Synthesis of Cyclic and Acyclic Pyrimidine Nucleosides Analogues with Anticipated Antiviral Activity

Mohamed F. El-Shehry, 1,* Emad M. El Telbani 2,3 and Mohamed I. Hegab 4,5

1 Pesticides Chemistry Department, National Research Centre, Dokki, 12622 Giza, Egypt
2 Green Chemistry Department, National Research Centre, Dokki, 12622 Giza, Egypt
3 Chemistry Department, Faculty of Science, Jazan University, Jazan, Saudi Arabia
4 Photochemistry Department, National Research Centre, Dokki, 12622 Giza, Egypt
5 Chemistry Department, Faculty of Science & Arts, Qurayat, Al-Jouf University, Saudi Arabia

* Corresponding author: E-mail: moh_elshhery2000@yahoo.com

Received: 25-12-2017

Abstract

A convenient method for preparation of cyclic and acyclic nucleosides was achieved by alkylation of 6-(2,4-dichlorophenoxymethyl)pyrimidine-2,4-dione (1) with a variety of acyclic and cyclic activated sugar analogues, namely (2-acetoxyethoxy)methyl acetate (3), 2-(acetoxymethoxy)propane-1,3-diyldibenzoate (4), benzyloxymethyl acetate (5), 2-acetoxy-5-(benzyloxymethyl)tetrahydrofuran-3,4-diyldibenzoate (12), 5-chloro-2-(4-chlorobenzoxoxy)methyl tetrahydrofuran-3-yl 4-chlorobenzoate (13) and 2-(acetoxymethyl)-6-bromotetrahydro-2H-pyran-3,4,5-triydriacetate (14), respectively. Deprotection of the synthesized nucleosides was achieved by using methanolic ammonia. The structures of the newly synthesized nucleoside analogues were fully characterized by analytical methods (mass spectrometry, 1H NMR, 13C NMR, and elemental analysis).

Keywords: Pyrimidines, nucleosides, vorbrüggen and niedballa’s procedure, antiviral activity

1. Introduction

A number of base-modified nucleosides have been playing a vital and important role as therapeutic agents in the treatment of patients infected with different viruses including human immunodeficiency virus (HIV), herpes simplex virus (HSV), hepatitis B virus (HBV), hepatitis C virus (HCV) and cytomegalovirus (CMV) infections.1 According to U.S. Food and Drug Administration (FDA), many cyclic and acyclic nucleoside analogues, such as 3’-azido-3’-deoxythymidine (AZT), 2,3’-dideoxyinosidin (DDI), 2,3’-didehydro-3’-deoxythymidine (D4T), 1’-(2-hydroxyethoxy)methyl-6-(phenylthio)thymine (HEPT), acyclovir, and penciclovir (Fig. 1) are effective in treatment of various viruses.2

Moreover, it is well known that functionalized nitrogen heterocycles play an interesting role in drug chemistry and therefore they have been intensively studied and used as scaffolds for searching and developing new drugs.3 Pyrimidine-incorporating sugar residues represent an interesting class of nucleosides which have a promising antiviral chemotherapy potential, especially that class in which the cyclic sugar residue is replaced with open-chain “acyclic” sugar moieties. Moreover, heterocycles possessing pyrimidine nucleus are of great interest because they constitute an important class of natural and non-natural products which possess diverse biological activities and medicinal applications.4 Additionally, pyrimidine skeleton is also present in many natural products, such as vitamin B1 (thiamine) and a lot of synthetic compounds which possess a wide spectrum of biological activities including polio herpes viruses,5 diuretic, anti-HIV, cardiovascular,6 antibacterial,7–9 antifungal,10,11 antihypertensive,12 antipyretic,13 antiviral,14–15 anti diabetic,16 antioxidant,17–18 anticancer activities,19–20 antilishmanial,21 anti-inflammatory,22 analgesic,23 antiallergic,24 anticonvulsant,25 antihistaminic,26 herbicidal,27 antidepressant,28 and also act as calcium...
channel blockers. On the other side, fusion of pyrimidine moiety with different heterocycle scaffolds gives rise to a new class of hybrid heterocycles possessing improved biological activity. Fused pyrimidines like purines, quinazolines, pteridines, pyridopyrimidines, pyrazopyrimidines, pyrimidoazepines, triazolopyrimidines, furopyrimidines and pyrrolopyrimidines were studied in the past decade and were found to possess remarkable pharmacological properties, such as antibacterial activity, antifungal activity, anti-cancer agents, antihyperlipidemic activity, blood related disorders, analgesic and anti-inflammatory activities, anti-HIV agents, CNS related agents, and immunosuppressants.

