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Synthesis and biological evaluation of analogues of M6G

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ABSTRACT

Synthesis and biological evaluation of new derivatives of Morphine-6-Glucuronide (M6G) are described. M6G is an active metabolite of morphine which displays more analgesia than morphine with a superior side effect profile but with a less efficiently BBB penetration. These phenomena could be explained by the presence of the glucuronide moiety, which confers a higher hydrophilic character compare to morphine. In this context, we have prepared three analogues of M6G possessing a tetrazole, an oxadiazole, and a triazolopyrimidine moiety instead of the carboxylic acid function on position 5 of the sugar. These three analogues showed higher analgesic properties than morphine and M6G even by oral administration.

1. Introduction

Morphine is the most widely used opiate treatment for moderate to severe pain in spite of several side effects as constipation, respiratory depression and chemical dependency. Several studies have showed that the analgesic effect of morphine was not produced by the parent drug but by its active metabolite M6G, which is formed upon administration of morphine in human. Indeed, after administration, morphine is metabolized chiefly through glucuronidation by uridine diphosphate glucuronosyl transferase (UGT) enzymes. Morphine has two main metabolites, namely morphine-3-glucuronide (M3G, 50%) and morphine-6-glucuronide (M6G, 10%) [1,2]. Systematic studies on M3G and M6G have been undertaken and showed, after intracerebroventricular injection, that M3G, with its low affinity for μ receptors, was devoid of significant analgesic properties, when M6G was more than 100-fold higher than morphine itself and have reduced side effects [3,4] which were generally associated with the uptake of morphine [5]. In apparent contradiction to its polar properties, M6G, which is a more potent analgesic drug than morphine itself, is able to penetrate the BBB, although to a lesser extent than morphine. A lot of work has been devoted to the synthesis of new analogues, such as chemically modified opiate alkaloids, peptides and non-peptide derivatives but with limited therapeutic success [6]. In this context we wish to describe here new derivatives of M6G in which the acid function of the glucuronide moiety is replaced by various heterocyclic rings and particularly by a tetrazole unit. Despite of their physical and chemical differences it has been showed that they exhibited a remarkable similarity in their respective topology and geometrical disposition [7]. Moreover we could hope that these new derivatives have a better pharmacological profile by notably limiting the metabolism and thus improving its "*in vivo*" stability. We describe herein the synthesis of three new derivatives of M6G, for which the carboxylic acid is replaced by a tetrazole, an oxadiazole ring and a triazolopyrimidine moiety together with the evaluation of the analgesic activity.

2. Results and discussion

We first envisaged the synthesis of the tetrazole derivative. For its preparation we first needed to prepare a glycosidic donor, possessing a tetrazole moiety in position 5 of the sugar. Starting from commercially available glucuronamide **1** we chose the sterically hindered benzoyl protective group rather than the classical acetyl group in order to avoid acyl transfer reaction [8], a side reaction often observed on glucuronidation, which strongly decreased the yield. So, treatment of compound **1** with benzoyl chloride in presence of pyridine led directly to a mixture of the cyano derivatives **2a** and **2b** in a 2:1 ratio and 57% yield. In this case concomitant dehydration was observed, reaction which traditionally occurred by the use of thionyl chloride [9] or trifluoroacetic acid (Scheme 1) [10].

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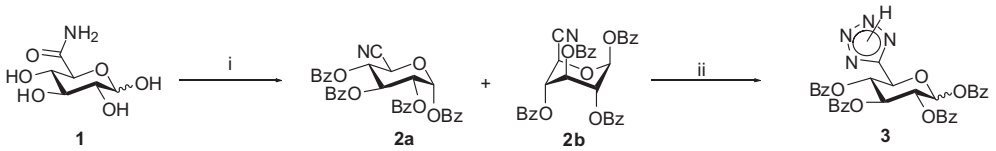
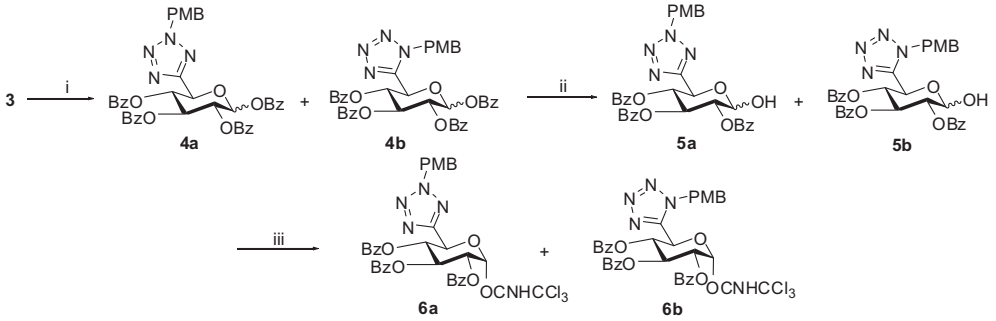


Scheme 1. Synthesis of glucuronamide derivative (**3**). Reagents and conditions : (i) BzCl, pyridine, CH_2Cl_2, 25 °C, 12 h (57%); (ii) $TMSN_3$, $(Bu_3Sn)_2O$, toluene, reflux, 12 h (59%).



Scheme 2. Synthesis of trichloroacetimidates derivatives (**6a-6b**). Reagents and conditions : (i) PMBCl, NEt_3, THF, reflux 12 h (73%); (ii) NH_2NH_2, AcOH, DMF, 25 °C 4 h (70%); (iii) CCl_3CN, DBU, CH_2Cl_2, 25 °C, 1 h (65%).

The ratio **2a/2b** was determined by NMR, considering the signal of each anomeric proton (respectively H-1α ($J = 3.5$ Hz) at 6.88 ppm for **2a** and H-1β ($J = 3.0$ Hz) at 6.57 ppm for **2b**). This unusual coupling constant for **2b** led us to undertake modeling calculations using the Batchmin®; program within the MM2 force field of the Macromodel package [11] in order to confirm the $^1C_4$ conformation. Unfortunately, no significant difference of energy between the two conformations was observed (Scheme 1).

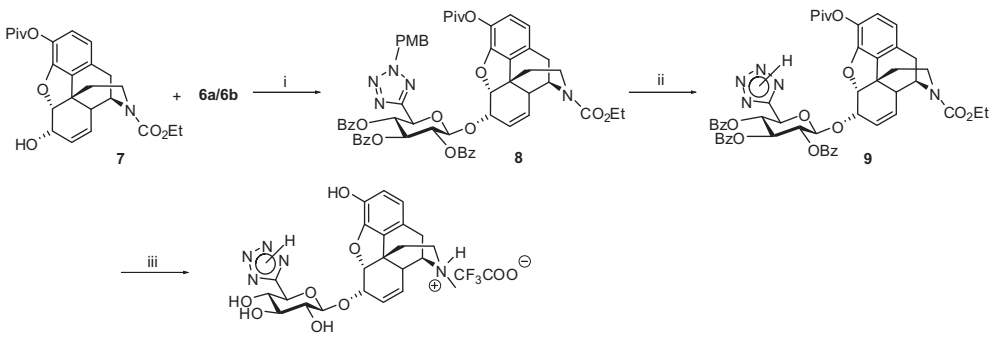
Among all the methods described to create the tetrazole ring [12] the treatment of mixture of cyano derivatives **2a** and **2b** with combination of trimethylsilylazide and bis(tributyltin) oxide gave the best results. Using this experimental procedure, the tetrazole glucuronide **3** [13] was obtained in 59% yield (Scheme 1). At this step of the synthesis it was necessary to protect the tetrazole moiety. We chose the *p*-methoxybenzyl group, stable in glycosylation conditions, introduced in soft conditions (PMBCl, Et_3N) [14] and cleaved in acidic media (TFA) [15], as protection of the tetrazole with a carbamate or an amide moiety was not possible, due to a Huisgen rearrangement often encountered in tetrazole chemistry [16] (Scheme 2).

Treatment of compound **3** with *para*-methoxybenzyl chloride in presence of triethylamine led to a mixture of protected tetrazoles **4a** and **4b** in a 2:1 ratio (73% combined yield, for **4a** and **4b** α/β : 2/1).

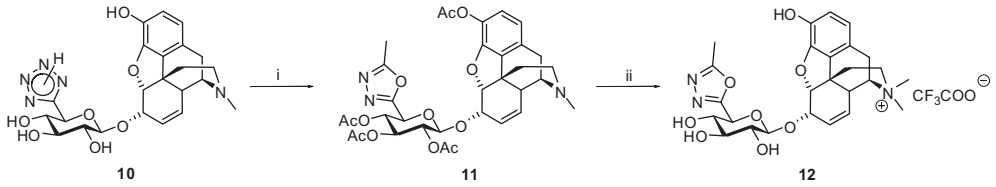
Among all the methods described in literature to perform glycosydation, we chose the trichloroacetimidate method developed by Schmidt [17].

