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ORIGINAL PAPER

Synthesis of morphinans with diversely functionalized benzoxazole moieties

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Abstract Three independent strategies have been established for the synthesis of morphinans with oxazole moieties derived from the aminophenol function of 2-aminomorphine. All the procedures possess the ability to furnish diversely substituted 2′-oxazole moieties which are considered significant in view of the presented density functional studies on the spatial and electrostatic properties of the proximal functions of the 3-hydroxyl of the morphinan backbone. These data are considered important for neuropharmacological development of potential kappa antagonist morphinans. The second strategy was extended to the direct vinylation of oxazoles to form more complex benzoxazole-type morphinans.

Keywords Alkaloids · Density functional calculations · Heterocycles · Opioid receptor · Palladium-catalyzed direct vinylation

Dedicated to Prof. Sándor Makleit to mark his 80th birthday.

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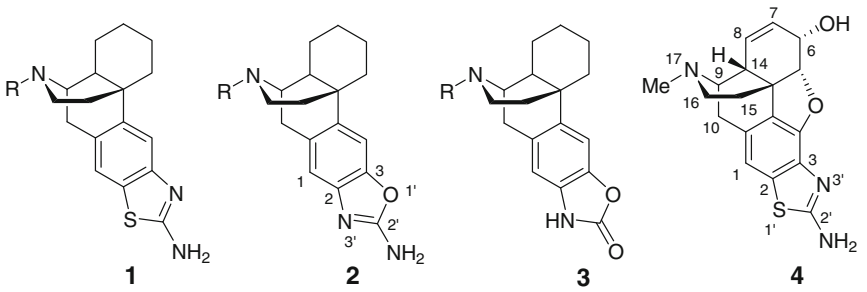
Introduction

The synthesis of morphinan derivatives with blocked or substituted 3-hydroxyl functions is a new and important challenge in the medicinal chemistry of opioid alkaloids. Neumeyer et al. [1, 2] reported the synthesis and complete pharmacological characterization of thiazole- and oxazole-fused levorphanols **1**–**3** and thiazolomorphine **4** (Fig. 1). Compound **1** possesses high affinity and selectivity at the kappa receptor. Functional assays showed that this congener was a full kappa but partial mu agonist. Ligands **2** and **3** showed lower affinities at mu and kappa receptors in comparison to the thiazolo derivative **1**. Thiazolomorphinan **4** possessed moderate affinities at mu and delta receptors without selectivity toward either subtype.

Besides these efforts several N-heterocycle-fused morphinans have been synthesized with divergent pharmacological profiles with respect to subtype selectivity and efficacy. The main approaches involve the formation of N-heterocyclic ring-fused morphinans with [3–9] or without [10–17] the presence of a 6,14-endoetheno-type C-ring bridged moiety.

Results and discussion

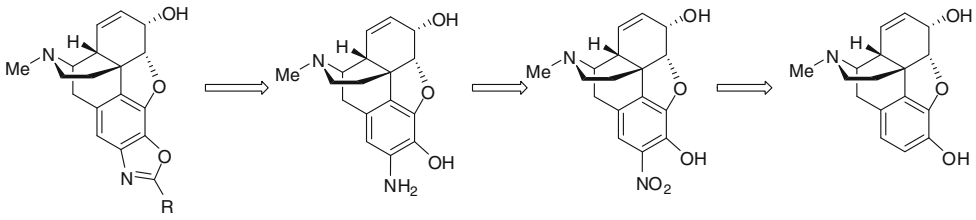
Herewith we report the design and synthesis of a set of novel oxazolomorphinans based on natural morphine instead of the synthetic analgesic levorphanol. These derivatives were designed on the basis of computational chemistry considerations to mimic the electronic profile of the pharmacologically more significant members of the presented series of morphinans **1**–**4**. Scheme 1 presents the retrosynthetic analysis of the proposed procedure.



	K_i (nM)		
	μ	δ	κ
1	1.5	29	0.049
2	150	-	52
3	160	-	47
4	30	32	220

Fig. 1 Recent representatives of 3-OH blocked or substituted morphinans and their affinities to opioid receptor subtypes (data from Refs. [1, 2])

Scheme 1



5a R = NH_2
5b R = H
5c R = Ph
5d R = 2-HO-Ph
5e R = 3-O_2N-Ph
5f R = 3-CH_3O-Ph
5g R = 2-CH_3-Ph
5h R= 4-HO-Ph

6 **7** Morphine

Design of novel derivatives

The affinity and selectivity of morphinans toward the target subtypes of opioid receptors are determined by two important factors. Firstly the relative distance of the important pharmacophores of the backbone and secondly the quality of the pharmacologically important moieties (i.e., the potential to interact with determining regions of peptide moieties of the active site). Therefore, an extended density functional theory (DFT) study was performed to explore and compare the spatial and electrostatic properties of compounds **1** and **2** and the outlined oxazolomorphinans **5** derived from 2-aminomorphine (**6**).