For the design and search of new drugs, the development of hybrid molecules through the binding of various pharmacophores in one frame could lead to molecules with interesting pharmaceutical properties. Based on above information and continuations of our interest in the synthesis of bioactive molecules derived from the pyrimidine moiety, our investigation aimed to synthesize new cyclic and acyclic nucleosides using available cyclic and acyclic moieties, which will be coupled with pyrimidine base, hoping to increase their antiviral activities. The effective method of protection and deprotection will also be examined.

2. Experimental

2.1. Chemistry

All the reagents were purchased from Sigma-Aldrich and the solvents from Merck and were used without further purification. Melting points were measured on an Apotec apparatus and are uncorrected. NMR spectra were recorded on Bruker AMX400 and Bruker Current AV400 Data spectrometers (400 MHz for $^1$H, 100.6 MHz for $^{13}$C). ESI mass spectra were determined with a Finnigan Thermo Quest MAT 95XL spectrometer and FAB high-resolution (HR) mass spectra with a VG Analytical 70-250S spectrometer using an MCA method and poly(ethylene glycol) as the support. The reactions were monitored by thin layer chromatography (TLC) using silica gel (60 F254) coated aluminium plates (Merck) which were visualized by UV irradiation (254 nm) and iodine vapoors. Column chromatography was performed by using silica gel (60–120 mesh). All reactions were carried out under dry nitrogen. 6-(2,4-Dichlorophenoxy)methyl)pyrimidine-2,4-dione (1) was prepared according to our previous report.

2.1.1. Preparation of Nucleosides 6, 8, 10, 11, 15, 17 and 19

A suspension of uracil derivative 1 (10 mmol) and ammonium sulphate (10 g) in HMDS (50 mL) was stirred and refluxed for 4 h. HMDS in excess was evaporated under reduced pressure to give bis(trimethylsilyl) compound 2. A solution of acylated acyclic reagents (10 mmol): (2-acetoxyethoxy)methyl acetate (3), (2-acetoxyethoxy)methylpropan-1,3-diyldibenzoxide (4), benzoyloxymethyl acetate (5), 2-acetoxy-5-(benzoyloxymethyl)tetrahydrofuran-3,4-diyldibenzoxide (12), 5-chloro-2-((4-chlorobenzoyloxy)methyl)tetrahydrofuran-3-yl 4-chlorobenzoate (13) and 2-(acetoxymethyl)-6-bromotetrahydro-2H-pyran-3,4,5-triyldiacetate (14), in dry acetonitrile (30 mL) and tin(IV) chloride (2 mL) was individually added to the residue of 2 and stirred at –30 °C for 24 h. After addition of pyridine (4 mL) the mixture was filtered to remove inorganic materials. The filtrate was diluted with chloroform (40 mL). The organic layer was washed with a saturated solution of sodium hydroxide carbonate (50 mL) followed by 1N solution of hydrochloric acid (50 mL), then brine (50 mL) and water successively, dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. The resulting crude nucleosides 6, 8, 10, 11, 15, 17 and 19 were separated by silica gel column chromatography (graduated mixture of ethyl acetate and petroleum ether, 9:1) as white solid.

Figure 1: Some examples of cyclic and acyclic antiviral agents
2-((6-(2,4-Dichlorophenoxy)methyl)-2,4-dioxo-3,4-di-hydropyrimidin-1(2H)-yl)ethoxy)ethyl Acetate (6)

Yield 2.8 g (70%), m.p. 166–168 °C. 1H NMR (DMSO-d6) δ 4.91 (s, 2H, CH2 phenoxy), 5.71 (s, 1H, CH uracil), 7.10–7.93 (m, 13H, Ar-H), 12.10 (br s, 1H, NH). 13C NMR (DMSO-d6) δ 46.56; H, 4.13; N, 4.53. Found: C, 48.59; H, 4.31; N, 4.60.

