# Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis of pharmacophores containing a prolinate core using a multicomponent 1,3-dipolar cycloaddition of azomethine ylides Elisabet Selva, Luis M. Castelló, Juan Mancebo-Aracil, Verónica Selva, Carmen Nájera, Francisco Foubelo, José M. Sansano	Leave this area blank for abstract info.
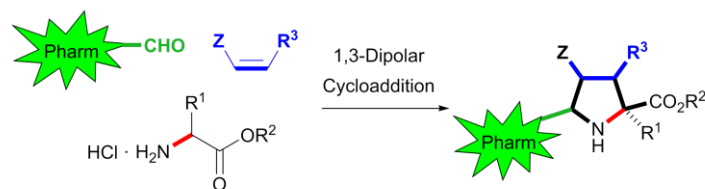
Synthesis of pharmacophores containing a prolinate core using a multicomponent 1,3-dipolar cycloaddition of azomethine ylides

Elisabet Selva,[a,b,c] Luis M. Castelló,[c] Juan Mancebo-Aracil,[d] Verónica Selva,[a,b] Carmen Nájera,[a] Francisco Foubelo[*a,b] and José M. Sansano[*a,b]

[a] *Departamento de Química Orgánica and Centro de Innovación en Química Avanzada (ORFEO-CINQA), Facultad de Ciencias, Universidad de Alicante 03080-Alicante, Spain.*

[b] *Instituto de Síntesis Orgánica, Facultad de Ciencias, Universidad de Alicante 03080-Alicante, Spain. Fax: +34-965903549 ; Tel : +34-965903728.*

[c] *Medalchemy, S. L. Avenida Ancha de Castelar, 46 – EA, San Vicente del Raspeig, 03690, Alicante*

[d] *Departamento de Química, Universidad Nacional del Sur (UNS), Av. Alem 1253, CP: 8000, Bahía Blanca, Buenos Aires, Argentina.*

* indicates the main/corresponding author, foubelo@ua.es, jmsansano@ua.es

ABSTRACT

A multicomponent 1,3-dipolar cycloaddition between heterocyclic aldehydes, amino esters and dipolarophiles is efficiently promoted by silver acetate as catalyst, and depending on the nature of the heterocycle and its reactivity the reaction requires 70 °C or rt to complete. Selected pharmacophores anchored to a formyl group are chromone, 5-methoxyindole, pyridoxal surrogates and a very attractive uracyl derivative. The preference of each tested amino esters towards different dipolarophiles is discussed. At the end, a selective reduction of the ester group allows to obtain a very interesting dideoxiazanucleoside derivative.

1. Introduction

The alarm of a drug antimicrobial resistance reported case reminds scientists the powerful evolution machinery in nature. Infections with resistant organisms are very difficult to treat, requiring costly and sometimes toxic alternatives. Bacteria, viruses, fungi, and parasites can cause disease among humans, other animals, and plants and have the ability to develop resistance to the drugs created against them. To face this problem when vaccines are not available, the development of new drugs as well as new diagnostic tests to track the origin and mechanism of resistance are prioritary.

Drug targets are usually proteins but are in some cases small regions of DNA or RNA. Synthetic nucleotides and nucleosides are currently being used to modify natural DNA/RNA sequences, altering specifically gene expression.[1] With this idea commercially available antiviral agents such as, for example, AZT, ribavirin, lamivudine, emtricitabine and stavudine incorporate mimetic heterocycles at the 2 position.[2,3] In addition, another different (non-commercial) compounds have shown interesting antiviral properties due to the presence of substituted pyridine/quinoline/quinazoline nucleus[4] or substituted indole/benzimidazole rings.[5] The synthesis of all these compounds require several steps and occasionally chemical yields are low.
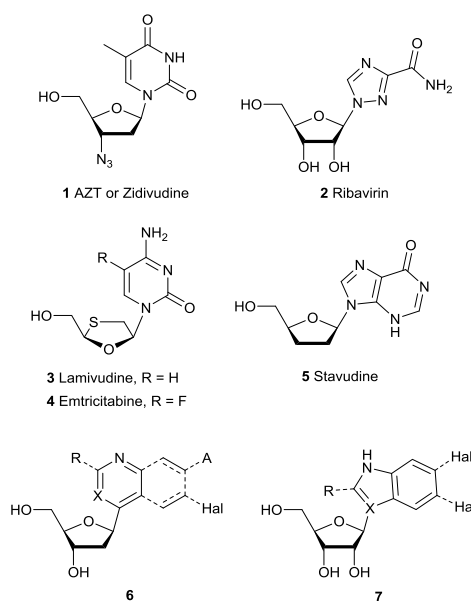

Figure 1. Synthetic nucleosides possessing high antiviral inhibition.

In this work, the synthesis of prolinates and pseudo-azanucleosides bearing a mimetic nucleo-base anchored in the strategic position 5 and a nitrogen atom instead of the furan oxygen is designed.[6] The multicomponent[7,8] 1,3-dipolar cycloaddition (1,3-DC)[9] between heterocyclic aldehydes, amino esters and the corresponding dipolarophile was choiced as straightforward way[10] to access this new family of compounds 8.[11] Apart from conventional hydrogen bonds between heterocycle and the genetic material of the microorganism, new additional biological interactions through the proline nitrogen atom can be envisaged.

2. Results and Discussion

This operationally simple multicomponent 1,3-DC started with the selection of four biologically attractive commercially available heterocyclic aldehydes 9-12 (Figure 2) based on the important role in nature of chromones,[12] 5-methoxyindole,[13] pyridoxal[14] and uracyl[15] surrogates.
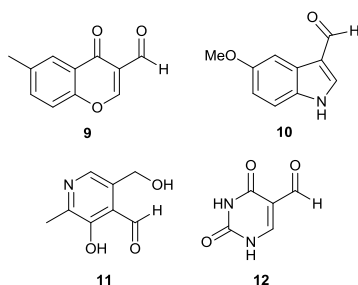
Figure 2. Commercially available formylheterocycles used in this work.