The optimized structures of compounds **1**, **2**, and **5a** were obtained at the B3LYP/6-31G(d,p) level of theory. On the basis of the superimpositions of compounds **2** versus **5a** and **1** versus **5a** made with overlaying carbons of ring A (Fig. 2, a and b, respectively) we concluded that the most important pharmacophores of the morphinan backbone (N17 for ionic interactions, C3-OH/X for hydrogen bonding) are very much in the same regions relative to each other irrespective of the quality of the new heterocycle and the presence of the 4,5-epoxy bridge between rings A and C [18, 19]. Besides of these considerations we also concluded that the spatial size of thiazole and oxazole rings are very close.

In order to study the electrostatic properties calculations were performed on the optimized geometries at the same level of the DFT theory. Table 1 lists the Gasteiger–Hückel charges [20, 21] of the most important moieties of compounds **1**, **2**, and **5**. Gasteiger–Hückel charges are empirical atomic partial charges widely used in docking and quantitative structure–activity relationship (QSAR) studies on the basis of their precise correlations with observed dipole moments. These charges were obtained with a distance-dependent dielectric and conjugate gradient method.

It can be concluded from these data that the charges on the O atom of the oxazole ring vary on a broad range which could have an interesting effect on the subtype selectivity of ligands **5a**–**5h**. The reason for this is the importance of the hydrogen bond forming ability of moieties in the proximity of position 3 of the morphinan skeleton. In addition to this, the substitution pattern of the 2′-aryl function could also have significant impact on the spatial position of these ligands as they can act as hydrogen bond donors (e.g., OH, NH_2) or hydrogen bond acceptors (e.g., OCH_3, NO_2).

Synthesis

Three approaches have been elaborated for the preparation of morphine analogues possessing an oxazole moiety

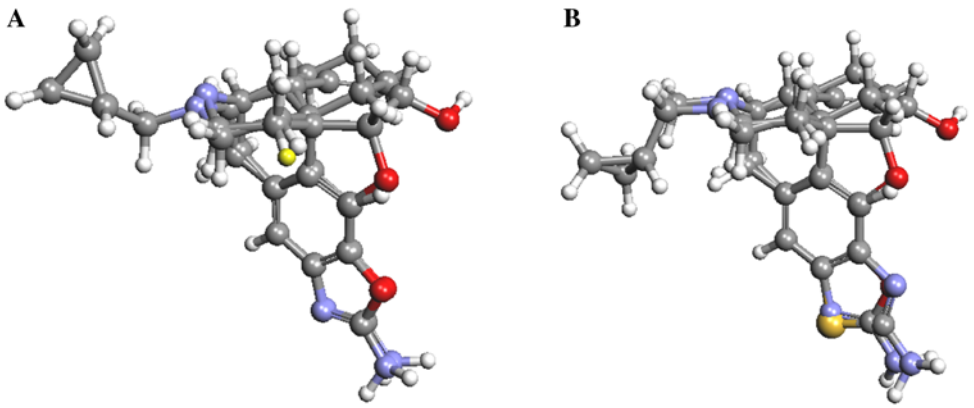
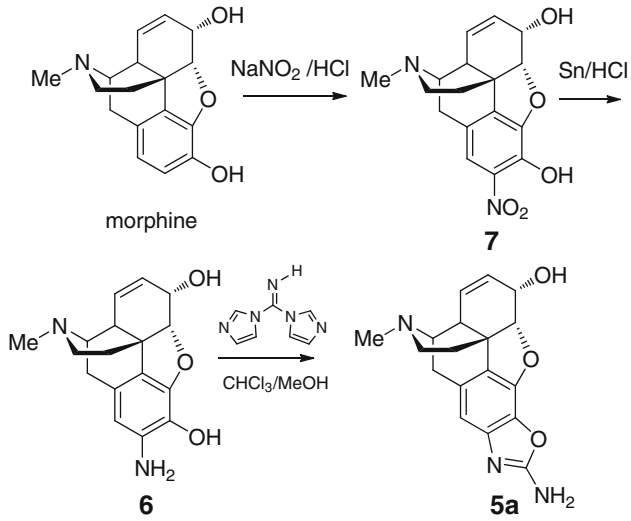


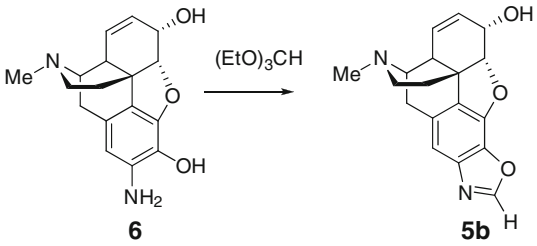
Fig. 2 Superimposition of optimized structures of compounds **2** and **5a** (**a**) and compounds **1** and **5a** (**b**)