Selective debenzoylation using hydrazine acetate in DMF gave the two acetals **5a** and **5b** (70%, **5a**/**5b** 2:1). The corresponding alpha imidates **6a** and **6b** were obtained after treatment with trichloroacetonitrile and DBU in a 3/1 ratio. The structure of these two imidates and the ratio of the two tetrazoles were confirmed by NMR spectroscopy. Isomerisation of tetrazoles during the reaction could explain the difference between the ratio observed for **5a**/**5b** and **6a**/**6b** as Lwowski and *coll.* have showed that this isomerization is strongly dependent of the solvent and of the steric hindrance [18].

The next step of the synthesis consisted of a glycosylation using a morphine derivative. As morphine is strongly scheduled substance controlled by French authorities, we have used the 3-*O*-pivaloyl *N*-ethylcarbamate morphine derivative **7** [19], which we were allowed to use in academic laboratory, furnished by Francopia®;, even if we should use drastic reduction conditions to transform the carbamate moiety into a methyl group. Thus, glycosylation of **7** with an excess of donor (**6a**/**6b**, 2.eq.) and promotor (TMSOTf, 4eq.) at 0 °C without anhydrous conditions, afforded the compound **8** as a unique β anomer in a good yield of 69%. Structure of compound **8** was determined by NMR, considering the anomeric proton (H-1β at 5.43 ppm with a coupling constant of 7 Hz). Cleavage of the *p*-methoxybenzyl group was performed using TFA, to give the tetrazole **9** in a 60% yield. Simultaneous reduction of the carbamate moiety and of the benzoate group was performed in presence of LAH. Purification of the crude product on reverse phase



Scheme 3. Synthesis of morphinan derivative (**10**). Reagents and conditions : (i) TMSOTf, CH_2Cl_2, 0 °C 30 mn (69%); (ii) TFA, reflux 15 mn (60%); (iii) $LiAlH_4$, THF, reflux 1 h (16%).



Scheme 4. Synthesis of morphinan derivative (**12**). Reagents and conditions : (i) Ac_2O, reflux 12 h (55%); MeONa, IR-120 resin, 3 h (46%).

flash chromatography afforded compound **10** in a 16%yield, as its trifluoroacetate salt. This low yield could be explained by the lot of purifications necessary to obtain purity higher than 95% for biological evaluation [20] (Scheme 3).

Starting from the tetrazole **10** (Scheme 4) we prepared the corresponding 1,3,4-oxadiazole **11** by treatment with acetic anhydride. The Huisgen rearrangement [16,21] of the tetrazole **10** gave the corresponding oxadiazole, with a methyl group in position 2, in 55% yield. Complete deacetylation of compound **11** using sodium methoxyde gave, after purification on HPLC, the oxadiazole **12** in 46% yield (Scheme 4).

The preparation of a triazolopyrimidine derivative was also envisaged by transformation of the tetrazole ring through reaction with an imidoyl chloride *via* a Huisgen reaction. Only a few couple of examples of this type of rearrangement has already been described [22,23]. Transformation of a tetrazole ring into a triazolopyrimidine has already been described by Karkas and *coll* [23]. on the anomeric position of a galactopyranoside.

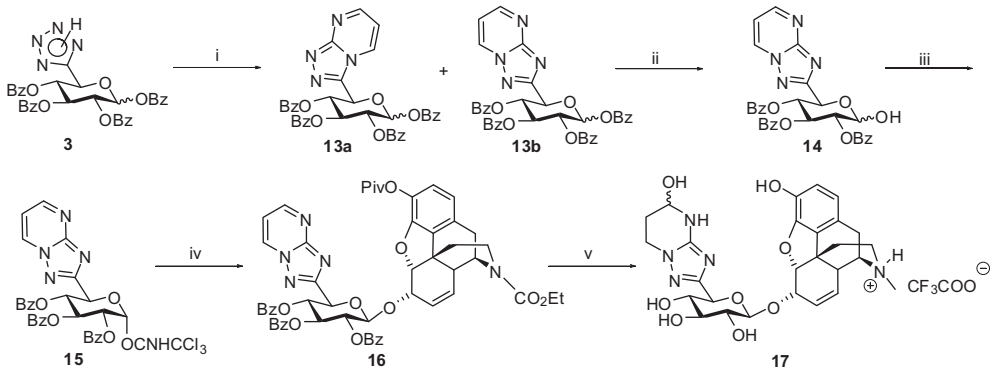
Treatment of the tetrazole **3** (Scheme 5) with 2-chloropyrimidine and pyridine led to the corresponding triazolopyrimidines **13a** and **13b** in a 3:1 ratio. Here too, the presence of these two isomers could be explained by a Huisgen rearrangement on the two isomeric forms of the tetrazole. The *N*-H1 isomer furnished the pyrimidine **13a** as the *N*H2 form gave the pyrimidine **13b**. Selective anomeric deprotection of the mixture of compounds **13a** and **13b** using hydrazine acetate in DMF led to the unique triazolopyrimidine hemiacetal **14**. Isomerisation of [4,3-a]pyrimidine into the [1,5-a]pyrimidine could be explained by a Dimroth [24] rearrangement which was also observed when **13a** was stored at room temperature under atmospheric pressure.

Formation of the alpha trichloroacetimidate [22] was performed, as previously described, using trichloroacetonitrile and DBU as a base. The presence of a single anomer was confirmed by NMR according to the anomeric proton at 7.00 ppm with a coupling constant of 3.5 Hz. Glycosylation of the acceptor 7 with the donor **15** in the conditions previously described furnished the compound **16** in 31% yield. Complete reduction of the triazolopyrimidine **16** with LAH didn't furnish the desired triazolopyrimidine but the M6G analogue **17** in 40% yield. The structure of compound **17** was established by NMR spectroscopy. The presence of a multiplet at 5.36 ppm corresponding to the proton *gem* to the hydroxyl group and two multiplets at 4.30 and 4.10 ppm corresponding to the hydrogens in alpha position of the hydroxyl group confirm the structure of **17**. The ^{13}C spectra also showed the presence of two secondary carbons at 40.1 and 26.2 ppm and a tertiary carbon at 71.1 ppm. The formation of this tetrahydrotetrazolopyrimidine derivative could be explained by a partial reduction of the pyridine ring to give the corresponding imine which is directly hydrated to give the compound **17**. Such partial reduction has already been described on phenanthroline, pteridine [25–27] and uracile [28] derivatives, but never on a pyrimidine moiety. We envisaged that, in this case, the hydride transfer was not possible due to a complexation of the nitrogen atoms of the pyrimidine and morphine moiety with aluminum, as the reduction of the sugar **14**, led to the complete reduction of the pyrimidine.

In summary, we have synthesized three analogues of M6G for which the carboxylic acid moiety was respectively replaced by a tetrazole ring (compound **10**), by a 1,3,4-oxadiazole moiety (compound **12**) and by a tetrahydrotriazolopyrimidine (compound **17**).

3. Biological evaluations

The anti-nociceptive activity was determined using the tail-flick procedure in Swiss mice male (Iffa Credo, group of 12 animals for each test). In the experiment, the tail reflex was elicited by placing the tip of the tail over a slit through which the light of an infra-red source was focused (55–60 °C) and the time to tail withdrawal was recorded. Heat intensity was settled for a withdrawal reflex within 0.5–3.5 s for basal recording of each animal. The cut-off time was set at 8 s for this test in order to avoid tissue damage. Responsiveness to drug treatments was measured several times from 20 to 120 min after administration. The compounds were tested at various doses between 1.25 and 30 mg/kg by subcutaneous administration. The inhibition of tail-flick was expressed as "percent maximum possible effect (%MPE) calculated using the method previously described by D'Amour and Smith [29].



Scheme 5. Synthesis of morphinan derivative (**17**). Reagents and conditions : (i) 2-chloropyrimidine, pyridine, reflux 12 h (74%); (ii) NH_2NH_2.AcOH, DMF, 0 °C, 1 h then room temperature 2 h (68%); (iii) CCl_3CN, DBU, CH_2Cl_2, room temperature 1.5 h (70%); (**7**), TMSOTf, CH_2Cl_2, 0 °C 0.5 h (31%); $LiAlH_4$, THF, reflux 1h (40%).

