds **3**, and **4** show absorption band of carbonyl group at 1710 and 1720 cm^{-1} respectively. The ^{1}H NMR of compound **4** shows chemical shift at 2.10 (singlet) corresponding to CH_3. The ^{13}C NMR of compounds **3**, and **4** show chemical shift (δ) at 165.4 and 171.2 corresponding to carbonyl group. Compounds **3** and **4** reacts with hydrazine hydrate to afford compounds **5a,b**. Spectral data (IR, mass spectra, ^{1}H NMR) of compounds **5a,b** are in agreement with the suggested structures. The IR of compounds **5a,b** show disappearance of absorption band for cyano group and carbonyl group. Mass spectra of compounds **5a,b** show molecular ion peak at m/z 429.9 and 367.8. 5-(4-Chlorophenyl)-4-imino-2-phenyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-amine **5a** and 5-(4-Chlorophenyl)-4-imino-2-methyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-amine **5b** reacts with D-glucose and D-ribose to produce compounds **6a-d**. Compounds **6a,b** react with acetic anhydride to afford acetylated derivative **7a,b**. The structures of compounds **6a-d** and **7a,b** were confirmed by spectral data (mass spectra, IR, ^{1}H NMR). Compounds **6a-d** show absorption band for hydroxyl group in the IR spectra. The ^{1}H NMR of compound **6a** show chemical shift at 7.80 ppm corresponding to function group CH=N. Compound **7a** shows absorption band for carbonyl group in the IR spectrum. The IR of compound **7a** shows disappearance of absorption band for hydroxyl group. The ^{1}H NMR of compound **7a** shows chemical shift at 2.16 (singlet) corresponding to methyl group of acetyl function group (Figure 2)

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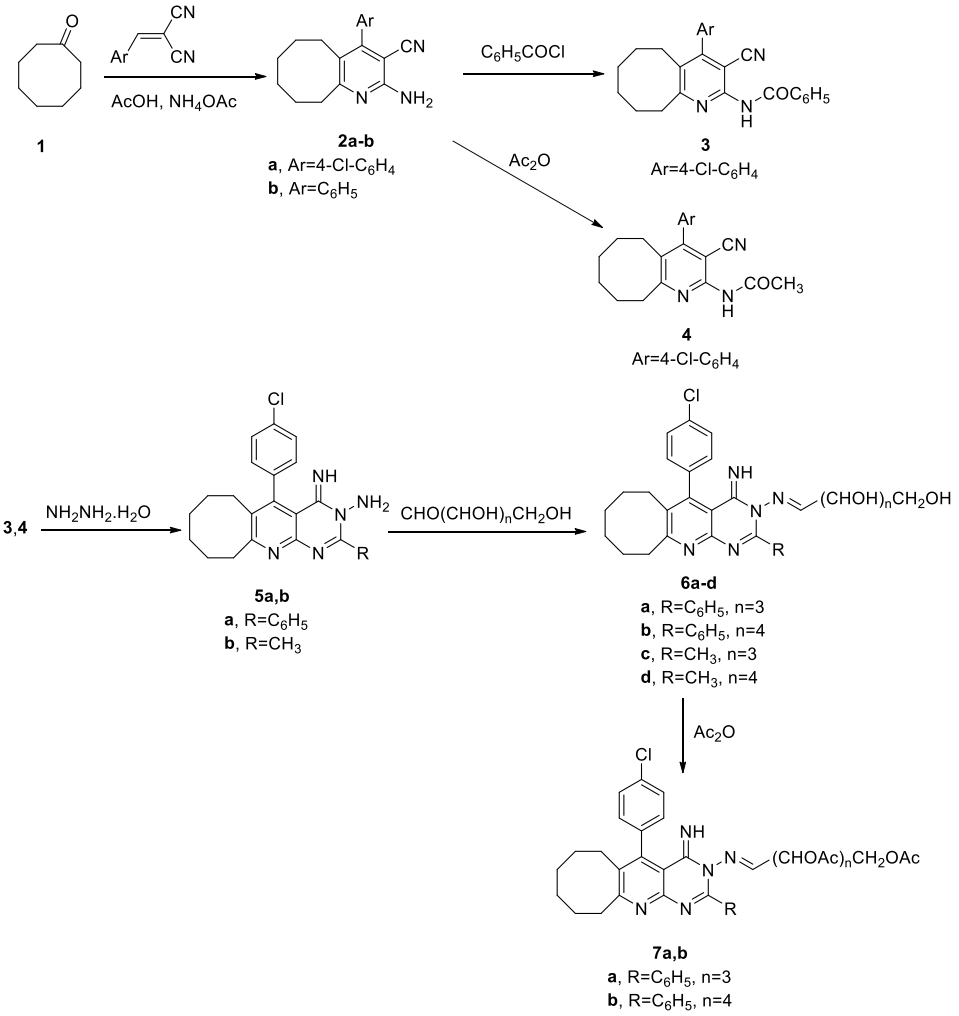