Table 1 Gasteiger–Hückel charges of atoms in the proximity of position 3 of the morphinan skeleton calculated at the B3LYP/6-31G(d,p) level of DFT

Compounds	Gasteiger–Hückel charges (*e*) on new heterocycles		
	Position 1′	Position 2′	Position 3′
1	0.1898	0.1672	−0.1567
2	−0.1580	0.1519	−0.1868
5a	−0.1599	0.1521	−0.1878
5b	−0.1643	−0.0340	−0.1811
5c	−0.1210	0.1047	−0.1413
5d	−0.1164	0.1227	−0.1876
5e	−0.1209	0.0873	−0.1222
5f	−0.1235	0.0924	−0.1212
5g	−0.1275	0.1066	−0.1209
5h	−0.1247	0.1103	−0.1445



Scheme 2



Scheme 3

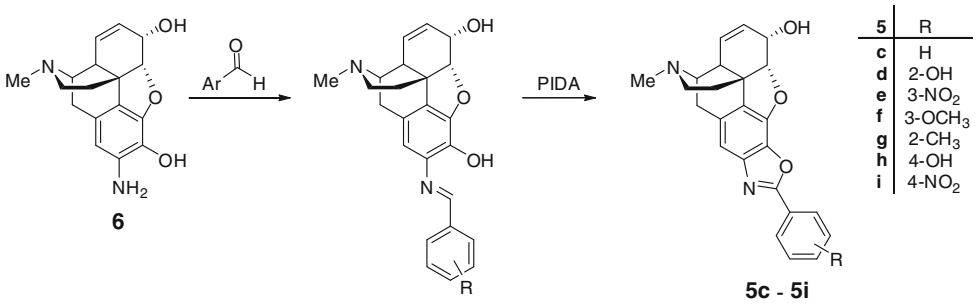
derived from the phenolic hydroxy group of morphinans. These procedures were initiated from a natural starting material, i.e., morphine, which was first nitrated. The synthesis and structure elucidation of 2-nitromorphine (**7**) [22] were started in 1911 and were undoubtedly clarified decades later [23, 24]. We applied these classical methods for the synthesis of 2-nitromorphine (**7**) [22–24]. The reduction of compound **7** to 2-aminomorphine (**6**) was performed in accordance with our previously published procedure [25] or with the classic tin–hydrochloric acid reagent combination [26].

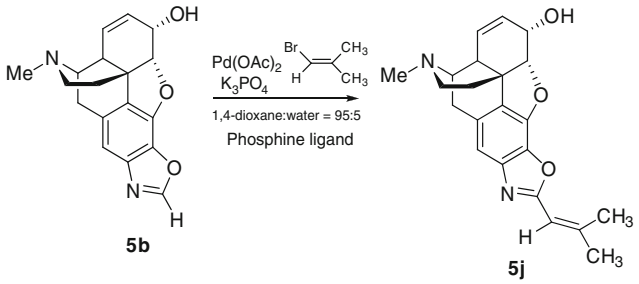
The synthesis of aminooxazole-derived morphinan **5a** was realized in accordance with the procedure disclosed by Wu et al. [27] using di(imidazol-1-yl)methanimine (Scheme 2). However, the original procedure and its applications for morphinans [2] applied THF as solvent, in which compound **6** is practically insoluble; therefore the reaction was carried out in a mixture of chloroform and methanol with significantly higher yields as previously reported, which may suggest the importance of the proper solvation.

In the second oxazole-forming strategy *o*-aminophenol-type **6** was treated with triethyl orthoformate to form unsubstituted oxazolomorphine **5b** in accordance with the procedure reported for aporphine alkaloids [28] (Scheme 3).

No formation of by-products was observed during reaction. After separation of the crude product mixture of unreacted aminomorphine **6** and product **5b** by column chromatography, compound **5b** was obtained in 56% yield.

Scheme 4





Scheme 5

The third strategy was based on the observations of Prakash et al. [29] in connection with the oxidative ring-closure of Schiff bases *ortho* to an unprotected phenolic hydroxyl function. The oxidative ring-closure was efficiently achieved with the application of (diacetoxyiodo)benzene (PIDA). The two-step procedure afforded a series of novel oxazolomorphinans **5c**–**5i** in high yields (Scheme 4).

The palladium-catalyzed derivatization of unsubstituted oxazolomorphine **5b** was identified as an interesting opportunity to significantly expand the range of moieties in terms of steric and electronic properties similarly to the previous application of Suzuki cross-coupling of halogen-containing morphinans [30–33]. The optimization of the direct vinylation of oxazolomorphinan **5b** was based on a recently reported protocol (Scheme 5) [34]. However, we aimed to use microwave (MW) initiation besides the traditional thermal procedure and to test some structurally similar phosphine ligands of the previously suggested 2-(dicyclohexylphosphino)biphenyl. The solvent mixture and the base were chosen in line with our previous experience with Pd-catalyzed cross-coupling of morphinans [30–33], whereas the reaction time and the target temperature (together with MW power) were carefully optimized with 2-(dicyclohexylphosphino)biphenyl as the phosphine ligand and 1-bromo-2-methylpropene as the vinyl source for both thermal and MW procedures (see footnote to Table 2).