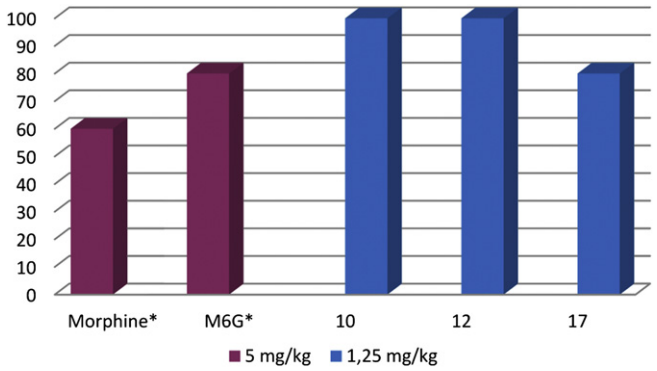


Fig. 1. Tail-Flick (%MPE max), s.c. administration. *The anti-nociceptive activity of morphine and M6G was in accordance with literature [19].

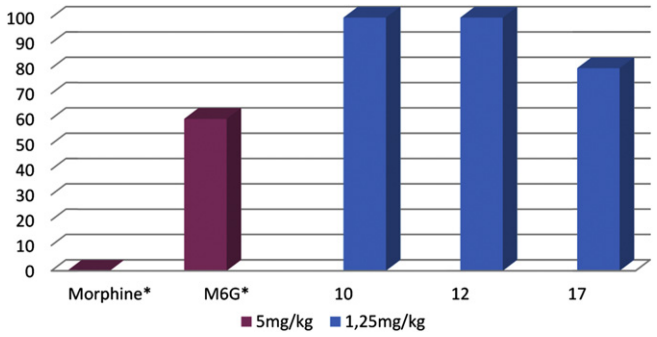


Fig. 2. Duration (%MPE 120 min after s.c. administration) * The results obtained for morphine and M6G was in accordance with literature [19].

The results of the tail-flick test on compounds **10**, **12** and **17** are summarized in Fig. 1 [30]. The DE_{50} correspond to the efficient dose of compound to obtain an analgesic activity of 50% of the MPE.

All the compounds tested showed powerful analgesic activity starting at low doses. The % MPE was superior to 80% after acute administration within doses of 1.25 mg/kg s.c. The three tested analogues of M6G have long duration analgesic activity (>120 min, Fig. 2) after unique dose injection. For comparison, the DE_{50} of morphine is about 4.4 mg/kg (s.c., 30 min post injection) [31,32], and about 2.7 mg/kg (s.c., 60 min post administration) for M6G.

The anti-nociceptive activity of compound **10** was also tested by oral administration. The value of percent MPE max obtained is about 78% at a dose of 10 mg/kg, p.o. and the DE_{50} was inferior to 2.5 mg/kg.

4. Conclusion

In summary, we have prepared three analogues of M6G with various heterocyclic rings (tetrazole, oxadiazole, and triazolopyrimidine) possessing powerful analgesic activity. The results of the tail-flick tests showed that the analgesic effect of the three synthesized compounds have higher analgesic effect than morphine and M6G by subcutaneous and oral administration. The low doses necessary for long duration anti-nociceptive effects by oral administration allowed us to envisage the use of this compound as drug for treatment of severe pain.

5. Experimental section

^1H and ^{13}C NMR spectra were recorded on a Brüker 400 MHz apparatus using $CDCl_3$ CD_3OD or D_2O. The chemical shifts are reported in ppm (δ scale) and all J values are in Hz. The following abbreviations are used: singlet (s), doublet (d), doubled doublet (dd), triplet (t), multiplet (m). Melting points are uncorrected. Mass spectra (Ion Spray) were performed on a Perkin Elmer Sciex PI300, HRMS. Monitoring of the reactions was performed using silica gel TLC plates (silica Merck 60 F254). Spots were visualized by UV light at 254 nm. Flash chromatography columns were performed using silica gel 60 (70–230 mesh). The reverse phase chromatographies were performed either on a CombiFlash (Retrieve®;) apparatus with a Redi Step C-18 column (Teledyne Isco®;), 43 g or with a preparative apparatus Novacep®; equipped with a diode array detector (230 nm) on Hyperprep 10 μm HSC8 column.

5.1. Synthesis of tetrazole (**10**)

5.1.1. 1,2,3,4-Tetra-O-benzoyl-α/β-D-glucurononitrile (**2a**/**2b**)

To a suspension of D-glucuronamide **1** (25.0 g, 0.129 mol) in pyridine (100 mL) was added over a period of 30 min, a solution of benzoyl chloride (102 mL, 0.878 mol) in CH_2Cl_2 (90 mL). The mixture was stirred overnight at room temperature, then CH_2Cl_2 (200 mL) and water (200 mL) were added. The organic layer was washed with HCl 1N (200 mL), saturated $NaHCO_3$ (3 × 200 mL), brine (200 mL) and was dried over Na_2SO_4. The concentrated residue was triturated with EtOH (200 mL) to give the nitrile **2a** and **2b** (43.4 g, 57%) as pale yellow solid. The α:β (2:1) ratio was determined by ^1H NMR. mp 209–212 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10-7.30 (m, 20Hα + 20Hβ, H-*aro*), 6.88 (d, 1Hα, *J* 3.5 Hz, H-1α), 6.57 (d, 1Hβ, *J* 3.0 Hz, H-1β), 6.21 (t, 1Hα, *J* 9.5 Hz, H-3α), 5.93 (t, 1Hα, *J* 9.5 Hz, H-4α), 5.84 (t, 1Hβ, *J* 4.0 Hz, H-3β), 5.71-5.65 (m, 1Hα + 1Hβ, H-2α, H-4β), 5.64 (m, 1Hβ, H-2β), 5.16 (d, 1Hβ, *J* 4.0 Hz, H-5β), 5.11 (d, 1Hα, *J* 9.5 Hz, H-5α); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 165.1, 164.8, 164.6, 164.3, 163.8 (C=O), 134.4-128.0 (C-*aro*), 115.3 (C-6β), 114.1 (C-6α), 90.9 (C-1β), 89.4 (C-1α), 69.3, 69.2, 69.0 (C-2α, C-3α, C-4α), 67.4 (C-4β), 66.7, 66.5 (C-2β, C-3β), 61.9 (C-5α), 60.8 (C-5β); HRMS (ES) $C_{34}H_{25}NO_9Na$ $[M + Na]^+$ calc. 614.1427, found 614.1422.

5.1.2. 1,2,3,4-Tetra-O-benzoyl-5-C-(tetrazol-5-yl)-α/β-D-xylopyranose (**3**)

To a solution of nitrile **2a**/**2b** (43.0 g, 72.8 mmol) in toluene (500 mL) were added $(Bu_3Sn)_2O$ (3.70 mL, 7.26 mmol) and $TMSN_3$ (28.7 mL, 216 mmol) and the mixture was refluxed overnight. The concentrated residue was purified by flash chromatography on silica gel (Cyclohexane-Ethyl acetate 1:1 to 0:1) to give the tetrazole **3** (27.0 g, 59%) as a brown solid. The α:β (2:1) ratio was determined by ^1H NMR. mp 144–147 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.19-7.28 (m, 20Hα + 20Hβ, H-*aro*), 7.06 (d, 1Hα, *J* 3.5 Hz, H-1α), 6.50-6.44 (m, 1Hβ + 1Hα, H-1β, H-3α), 6.21 (t, 1Hβ, *J* 9.0 Hz, H-3β), 6.13-6.01 (m, 2Hβ + 1Hα, H-4β, H-4α, H-2β), 5.90-5.85 (m, 2Hα, H-2α, H-5α), 5.66 (d, 1Hβ, *J* 9.0 Hz, H-5β). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.79, 165.2, 164.7 (C=O, C=N), 134.4-128.1 (C-*aro*), 93.0 (C-1β), 89.9 (C-1α), 72.0, 70.5, 70.4, 70.3, 69.5 (C-2α, C-2β, C-3α, C-3β C-4α, C-4β), 68.9 (C-5β), 67.0 (C-5α); HRMS (ES) $C_{34}H_{26}N_4O_9Na$ $[M + Na]^+$ calc. 657.1597, found 657.1595.