The optimization of the reaction was very simple[16] and only solvents (DCM, EtOH, PhMe, THF) and temperature (rt-110 °C range) were studied for all the formylheterocycles involved, silver acetate being necessary for the completion of the reaction. In general, to the solution (or suspension) of the free amino ester (or its hydrochloride), the aldehyde and triethylamine (1.1 equiv) in the corresponding solvent, the dipolarophile and silver acetate (5 mol%) were added in this order. Thus, 3-formyl-6-methylchromone (9) was tested in the presence of phenylalanine ethyl ester hydrochloride and N-methylmaleimide (NMM) as dipolarophile. Whilst the reaction did not occur neither at room temperature nor 70 °C in toluene, the expected endo-cycloadduct 8aa was obtained in 75% yield and 92:8 endo:exo ratio, after flash chromatography when the reaction was performed in refluxing ethanol (the best solvent for these series of compounds) for 10 h (Scheme 1). N-Benzylmaleimide (NBM) and methyl acrylate also gave good yields of cycloadducts 8ab (65%) and 8ac (76%), respectively (Scheme 1). Alanine methyl ester hydrochloride was allowed to react under this reaction conditions with maleimides giving rise to polycyclic compounds endo-8ad and endo-8ae in 70 and 65% yields (Scheme 1). Unfortunately, the in situ generated imine from glycine methyl ester hydrochloride and aldehyde 9 afforded the expected cycloadduct in very low yield (<10% by analysis of ^{1}H NMR spectra of the crude mixture) unpurified with decomposed compounds and a noticeable amount (approx. 20% by ^{1}H NMR) of several stereoisomers of imidazolidine 13a as a result of the reaction of the imine with itself (Scheme 1). Compouds 8ab-8ae were isolated as unique endo-diastereoisomer (>95:5 dr).
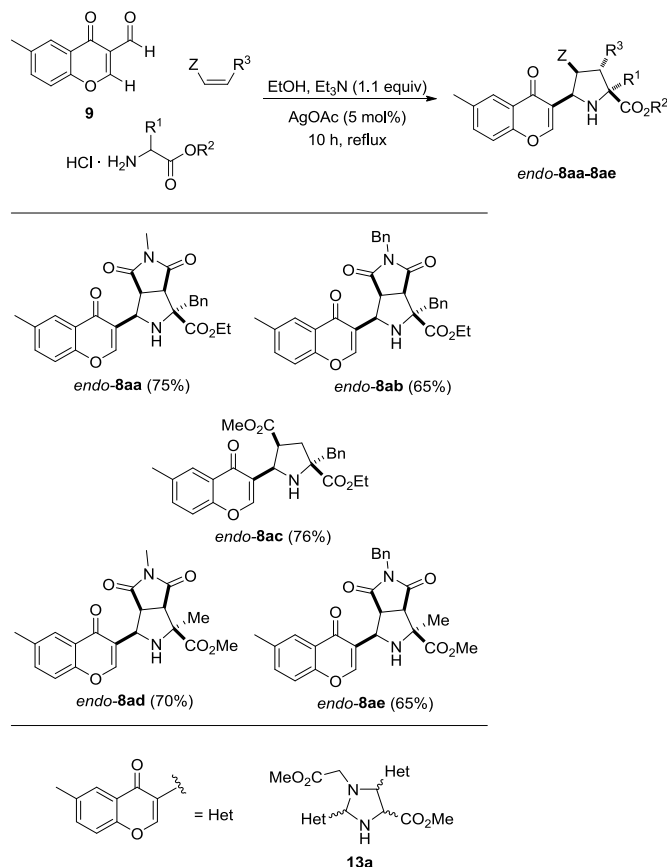
Scheme 1. Synthesis of compound 8a series bearing 4-chromenone nucleus.

5-Methoxyindole-3-carbaldehyde (10) behaved similarly to chromone 9. The cleanest reaction occurred in toluene at 70 °C in the presence of α-substituted amino esters with maleimides, triethylamine (1.1 equiv) and silver acetate (5 mol%) (Scheme 2). Thus, the combination with NMM and NBM with phenylalanine ethyl ester hydrochloride gave endo-cycloadducts 8ba and 8bb in moderate yield (52 and 55%, respectively). Alanine methyl ester hydrochloride also underwent 1,3-DC under standard conditions with NMM furnishing product endo-8bc in 60% yield (Scheme 2). Glycine methyl ester hydrochloride gave the corresponding mixture of stereoisomeric imidazolidines 13b (not drawn, approx. 20% by ^{1}H NMR) together with decomposed compounds and a small amount of the desired cycloadduct (<10% by analysis of ^{1}H NMR spectra of the crude mixture). Acrylates are not appropriate dipolarophiles in this particular transformation. As well as occurred in the last series, compouds 8ba-8ac were isolated as unique endo-diastereoisomer (>95:5 dr).

endo-8ba-8bc
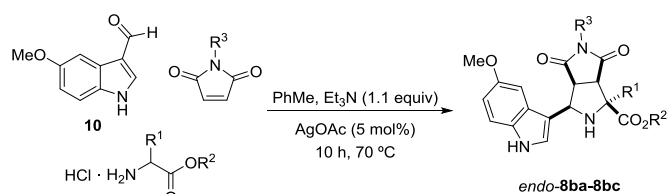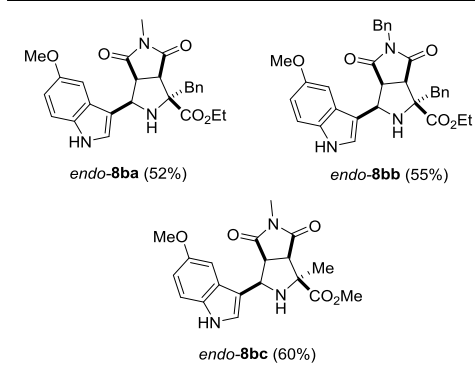
Scheme 2. Synthesis of compound **8b** series bearing 5-methoxyindole nucleus.

Pyridoxal hydrochloride (**11·HCl**) was the first example of a formylheterocycle able to react with glycine methyl ester hydrochloride under the standard reaction conditions in refluxing ethanol (best solvent). When this two reagents were combined with triethylamine (2.2 equiv), NMM and silver acetate (5 mol%) in refluxing ethanol, cycloadduct *endo*-**8ca** was isolated in 96% yield (Scheme 3) and no traces of imidazolidine **13c** were detected. Phenylalanine ethyl ester hydrochloride reacted with maleimides producing *endo*-**8cb** and *endo*-**8cc** in excellent yields and more than 95:5 *endo*:*exo* ratio (Scheme 3). Ethyl acrylate was required in order to prevent transesterification from the solvent. The reaction with **11·HCl**, the already mentioned acrylate and ethyl phenylalaninate furnished molecule **8cd** in very high yield (92%) and high diastereomeric ratio (90:10 *endo*:*exo*) (Scheme 3). It is noteworthy that the two hydroxyl groups of the pyridoxal **11** were not protected previously to the cycloaddition, which demonstrated a high functional group tolerance.
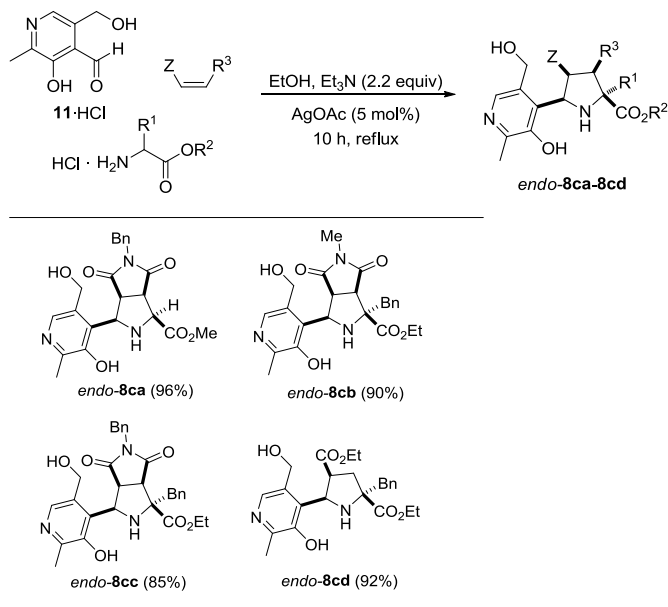
Scheme 3. Synthesis of compound **8c** series bearing a pyridoxal surrogate nucleus.