In view of the isolated yields reported in Table 2 it could be emphasized that the application of MW promotion had no advantage over the thermal method; however, it is worthwhile to note that the significantly shorter reaction time could make the MW procedure a tempting choice, even though there is a well-known limitation regarding reaction volumes. Tricyclohexyl phosphine, as a simpler and cheaper analogue of cyclohexyl JohnPhos, was found to be completely ineffective in our catalytic systems, whereas bis(*t*-butyl)phosphine (JohnPhos) was similarly effective compared with the original choice. The spatially more hindered X-Phos was found to be less effective under the applied conditions (Scheme 6).

On the basis of previous observations, the synthesis of 2-vinyloxazole-type derivatives **5j**–**5l** was realized under thermal conditions at 110 °C. Isolated yields were found to be in the range of 54–75%. Lower conversions were observed for spatially hindered vinyl derivative **5k** and the highest conversion was detected for the coupling with (*E*)-*β*-bromostyrene due to electronic reasons.

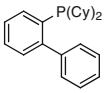
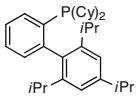
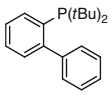
Conclusion

Oxazole rings were formed in three independent methods on morphinan backbone utilizing its 3-hydroxyl function. These derivatives and their *N*-cylopropylmethyl-nor counterparts could be interesting pharmacologically based on DFT-supported calculations. Versatile derivatization was made possible by Pd-catalyzed direct vinylation of the unsubstituted oxazolomorphinan. The optimization of the procedure was extended to microwave-promoted conditions as well.

Experimental

Melting points were determined with a Kofler hot-stage apparatus. Thin-layer chromatography (TLC) was performed on pre-coated Merck 5554 Kieselgel 60 F254 foils using chloroform/methanol (8:2) mobile phase. The spots were visualized with Dragendorff's reagent. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DX 360 spectrometer, chemical shifts are reported in parts per million (δ) from internal TMS, and coupling constants

Table 2 Details of the optimization of the direct vinylation

Applied phosphine	Isolated yield for **5j** under thermal conditions (%)[a,c]	Isolated yield for **5j** under MW conditions (%)[b,c]
PCy_3	3	Traces
 Cyclohexyl JohnPhos	63	60
 X-Phos	52	44
 JohnPhos	58	52

[a] 1 equiv. of oxazole, 2 equiv. of vinyl bromide, 2 eq. of K_3PO_4, 5 mol% of $Pd(OAc)_2$, and 10 mol% of phosphine in dioxane/water (95:5) stirred in a sealed tube at 110 °C for 18 h under nitrogen

[b] 1 equiv. of oxazole, 2 equiv. of vinyl bromide, 2 equiv. of K_3PO_4, 5 mol% of $Pd(OAc)_2$, and 10 mol% of phosphine in dioxane/water (95:5) irradiated in CEM Discover MW reactor at 140 °C (150 W in PowerMax mode) for 10 min under nitrogen

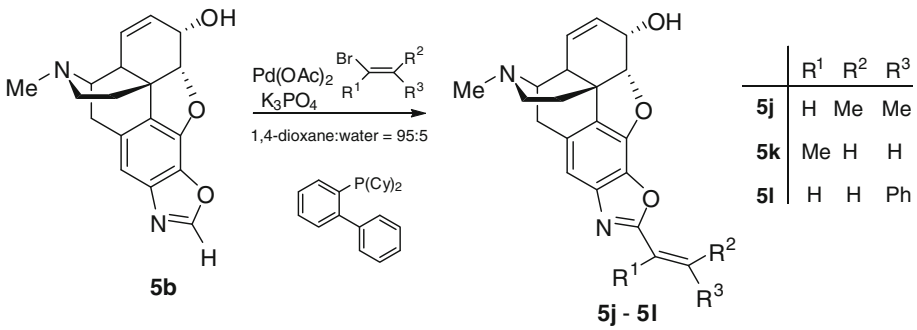
[c] The reported yields are averages of three runs

(*J*) are measured in Hertz. MALDI-TOF MS spectra were recorded on a Bruker Biflex III spectrometer in the positive, linear mode using 2,4,6-trihydroxyacetophenone as matrix. High resolution mass spectral measurements were performed with a Bruker micrOTOF-Q instrument in the ESI mode. Optical rotation was determined with a PerkinElmer Model 241 polarimeter with a water-jacketed 10-cm cell and is given in units of deg cm^2 g^{-1}. IR spectra were recorded on PerkinElmer 16 PC FTIR spectrometer. Elemental analyses (C, H, N) were obtained on a Carlo Erba EA1108 analyzer, and the results agreed favorably with calculated values. The MW-induced reactions were carried out in a Discover model microwave reactor manufactured by CEM Corporation. Controlled temperature, power, pressure, and time settings were used for all reactions.