5.1.3. 1,2,3,4-Tetra-O-benzoyl-5-C-[2-(4-methoxybenzyl)-2H-tetrazol-5-yl]-α/β-D-xylopyranose and 1,2,3,4-tetra-O-benzoyl-5-C-[1-(4-methoxybenzyl)-1H-tetrazol-5-yl]-α/β-D-xylopyranose (**4a**/**4b**)

A solution of tetrazole **3** (21.0 g, 33.1 mmol) in THF (210 mL) triethylamine (5.5 mL, 39.5 mmol) and 4-methoxybenzyl chloride (5.0 mL, 36.7 mmol) was refluxed overnight. The concentrated residue was purified on flash chromatography (Cyclohexane-Ethyl acetate 4:1) to give the mixture of isomers **4a** and **4b** (18.5 g, 73%) as pale yellow solid. The **4a**:**4b** (2:1) ratio was determined by ^1H NMR with a 2:1 α:β ratio for **4a** and a 2:1 α:β ratio for **4b**. ^1H NMR

(400 MHz, $CDCl_3$) for α anomers : δ 8.21-7.29 (m, 20Ha + 20Hb, H-*aro*), 7.23 (d, 2Hb, *J* 8.5 Hz, H-*aroPMB*b), 7.17 (d, 2Ha, *J* 8.5 Hz, H-*aroPMB*a), 6.98 (d, 1Ha, *J* 3.5 Hz, H-1a), 6.96 (d, 1Hb, *J* 3.5 Hz, H-1b), 6.86 (d, 2Hb, *J* 8.5 Hz, H-*aroPMB*b), 6.75 (d, 2Ha, *J* 8.5 Hz, H-*aroPMB*a), 6.42 (t, 1Ha, *J* 10.0 Hz, H-3a), 6.33 (t, 1Hb, *J* 10.0 Hz, H-3b), 6.13 (t, 1Ha, *J* 10.0 Hz, H-4a), 5.84 (dd, 1Ha, *J* 3.5 Hz, *J* 10.0 Hz, H-2a), 5.76-5.63 (m, 3Ha + 5Hb, CH_2PhOCH_3a, CH_2PhOCH_3b, H-5a, H-2b, H-4b, H-5b), 3.79 (s, 3Hb, OCH_3b), 3.75 (s, 3Ha, OCH_3a); NMR ^{13}C (100 MHz, $CDCl_3$) for α anomers : δ 165.8, 165.2, 164.5, 164.3, 164.2, 162.1 (C=O, C=N), 134.4-124.7 (C-*aro*), 114.5 (C-*aroPMB*a), 114.3 (C-*aroPMB*b), 90.0 (C-1a), 89.7 (C-1b), 71.1 (C-4a), 70.4, 70.2, (C-2a, C-3a), 69.9, 69.6, 69.5 (C-2b, C-3b, C-4b), 67.0 (C-5a), 66.0 (C-5b), 56.7 (CH_2PhOCH_3a), 55.3 (OCH_3b), 55.2 (OCH_3a), 52.1 (CH_2PhOCH_3b); HRMS (ES) $C_{42}H_{34}N_4O_{10}Na$ $[M + Na]^+$ calc. 777.2173, found 777.2181.

5.1.4. 2,3,4-Tri-O-benzoyl-5-C-[2-(4-(methoxybenzyl)-2H-tetrazol-5-yl]-α/β-D-xylopyranose and 2,3,4-tri-O-benzoyl-5-C-[1-(4-(methoxybenzyl)-1H-tetrazol-5-yl]-α/β-D-xylopyranose (**5a**/**5b**)

To a solution of tetrazoles **4a** and **4b** (13.4 g, 17.8 mmol) in DMF (100 mL) at 0 °C was added hydrazine acetate (2.45 g, 26.6 mmol) in small portions over 15 min. The mixture was stirred for 1h at 0 °C then for 4 h at room temperature. The concentrated residue was purified on flash chromatography (Cyclohexane-Ethyl acetate 7:3) to give the hemiacetals **5a** and **5b** (8.0 g, 70%) as a pale yellow solid.

The **5a**:**5b** (2:1) ratio was determined by ^1H NMR with a 5:1 α:β ratio for **5a** and a 5:1 α:β ratio for **5b**. ^1H NMR (400 MHz, $CDCl_3$) for α anomers : δ 8.14-7.15 (m, 17Ha + 17Hb, H-*aro*), 6.96 (d, 2Ha, *J* 9.0 Hz, H-*aroPMB*a), 6.71 (d, 2Hb, *J* 9.0 Hz, H-*aroPMB*b), 6.36-6.26 (m, 1Ha + 1Hb, H-3a, H-3b), 6.02 (t, 1Ha, *J* 10.0 Hz, H-4a), 5.88 (d, 1Ha, *J* 3.5 Hz, H-1a), 5.86 (d, 1Hb, *J* 3.5 Hz, H-1b), 5.85-5.74 (m, 1Ha + 3Hb, H-5a, H-5b, CH_2PhOCH_3b), 5.63 (s, 2Ha, CH_2PhOCH_3a), 5.51-5.42 (m, 1Ha + 1Hb, H-4b, H-2a), 5.31 (dd, 1Hb, *J* 3.5 Hz, *J* 10.0 Hz, H-2b), 3.82 (s, 3Hb, OCH_3b), 3.75 (s, 3Ha, OCH_3a); ^{13}C NMR (100 MHz, $CDCl_3$) for α anomeres : δ 165.8, 165.5, 164.7, 162.9, 150.5 (C=O, C=N), 133.7-124.8 (C-*aro)*, 114.5 (C-*aroPMB*b), 114.2 (C-*aroPMB*a), 90.9 (C-1a), 90.8 (C-1b), 72.1 (C-2a), 71.8 (C-2b ou C-3b ou C-4b), 71.2 (C-4a), 70.2 (C-2b ou C-3b ou C-4b), 70.0 (C-3a), 69.3 (C-2b ou C-3b ou C-4b), 64.1 (C-5a), 63.4 (C-5b), 56.7 (CH_2PhOCH_3a), 55.4 (OCH_3b), 55.2 (OCH_3a), 52.0 (CH_2PhOCH_3b); HRMS (ES) $C_{35}H_{31}N_4O_9$ $[M + H]^+$ calc. 651.2091, found 651.2111.

5.1.5. 2,3,4-Tri-O-benzoyl-5-C-[2-(4-(methoxybenzyl)-2H-tetrazol-5-yl]-α-D-xylopyranosyle trichloroacetimidate and 2,3,4-tri-O-benzoyl-5-C-[1-(4-methoxybenzyl)-1H-tetrazol-5-yl]-α-D-xylopyranosyle trichloroacetimidate (**6a**/**6b**)

To a solution of hemiacetal **5a** and **5b** (6.0 g, 9.23 mmol) in CH_2Cl_2 (170 mL) were added DBU (278 μL, 1.86 mmol) and trichloroacetonitrile (14.6 ml, 184 mmol). The mixture was stirred for 1h then a solution of acetic acid (105 μL, 1.83 mmol) in water (50 mL) was added. The organic layer was washed with water (50 mL) dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (silica gel previously washed with a 5% solution of Et_3N in ethyl acetate) (Cyclohexane-Ethyl acetate 7:3) to afford the imidates **6a** and **6b** (4.7 g, 65%) as pale yellow solid. The **6a**:**6b** (3:1) ratio was determined by ^1H NMR. ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H-b, N*H*b), 8.69 (s, 1Ha, N*H*a), 8.20-7.29 (m, 15Ha + 17Hb, H-*aro*), 7.18 (d, 2Ha, *J* 8.5 Hz, H-*aroPMB*a), 6.99 (d, 2Hb, *J* 8.5 Hz, H-*aroPMB*b), 6.94 (m, 1Ha + 1Hb, H-1a, H-1b), 6.74 (d, 2Ha, *J* 8.5 Hz, H-*aroPMB*a), 6.36 (t, 1Ha, *J* 10.0 Hz, H-3a), 6.29 (t, 1Hb, *J* 10.0 Hz, H-3b), 6.10 (t, 1Ha, *J* 10.0 Hz, H-4a), 5.80-5.69 (m, 2Ha + 3Hb, H-2a, CH_2PhOCH_3b, H-5a, H-5b), 5.64 (s, 2Ha, CH_2PhOCH_3a), 5.62-5.55 (m, 2Hb, H-4b, H-2b), 3.84 (s, 3Hb, OCH_3b), 3.75 (s, 3Ha, OCH_3a); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 165.4, 164.4, 162.0, 160.5, 159.9 (C=O, C=N), 134.0-124.8 (C-*aro*), 114.6 (C-*aroPMB*b), 114.3 (C-*aroPMB*a), 93.1 (C-1a), 92.8 (C-1b), 70.9 (C-2b ou C-3b ou C-4b), 70.7 (C-4a), 70.5 (C-2a), 70.0 (C-2b ou C-3b ou C-4b), 69.8 (C-3a), 69.3 (C-2b ou C-3b ou C-4b), 66.9 (C-5a), 66.0 (C-5b), 56.5 (CH_2PhOCH_3a), 55.3 (OCH_3b), 55.1 (OCH_3a), 51.8 (CH_2PhOCH_3b).