Figure 2: Chemicals synthesis

Anticancer evaluation

Anticancer activity of prepared compounds was done against three tumor cell lines (adenocarcinomic human alveolar basal epithelial cells A-549, human epithelial colorectal adenocarcinoma cells CaCo-2, and human colorectal adenocarcinoma cell line HT-29) using (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay [22]. The results are shown in Table 1 as anticancer activity of prepared compounds at 100 µM on three cell lines. The results exhibits that compound **7a** have highest activity toward A-549 cell lines. Compounds **5a**, **6d**, **7a** have medium activity towards A-549 cell lines as compared with doxorubicin. Compounds **2a, b**, **3**, **4**, **6a, b** have weak activity toward A-549 cell lines as compared with doxorubicin. Compound **2a** has highest activity toward CaCo-2 cell lines as compared with doxorubicin. Compounds **5a**, **7a** have medium activity toward CaCo-2 cell lines as compared with doxorubicin. Compounds **5a**, **6c**, **d**, **7a** show weak activity toward CaCo-2 cell lines as compared with doxorubicin. Compound **2a** shows highest activity towards HT-29 cell lines as compared with doxorubicin. Compounds **2b**, **4**, **5a, b**, **6a-d**, **7a,b** have weak activity towards HT-29 cell lines against doxorubicin. (Table 1)

Table 1: Anticancer evaluation of compounds on human tumor cell lines at 100 µM

Compound No.	A-549	CaCo-2	HT-29
2a	3.3	92.3	92.4
2b	15.6	0	35.1
3	19.3	0	0
4	29.4	0.9	12.0
5a	50.4	25.6	25.4
5b	0	0	15.1
6a	25.0	0	13.3
6b	17.2	0	18.3
6c	25.3	5.2	26.9
6d	45.9	17.5	31.5
7a	47.8	7.9	32.9
7b	88.5	71	8.7
Doxorubicin	1oo	100	100

$p \leq 0.01$, n = 3

From the results, we can conclude structure activity relationship. Acetylated sugar in compound **7a** enhances greatly the anticancer activity towards adenocarcinomic human alveolar basal epithelial cells A-549. Presence of sugar moiety linked to pyrimidine ring in compound **6d** and presence of pyrimidine ring in compound **5a** give medium activity toward A-549 cell lines. Presence of amino cyano function group in compounds **2a,b** and presence of benzoyl and acetyl group linked to amino cyano function group in compounds **3**, and **4** give weak activity towards A-549 cell lines. Presecne of sugar moiety linked to pyrimidine ring in compound 6a, b give weak activity towards A-549 cell lines. Amino cyano function group in compounds **2a, b** give high activity towards CaCo-2 cell lines. Presence of 2-phenyl-diaminopyrimidine ring in compound **5a** and acetylated sugar linked to 2-phenyl-pyrimidine ring in compound **7a** make medium activity towards CaCo-2 cell lines. Sugar moiety linked to diamino-pyrimidine ring in compounds **6c, d** make weak activity toward CaCo-2 cell lines. Amino cyano function group linked to pyridine ring in compound **2a** give high activity toward HT-29 cell lines.

EXPERIMENTAL

The instruments used were as previously reported paper [22].

General method for preparation of compounds 2a,b

A mixture of arylidene malononitrile (0.01 mole), cyclooctanone (0.01 mole), 4 gm anhydrous ammonium acetate in 20 mL acetic acid are heated under reflux for 3 hours. After cooling the reaction mixture to room temperature, the reaction mixture is poured into cold water. The formed solid collected and crystallized from ethanol to give compounds **2a,b**.