1.3-Bis(benzoxylmethyl)-6-((2,4-dichlorophenoxy)methyl)pyrimidine-2,4-(1H,3H)-dione (11)

Yield 3 g (58%), m.p. 158–160 °C. 1H NMR (DMSO-d6, 400 MHz) δ 2.11 (s, 3H, COCH3), 3.83, 4.42 (t, 4H, OCH2CH2O), 5.45 (s, 2H, CH2 phenoxy), 5.62 (s, 2H, OCH2N), 6.10 (s, 1H, CH uracil), 7.48–7.90 (m, 3H, Ar-H), 12.50 (br s, 1H, NH). 13C NMR (DMSO-d6, 100 MHz) δ 20.9, 63.2, 66.8, 72.1, 100.7, 115.9, 116.0, 122.9, 126.1, 128.6, 129.9, 151.5, 152.1, 162.7, 170.6. MS m/z = 402 [M–1]. Anal. Calcd for C27H24Cl2N2O5: C, 61.49; H, 4.59; N, 5.39.

2-(Benzyloxymethyl)-5-((2,4-dichlorophenoxy)methyl)-2,4-dioxo-3,4-di-hydropyrimidin-1(2H)-yl)tetrahydrofuran-3,4-diyi Dibenzoate (15)

Yield 4.5 g (62%), m.p. 113–115 °C. 1H NMR (DMSO-d6, 400 MHz) δ 4.31–4.40 (m, 2H, H-5’S’), 4.51–4.60 (m, 1H, H-4’), 4.91 (s, 2H, CH2 phenoxy), 5.71 (s, 1H, CH uracil), 5.90–6.11 (m, 2H, H-2’, H-3’), 6.40 (d, 1H, J = 9.10 Hz, H-1’), 7.10–7.98 (m, 18H, Ar-H), 12.01 (br s, 1H, NH). 13C NMR (DMSO-d6, 100 MHz) δ 63.7, 65.7, 70.7, 73.8, 78.2, 98.0, 115.7, 122.9, 125.9, 128.6, 128.8, 129.9, 129.1, 129.5, 126.9, 129.9, 133.7, 134.0, 134.2, 151.1, 152.2, 162.5, 164.9, 165.1, 165.8. MS m/z = 730 [M–1]. Anal. Calcd for C37H28Cl2N2O16: C, 60.75; H, 3.86; N, 3.83. Found: C, 60.63; H, 3.94; N, 3.75.

(3-(4-Chlorobenzoyloxy)-5-((2,4-dichlorophenoxy)methyl)-2,4-dioxo-3,4-di-hydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl 4-Chlorobenzoate (17)

Yield 3.9 g (58%), m.p. 85–87 °C. 1H NMR (DMSO-d6) δ 2.21–2.30 (m, 2H, H-2’’), 4.81–4.25 (m, 2H, H-5’S’’), 4.72 (m, 1H, H-4’’), 4.90 (s, 2H, CH2 phenoxy), 5.40 (m, 1H, H-3’’), 5.61 (s, 1H, CH uracil), 6.51 (m, 1H, H-1’’), 7.10–8.00 (m, 11H, Ar-H), 11.93 (br s, 1H, NH). 13C NMR (DMSO-d6, 100 MHz) δ 66.4, 67.4, 74.9, 75.6, 79.5, 81.2, 82.3, 98.2, 102.9, 115.6, 128.5, 129.2, 129.8, 129.9, 130.6, 131.1, 131.4, 138.6, 150.4, 150.8, 151.1, 162.8, 163.0, 164.9. MS m/z = 678 [M–2]. Anal. Calcd for C39H28Cl2N2O12: C, 52.96; H, 3.26; N, 4.12. Found: C, 52.87; H, 3.31; N, 4.20.