5.1.6. 3-O-Pivaloyl-N-ethoxycarbonylnormorphin-6-yl 2,3,4-tri-O-benzoyl-5-C-[2-(4-methoxybenzyl)-2H-tetrazol-5-yl]-β-D-xylopyranoside (**8**)

To a solution of imidate **6a**/**6b** (3.6 g, 4.54 mmol) and acceptor **7** (1.0 g, 2.34 mmol) in CH_2Cl_2 (50 mL) at 0 °C, under argon, was added TMSOTf (1.7 mL, 9.38 mmol). The mixture was stirred at 0 °C for 30 min, then at room temperature for 30 min. After addition of DIEA (1 mL) the mixture was stirred for 15 min then concentrated. The residue was purified by chromatography on silica gel (Cyclohexane-AcOEt 3:2) to afford the compound **8** (1.7 g, 69%) as a white powder. mp 185–188 °C; $[\alpha]_D^{23} = -77$ (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.97-7.28 (m, 15H, H-*aro*), 7.17 (m, 2H, H-*aroPMB*), 6.72 (m, 3H, H-*aroPMB*, H-1), 6.54 (d, 1H, *J* 8.5 Hz, H-2), 6.13 (t, 1H, *J* 10.0 Hz, H-4′), 5.90 (t, 1H, *J* 10.0 Hz, H-3′), 5.72 (m, 1H, H-8), 5.67 (m, 1H, H-2′), 5.61 (d, 2H, *J* 5.0 Hz, CH_2PhOCH_3), 5.43 (d, 1H, *J* 7.0 Hz, H-1′), 5.32 (d, 1H, *J* 10.0 Hz, H-5′), 5.25 (m, 1H, H-7), 5.00-4.80 (m, 2H, H-9, H-5), 4.40 (m, 1H, H-6), 4.20 (m, 2H, OCH_2CH_3), 4.00 (m, 1H, H-16a), 3.74 (s, 3H, OCH_3), 3.00 (m, 1H, H-16b), 2.84-2.74 (m, 2H, H-10), 2.48 (m, 1H, H-14), 1.89 (m, 2H, H-15), 1.30 (m, 12H, $C(CH_3)_3$, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 165.7, 165.1, 164.5, 159.9 (C=O, C=N), 155.0, 150.5, 133.1, (C-*aro*), 130.7 (C-8), 129.8, 129.7, 129.6, 128.3, 128.2, 128.1, (C-*aro*), 127.4 (C-7), 122.2 (C-1), 119.3 (C-2), 114.3 (C-*aroPMB*), 99.4 (C-1′), 89.9 (C-5), 72.9 (C-3′, C-6), 72.5 (C-2′), 71.5 (C-4′), 68.7 (C-5′), 61.6 (OCH_2CH_3), 56.6 (CH_2PhOCH_3), 55.2 (OCH_3), 50.2 (C-9), 44.3 (C-13), 39.8 (C-14), 37.2 (C-16), 35.3 (C-15), 35.0 ($C(CH_3)_3$), 30.2 (C-10), 29.8 ($C(CH_3)_3$), 14.7 (OCH_2CH_3); HRMS (ES) $C_{59}H_{57}N_5O_{14}Na$ $[M + Na]^+$ calc. 1082.3800, found 1082.3802.

5.1.7. 3-O-Pivaloyl-N-ethoxycarbonylnormorphin-6-yl 2,3,4-tri-O-benzoyl-5-C-(tetrazol-5-yl)-β-D-xylopyranoside (**9**)

A solution of compound **8** (1.6 g, 1.51 mmol) in TFA (4.5 mL, 60.6 mmol) was refluxed for 15 min. The mixture was concentrated then *co*-concentrated with toluene (2 × 10 mL). The residue was purified by chromatography on silica gel (Cyclohexane-Ethyl acetate 1:2) to give the tetrazole **9** (850 mg, 60%) as a pale yellow solid. mp 169–171 °C; $[\alpha]_D^{23} = -66$ (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.98-7.24 (m, 15H, H-*aro*), 6.76 (d, 1H, *J* 8.0 Hz, H-1), 6.58 (d, 1H, *J* 8.0 Hz, H-2), 6.01 (t, 1H, *J* 10.0 Hz, H-3′), 5.98-5.95 (m, 1H, H-8), 5.72 (m, 1H, H-4′), 5.62 (m, 1H, H-2′), 5.41 (d, 1H, *J* 10.0 Hz, H-5′), 5.34-5.26 (m, 2H, H-1′ et H-7), 5.02-4.96 (m, 1H, H-9), 4.85 (m, 1H, H-5), 4.38-4.31 (m, 1H, H-6), 4.22-4.13 (m, 2H, OCH_2CH_3), 4.07-3.98 (m, 1H, H-16a), 3.10-2.83 (m, 2H, H-16b, H-10a), 2.82-2.72 (m, 1H, H-10b), 2.47 (m, 1H, H-14), 1.93-1.85 (m, 2H, H-15), 1.47 (s, 12H, $C(CH_3)_3$), 1.33-1.25 (m, 3H, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 165.1, 165.0 (C=O, C=N), 133.5, 132.4, 130.0, 129.8, 128.5, 128.4, 128.3 (C-*aro,* C-8, C-7), 122.5 (C-1), 119.9 (C-2), 90.9 (C-1′), 77.0 (C-6), 72.03 (C-2′ ou C-3′), 71.9 (C-2′ ou C-3′), 70.7 (C-4′), 68.3 (C-5′), 61.8 (OCH_2CH_3), 49.7 (C-9), 44.5 (C-13), 40.0 (C-14), 37.1 (C-16), 35.5 (C-15), 29.7 (C-10), 27.2 ($C(CH_3)_3$), 14.7 (OCH_2CH_3); HRMS (ES) $C_{51}H_{49}N_5O_{13}Na$ $[M + Na]^+$ calc. 962.3225, found 962.3211.

5.1.8. Morphin-6-yl-5-C-(tetrazol-5-yl)-β-D-xylopyranoside (**10**)

To a suspension of LAH (300 mg, 7.91 mmol) in THF (12 mL), was added a solution of tetrazole **9** (500 mg, 0.532 mmol) in THF (12 mL). The mixture was refluxed for 1h, ethyl acetate was added and the pH was adjusted to 1 with HCl 1N. The mixture was

concentrated and the residue was purified by reverse-phase chromatography (C18) (H_2O pure then (H_2O + 0.1%TFA)–CH_3CN 80:20). A second purification ((H_2O + 0.1%TFA)–CH_3CN from 95:5 to 20:80) was necessary to obtained the final compound **10** as a withe solid (42 mg, 16%). mp 204–207 °C; $[\alpha]_D^{23} = -116$ (c 0.5, MeOH); ^{1}H NMR (400 MHz, D_2O): δ 6.74 (d, 1H, *J* 8.0 Hz, H-1), 6.65 (d, 1H, *J* 8.0 Hz, H-2), 5.73 (m, 1H, H-8), 5.30 (m, 1H, H-7), 5.23 (d, 1H, *J* 5.5 Hz, H-5), 4.94-4.88 (m, 2H, H-1′, H-5′), 4.48 (m, 1H, H-6), 4.15 (m, 1H, H-9), 3.80 (t, 1H, *J* 9.5 Hz, H-4′), 3.69 (t, 1H, *J* 9.5 Hz, H-3′), 3.54 (m, 1H, H-2′), 3.37 (m, 1H, H-16a), 3.24 (m, 1H, H-10a), 3.10 (m, 1H, H-16b), 2.95 (s, 3H, N*CH*$_3$), 2.95-2.83 (m, 2H, H-10b, H-14), 2.32-2.02 (m, 2H, H-15); ^{13}C NMR (100 MHz, D_2O): δ 145.5 (C=N), 137.8, 134.0 (C-*ipso*), 131.1 (C-8), 129.0 (C-*ipso*), 126.0 (C-7), 123.3 (C-*ipso*), 120.4 (C-2), 117.7 (C-1), 102.3 (C-1′), 88.1 (C-5), 75.0 (C-3′), 73.3 (C-6), 73.0 (C-2′), 72.4 (C-4′), 69.3 (C-5′), 60.5 (C-9), 47.1 (C-16), 41.5 (C-13), 40.9 (N*CH*$_3$), 38.4 (C-14), 32.4 (C-15), 20.8 (C-10); HMRS (ES) $C_{23}H_{28}N_5O_7$ $[M + H]^+$ calc.486.1989, found 486.1982.