2-Amino-4-(4-chlorophenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carbonitrile 2a

Yield: 65%; m.p. 240-242 °C; IR (KBr) cm^{-1}, ν: 3320 (NH_2), 2235 (CN); ^{1}H NMR (DMSO) δ/ppm: 1.20 (t, 2H, *J* =7.1 Hz, CH_2), 1.25 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.70 (m, 2H, CH_2), 3.40 (t, 2H, J =7.1 Hz, CH_2), 6.80 (brs, 2H, NH_2), 7.40 (d, 2 H, J =7.5 Hz, Ar), 7.60 (d, 2H, *J* =7.5 Hz, Ar). ^{13}C NMR (DMSO) δ/ppm: 22.3, 24.2, 26.3, 28.5, 29.2, 29.6 (6 CH_2), 115.1 (CN), 120.2, 121.4, 123.1, 125.2, 125.9, 130.7, 132.6, 135.2, 137.9, 152.3, 155.3 (11 C=). MS (m/z): 311.8 (M^+, 31%). Anal. Calcd. for $C_{18}H_{18}ClN_3$: C, 69.34; H, 5.82; N, 13.48; Found: C, 69.39; H, 5.90; N, 13.53.

2-Amino-4-(phenyl)-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine-3-carbonitrile 2b

Yield: 70%; m.p. 225-227 °C; IR (KBr) cm^{-1}, ν: 3330 (NH_2), 2250 (CN); ^{1}H NMR (DMSO) δ/ppm: 1.25 (t, 2H, *J* =7.1 Hz, CH_2), 1.29 (m, 2H, CH_2), 1.71 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 2.76 (m, 2H, CH_2), 3.21 (t, 2H, *J* =7.1 Hz, CH_2), 6.72 (brs, 2H, NH_2), 7.30 (d, 2 H, *J* =7.5 Hz, Ar), 7.51 (d, 2H, *J* =7.5 Hz, Ar). ^{13}C NMR (DMSO) δ/ppm: 21.10, 25.12, 27.15, 28.10, 28.90, 29.10 (6 CH_2), 112.28 (CN), 121.1, 122.7, 123.2, 123.6, 125.8, 128.3, 129.2, 130.7, 132.7, 135.1, 136.8 (11 C=). MS (m/z): 277.3 (M^+, 41%). Anal. Calcd. for $C_{18}H_{19}N_3$: C, 77.95; H, 6.90; N, 15.15; Found: C, 78.04; H, 6.98; N, 15.19.

N-(4-(4-Chlorophenyl)-3-cyano-5,6,7,8,9,10-hexahydrocycloocta[b]pyridin-2-yl)benzamide 3

A mixture of compound **2a** (0.01 mole) and benzoyl chloride (0.01 mole) in 20 mL pyridine was refluxed for 3 hours. Then, the reaction mixture is acidified with 10 % HCl. The precipitate formed was collected, dried a recrystallized from ethanol to give compound **3**.

Yield: 65%; m.p. 105-107 °C; IR (KBr) cm^{-1}, ν: 3350 (NH), 2230 (CN), 1710 (C=O); ^{1}H NMR (DMSO) δ/ppm: 1.20 (t, 2H, *J* =7.1 Hz, CH_2), 1.30 (m, 2H, CH_2), 1.40 (brs, 1H, NH), 1.70 (m, 2H, CH_2), 2.20 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 3.00 (t, 2H, *J* =7.1 Hz, CH_2), 7.40-7.60 (m, 9H, Ar). ^{13}C NMR (DMSO) δ/ppm: 21.1, 23.2, 24.1, 25.4, 26.7, 27.9 (6 CH_2), 118.5 (CN), 125.1, 125.9, 127.1, 128.2, 128.9, 129.3, 129.9, 130.1, 130.8, 132.4, 135.1, 136.8, 137.4, 138.2, 140.2, 143.7, 145.9 (17 C=), 165.4 (C=O). MS (m/z): 415.9.7 (M^+, 51%). Anal. Calcd. for $C_{25}H_{22}ClN_3O$: C, 72.20; H, 5.33; N, 10.10; Found: C, 72.28; H, 5.39; N, 10.18.

N-(4-(4-Chlorophenyl)-3-cyano-5,6,7,8,9,10-hexahydrocycloocta[b]pyridin-2-yl)acetamide 4

A mixture of compound **2a** (0.01 mole) and 20 mL acetic anhydride is heated under reflux for 2 hours. The reaction mixture is poured into cold water. The formed solid collected and crystallized from ethanol to give compound **4**.