2′-Amino-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxymorphine (**5a**, $C_{18}H_{19}N_3O_3$)

A solution containing 739 mg di(imidazol-1-yl)methanimine (4.59 mmol) and 460 mg 2-aminomorphine (**6**, 1.53 mmol) in 60 cm^3 chloroform/methanol (2:1) was heated at reflux under nitrogen overnight. After cooling to room temperature, the reaction mixture was diluted with 80 cm^3 ethyl acetate and washed successively with water, saturated aqueous NH_4Cl solution, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford the crude product. Further purification by silica gel chromatography gave the desired product **5a** as a yellow solid (yield 310 mg, 60%). M.p.: 244–246 °C; $[\alpha]_D^{25} = -16.4$ ($c = 0.1$, chloroform); $R_f = 0.40$ ($CHCl_3$/MeOH = 8:2); IR (KBr): $\bar{\nu} = 3{,}520$, 3,460, 3,370, 2,960, 1,620, 1,350, 1,240, 1,160 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): $\delta = 6.52$ (1H, s, H1), 5.59–5.56 (1H, m, H7), 5.34–5.32 (1H, m, H8), 5.02 (2H, br s, 2′-NH_2), 4.87 (1H, dd, H5, $J_{5,6} = 6.3$ Hz, $J_{5,7} = 1.4$ Hz), 4.25–4.21 (1H, m, H6), 3.31 (1H, dd, H9, $J_{9,10a} = 6.9$ Hz, $J_{9,14} = 2.8$ Hz), 3.22 (1H, d, H10b, $J = 18.3$ Hz), 2.84–2.81 (1H, m, H14), 2.65 (1H, dd, H16b, $J_{16b,16a} = 13.7$ Hz, $J_{16b,15b} = 4.4$ Hz), 2.43 (3H, s, N-CH_3), 2.30–2.27 (2H, m, H10a, H16a), 2.06 (1H, td, H15a, $J_{15a,15b;15a,16a} = 12.3$ Hz, $J_{15a,15b} = 5.4$ Hz), 1.83–1.79 (2H, m, H15b, C6-OH) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 165.34$ (C2′), 140.69 (C2), 137.41 (C4), 133.60, 133.20, 133.16, 132.45, 130.51 (C3, C7, C8, C11, C12), 109.90 (C1), 94.54 (C5), 68.12 (C9), 67.56 (C6), 48.67 (C16), 43.76, 43.54 (C13, NCH_3), 41.09 (C14), 35.78 (C15), 24.90 (C10) ppm; HRMS: *m/z* (%) = 348.1329 ($M + Na^+$, 100), calculated for $C_{18}H_{19}N_3O_3Na$ 348.1324.

Scheme 6



1′,3′-Oxazolo-(4′,5′:2,3)-3-deoxymorphine (**5b**, $C_{18}H_{18}N_2O_3$)

2-Aminomorphine (**6**, 500 mg, 1.66 mmol) was dissolved in 25 cm^3 of ethanol, and 0.5 cm^3 of triethyl orthoformate (5.5 mmol) was added to the slurry solution. This mixture was refluxed overnight under nitrogen. The resulting solution was evaporated to dryness, and the residue was dissolved in ethyl acetate. The organic solution was washed with 2 × 10 cm^3 of 10% NaOH solution, dried over $MgSO_4$, and was evaporated to dryness to yield the oxazole **5b** as yellow, pyramidal crystals. Yield 287 mg (56%), m.p.: 218 °C (dec.); $[\alpha]_D^{25} = -24.5$ ($c = 0.1$, chloroform); IR (KBr): $\bar{\nu} = 3{,}540, 3{,}310, 2{,}970, 1{,}610, 1{,}340, 1{,}240, 1{,}150\ cm^{-1}$; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 7.65$ (1H, s, H2′), 6.63 (1H, s, H1), 5.61–5.58 (1H, m, H7), 5.31–5.28 (1H, m, H8), 4.81 (1H, dd, H5, $J_{5,6} = 6.4$ Hz, $J_{5,7} = 1.4$ Hz), 4.30–4.27 (1H, m, H6), 3.33 (1H, dd, H9, $J_{9,10a} = 7.0$ Hz, $J_{9,14} = 2.6$ Hz), 3.27 (1H, d, H10b, $J = 17.9$ Hz), 2.87–2.82 (1H, m, H14), 2.55 (1H, dd, H16b, $J_{16b,16a} = 14.1$ Hz, $J_{16b,15b} = 4.4$ Hz), 2.50 (3H, s, N-CH_3), 2.31–2.27 (2H, m, H10a, H16a), 2.04 (1H, td, H15a, $J_{15a,15b;15a,16a} = 12.7$ Hz, $J_{15a,15b} = 5.9$ Hz), 1.91–1.85 (2H, m, H15b, C6-OH) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 154.19$ (C2′), 138.28 (C2), 137.56 (C4), 133.90, 133.45, 132.76, 132.35, 131.66 (C3, C7, C8, C11, C12), 107.38 (C1), 93.71 (C5), 67.92 (C9), 66.50 (C6), 47.91 (C16), 43.70, 43.24 (C13, NCH_3), 41.79 (C14), 36.07 (C15), 25.09 (C10) ppm; HRMS: *m/z* (%) = 333.1221 ($M + Na^+$, 100), calculated for $C_{18}H_{18}N_2O_3Na$ 333.1215.