The 1,3-DC involving 5-formyluracil (**12**) are perhaps the most attractive series because it resembles the natural uridine nucleoside. The multicomponent reaction was implemented at room temperature in a different way to the reactions run before. Toluene was the most appropriate solvent. Glycine methyl ester hydrochloride reacted with maleimides and **12** to give *endo*-cycloadducts **8da** and *endo*-**8db** in 82 and 88% yield, respectively (Scheme 4, eq. 1). When phenylalanine ethyl ester was employed as free amine, base was not needed and the reaction was completed in 10 h. NMM, NBM and ethyl acrylate were appropriate dipolarophiles to access the interesting azanucleosidic agents **8dc**-**8de** (Scheme 4, eq. 2). The high yields achieved in all these examples were obtained after recrystallization/precipitation from warm ethanol taking advantage of the poor solubility of molecules **8da**-**8de**. The preparation of compound *endo*-**8da** was also attempted in a 1.5 g scale obtaining the same chemical yield. All of the cycloadducts containing the uracyl moiety were isolated as unique *endo*-diastereoisomers (>95:5 dr).
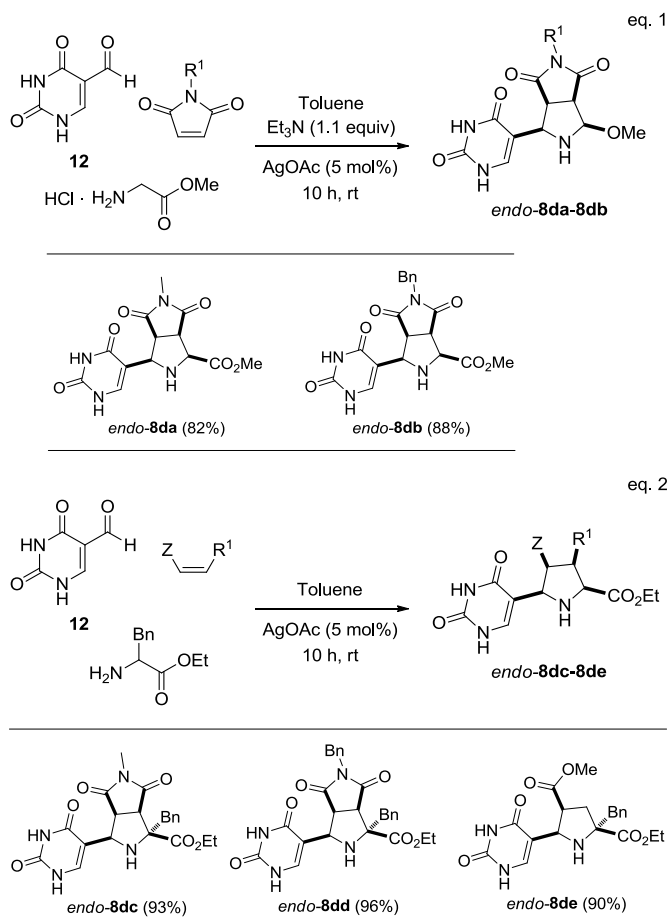
Scheme 4. Synthesis of compound **8d** series bearing a uracil nucleus.

The relative configuration of products **8** were determined by selective nOe experiments identifying clearly in the most representative examples of each series the all *cis*-arrangement typical of the major *endo*-approach of the dipolarophile to the intermediate W-shape conformer of the azomethine ylide. Moreover, all compounds described in this article are being tested as potential antibacterial, antitumor and antiviral agents.

To demonstrate the utility of this methodology the preparation of more similar structures to natural scaffolds such as *endo*-**14dc** was achieved by selective reduction of the ester group of the uracil derivative *endo*-**8dc** in good yield (80%) using NaBH$_4$ in methanol under reflux of THF for 10 h (Scheme 5).[17,18]
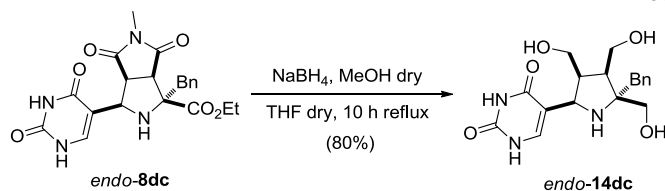
Scheme 5. Synthesis of mimetic dideoxiazanucleoside *endo*-**14dc**.

3. Conclusions

According to all these results we can conclude that a large family of azanucleosides can be efficiently and easily prepared in a multicomponent process from readily accessible starting compounds. The versatility of the 1,3-DC has been demonstrated once more allowing the presence of many functional groups ensuring a 2,4,5-*cis*-arrangement or *all*. Among this, the operational simplicity of this procedure permits its implementation in a larger scale. A reduction of the ester group can be the key to new family of potential drugs whose study of activity is in their infancy. The asymmetric 1,3-DC version of these transformations is a difficult task and are currently underway.

4. Experimental Section

4.1. General

All commercially available reagents and solvents were used without further purification, only aldehydes were also distilled prior to use. Analytical TLC was performed on Schleicher & Schuell F1400/LS 254 silica gel plates, and the spots were visualised under UV light (λ = 254 nm). Flash chromatography was carried out on handpacked columns of Merck silica gel 60 (0.040-0.063 mm). Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT) are listed and wave numbers are given in cm^{-1}. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^{1}H NMR and 75 or 100 MHz for ^{13}C NMR, using CDCl$_3$ or DMSO-d$_6$ as solvent and TMS as internal standard (0.00 ppm). The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and br s = broad signal. All coupling constants (J) are given in Hz and chemical shifts in ppm. ^{13}C NMR spectra were referenced to CDCl$_3$ at 77.16 ppm. DEPT-135 experiments were performed to assign CH, CH$_2$ and CH$_3$. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV using a Shimadzu QP-5000 by injection or DIP; fragment ions in m/z are given with relative intensities (%) in parentheses. High-resolution mass spectra (HRMS) were measured on an instrument using a quadrupole time-of-flight mass spectrometer (QTOF) and also through the electron impact mode (EI) at 70 eV using a Finnigan VG Platform or a Finnigan MAT 95S. Microanalyses were performed in a Thermo Finnigan Flash 1112 Series.