Yield: 55%; m.p. 150-152 °C; IR (KBr) cm^{-1}, ν: 3410 (NH), 2230 (CN), 1720 (C=O); ^{1}H NMR (DMSO) δ/ppm: 1.25 (t, 2H, *J* =7.1 Hz, CH_2), 1.34 (m, 2H, CH_2), 1.52 (brs, 1H, NH), 1.78 (m, 2H, CH_2), 2.10 (s, 3H, CH_3), 2.60 (m, 2H, CH_2), 3.05 (m, 2H, CH_2), 3.20 (t, 2H, *J* =7.1 Hz, CH_2), 7.34-7.53 (m, 4H, Ar). ^{13}C NMR (DMSO) δ/ppm: 19.2 (CH_3), 22.3, 23.9, 24.2, 26.1, 26.9, 29.1 (6 CH_2), 116.1 (CN), 121.2, 122.3, 124.5, 125.1, 127.2, 129.1, 129.5, 131.2, 133.1, 151.2, 153.4 (11 C=), 171.2 (C=O). MS (m/z): 353.8 (M^+, 33%). Anal. Calcd. for $C_{20}H_{20}ClN_3O$: C, 67.89; H, 5.70; N, 11.88; Found: C, 67.93; H, 5.78; N, 11.93.

General method for preparation of compounds 5a,b

A mixture of compounds **3** and **4** (0.01 mole), and 50 mL ethanol containing 3 mL hydrazine hydrate was refluxed for 3 hours. The reaction mixture was cooled to room temperature. Then, the reaction mixture is poured to cold water. The formed solid is recrystallized from ethanol to give compounds **5a,b**.

5-(4-Chlorophenyl)-4-imino-2-phenyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-amine 5a

Yield: 45%; m.p. 251-253 °C; IR (KBr) cm^{-1}, ν: 3340, 3410 (NH, NH_2); ^{1}H NMR (DMSO) δ/ppm: 1.30 (t, 2H, *J* =7.1 Hz, CH_2), 1.34 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 2.30 (m, 2H, CH_2), 2.90 (m, 2H, CH_2), 3.20 (t, 2H, *J* =7.1 Hz, CH_2), 6.80 (brs, 3H, NH_2, NH), 7.31-7.60 (m, 9H, Ar). ^{13}C NMR (DMSO) δ/ppm: 22.5, 22.8, 24.5, 25.1, 25.9, 26.1 (6 CH_2), 121.7, 122.7, 122.9, 124.1, 126.1, 126.8, 128.1, 128.9, 129.1, 130.3, 134.5, 137.5, 138.4, 138.9, 139.1, 142.4, 145.9, 147.3 (18 C=), 155.2 (C=N). MS (m/z): 429.9 (M^+, 51%). Anal. Calcd. for $C_{25}H_{24}ClN_5$: C, 69.84; H, 5.63; N, 16.29; Found: C, 69.89; H, 5.69; N, 16.34.

5-(4-Chlorophenyl)-4-imino-2-methyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-amine 5b

Yield: 42%; m.p. 240-242 °C; IR (KBr) cm^{-1}, ν: 3350, 3426 (NH, NH_2); ^{1}H NMR (DMSO) δ/ppm: 1.34 (t, 2H, *J* =7.1 Hz, CH_2), 1.37 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.40 (m, 2H, CH_2), 2.98 (m, 2H, CH_2), 3.12 (s, 3H, CH_3), 3.28 (t, 2H, *J* =7.1 Hz, CH_2), 6.73 (brs, 3H, NH2, NH), 7.30 (d, 2H, *J*=7.5 Hz, Ar), 7.50 (d, 2H, *J*=7.5 Hz, Ar). ^{13}C NMR (DMSO) δ/ppm: 20.3 (CH_3), 21.3, 22.9, 24.6, 26.2, 26.1, 26.9 (6 CH_2), 124.1, 126.2, 127.1, 129.3, 130.2, 133.1, 135.4, 137.9, 141.3, 145.4 (10 C=), 149.6, 153.7, 155.2 (3 C=N). MS (m/z): 367.8 (M^+, 43%). Anal. Calcd. for $C_{20}H_{22}ClN_5$: C, 65.30; H, 6.03; N, 19.04; Found: C, 65.38; H, 6.09; N, 19.09.