General method for the formation of Schiff bases

2-Aminomorphine (**6**, 500 mg, 1.66 mmol) was dissolved in 25 cm^3 of absolute ethanol. After addition of 1.83 mmol of the appropriate benzaldehyde the solution was refluxed for 3 h. The ethanolic solution was evaporated to dryness, and the crude yellow oily product was found to be pure enough according to TLC monitoring to use it in the following step without further purification.

*General method for the synthesis of 2′-aryl-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxymorphine hydrochlorides (**5c–5i**) from Schiff bases*

The Schiff base (1.66 mmol) was dissolved in 10 cm^3 methanol and 550 mg (diacetoxyiodo)benzene (1.75 mmol) was added and the mixture was stirred overnight at room temperature. The solution was evaporated to dryness and the residual mass was dissolved in absolute ethanol. On dropwise addition of ethanol saturated with hydrogen chloride the product precipitated in salt form. The HCl salt was filtered off and was washed with ether to yield the corresponding 2′-aryloxazolo product.

2′-Phenyl-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxymorphine dihydrochloride (**5c**, $C_{24}H_{24}Cl_2N_2O_3$)

Pale yellow solid, yield 545 mg (85%); m.p.: >250 °C; $[\alpha]_D^{25} = -6.9$ ($c = 0.1$, methanol); IR (KBr): $\bar{\nu} = 3{,}570, 3{,}380, 2{,}950, 1{,}630, 1{,}350, 1{,}250, 1{,}120\ cm^{-1}$; ^{1}H NMR (360 MHz, DMSO-d_6): $\delta = 10.41$–10.21 (2H, br s, 2 NH^+), 7.87 (2H, dd, 2 phenyl-H, $J = 8.4$, 3.4 Hz), 7.42–7.31 (3H, m, 3 phenyl-H), 6.52 (1H, s, H1), 5.73–5.70 (1H, m, H7), 5.45–5.43 (1H, m, H8), 4.92 (1H, dd, H5, $J_{5,6} = 6.6$ Hz, $J_{5,7} = 1.6$ Hz), 4.30–4.25 (2H, m, H6, C6-OH), 3.38 (1H, dd, H9, $J_{9,10a} = 7.2$ Hz, $J_{9,14} = 2.7$ Hz), 3.28 (1H, d, H10b, $J = 18.0$ Hz), 2.86–2.82 (1H, m, H14), 2.57 (1H, dd, H16b, $J_{16b,16a} = 14.4$ Hz, $J_{16b,15b} = 3.9$ Hz), 2.46 (3H, s, N-CH_3), 2.33–2.28 (2H, m, H10a, H16a), 2.10 (1H, td, H15a, $J_{15a,15b;15a,16a} = 12.2$ Hz, $J_{15a,15b} = 6.0$ Hz), 1.97–1.91 (1H, m, H15b) ppm; ^{13}C NMR (90.6 MHz, DMSO-d_6): $\delta = 163.71$ (C2′), 138.84 (C2), 137.55 (C4), 134.11, 133.86, 133.55, 132.89, 132.50, 132.35, 131.88, 131.66, 130.60, 129.75, 128.77 (C3, C7, C8, C11, C12, 6 phenyl-C), 107.78 (C1), 94.24 (C5), 68.21 (C9), 66.73 (C6), 47.33 (C16), 43.59, 43.04 (C13, NCH_3), 41.44 (C14), 38.01 (C15), 25.49 (C10) ppm; HRMS: *m/z* (%) = 409.1533 ($M + Na^+$, 100), calculated for $C_{24}H_{22}N_2O_3Na$ 409.1528.