4.2. General procedure for the synthesis of products 8a and 8b.

To a stirred solution of amino ester hydrochloride (1.1 equiv, 0.6 mmol) in EtOH (3 mL, for **8a**) or toluene (3 mL, for **8b**), aldehyde (1 equiv, 0.5 mmol) was added. After that, Et$_3$N (1.1 equiv, 70 µL), the dipolarophile (1 equiv, 0.5 mmol) and AgOAc (5 mol%) were added in this order. The reaction mixture was stirred overnight at 70 °C. The solvent was evaporated under reduced pressure. The crude mixture was extracted with ethyl acetate and washed with brine. The organic phase was dried (MgSO$_4$), filtrated and evaporated. The corresponding pyrrolidines were obtained in good yields after purification by flash chromatography (Hex/AcOEt).

4.2.1.   (1S,3R*,3aS*,6aR*)-Ethyl   1-benzyl-5-methyl-3-(6-methyl-4-oxo-4H-chromen-3-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8aa)*: White solid, (178 mg, 75% yield). IR (neat) v_{max}: 730, 1098, 1288, 1436, 1484, 1642, 1703, 1736, 2959 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.41 (t, J = 7.2 Hz, 3H), 2.45 (s, 3H), 2.84 (s, 3H), 3.19 (d, J = 13.7 Hz, 1H), 3.48 (d, J = 7.2 Hz 1H), 3.57 (d, J = 13.7 Hz, 1H), 3.75 (br s, 1H), 4.35 (q, J = 8.5 Hz, 2H), 4.90 (d, J = 9.0 Hz, 1H), 7.20-7.26 (m, 5H), 7.33 (d, J = 8.6 Hz, 1H), 7.48 (dd, J = 8.6, 2.3 Hz, 1H) 7.96 (s, 1H), 8.01 (d, J = 0.9 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.1, 21.0, 25.1, 40.1, 47.5, 54.1, 62.0, 71.3, 77.3, 118.0, 123.0, 125.1, 127.6, 128.9, 129.6, 129.8, 134.9, 135.2, 135.4, 152.9, 154.7, 170.3, 174.6, 175.2, 177.6. LRMS (EI): m/z = 474 (M$^+$, >1%), 401 (14), 384 (23), 383 (100), 337 (34), 252 (14), 91 (22). HRMS (EI): calcd. for [C$_{27}$H$_{26}$N$_2$O$_6$] 474.1791; found 474.1781.

4.2.2.   (1S,3R*,3aS*,6aR*)-Ethyl 1,5-dibenzyl-3-(6-methyl-4-oxo-4H-chromen-3-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8ab)*: Yellow solid, (179 mg, 65% yield). IR (neat) v_{max}: 709, 1173, 1345, 1398, 1484, 1640, 1707, 1736, 2933 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.42 (t, J = 7.2 Hz, 3H), 2.48 (s, 3H), 3.15 (d, J = 13.7 Hz, 1H), 3.47 (d, J = 7.7 Hz, 1H), 3.59 (d, J = 13.7 Hz, 1H), 3.87 (d, J = 7.6 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 4.54 (q, J = 14.1 Hz, 2H), 4.98 (d, J = 8.8 Hz, 1H), 7.16-7.32 (m, 11H), 7.49 (dd, J = 8.6, 2.1 Hz, 1H) 7.62 (s, 1H), 8.06 (d, J = 2.2 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.2, 21.0, 40.1, 42.5, 46.9, 53.9, 61.8, 71.1, 77.3, 117.9, 123.0, 125.2, 127.5, 127.9, 128.5, 128.6, 128.7, 128.9, 129.6, 135.0, 135.1, 135.2, 135.7, 152.7, 154.6, 170.5, 174.2, 174.9, 177,4. LRMS (EI): m/z = 550 (M$^+$, >1%), 447 (16), 460 (31), 459 (100), 413 (46), 252 (26), 91 (92). HRMS (EI): calcd. for [C$_{33}$H$_{30}$N$_2$O$_6$] 550.2104; found 550.2078.

4.2.3.   (2R,4S*,5R*)-2-Ethyl   4-methyl   2-benzyl-5-(6-methyl-4-oxo-4H-chromen-3-yl)pyrrolidine-2,4-dicarboxylate   (8ac)*: Yellow oil, (170 mg, 76% yield). IR (neat) v_{max}: 1198, 1437, 1485, 1619, 1645, 1733, 2251, 2950, 2981, 3339 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.25 (t, J = 7.1 Hz, 3H), 2.26 (dd, J = 13.6, 7.7 Hz, 1H), 2.42 (s, 3H), 2.75 (dd, J = 13.6, 4.7 Hz, 1H), 3.01 (d, J = 13.4 Hz, 1H), 3.18 (d, J = 13.4 Hz, 1H), 3.31 (s, 3H), 3.54 (td, J = 7.5, 4.8 Hz, 1H), 4.18 (tq, J = 7.2, 3.4 Hz, 3H), 4.79 (d, J = 7.5 Hz, 1H), 7.14-7.33 (m, 5H), 7.32 (d, J = 8.6 Hz, 1H), 7.45 (dd, J = 8.6, 2.0 Hz, 1H), 7.97 (d, J = 1.3 Hz, 1H), 8.08 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.2. 21.0, 38.9, 45.0, 47.1, 51.5, 56.5, 61.3, 69.3, 117.9, 123.1, 125.1, 127.0, 128.2, 128.3, 130.0, 135.0, 135.1, 136.5, 153.5, 154.6, 173.1, 174.8, 177.2. LRMS (EI): m/z = 449 (M$^+$, >1%), 376 (27), 359 (21), 358 (100), 280 (15), 259 (52), 252 (26), 226 (15), 91 (33). HRMS (EI): calcd. for [C$_{26}$H$_{27}$NO$_6$] 449.1838; found 449.1840.

4.2.4.   (1S,3R*,3aS*,6aR*)-Methyl   1,5-dimethyl-3-(6-methyl-4-oxo-4H-chromen-3-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8ad)*: Pale brown solid, (134 mg, 70% yield). IR (neat) v_{max}: 709, 1173, 1345, 1398, 1484, 1640, 1707, 1736, 2933. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.70 (s, 3H), 2.44 (s, 3H), 2.86 (s, 3H), 3.35 (d, J = 7.7 Hz, 1H), 3.78 (t, J = 8.2 Hz, 1H), 3.88 (s, 3H), 4.88 (d, J = 8.9

Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.49 (dd, J = 8.6, 2.2 Hz, 1H), 7.95 (dd, J = 2.0, 1.0 Hz, 1H), 8.08 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.1, 23.0, 25.4, 48.2, 53.4, 55.8, 57.6, 68.5, 118.1, 123.1, 125.1, 135.7, 135.9, 154.2, 154.8, 171.2, 174.5, 175.0, 178.5. LRMS (EI): m/z = 384 (M$^+$, >1%), 369 (18), 326 (20), 325 (100), 273 (19), 266 (26), 213 (23), 119 (21). HRMS (EI): calcd. for [C$_{20}$H$_{20}$N$_2$O$_6$] 384.1321; found 384.1305.