2-(Acetoxyethyl)methyl-6-((6-(2,4-dichlorophenoxy)methyl)-2,4-dioxo-3,4-di-hydropyrimidin-1(2H)-yl)tetrahydrofuro-2H-pyran-3,4,5-triyli Triacetate (19)

Yield 4.1 g (67%), m.p. 137–139 °C. 1H NMR (DMSO-d6, 400 MHz) δ 1.80–2.10 (4xs, 12H, 4 x COCH3), 3.31 (m, 1H, H-5’), 4.18 (m, 2H, H-6’’’), 5.02 (m, 4H, H-3’, H-4’;CH2 phenoxy), 5.42 (dd, 1H, J1,2 = 9.50, J2,3 = 9.10 Hz, H-2’’’), 5.60 (s, 1H, CH uracil), 6.20 (d, 1H, J1,2 = 9.50 Hz, H-1’’’), 7.10–8.71 (m, 3H, Ar-H, Ar-H), 12.01 (br s, 1H, NH). 13C NMR (DMSO-d6, 100 MHz) δ 65.2, 67.9, 73.0, 77.8, 79.5, 96.6, 99.1, 115.7, 122.9, 125.9, 149.8, 151.7, 152.1, 162.1, 162.7, 169.3, 170.3. MS m/z = 617.3 [M+]. Anal. Calcd for C35H27Cl2N2O12: C, 48.64; H, 4.24; N, 4.54. Found: C, 48.59; H, 4.31; N, 4.60.

2.1.2. General Procedure for the Preparation of Deprotected Nucleosides 7, 9, 16, 18 and 20

Each protected nucleoside was dissolved individually in methanol saturated with ammonia and stirred for two days at room temperature. Then the solution was concentrated to dryness and the residue recrystallized in methanol to give deprotected nucleosides 7, 9, 16, 18 and 20.
6-((2,4-Dichlorophenoxy)methyl)-1-(1,3-dihydroxypropan-2-ol)pyrimidine-2,4(1H,3H)-dione (9)
Yield 3.2 g (84%), m.p. 190–192 °C. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 3.40–3.58 (m, 5H, 2CH$_2$, CH), 4.53 (m, 2H, OH), 5.33 (s, 2H, CH$_2$ phenoxy), 5.42 (s, 2H, OCH$_2$N), 5.69 (s, 1H, CH uracil), 7.31–7.64 (m, 3H, Ar-H), 12.10 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 61.0, 65.1, 70.2, 80.6, 110.1, 115.4, 116.0, 122.8, 125.9, 128.6, 151.9, 152.0, 152.2, 163.2. MS $m/z$ = 390 [M–1]. Anal. Calcd for C$_{15}$H$_{16}$Cl$_2$N$_2$O$_6$: C, 46.05; H, 4.12; N, 7.16. Found: C, 46.14; H, 4.20; N, 7.09.

6-((2,4-Dichlorophenoxy)methyl)-1-(3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (16)
Yield 2.7 g (65%), m.p. 128–130 °C. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 3.40–3.44 (m, 2H, H-5',5''), 3.58–3.60 (m, 1H, H-4'), 3.70–3.85 (m, 1H, H-3'), 4.10–4.25 (m, 1H, H-2'), 4.15 (d, 1H, OH), 4.60 (d, 1H, OH), 4.90 (s, 2H, CH$_2$ phenoxy), 5.13 (m, 1H, OH), 5.72 (s, 1H, CH uracil), 6.08 (d, 1H, $J$ = 7.75 Hz, H-1'), 7.20–7.62 (m, 3H, Ar-H), 11.91 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 62.6, 65.7, 70.52, 71.1, 84.7, 87.7, 98.0, 115.6, 122.9, 125.8, 128.5, 129.0, 133.7, 150.6, 151.1, 152.2, 163.1. MS $m/z$ = 421.1 [M+2]. Anal. Calcd for C$_{16}$H$_{16}$Cl$_2$N$_2$O$_7$: C, 45.84; H, 3.85; N, 6.68. Found: C, 45.92; H, 3.93; N, 6.76.