5.2. Synthesis of 1,3,4-oxadiazole (**12**)

5.2.1. 3-O-Acetylmorphin-6-yl 2,3,4-tri-O-acetyl-5-C-(2-methyl-1,3,4-oxadiazol-5-yl)-β-D-xylopyranoside (**11**)

A solution of tetrazole **10** (134 mg, 0.28 mmol) in acetic anhydride (3 mL) was refluxed overnight then the reaction mixture was concentrated. The residue was co-concentrated with toluene (2 × 10 mL) and purified by chromatography on silica gel ($CHCl_3$-MeOH 98:2 to 95:5) to give the oxadiazole **11** (102 mg, 55%) as pale yellow solid. mp 180–186 °C; $[\alpha]_D^{23} = -82$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, 1H, *J* 8.0 Hz, H-1), 6.59 (d, 1H, *J* 8.0 Hz, H-2), 5.71 (m, 1H, H-8), 5.37 (m, 2H, H-4′ et H-3′), 5.27 (m, 1H, H-7), 5.18 (m, 1H, H-2′), 4.99 (d, 1H, *J* 7.5 Hz, H-1′), 4.95 (d, 1H, *J* 5.5 Hz, H-5), 4.87 (m, 1H, H-5′), 4.31 (m, 1H, H-6), 3.71 (m, 1H, H-9), 3.07 (m, 1H, H-10a), 2.97-2.89 (m, 2H, H-16a, H-14), 2.62-2.52 (m, 8H, H-10b, *CH*$_3$-oxadiazole, N*CH*$_3$, H-16b), 2.33 (s, *CH*$_3$CO), 2.28 (m, 1H, H-15a), 2.14 (s, 3H, *CH*$_3$CO), 2.04 (s, 3H, *CH*$_3$CO), 1.98 (m, 1H, H-15b), 1.93 (s, 3H, *CH*$_3$CO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 170.0, 169.4, 169.3, 165.3, 161.2 (C=O, C=N), 150.3, 132.0 (C-*ipso*), 130.9 (C-8), 130.6, 130.4 (C-*ipso*), 127.5 (C-7), 122.6 (C-1), 119.5 (C-2), 100.0 (C-1′), 89.1 (C-5), 73.6 (C-6), 71.8 (C-3′ or C-4′), 71.0 (C-2′), 69.6 (C-3′ or C-4′), 67.9 (C-5′), 58.5 (C-9), 46.0 (C-16), 42.7 (C-13), 41.7 (N*CH*$_3$), 38.9 (C-14), 33.8 (C-15), 21.5 (C-10), 20.7, 20.6, 20.4 (*CH*$_3$CO), 11.0 (*CH*$_3$-oxadiazole). HRMS (ES) $C_{33}H_{38}N_3O_{12}$ $[M + H]^+$ calc. 668.2455, found 668.2560.

5.2.2. Morphin-6-yl 5-C-(2-methyl-1,3,4-oxadiazol-5-yl)-β-D-xylopyranoside (**12**)

To a solution of oxadiazole **11** (100 mg, 0.15 mmol) in methanol (2 mL) was added, at room temperature, sodium methoxyde (32 mg, 0.59 mmol). The reaction mixture was stirred for 3 h then resine Amberlyte H^+ was added. The mixture was filtered, the filtrate was concentrated under reduced pressure and the residue was purified by reverse-phase chromatography (C18) (H_2O + 0.1% TFA)-CH_3CN 95:5 to 20:80) to give the oxadiazole **12** (34 mg, 46%) as white crystals. mp 215–218 °C; ^{1}H NMR (300 MHz, D_2O): δ 6.83 (d, 1H, *J* 8.0 Hz, H-1), 6.74 (d, 1H, *J* 8.0 Hz, H-2), 5.84 (m, 1H, H-8), 5.46 (m, 1H, H-7), 5.32 (d, 1H, *J* 6.5 Hz, H-5), 5.00 (d, 1H, *J* 8.0 Hz, H-1′), 4.90 (m, 1H, H-5′), 4.59 (m, 1H, H-6), 4.26 (m, 1H, H-9), 3.92 (t, 1H, *J* 9.5 Hz, H-4′), 3.74 (t, 1H, *J* 9.5 Hz, H-3′), 3.59 (m, 1H, H-2′), 3.45-3.38 (m, 1H, H-16a), 3.29 (d, 1H, H-10a), 3.17 (m, 1H, H-16b), 3.03-2.92 (m, 5H, *NCH*$_3$, H-10b, H-14), 2.63 (s, 3H, *CH*$_3$-oxadiazole), 2.40-2.11 (m, 2H, *H*-15); ^{13}C NMR (75 MHz, D_2O): δ 131.2 (C-8), 126.3 (C-7), 120.6 (C-2), 118.2 (C-1), 102.5 (C-1′), 88.2 (C-5), 75.0 (C-3′), 73.5 (C-6), 73.0 (C-2′ or C-4′), 71.4 (C-2′ or C-4′), 69.3 (C-5′), 60.7 (C-9), 47.4 (C-6), 41.1 (N*CH*$_3$), 38.7 (C-14), 32.6 (C-15), 21.1 (C-10), 10.2 (*CH*$_3$-oxadiazole). HRMS (ES) $C_{25}H_{30}N_3O_8$ $[M + H]^+$ calc. 500.2033, found 500.2021.

5.3. Synthesis of pyrimidine (**17**)

5.3.1. 1,2,3,4-Tetra-O-benzoyl-5-C-([1,2,4]triazolo [4,3-a]pyrimidin-3-yl)-α/β-D-xylopyranose (**13a**) and 1,2,3,4-tetra-O-benzoyl-5-C-([1,2,4]triazolo [1,5-a]pyrimidin-3-yl)-α/β-D-xylopyranose (**13b**)

A solution of 1,2,3,4-tetra-O-benzoyl-5-C-(tetrazol-5-yl)-α/β-D-xylopyranose **3** (3.0 g, 4.73 mmol) and 2-chloropyrimidine (813 mg, 7.10 mmol) in pyridine (38 mL) was refluxed overnight. The reaction mixture was concentrated and the residue was purified by chromatography on silica gel (Cyclohexane-AcOEt 3:7) to give the mixture of pyrimidines **13a** and **13b** (2.4 g, 74%) as pale yellow solid. The α:β ratio (2/1 for **13a** and 7/3 for **13b**) were determined on the ^{1}H NMR spectra.

For **13a** : ^{1}H NMR(400 MHz, $CDCl_3$): δ 8.93 (m, 1Hα, H-5′α or H-7′α), 8.87 (m, 1Hβ, H-5′β or H-7′β), 8.73 (m, 1Hα, H-5′α or H-7′α), 8.64 (m, 1Hβ, H-5′β or H-7'β), 8.22-7.25 (m, 20Hα + 20Hβ, H-*aro*), 7.04 (d, 1Hα, *J* 3.5 Hz, H-1α), 7,00 (dd, 1Hα, *J* 4.0 Hz, *J* 7.0 Hz, H-6′α), 6.93 (dd, 1Hβ, *J* 3.5 Hz, *J* 6.5 Hz, H-6′β), 6.57 (t, 1Hα, *J* 9.5 Hz, H-3α), 6.52 (d, 1Hβ, *J* 7.5 Hz, H-1β), 6.29 (m, 2Hβ, H-3β, H-4β), 6.11-6.01 (m, 2Hα + 1Hβ, H-4α, H-5α, H-2β), 5.93 (dd, 1Hα, *J* 3.5 Hz, *J* 10.0 Hz, H-2α), 5.90-5.86 (m, 1Hβ, H-5β); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 165.2, 165.1, (C=O), 164.6 (C-3′β), 164.4 (C-3′α), 155.1 (C-8a′α, C-8a′β), 154.2 (C-5′α or C-7′α), 154.0 (C-5′β or C-7′β), 140.3 (C-5′β or C-7′β), 140.1 (C-5′α or C-7′α), 134.4, 134.2, 133.8, 133.7, 133.5, 132.5, 132.4, 130.2-128.3 (C-*aro*), 110.4 (C-6'α, C-6'β), 93.0 (C-1β), 89.7 (C-1α), 71.4 (C-2β or C-3β or C-4β), 70.7 (C-2β or C-3β or C-4β), 70.4 (C-2α), 70.1 (C-2β or C-3β or C-4β), 69.4 (C-3α or C-4α), 69.1 (C-3α or C-4α), 68.7 (C-5α, C-5β). HRMS (ES) $C_{38}H_{29}N_4O_9$ $[M + H]^+$ calc. 685.1935 found 685.1985.