4.2.5. (1S*,3R*,3aS*,6aR*)-Methyl 5-benzyl-1-methyl-3-(6-methyl-4-oxo-4H-chromen-3-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8ae): Yellow solid, (150 mg, 65% yield). IR (neat) υ$_{max}$: 700, 1170, 1344, 1399, 1485, 1640, 1705, 1740, 2952. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.72 (s, 3H), 2.46 (s, 3H), 3.35 (d, J = 7.9 Hz, 1H), 3.79 (d, J = 8.6 Hz, 1H), 3.85 (s, 3H), 4.50 (d, J = 4.8 Hz, 1H), 5.01 (d, J = 6.3 Hz, 1H), 7.26-7.30 (m, 6H), 7.34 (d, J = 8.6 Hz, 1H), 7.50 (dd, J = 8.6, 2.0 Hz, 1H), 7.95 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 21.0, 22.8, 42.9, 47.6, 53.3, 55.2, 56.7, 68.2, 118.0, 122.9, 125.1, 128.0, 128.5, 128.7, 128.9, 135.4, 135.6, 135.7, 154.2, 154.7, 171.0, 174.0, 174.6, 178.2. LRMS (EI): m/z = 460 (M$^+$, >1%), 445 (24), 402 (27), 401 (100), 273 (33), 266 (70), 240 (28), 213 (26), 91 (74). HRMS (EI): calcd. for [C$_{26}$H$_{24}$N$_2$O$_6$] 460.1634; found 460.1629.

4.2.6. (1S*,3R*,3aS*,6aR*)-Ethyl 1-benzyl-3-(5-methoxy-1H-indol-3-yl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8ba): Grey solid, (119 mg, 52% yield). IR (neat) υ$_{max}$: 703, 1214, 1381, 1283, 1437, 1485, 1704, 2938, 3375. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.26 (t, J = 7.2 Hz, 3H), 2.98 (s, 3H), 3.30 (d, J = 13.4 Hz, 1H), 3.37-3.44 (m, 1H), 3.48-3.54 (m, 1H), 3.51 (d, J = 13.7 Hz, 1H), 3.82 (s, 3H), 4.16 (q, J = 7.2 Hz, 2H), 4.86 (d, J = 6.4 Hz, 1H), 6.85 (dd, J = 8.9, 2.4 Hz, 1H), 7.16 (s, 1H), 7.22-7.36 (m, 7H), 8.18 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.1, 25.2, 40.0, 48.9, 54.0, 55.7, 56.5, 62.5, 71.5, 100.3, 112.3, 112.7, 126.0, 127.8, 128.3, 128.9, 130.1, 131.1, 131.5, 134.7, 153.9, 174.2, 174.5, 175.1. LRMS (EI): m/z = 461 (M$^+$, >1%), 388 (67), 371 (23), 370 (100), 350 (28), 212 (20), 185 (30), 147 (22), 91 (27). HRMS (EI): calcd. for [C$_{26}$H$_{27}$N$_3$O$_5$] 461.1951; found 461.1941.

4.2.7. (1S*,3R*,3aS*,6aR*)-Ethyl 1,5-dibenzyl-3-(5-methoxy-1H-indol-3-yl)-4,6- dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8bb): Brown solid, (148 mg, 55% yield). IR (neat) υ$_{max}$: 701, 1174, 1211, 1396, 1704, 2932, 3348. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.43 (t, J = 7.2 Hz, 3H), 3.18 (d, J = 13.5 Hz, 1H), 3.48-3.60 (m, 3H), 3.87 (s, 3H), 4.32 (d, J = 14.1 Hz, 1H), 4.39 (qd, J = 7.2, 1.0 Hz, 2H), 4.47 (d, J = 14.1 Hz, 1H), 5.17 (d, J = 8.9 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 8.9, 2.5 Hz, 1H), 7.22-7.30 (m, 12H), 8.36 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.2, 40.1, 42.6, 49.0, 54.9, 52.2, 55.9, 61.7, 71.1, 100.9, 111.8, 112.2, 112.4, 127.4, 127.8, 128.5, 128.8, 128.9, 129.8, 135.4, 135.7, 153.9, 171.2, 174.7, 175.6. LRMS (EI): m/z = 537 (M$^+$, >1%), 464 (13), 447 (16), 446 (57), 444 (20), 351 (23), 350 (100), 276 (29), 212 (22), 185 (37), 158 (21), 91 (65). HRMS (EI): calcd. for [C$_{32}$H$_{31}$N$_3$O$_5$] 537.2264; found 537.2244.

4.2.8. (1S*,3R*,3aS*,6aR*)-Methyl-3-(5-methoxy-1H-indol-3-yl)-1,5-dimethyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8bc): Brown solid, (110 mg, 60% yield). IR (neat) υ$_{max}$: 1289, 1439, 1702, 1751, 2957, 3265. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.62 (s, 3H), 2.72 (s, 3H), 3.33 (d, J = 7.6 Hz, 1H), 3.57 (dd, J = 9.1, 7.5 Hz, 1H), 3.82 (s, 3H), 3.89 (s, 3H), 5.04 (d, J = 9.1 Hz, 1H), 6.80 (dd, J = 8.8, 2.4 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 7.05 (d, J = 2.1 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 8.45 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 23.9,

25.1, 50.4, 52.8, 55.8, 56.5, 56.9, 67.4, 100.8, 111.6, 112.4, 112.5, 123.4, 126.5, 131.8, 154.0, 173.2, 175.3, 176.3. LRMS (EI): m/z = 371 (M$^+$, >1%), 269 (20), 261 (16), 260 (100), 200 (62), 185 (63), 169 (29), 159 (40). HRMS (EI): calcd. for [C$_{19}$H$_{21}$N$_3$O$_5$] 371.1481; found 371.1473.

4.3. General procedure for the synthesis of product 8c.

To a stirred solution of ester hydrochloride as amine (1.1 equiv, 0.5 mmol) in EtOH (3 mL) was added pyridoxal hydroclorhide (1 equiv, 0.5 mmol). After, Et$_3$N (2 equiv, 140 µL), dipolarophile (1 equiv, 0.5 mmol) and AgOAc (5 mol%). The reaction mixture was stirred overnight at 70 °C. The solvent was removed under reduced pressure. The crude mixture was extracted with ethyl acetate and was washed with brine. The organic phase was dried (MgSO$_4$) and after filtration and evaporation, the corresponding pyrrolidines were obtained without purification.