6-((2,4-Dichlorophenoxy)methyl)-1-(4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (18)
Yield 2.8 g (69.7%), m.p. 195–197 °C. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 2.15–2.21 (m, 2H, H-2',2''), 3.22–3.31 (m, 2H, H-5',5''), 3.81 (br s, 2H, 2 × OH), 4.50 (m, 1H, H-3'), 4.80 (s, 2H, CH$_2$ phenoxy), 5.08 (m, 1H, H-4'), 5.40 (s, 1H, CH uracil), 5.51 (m, 1H, H-1'), 7.06–7.70 (m, 3H, Ar-H), 12.10 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 61.7, 65.6, 71.5, 81.1, 86.0, 87.7, 98.3, 115.6, 122.9, 125.8, 128.6, 129.9, 150.1, 151.1, 152.2, 163.1. MS $m/z$ = 405.2 [M+2]. Anal. Calcd for C$_{16}$H$_{16}$Cl$_2$N$_2$O$_6$: C, 47.66; H, 4.00; N, 6.95. Found: C, 47.59; H, 4.05; N, 6.87.

6-((2,4-Dichlorophenoxy)methyl)-1-(3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)pyrimidine-2,4(1H,3H)-dione (20)
Yield 2.5 g (55.7 %), m.p. 214–216 °C. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 2.80–2.90 (m, 1H, H-3'), 3.19–3.45 (m, 4H, H-4', H-5', H-6',6''), 4.10 (dd, 1H, $J_{1,2}$ = 9.95 Hz, $J_{1,3}$ = 9.15 Hz, H-2'), 4.10 (m, 4H, 4 × OH), 4.71 (s, 2H, CH$_2$ phenoxy), 5.30 (d, 1H, $J$ = 9.95 Hz, H-1'), 5.55 (s, 1H, CH uracil), 7.02–7.55 (m, 3H, Ar-H), 8.20 (br s, 1H, NH). $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 61.4, 65.8, 68.4, 70.4, 78.3, 81.2, 83.3, 96.9, 99.1, 115.6, 122.8, 125.7, 128.6, 129.8, 152.2, 163.7, 166.5. MS $m/z$ = 451.1 [M+2]. Anal. Calcd for C$_{17}$H$_{18}$Cl$_2$N$_2$O$_8$: C, 45.45; H, 4.04; N, 6.24. Found: C, 45.51; H, 4.09; N, 6.17.

3. Results and Discussion
Our strategy to design and synthesize pyrimidine nucleoside analogues was based on the alkylation of si-


4. Conclusions

A series of cyclic and acyclic nucleosides were prepared with moderate yields by alkylation of 6-(2,4-dichlorophenoxy)methyl)pyrimidine-2,4-dione with various acyclic and cyclic activated sugars by performing Vorbrüggen and Niedballa's procedure. Deprotection of the synthesized nucleosides was achieved by using methanolic ammonia solution.

5. Acknowledgments

The authors acknowledge Professor Chris Meier and Innovative Research Team in State Key laboratory of Organic Chemistry, Hamburg University, for their help during performing this work.

6. References

1. E. De Clercq, A. Holý, Nat. Rev. Drug Discovery. 2005, 4, 928–940. DOI:10.1038/nrd1877
Povzetek

V članku predstavljamo priročno metodo za pripravo cikličnih in acikličnih nukleozidov s pomočjo alkiliranja 6-(2,4-diklorofenoksimetil)pirimidin-2,4-diona (1) s širokim izborom acikličnih in cikličnih aktiviranih analogov sladkorjev: (2-acetoksimetil)metil acetat (3), (2-acetoksimetil)propan-1,3-dii dibenzoot (4), benziloksiacet il acetil (5), 2-acetoksi-5-(benziloksiacet il)tetrahidrofur ran-3,4-dii dibenzoot (12), 5-kloro-2-((4-klorobenziloksi)metil)tetrahidrofur ran-3-ii 4-klorobenzoot (13) in 2-(acetoksimetil)-6-bromotetrahidro-2H-piran-3,4-trill triacetat (14). Odstranitev zaščitne skupine iz tako pripravljenih nukleozidov smo dosegl z uporabo amoniakja v metanalnol. Nove nukleozide, ki smo jih na ta načini sintetizirali, smo tudi karakterizirali z analitskimi metodami (masna spektrometrija, 1H NMR, 13C NMR in elementna analiza).