For **13b** : ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80-8.71 (m, 2Hα + 2Hβ, H-5′α, H-7′α, H-5′β, H-7′β), 8.22-7.30 (m, 20Hα + 20Hβ, H-*aro*), 7.10 (dd, 1Hα, *J* 6.5 Hz, *J* 4.5 Hz, H-6′α), 7.07-7.02 (m, 1Hα + 1Hβ, H-6′β, H-1α), 6.47 (m, 1Hα + 1Hβ, H-1β, H-3α), 6.27-6.16 (m, 1Hα + 2Hβ, H-4α, H-3β, H-4β), 6.06 (m, 1Hβ, H-2β), 5.89 (dd, 1Hα, *J* 3.5 Hz, *J* 10.0 Hz, H-2α), 5.73 (d, 1Hα, *J* 10.0 Hz, H-5α), 5.53 (d, 1Hβ, *J* 9.0 Hz, H-5β). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 165.6, 165.3, 165.0, 164.8, 164.5, 164.2 (C=O), 164.0 (C-2′α), 163.8 (C-2′β), 155.3 (C-3a′α, C-3a′β), 155.1 (C-7′α), 155.0 (C-7′β), 136.0 (C-5′α, C-5′β), 134.0, 133.7, 133.4-133.2, 130.2-128.2 (C-*aro*), 110.7 (C-6′α), 110.6 (C-6′β), 92.9 (C-1β), 90.0 (C-1α), 72.5 (C-3β or C-4β), 72.0 (C-3β or C-4β), 71.3 (C-4α), 70.6 (C-2β), 70.4 (C-2α, C-3α), 69.4 (C-5α, C-5β). HRMS (ES) $C_{38}H_{29}N_4O_9$ $[M + H]^+$ calc. 685.1935, found 685.1953.

5.3.2. 3,4-Tri-O-benzoyl-5-C-([1,2,4]triazolo [1,5-a]pyrimidin-2-yl)-α/β-D-xylopyranose (**14**)

To a solution of a mixture of pyrimidines **13a** and **13b** (500 mg, 0.73 mmol) in DMF (19 mL) was added, at 0 °C, hydrazine acetate (101 mg, 1.10 mmol) in small portions over a period of 10 min. The reaction mixture was stirred at 0 °C for 1 h then 2 h at room temperature. The mixture was concentrated and the residue was purified by chromatography on silica gel (Cyclohexane-AcOEt 1:4) to give the corresponding hemiacetal **14** (284 mg, 67%) as white crystals. The NMR spectra showed an α:β ratio of 4:1; ^{1}H NMR (400 MHz, $CDCl_3$) for α anomer : δ 8.77 (dd, 1H, *J* 2.0 Hz, *J* 7.0 Hz, H-5′ or H-7′), 8.69 (m, 1H, H-5′ or H-7′), 8.02-7.27 (m, 15H, H-*aro*), 7.04 (m, 1H, H-6′), 6.43 (t, 1H, *J* 10.0 Hz, H-3), 6.11 (t, 1H, *J* 10.0 Hz, H-4), 5.95 (d, 1H, *J* 3.5 Hz, H-1), 5.88 (d, 1H, *J* 10.0 Hz, H-5), 5.49 (dd, 1H, *J* 3.5 Hz, *J* 10.0 Hz, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) for α anomer : δ 165.8, 165.7, 165.0 (C=O), 164.9 (C-2′), 155.2 (C-3a′), 155.1 (C-7′), 136.1 (C-5′), 133.2-132.9, 129.3-128.2 (C-*aro*), 110.8 (C-6′), 90.8 (C-1), 72.2 (C-2), 71.7 (C-4), 70.5 (C-3), 66.3 (C-5). HRMS (ES) $C_{31}H_{25}N_4O_8$ $[M + H]^+$ calc. 581.1672, found 581.1661.

*5.3.3. 2,3,4-Tri-O-benzoyl-5-C-([1,2,4]triazolo [1,5-a]pyrimidin-2-yl)-α-D-xylopyranosyle trichloroacetimidate (**15**)*

To a solution of hemiacetal **14** (650 mg, 1.12 mmol) in CH_2Cl_2 (15 mL) were added, at room temperature, DBU (186 μL, 1.24 mmol) and trichloroacetonitrile (2.20 mL, 21.9 mmol). The reaction mixture was stirred for 1.5 h at room temperature and an aqueous solution of acetic acid (70 μL, 1.22 mmol in 7 mL of water) was added. The layers were separated, the organic layer was washed with water (7 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by chromatography on silica gel (silica previously washed with a 5% solution of NEt_3 in AcOEt) (Cyclohexane-AcOEt 1:1) to afford the imidate **15** (565 mg, 70%) as a yellow solid. mp 72–73 °C $[\alpha]_D^{23} = 117$ (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81-8.76 (m, 2H, H-5′, H-7′), 8.69 (s, 1H, NH), 8.00-7.29 (m, 15H, H-*aro*), 7.11 (dd, 1H, *J* 4.0 Hz, *J* 7.0 Hz, H-6′), 7.00 (d, 1H, *J* 3.5 Hz, H-1), 6.43 (t, 1H, *J* 10.0 Hz, H-3), 6.20 (t, 1H, *J* 10.0 Hz, H-4), 5.81 (dd, 1H, *J* 3.5 Hz, *J* 10.0 Hz, H-2), 5.71 (d, 1H, *J* 10.0 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 165.3, 164.7 (C=O), 164.0 (C-2′), 160.4 (C=N), 155.4 (C-3a'), 155.1 (C-7′), 135.9 (C-5′), 133.5-133.2, 129.9-128.2 (C-*aro*), 110.7 (C-6′), 93.3 (C-1), 71.1 (C-4), 70.6 (C-2), 70.1 (C-3), 69.4 (C-5).

*5.3.4. 3-O-Pivaloyl-N-ethoxycarbonylnormorphin-6-yl 2,3,4-tri-O-benzoyl-5-C-([1,2,4]triazolo [1,5-a]pyrimidin-2-yl)-β-D-xylopyranoside (**16**)*

To a solution of the imidate **15** (1.5 g, 2.07 mmol) and morphine derivative **7** (738 mg, 1.73 mmol) in CH_2Cl_2 (24 mL), cooled at 0 °C, was added TMSOTf (1.2 mL, 6.61 mmol). The reaction mixture was stirred at 0 °C for 30 min then at room temperature for 1 h. DIEA (1.1 mL) was added, the mixture was stirred for 15 min and then concentrated. The residue was purified by chromatography on silica gel (Cyclohexane-AcOEt 1:4) to give the triazolopyrimidine **16** (470 mg, 31%) as a yellow solid. mp 171.5 °C $[\alpha]_D^{23} = -65$ (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (dd, 1H, *J* 2.0 Hz, 4.0 Hz, H-5″ or H-7″), 8.75 (dd, 1H, *J* 2.0 Hz, 7.0 Hz, H-5″ or H-7″), 8.02-7.29 (m, 15H, H-*aro*), 7.10 (dd, 1H, *J* 4.0 Hz, *J* 7.0 Hz, H-6″), 6.71 (d, 1H, *J* 8.0 Hz, H-1), 6.52 (d, 1H, *J* 8.0 Hz, H-2), 6.21 (m, 1H, H-4′), 5.95 (t, 1H, *J* 9.0 Hz, H-3′), 5.75-5.69 (m, 2H, H-2′, H-8), 5.47 (d, 1H, *J* 7.0 Hz, H-1′), 5.34 (d, 1H, *J* 9.5 Hz, H-5′), 5.23 (m, 1H, H-7), 4.98 (d, 1H, *J* 5.5 Hz, H-5), 4.93 (m, 1H, H-9), 4.46 (m, 1H, H-6), 4.20-4.05 (m, 2H, OCH_2CH_3), 3.99 (m, 1H, H-16a), 3.00 (m, 1H, H-16b), 2.90-2.70 (m, 2H, H-10), 2.48 (m, 1H, H-14), 1.88 (m, 2H, H-15), 1.31-1.25 (m, 12H, $C(CH_3)_3$, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 165.2, 164.7 (C=O), 155.4 (C-3a″), 154.9 (C-7′), 136.0 (C-5′), 133.1-128.2 (C-*aro*, C-7, C-8), 122.2 (C-1), 119.2 (C-2), 110.6 (C-6′), 99.4 (C-1′), 89.9 (C-5), 73.0 (C-6), 72.7 (C-3′), 72.2 (C-2′), 71.3 (C-4′, C-5′), 61.5 (OCH_2CH_3), 49.8 (C-9), 44.3 (C-13), 39.8 (C-14), 37.2 (C-16), 35.3 (C-15), 30.0 (C-10), 27.2 ($C(CH_3)_3$), 14.7 (OCH_2CH_3). HRMS (ES) $C_{55}H_{52}N_5O_{13}$ $[M + H]^+$ calc. 990.3562 found 990.3596.