2′-(2-Hydroxyphenyl)-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxymorphine dihydrochloride (**5d**, $C_{24}H_{24}Cl_2N_2O_4$)

Yellow solid, yield 547 mg (82%); m.p.: >250 °C; $[\alpha]_D^{25} = -6.2$ ($c = 0.1$, methanol); IR (KBr): $\bar{\nu} = 3{,}620, 3{,}580, 3{,}370, 2{,}950, 1{,}630, 1{,}400, 1{,}340, 1{,}250, 1{,}130\ cm^{-1}$; ^{1}H NMR (360 MHz, DMSO-d_6): $\delta = 10.30$–10.15 (2H, br s, 2 NH^+), 9.30 (1H, br s, 2″-OH), 7.45 (1H, dd, aryl-H, $J = 8.1$, 4.2 Hz), 7.24–7.09 (3H, , 3 aryl-H), 6.59 (1H, s, H1), 5.81–5.77 (1H, m, H7), 5.50–5.44 (1H, m, H8), 4.85 (1H, dd, H5, $J_{5,6} = 7.0$ Hz, $J_{5,7} = 2.2$ Hz), 4.27–4.22 (2H, m, H6, C6-OH), 3.76–3.31 (2H, m, H9, H10b), 2.91–2.86 (1H, m, H14), 2.64 (1H, dd, H16b, $J_{16b,16a} = 14.7$ Hz, $J_{16b,15b} = 4.0$ Hz), 2.51 (3H, s, N-CH_3), 2.33–2.26 (2H, m, H10a, H16a), 2.17 (1H, td, H15a, $J_{15a,15b;15a,16a} = 13.1$ Hz, $J_{15a,15b} = 6.0$ Hz), 1.88–1.84 (1H, m, H15b) ppm; ^{13}C NMR (90.6 MHz, DMSO-d_6): $\delta = 162.41$ (C2′), 157.34 (C2″), 138.52, 138.29 (C2, C6″), 137.61 (C4), 135.01, 134.22, 133.65, 132.65, 131.88, 130.66, 128.79 (C3, C7, C8, C11, C12, 2 aryl-C), 117.43 (C3″), 112.51 (C1″), 107.66 (C1), 94.10 (C5), 68.66 (C9), 66.39 (C6), 47.37 (C16), 43.69, 43.24 (C13, NCH_3), 41.14 (C14), 38.63 (C15), 25.40 (C10) ppm; MALDI TOF: *m/z* = 425.3 ($M + Na^+$), calculated for $C_{24}H_{22}N_2O_4Na$ 425.1.

2′-(3-Nitrophenyl)-1′,3′-oxazolo-(4’,5′:2,3)-3-deoxymorphine dihydrochloride (**5e**, $C_{24}H_{23}Cl_2N_3O_5$)

Bright yellow solid, yield 601 mg (84%); m.p.: >250 °C; $[\alpha]_D^{25} = -3.0$ ($c = 0.1$, methanol); IR (KBr): $\bar{\nu} = 3{,}550, 3{,}370, 2{,}960, 1{,}640, 1{,}550, 1{,}400, 1{,}350, 1{,}330, 1{,}260, 1{,}140$

cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6): δ = 10.08–9.95 (2H, br s, 2 NH^+), 7.87–7.73 (2H, m, 2 aryl-H), 7.66–7.54 (2H, m, 2 aryl-H), 6.51 (1H, s, H1), 5.87–5.82 (1H, m, H7), 5.59–5.54 (1H, m, H8), 4.91 (1H, dd, H5, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 2.4 Hz), 4.30–4.25 (2H, m, H6, C6-OH), 3.38 (1H, dd, H9, $J_{9,10a}$ = 6.6 Hz, $J_{9,14}$ = 2.7 Hz), 3.30 (1H, d, H10b, J = 18.3 Hz), 2.88–2.83 (1H, m, H14), 2.63 (1H, dd, H16b, $J_{16b,16a}$ = 14.7 Hz, $J_{16b,15b}$ = 3.7 Hz), 2.50 (3H, s, N-CH_3), 2.36–2.29 (2H, m, H10a, H16a), 2.19 (1H, td, H15a, $J_{15a,15b;15a,16a}$ = 12.7 Hz, $J_{15a,15b}$ = 5.8 Hz), 1.84–1.79 (1H, m, H15b) ppm; ^{13}C NMR (90.6 MHz, DMSO-d_6): δ = 162.67 (C2′), 146.94 (C3″), 138.27, 137.29 (C2, C4), 135.05, 134.71, 133.92, 133.60, 132.35, 132.09, 131.88, 129.45, 128.92, 127.60 (C3, C7, C8, C11, C12, 5 aryl-C), 107.70 (C1), 94.51 (C5), 68.14 (C9), 66.08 (C6), 46.73 (C16), 43.60, 43.42 (C13, NCH_3), 42.43 (C14), 39.07 (C15), 25.28 (C10) ppm; MALDI TOF: m/z = 454.1 (M + Na^+), calculated for $C_{24}H_{21}N_3O_5Na$ 454.1.