General method for preparation of compounds 6a-d

To a well stirred solution of compounds **5a,b** (0.01 mole) in 50 mL ethanol containing 3 drops of glacial acetic acid, D-glucose and D-ribose (0.015 mole) dissolved in distilled water was added. The reaction mixture was headed under reflux for 5 hours, and then the half of the solvent was evaporated under reduced pressure. The precipitated solid was filtered, washed with water and recrystalized from ethanol to give compounds **6a-d**.

5-((5-(4-Chlorophenyl)-4-imino-2-phenyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-yl)imino)pentane-1,2,3,4-tetraol 6a

Yield: 60%; m.p. 261-263 °C; IR (KBr) cm-1, ν: 3360 (NH), 3420 (OH); ^{1}H NMR (DMSO) δ/ppm: 1.10 (t, 2H, *J* =7.1 Hz, CH_2), 1.27 (m, 2H, CH_2), 1.39 (m, 2H, CH_2),1.60 (brs, 4H, OH), 1.61 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.12 (t, 2H, *J* =7.1 Hz, CH_2), 3.50 (m, 5H, 3CHOH, CH_2OH), 7.30 (brs, 1H, NH), 7.34-7.65 (m, 9 H, Ar), 7.80 (d, 1H, *J*=6.2 Hz, CH=N). ^{13}C NMR (DMSO) δ/ppm: 21.2, 22.2, 23.1, 23.9, 24.1, 25.6 (6 CH_2), 61.2, 63.2, 65.4, 70.1 (4 COH), 121.3 121.9, 122.1, 123.4, 124.1, 124.9, 126.1, 128.8, 129.1, 131.0, 132.9, 134.2, 135.8, 137.3, 138.2, 139.0 (16 C=), 153.1, 154.4, 156.1, 157.1 (4 C=N). MS (m/z): 562.07 (M^+, 47%). Anal. Calcd. for $C_{30}H_{32}ClN_5O_4$: C, 64.11; H, 5.74; N, 12.46; Found: C, 64.18; H, 5.79; N, 12.52.

6-((5-(4-Chlorophenyl)-4-imino-2-phenyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-yl)imino)hexane-1,2,3,4,5-pentaol 6b

Yield: 55%; m.p. 256-258 °C; IR (KBr) cm^{-1}, ν: 3410 (NH), 3530 (OH); ^{1}H NMR (DMSO) δ/ppm: 1.24 (t, 2H, *J* =7.1 Hz, CH_2), 1.40 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 2.10 (t, 2H, *J* =7.1 Hz, CH_2), 2.50 (brs, 6H, 5OH, NH), 3.64 (m, 6 H, 4CHOH, CH_2OH), 7.41-7.56 (m, 9H, Ar), 8.10 (d, 1H, *J*=6.2 Hz, CH=N). MS (m/z): 592.09 (M^+, 51%). Anal. Calcd. for $C_{31}H_{34}ClN_5O_5$: C, 62.89; H, 5.79; N, 11.83; Found: C, 62.93; H, 5.84; N, 11.89.

5-((5-(4-Chlorophenyl)-4-imino-2-methyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-yl)imino)pentane-1,2,3,4-tetraol 6c

Yield: 50%; m.p. 265-267 °C; IR (KBr) cm^{-1}, ν: 3430 (NH), 3510 (OH); ^{1}H NMR (DMSO) δ/ppm: 1.13 (t, 2H, *J* =7.1 Hz, CH_2), 1.35 (m, 2H, CH_2), 1.50 (m, 2H, CH_2), 1.71 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 2.05 (t, 2H, *J* =7.1 Hz, CH_2), 2.40 (s, 3H, CH_3), 3.52 (brs, 5H, 4OH, NH), 3.79 (m, 5H, 3CHOH, CH_2OH), 7.43 (d, 2H, *J*=7.5 Hz, Ar), 7.59 (d, 2H, *J*=7.5Hz, Ar), 8.25 (d, 1H, *J*=6.2 Hz, CH=N). MS (m/z): 500.0 (M^+, 61%). Anal. Calcd. for $C_{25}H_{30}ClN_5O_4$: C, 60.06; H, 6.05; N, 14.01; Found: C, 60.13; H, 6.14; N, 14.09.