*5.3.5. Morphin-6-yl-5-C-(5-hydroxy-4,5,6,7-tetrahydro [1,2,4] triazolo [1,5-a]pyrimidin-2-yl)-β-D-xylopyranoside (**17**)*

To a suspension of $LiAlH_4$ (140 mg, 3.69 mmol) in THF (6 mL) was added a solution of compound **16** (250 mg, 0.253 mmol) in THF (6 mL). The reaction mixture was refluxed for 1 h then cooled at room temperature and AcOEt was added. A solution of HCl 1N was added till pH 1 and the mixture was concentrated. The residue was purified once on reverse phase chromatography (H_2O then (H_2O + 0.1%TFA)-CH_3CN 80:20) to eliminate the aluminium salts. A second purification on preparative reverse phase chromatography (gradient (H_2O + 0.1%TFA)-CH_3CN from 95:5 to 20:80) afforded the tetrahydrotetrazolopyrimidine **17** as white crystals (61 mg, 40%). mp 201 °C $[\alpha]_D^{23} = -118$ (c 0.5, MeOH); ^{1}H NMR (300 MHz, D_2O): δ 6.80 (d, 1H, *J* 8.0 Hz, H-1), 6.72 (d, 1H, *J* 8.0 Hz, H-2), 5.83 (m, 1H, H-8), 5.43 (m, 1H, H-7), 5.36 (m, 1H, H-5′), 5.29 (d, 1H, *J* 5.5 Hz, H-5), 4.91 (d, 1H, *J* 8.0 Hz, H-1′), 4.52 (m, 1H, H-6), 4.51 (d, 1H, *J* 9.5 Hz, H-5′), 4.32-4.20 (m, 2H, H-9, H-6″a), 4.10 (m, 1H, H-6″b), 3.78 (t, 1H, *J* 9.5 Hz, H-4′), 3.68 (t, 1H, *J* 9.5 Hz, H-3′), 3.53 (dd, 1H, *J* 8.0 Hz, *J* 9.5 Hz, H-2′), 3.40 (m, 1H, H-16a), 3.25 (m, 1H, H-10a), 3.12 (m, 1H, H-16b), 3.05-2.89 (m, 5H, H-10b, H-14, NCH_3), 2.35-2.11 (m, 4H, H-15, H-7″); ^{13}C NMR (75 MHz, D_2O): δ 131.2 (C-8), 126.1 (C-7), 120.5 (C-2), 117.8 (C-1), 102.5 (C-1′), 88.3 (C-5), 74.9 (C-3′), 73.7 (C-6), 72.9 (C-2′), 71.7 (C-4′), 71.1 (C-5″), 70.4 (C-5′), 60.6 (C-9), 47.2 (C-16), 40.9 (NCH_3), 40.1 (C-6″), 38.5 (C-14), 32.4 (C-15), 26.2 (C-7″), 20.9 (C-10). HRMS (ES) $C_{27}H_{34}N_5O_8$ $[M + H]^+$ calc. 556.2407, found 556.2390.

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References

[1] L. Christrup, Acta Anaesthesiol Scand. (1997) 4–16.
[2] S. Donnelly, M.P. Davis, D. Walsh, M. Naughton, Support Care Cancer 10 (2002) 13–35.
[3] U. Bickel, O.P. Schumacher, Y.S. Kang, K. Voigt, J. Pharmacol. Exp. Ther. 278 (1996) 107–113.
[4] D. Wu, Y.S. Kang, W.M. Pardrige, Drug Metab. Dispos 41 (1997) 768–771.
[5] G.J. Kilpatrick, T.W. Smith, Med. Res. Rev. 25 (2005) 521–544.
[6] S. Hanessian, S. Parthasarathy, M. Maudit, K. Payza, J. Med. Chem. 46 (2003) 34–48 [and references cited therein].
[7] C.F. Matta, A.A. Arabi, D.F. Keaver, Eur. J. Med. Chem. 45 (2010) 868–872.
[8] T. Nukada, A. Berces, D.M. Whitfield, J. Org. Chem. 64 (1999) 9030–9045.
[9] H. Fukushima, A. Hiratate, M. Takahashi, M. Saito, E. Munetomo, K. Kitano, H. Saito, Y. Takaoka, K. Yamamoto, Bioorg. Med. Chem. 12 (2004) 6053–6061.
[10] B. Rickborn, F.R. Jensen, J. Org. Chem. 27 (1962) 4608–4610.
[11] W.C. Still, Macromodel/Batchmin Molecular Modeling Package. Schrödinger Inc, 1999, version 7.0.
[12] For examples: (a) J.G. Buchanan, A.P.W. Clelland, T. Johnson, R.A.C. Rennie, R.H. Wightman, J. Chem. Soc. Perkin Trans. 1 (1992) 2593–2596; (b) Z.P. Demko, K.B. Sharpless, J. Org. Chem. 66 (2001) 7945–7950; (c) S.J. Wittenberger, G.B. Donner, J. Org. Chem. 58 (1993) 4139–4141; (d) G. Garipova, A. Gautier, S.R. Piettre, Tetrahedron 61 (2005) 4755–4759.
[13] An analogue of compound (3) has already been prepared by Vasella and coll R. Hoos, J. Huixin, A. Vasella, P. Weiss, Helvetica Chim. Acta 79 (1996) 1757–1784.
[14] M. Begtrup, Bull. Soc. Chim. Belg 97 (1988) 573–598.
[15] E.R. Ford, P. Knowles, E. Lunt, S.M. Marshall, A. Penrose, C.A. Ramsden, A.J.H. Summers, L. Joyce, J.L. Walker, D.E. Wright, J. Med. Chem. 29 (1986) 538–549.
[16] R. Huisgen, H.J. Sturm, M. Seidel, Chem. Ber 94 (1961) 1555–1562.
[17] R.R. Schmidt, J. Michel, Angew. Chem. Int. Ed. 25 (1996) 212–235.
[18] H.A. Dabbagh, W.J. Lwowski, J. Org. Chem. 65 (2000) 7284–7290.
[19] A. Dlubala, I. Ripoche, C. Trécant, PCT WO 2010067010, (2010).
[20] The drastic reducing conditions (LAH) used to reduce both the benzoate and the N-ethyl carbamate into a N-methyl group were here necessary due to the compulsory starting material (**7**).
[21] R. Huisgen, J. Sauer, M. Seidel, Chem. Ber 93 (1960) 2885–2891.
[22] V.N. Nuriev, N.V. Zyk, S.Z. Vatsadze, Arkivoc (2005) 208–224.
[23] S.H. Mahmoud, L. Somsak, I. Karkas, Carbohydr. Res. 254 (1994) 91–104.
[24] A. Lauria, I. Abbate, C. Patella, N. Gambino, A. Silvestri, G. Barone, A.M. Almerico, Tetrahedron Lett. 49 (2008) 5125–5128.
[25] F. Terrier, M. Sebban, R. Goumont, J.C. Hallé, G. Moutiers, I. Cangelosi, E. Buncel, J. Org. Chem. 65 (2000) 7391–7398.
[26] K.R. Davis, R. Wolfenden, J. Org. Chem. 48 (1983) 2280–2281.
[27] A. Albert, D.J. Brown, H.C.S. Wood, J. Chem. Soc. (1956) 2066–2070.
[28] T.C. Thurber, L.B. Townsend, J. Heterocycl. Chem. 9 (1972) 629–636.
[29] F.E. d'Amour, D.L. Smith, J. Pharmacol. Exp. Ther. 72 (1941) 74–79.
[30] A. Dlubala, I. Ripoche, C. Trécant, PCT WO 2010067008 (2010).
[31] D. Paul, K.M. Standifer, C.E. Inturrisi, G.W. Pasternak, J. Pharmacol. Exp. Ther. 251 (1989) 477–483.
[32] J. Temsamani, C. Bonnafous, C. Rousselle, Y. Fraisse, P. Clair, L.A. Granier, A.R. Rees, M. Kaczorek, J.M. Scherrmann, J. Pharmacol. Exp. Ther. 313 (2005) 712–719.