4.3.1. (1R*,3S*,3aR*,6aS*)-Methyl 5-benzyl-3-(3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8ca): Yellow solid, (110 mg, 96% yield). IR (neat) υ$_{max}$: 1211, 1393, 1714, 1745, 2802, 3264. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.26 (s, 3H), 3.50-3.73 (m, 2H), 3.77 (s, 3H), 4.09 (d, J = 7.5 Hz, 1H), 4.40 (d, J = 14.3 Hz, 1H), 4.51 (d, J = 14.3 Hz, 1H), 4.90 (d, J = 8.9 Hz, 1H), 7.22-7.28 (m, 5H), 7.71 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 18.3, 43.1, 47.1, 48.4, 52.6, 59.3, 61.0, 61.3, 126.1, 128.0, 128.5, 129.0, 132.0, 134.9, 138.6, 148.6, 152.7, 169.6, 174.8, 175.0. LRMS (EI): m/z = 425 (M$^+$, >1%), 348 (30), 337 (30), 220 (44), 215 (22), 187 (40), 165 (18), 161 (100), 150 (31), 139 (17), 91 (95). HRMS (EI): calcd. for C$_{22}$H$_{23}$N$_3$O$_6$ [M - CH$_3$O, - CO$_2$CH$_3$] 336.1336; found 336.1348.

4.3.2. (1R*,3S*,3aR*,6aS*)-Ethyl 1-benzyl-3-(3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8cb): Pale green solid, (204 mg, 90% yield). IR (neat) υ$_{max}$: 731, 1096, 1198, 1288, 1385, 1437, 1702, 1739, 2664, 2942, 3302. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.38 (t, J = 7.1 Hz, 3H), 2.78 (s, 3H), 2.32 (s, 3H), 3.10 (d, J = 13.8 Hz, 1H), 3.50 (d, J = 7.9 Hz, 1H), 3.69 (d, J = 13.9 Hz, 1H), 3.98 (t, J = 8.6 Hz, 1H), 4.34 (q, J = 7.0 Hz, 2H), 4.63 (q, J = 13.2 Hz, 2H), 5.34 (d, J = 9.8 Hz, 1H), 7.17-7.28 (m, 5H), 7.74 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.1, 17.9, 25.1, 40.5, 48.5, 53.7, 57.0, 61.0, 62.4, 71.1, 127.9, 128.1, 129.4, 129.6, 133.0, 134.2, 137.3, 147.9, 153.2, 170.1, 174.3, 174.4. LRMS (EI): m/z = 453 (M$^+$, >1%), 362 (22), 345 (19), 344 (100), 187 (24), 91 (17). HRMS (EI): calcd. for [C$_{24}$H$_{27}$N$_3$O$_6$] 453.1900; found 453.1922.

4.3.3. (1S*,3R*,3aR*,6aS*)-Ethyl 1,5-dibenzyl-3-(3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8cc): Pale green solid, (225 mg, 85% yield). IR (neat) υ$_{max}$: 702, 1200, 1349, 1397, 1708, 1736, 2658, 2935, 3298. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.35 (t, J = 7.1 Hz, 3H), 2.31 (s, 3H), 2.99 (d, J = 14.0 Hz, 1H), 3.48 (d, J = 7.8 Hz, 1H), 3.72 (d, J = 13.8 Hz, 1H), 3.95 (t, J = 8.3 Hz, 1H), 4.34-4.36 (m, 1H), 4.53 (d, J = 14.0 Hz, 1H), 5.27 (d, J = 9.7 Hz, 1H), 7.14-7.34 (m, 10H), 7.81 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 14.0, 40.9, 43.1, 48.1, 53.8, 57.1, 59.4, 62.7, 71.5, 128.1, 128.6, 128.7, 129.1, 129.2, 129.4, 130.0, 134.3, 134.6, 135.7, 137.8, 142.2, 155.9, 170.1, 173.5, 173.9. LRMS (EI): m/z = 529 (M$^+$, >1%), 438 (14), 421 (26),

420 (100), 187 (26), 91 (65). HRMS (EI): calcd. for $C_{30}H_{31}N_3O_6$ [M - CH_3O] 498.2029; found 498.2026.

4.3.4. *(2R*,4S*,5R*)-Diethyl 2-benzyl-5-(3-hydroxy-5-(hydroxymethyl)-2-methylpyridin-4-yl)pyrrolidine-2,4-dicarboxylate (8cd)*: Yellow oil, (203 mg, 92% yield). IR (neat) υ_{max}: 702, 1029, 1189, 1378, 1735, 2664, 2981, 3322. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 0.81 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 2.27-2.42 (m, 4H), 2.90-2.99 (m, 2H), 3.39 (d, *J* = 13.7 Hz, 1H), 3.52 (td, *J* = 8.3, 4.6 Hz, 1H), 3.70 (qd, *J* = 7.2, 2.5 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.50 (d, *J* = 13.0 Hz, 1H), 4.62 (d, *J* = 13.0 Hz, 1H), 5.19 (d, *J* = 8.6 Hz, 1H), 6.87-7.39 (m, 5H), 7.68 (s, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ: 13.6, 14.1, 16.2, 38.5, 44.4, 47.6, 59.7, 59.9, 61.4, 61.9, 69.6, 127.8, 129.1, 129.1, 129.7, 132.1, 132.4, 135.0, 135.3, 154.9, 171.3, 173.9. LRMS (EI): m/z = 442 (M$^+$, >1%), 351 (23), 333 (53), 323 (31), 305 (100), 287 (62), 259 (17), 91 (41). HRMS (EI): calcd. for $C_{24}H_{30}N_2O_6$ [M - CH_3O, - OH] 394.1534; found 394.1529.

4.4. General procedure for the synthesis of products 8d.

8da-8db: to a stirred solution of ester hydrochloride as amine (1.1 equiv, 0.6 mmol) in toluene (2 mL) was added 5-formyluracile (1 equiv, 0.5 mmol) and Et$_3$N (1.1 equiv). After that, dipolarophile (1.0 equiv) and AgOAc (5 mol%). The reaction mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure. The crude mixture was filtrated through celite with warm EtOH to furnish the corresponding product. To remove the ammonium salt, it was washed with DCM.

8dc-8de: to a stirred solution of free amine ester (1 equiv was previously isolated: 1 equiv of the corresponding hydrochloride with 1.3 equiv K$_2$CO$_3$, in a mixture of AcOEt/H$_2$O during 1h. It was washed with water and the organic fase evaporated), in toluene (2 mL) was added 5-formyluracile (1 equiv, 0.5 mmol). After that, dipolarophile (1.0 equiv, 0.5 mmol) and AgOAc (5 mol%). The solvent was removed under reduced pressure. The crude mixture was filtrated through celite with warm EtOH to furnish the corresponding product.