6-((5-(4-Chlorophenyl)-4-imino-2-methyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-yl)imino)hexane-1,2,3,4,5-pentaol 6d

Yield: 40 %; m.p. 270-272 °C; IR (KBr) cm^{-1}, ν: 3390 (NH), 3510 (OH); ^{1}H NMR (DMSO) δ/ppm: 1.23 (t, 2H, *J* =7.1 Hz, CH_2), 1.40 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 1.92 (m, 2H, CH_2), 2.03 (brs, 6H, 5OH, NH), 2.17 (t, 2H, *J* =7.1 Hz, CH_2), 3.42 (m, 6H, 4CHOH, CH_2OH), 7.42 (d, 2H, *J* =7.5 Hz, Ar), 7.57 (d, 2H, *J*=7.5 Hz, Ar), 8.31 (d, 1H, J=6.2 Hz, CH=N). MS (m/z): 530.02 (M^+, 71%). Anal. Calcd. for $C_{26}H_{32}ClN_5O_5$: C, 58.92; H, 6.09; N, 13.21; Found: C, 59.01; H, 6.15; N, 13.28.

General method for preparation of compounds 7a,b

A solution of compound **6a,b** (0.01 mole) in 15 ml acetic anhydride was heated under reflux for 4 hours. The reaction mixture was then cooled to room temperature and was poured into cold water. The formed solid was collected and crystallized from ethanol to give compounds **7a,b**.

5-((5-(4-Chlorophenyl)-4-imino-2-phenyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-yl)imino)pentane-1,2,3,4-tetrayl tetraacetate 7a

Yield: 40 %; m.p. 150-152 °C; IR (KBr) cm^{-1}, ν: 3410 (NH), 1740 (C=O); ^{1}H NMR (DMSO) δ/ppm: 1.15 (t, 2H, *J* =7.1 Hz, CH_2), 1.31 (m, 2H, CH_2), 1.40 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 1.90 (t, 2H, *J* =7.1 Hz, CH_2), 2.16 (s, 12H, 4CH_3), 3.42 (m, 5H, 3CHOAc, CH_2OAc), 4.21 (brs, 1H, NH), 7.32-7.51 (m, 9H, Ar), 8.21 (d, 1H, J=6.2 Hz, CH=N). ^{13}C NMR (DMSO) δ/ppm: 20.1, 21.2, 21.9, 22.2 (4 CH_3), 23.2, 24.1, 24.8, 26.2, 27.2, 28.6 (6 CH_2), 120.1, 120.9, 122.3, 123.1, 124.6, 126.3, 128.1, 130.8, 132.2, 136.1, 137.0, 139.1, 141.4, 142.5, 143.1, 145.6 (16 C=), 153.1, 154.3, 155.9, 158.1 (4 C=N), 170.1 (4 C=O). MS (m/z): 730.22 (M^+, 52%). Anal. Calcd. for $C_{38}H_{40}ClN_5O_8$: C, 62.50; H, 5.52; N, 9.59; Found: C, 62.58; H, 5.59; N, 9.64.

6-((5-(4-Chlorophenyl)-4-imino-2-phenyl-6,7,8,9,10,11-hexahydrocycloocta[5,6]pyrido[2,3-d]pyrimidin-3(4H)-yl)imino)hexane-1,2,3,4,5-pentayl pentaacetate 7b

Yield: 45%; m.p. 145-147 °C; IR (KBr) cm^{-1}, ν: 3350 (NH), 1745 (C=O); ^{1}H NMR (DMSO) δ/ppm: 1.23 (t, 2H, *J* =7.1 Hz, CH_2), 1.41 (m, 2H,

CH_2), 1.53 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 1.91 (m, 2H, CH_2), 2.16 (t, 2H, *J*=7.1 Hz, CH_2), 2.34 (s, 15H, $5CH_3$), 3.72 (m, 6H, 4 CHOAc, CH_2OAc), 5.14 (brs, 1H, NH), 7.32-7.56 (m, 9 H, Ar), 8.21 (d, 1H, *J*=6.2 Hz, CH=N). MS (m/z): 802.28 (M^+, 33%). Anal. Calcd. for $C_{41}H_{44}ClN_5O_{10}$: C, 61.38; H, 5.53; N, 8.73; Found: C, 61.43; H, 5.61; N, 8.79.

CONCLUSION

Novel cycloocta[b]pyridine derivatives have been prepared and characterized. The anticancer activity of the prepared compounds was done in comparison of doxorubicin as reference drug. Several prepared compounds show good anticancer activity.

Conflict of interest

The authors confirm that no conflict of interest.

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