4.4.1. *(1S*,3R*,3aS*,6aR*)-Methyl 3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8da)*: Pale yellow solid, (132 mg, 82% yield). IR (neat) υ_{max}: 1098, 1223, 1439, 1694, 1741, 2978. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 2.66 (s, 3H), 3.39-3.44 (m, 1H), 3.53-3.56 (m, 1H), 3.67 (s, 3H), 3.92 (d, *J* = 7.1 Hz, 1H), 4.32 (d, *J* = 8.7 Hz, 1H), 7.19-7.27 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 24.6, 48.0, 49.1, 51.7, 61.0, 63.0, 127.4, 127.5, 128.0, 138.7, 171.8, 175.5, 176.9. LRMS (EI): m/z = 322 (M$^+$, >1%), 307 (30), 289 (46), 263 (69), 259 (17), 211 (93), 206 (51), 204 (41), 178 (24), 151 (93), 121 (46), 107 (28), 44 (100). LRMS (EI): calcd. for [$C_{13}H_{14}N_4O_6$] 322.0913; found 322.0924.

4.4.2. *(1S*,3R*,3aS*,6aR*)-Methyl 5-benzyl-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8db)*: Pale yellow solid, (175 mg, 88% yield). IR (neat) υ_{max}: 1157, 1211, 1400, 1445, 1659, 1693, 1740, 3029. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 3.42 (d, *J* = 3.4 Hz, 1H), 3.46 (d, *J* = 8.3 Hz, 1H), 3.64 (d, *J* = 3.4 Hz, 1H), 3.67 (s, 3H), 3.97 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.35 (dd, *J* = 7.1, 4.2 Hz, 1H), 4.41 (d, *J* = 4.0 Hz, 2H), 7.16-7.36 (m, 8H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 41.3, 47.6, 48.6, 51.4, 60.9, 62.7, 127.1, 127.3, 127.6, 128.2, 135.7, 138.2, 170.4, 174.9, 176.4.

LRMS (EI): m/z = 398 (M$^+$, >1%), 383 (3), 365 (38), 339 (33), 211 (100), 206 (23), 204 (32), 187 (15), 151 (70), 106 (17), 91 (75). HRMS (EI): calcd. for $C_{19}H_{18}N_4O_6$ [M - H$^+$] 397.1158; found 397.1148.

4.4.3. *(1S*,3R*,3aS*,6aR*)-Ethyl 1-benzyl-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-5-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8dc)*: Grey solid, (198 mg, 93% yield). IR (neat) υ_{max}: 1098, 1436, 1678, 1697, 3031. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.24 (t, *J* = 7.1 Hz, 3H), 2.65 (s, 3H), 2.89 (d, *J* = 6.7 Hz, 1H), 3.00 (d, *J* = 13.9 Hz, 1H), 3.16 (d, *J* = 14.0 Hz, 1H), 3.45-3.54 (m, 2H), 4.01-4.14 (m, 2H), 4.51 (d, *J* = 8.5 Hz, 1H), 7.11-7.23 (m, 8H), 7.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 15.2, 25.9, 50.5, 57.1, 57.6, 62.0, 62.2, 72.9, 126.6, 127.9, 128.1, 129.3, 129.6, 129.8, 130.2, 130.5, 131.4, 137.6, 165.8, 171.8, 177.1, 177.3. LRMS (EI): m/z = 426 (M$^+$, <1%), 353 (11), 336 (16), 335 (100), 289 (14), 206 (8), 91 (16). Elemental Analysis required for $C_{21}H_{22}N_4O_6$: C 59.20, H 5.20, N 13.10%; found: C 59.40, H 5.00, N 12.85%.

4.4.4. *(1S*,3R*,3aS*,6aR*)-Ethyl 1,5-dibenzyl-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4,6-dioxooctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (8dd)*: Yellow solid, (240 mg, 96% yield). IR (neat) υ_{max}: 1199, 1400, 1674, 1703, 3031. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.24 (t, *J* = 7.1 Hz, 3H), 3.09 (d, *J* = 13.9 Hz, 1H), 3.24 (d, *J* = 14.0 Hz, 1H), 3.57-3.68 (m, 2H), 4.04-4.12 (m, 2H), 4.37 (d, *J* = 14.0 Hz, 1H), 4.47 (d, *J* = 14.0 Hz, 1H), 4.61 (d, *J* = 8.5 Hz, 1H), 7.16-7.31 (m, 14H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 14.3, 42.1, 48.9, 55.6, 55.8, 61.2, 71.7, 127.1, 127.6, 127.7, 128.6, 128.8, 129.7, 130.5, 136.6, 136.2, 139.1, 151.5, 164.7, 170.8, 175.7, 176.1. LRMS (EI): m/z = 502 (M$^+$, <1%), 429 (9), 412 (23), 411 (100), 365 (9), 91 (63). Elemental Analysis required for $C_{27}H_{26}N_4O_6$: C 64.50, H 5.20, N 11.15%; found C 64.65, H 5.10, N 11.50%.

4.4.5. *(2R*,4S*,5R*)- Ethyl 4-methyl 2-benzyl-5-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)pyrrolidine-2,4-dicarboxylate (8de)*: Pale yellow solid, (180 mg, 90% yield). IR (neat) υ_{max}: 1202, 1438, 1676, 1719, 2977, 3061. ^{1}H NMR (300 MHz, DMSO-d$_6$) δ: 1.18 (t, *J* = 7.1 Hz, 3H), 2.09 (dd, *J* = 13.9 Hz, 1H), 2.46 (dd, *J* = 14.0 Hz, 1H), 2.86-3.02 (m, 2H), 3.14-3.21 (m, 1H), 3.38 (s, 3H), 4.04-4.11 (m, 2H), 4.39 (d, *J* = 8.5 Hz, 1H), 7.20-7.28 (m, 8H), 7.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d$_6$) δ: 8.9, 14.5, 45.9, 47.3, 51.6, 56.8, 60.9, 69.1, 111.9, 127.0, 128.4, 130.3, 137.4, 138.2, 151.3, 164.1, 173.1, 174.7. LRMS (EI): m/z = 401 (M$^+$, <1%), 328 (19), 311 (15), 310 (100), 232 (23), 211 (7), 204 (8), 91 (27). HRMS (EI): calcd. for $C_{20}H_{23}N_3O_6$ [M - CO_2CH_3], 342.1460; found 342.1454.

4.5. General procedure for the synthesis of product 14dc.

Finely powdered sodium borohydride (6 equiv, 1.3 mmol) was suspended in THF (4 mL) in presence of the respective ester (100 mg, 0.2 mmol) during a period of 15 minutes under reflux (70 °C) and stirring. Then methanol (0.45 mL) was added dropwise during a period of 5 minutes and effervescence was observed. Stirring and reflux were maintained during a period of 10 h. After the end of the reaction, the alcohol was cooled to room temperature and quenched with a saturated solution of NH$_4$Cl. For purification the organic layer was separated and the aqueous phase extracted with DCM. The organic phase was dried (MgSO$_4$) and concentrated under low pressure to give the corresponding triol **14dc**.

4.5.1. *5-[(2R*,3R*,4R*,5S*)-5-Benzyl-3,4,5-tris(hydroxymethyl)-pyrrolidin-2-yl]pyrimidine-2,4(1H,3H)-dione (14dc)*: Pale yellow

solid, (65 mg, 80% yield). IR (neat) v_{max}: 702, 1098, 1454, 1698, 1775, 2926, 3390. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.42 (dd, J = 13.2, 7.5 Hz, 1H), 2.55-2.59 (m, 1H), 2.64-2.67 (m, 3H), 2.81-2.84 (m, 1H), 3.03 (d, J = 10.5 Hz, 1H), 3.15-3.18 (m, 1H), 3.25 (td, J = 11.3, 10.5, 5.1 Hz, 4H), 3.45 (dd, J = 11.3, 3.3 Hz, 1H), 4.62 (d, J = 6.1 Hz, 1H), 4.88-5.07 (m, 3H), 7.20-7.32 (m, 8H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 34.8, 40.4, 54.6, 59.6, 60.5, 63.0, 66.0, 126.3, 126.7, 128.6, 128.9, 129.5, 129.6, 138.7, 140.1. LRMS (EI): m/z = 361 (M^+, <1%), 164 (29), 120 (21), 117 (37), 105 (13), 91 (100), 70 (25). HRMS (EI): calcd. for $C_{18}H_{23}N_3O_5$ [M − 2xCH$_2$O − H$_2$O]: 282.1249; found 282.1260.

Acknowledgements

Notes and references

1. *Organic Synthesis and Molecular Engineering*, (Ed. Nielsen MB) John Wiley & Sons, Hoboken, New Jersey, 2014.
2. For updated list of HCV inhibitors in the market, see: https://www.drugs.com/drug-class/antiviral-agents.html
3. De Clercq E. *Nature Rev.,* 2008; 4: 1001-1018.
4. (a) Calter MA, Zhu C. *J. Org. Chem.* 1999; 64: 1415-1419; (b) Chen JJ, Drach JC, Townsend LB. *J. Org. Chem.* 2003; 68: 4170-4178; (c) Li JS, Gold B. *J. Org. Chem.* 2005; 70: 8764-8771.
5. Chen JJ, Wei Y, Williams, JD, Drach JC, Townsend LB. *Nucleosides, Nucleotides, and Nucleic Acids*, 2005; 24: 1417-1437.
6. The introduction of these heterocyclic moieties (anchored to the dipolarophile) has been published after our patent application. Yang Q-L, Xie M-S, Xia C, Sun H-L, Zhang D-J, Huang K-X, Guo Z, Qu G-R, Guo H-M. *Chem. Commun.* 2014; 50: 14809-14812.
7. For recent reviews dealing with multicomponent reactions, see: (a) van der Heijden G, Ruijter E, Orru RVA. *Synlett* 2013; 24: 666-685; (b) Brauch S, van Berkel SS, Westermann B. *Chem. Soc. Rev.* 2013; 42: 4948-4962; (c) *Multicomponent Reactions in Organic Synthesis*, (Eds. Zhu J, Wang Q, Wang M-X) Wiley-VCH: Weinheim, 2014;(d) *Science of Synthesis*: *Multicomponent Reactions*, (Ed. Müller TJJ), Thieme: Stuttgart, 2014; (e) *Multicomponent Reactions: Concepts and Applications for Design and Synthesis*, (Ed. Pérez-Herrera R, Marqués-López E), Wiley-VCH: Weinheim, 2015.
8. (a) Mancebo-Aracil J, Cayuelas A, Nájera C, Sansano J. M. *Tetrahedron* 2015; 71: 8804-8816; (b) Mancebo-Aracil J, Castelló LM, Nájera C, Sansano JM, Larrañaga O, de Cózar A, Cossío FP. *Tetrahedron*, 2015; 71: 9645-9661.
9. For recent 1,3-DC general reviews, see: (a) Ryan JH. *Arkivoc* 2015; (i): 160-183; (b) T. Hashimoto, K. Maruoka, *Chem. Rev.* 2015; 115: 5366-5412; (c) Pavlovska TL, Redkin RGr, Lipson VV, Atamanuk DV. *Synth. Biol. Activ. Mol. Divers* 2016; 20: 299-344; (d) Meyer AG, Ryan JH. *Molecules*, 2016; 21: 935-989; (e) Singh MS, Chowdhury S, Koley S. *Tetrahedron* 2016; 72: 1603-1716; (f) Nájera C, Sansano JM. *Chem. Rec.* 2016; 16: 2430-2448; (g) Dondas HA, Retamosa MG, Sansano JM. *Synthesis* 2017; 49: 2819-2851; (h) Bdiri B, Zhao B-J, Zhou Z-M. *Tetrahedron: Asymmetry,* 2017; 28: 876-883.
10. (a) Nájera C, Sansano JM. *Org. Biomol. Chem.* 2009; 7: 4567-4581; (b) Nájera C, Sansano JM. *L'Actualité Chim.* 2013; 370: 28-30.
11. Preliminary results were previously patented. Mancebo-Aracil J, Castelló LM, Nájera C, Sansano JM. WO Patent P050644 A1, Apr 11, 2013.
12. 4-Chromenone nucleus is present in flavones, which can be considered anti-oxidant agents, have also effects on CYP (P450) activity, coronary heart disease prevention, hepatoprotective, anti-inflammatory, and anticancer activities, antiviral activitiy, etc. In plant systems, flavonoids help in combating oxidative stress and act as growth regulators. Kumar S, Pandey AK. *Scientific World J.* 2013; 2013: 1-8.
13. Serotonin is as a neurotransmitter that modulates neural activity and a wide range of neuropsychological processes. Berger M, Gray, JA, Roth BL. *Annu. Rev. Med.*, 2009, **60**, 355-366.
14. Pyridoxal phosphate represents the most versatile organic cofactor in biology, and is used by a variety of enzymes in all organisms. Percudani R, Peracchi A. *EMBO reports*, 2003, **4**, 850-854.
15. Antiviral and anti-tumor are the two most widely reported activities of uracil analogues Pałasz A, Cież D. *Eur. J. Med. Chem.*, 2015, **97**, 582-611.
16. Mancebo-Aracil J, Nájera C, Sansano JM. *Tetrahedron: Asymmetry*, 2015; 26: 674-678.
17. Castelló LM, Nájera C, Sansano JM, Larrañaga O, de Cózar A, Cossío FP. *Adv. Synth. Catal.* 2014, **356**, 3861-3870.
18. da Costa JCS, Pais KC, Fernandes EL, de Oliveira PSM, Mendonça JS, de Souza MVN, Peralta MA, Vasconcelos TRA. *Arkivoc* 2006; (i): 128-133.