2′-(3-Methoxyphenyl)-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxy-morphine dihydrochloride (**5f**, $C_{25}H_{26}Cl_2N_2O_4$)
Pale yellow solid, yield 512 mg (74%); m.p.: >250 °C; $[\alpha]_D^{25}$ = −4.9 (c = 0.1, methanol); IR (KBr): $\bar{\nu}$ = 3,540, 3,340, 2,950, 1,630, 1,340, 1,240, 1,120 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6): δ = 10.44–10.09 (2H, br s, 2 NH^+), 7.37–7.10 (4H, m, 4 aryl-H), 6.47 (1H, s, H1), 5.81–5.75 (1H, m, H7), 5.54–5.50 (1H, m, H8), 4.83 (1H, dd, H5, $J_{5,6}$ = 6.9 Hz, $J_{5,7}$ = 2.7 Hz), 4.33–4.29 (2H, m, H6, C6-OH), 3.91 (3H, s, OCH_3), 3.45–3.12 (2H, m, H9, H10b), 2.90–2.84 (1H, m, H14), 2.60 (1H, dd, H16b, $J_{16b,16a}$ = 14.5 Hz, $J_{16b,15b}$ = 4.0 Hz), 2.47 (3H, s, N-CH_3), 2.39–2.32 (2H, m, H10a, H16a), 2.14 (1H, td, H15a, $J_{15a,15b;15a,16a}$ = 12.4 Hz, $J_{15a,15b}$ = 5.5 Hz), 1.91–1.84 (1H, m, H15b) ppm; ^{13}C NMR (90.6 MHz, DMSO-d_6): δ = 162.37 (C2′), 157.04 (C3″), 138.14, 137.62 (C2, C4), 136.48, 136.21, 136.11, 133.66, 132.55, 129.69, 128.76 (C3, C7, C8, C11, C12, 2 aryl-C), 121.49, 119.71 (C5″, C2″), 110.28 (C1″), 106.97 (C1), 94.18 (C5), 69.04 (C9), 66.11 (C6), 56.18 (OCH_3), 46.32 (C16), 43.82, 43.67 (C13, NCH_3), 42.31 (C14), 39.80 (C15), 24.82 (C10) ppm; MALDI TOF: m/z = 439.1 (M + Na^+), calculated for $C_{25}H_{24}N_2O_4Na$ 439.2.

2′-(2-Methylphenyl)-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxy-morphine dihydrochloride (**5g**, $C_{25}H_{26}Cl_2N_2O_3$)
Yellow solid, yield 478 mg (72%); m.p.: >250 °C; $[\alpha]_D^{25}$ = −5.8 (c = 0.1, methanol); IR (KBr): $\bar{\nu}$ = 3,540, 3,330, 2,950, 1,640, 1,550, 1,340, 1,250, 1,130 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6): δ = 10.23–9.79 (2H, br s, 2 NH^+), 7.51–7.17 (4H, m, 4 aryl-H), 6.41 (1H, s, H1), 5.87–5.79 (1H, m, H7), 5.51–5.47 (1H, m, H8), 4.77 (1H, dd, H5, $J_{5,6}$ = 6.8 Hz, $J_{5,7}$ = 3.0 Hz), 4.29–4.24 (2H, m, H6, C6-OH), 3.40 (1H, dd, H9, $J_{9,10a}$ = 6.8 Hz, $J_{9,14}$ = 2.9 Hz), 3.33 (1H, d, H10b, J = 17.5 Hz), 2.94–2.87 (1H, m, H14), 2.58 (1H, dd, H16b, $J_{16b,16a}$ = 14.5 Hz, $J_{16b,15b}$ = 4.0 Hz), 2.47 (3H, s, N-CH_3), 2.39–2.32 (2H, m, H10a, H16a), 2.25 (3H, s, aryl-CH_3), 2.14 (1H, td, H15a, $J_{15a,15b;15a,16a}$ = 12.8 Hz, $J_{15a,15b}$ = 5.1 Hz), 1.90–1.84 (1H, m, H15b) ppm; ^{13}C NMR (90.6 MHz, DMSO-d_6): δ = 162.71 (C2′), 138.38, 137.51, 137.40, 136.83 (C2, C4, C1″, C2″), 133.80, 133.51, 133.40, 132.63, 129.55, 128.44, 128.23, 127.18, 126.93 (C3, C7, C8, C11, C12, 4 aryl-C), 107.12 (C1), 95.81 (C5), 69.64 (C9), 66.21 (C6), 46.07 (C16), 44.02, 43.87 (C13, NCH_3), 42.44 (C14), 39.72 (C15), 24.72 (C10), 21.76 (aryl-CH_3) ppm; MALDI TOF: m/z = 423.1 (M + Na^+), calculated for $C_{25}H_{24}N_2O_3Na$ 423.2.

2′-(4-Hydroxyphenyl)-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxy-morphine dihydrochloride (**5h**, $C_{24}H_{24}Cl_2N_2O_4$)
Pale yellow solid, yield 587 mg (88%); m.p.: >250 °C; $[\alpha]_D^{25}$ = −4.6 (c = 0.1, methanol); IR (KBr): $\bar{\nu}$ = 3,640, 3,590, 3,370, 2,960, 1,640, 1,330, 1,260, 1,140 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6): δ = 10.28–10.10 (2H, br s, 2 NH^+), 9.23 (1H, br s, 4″-OH), 7.58–7.52 (2H, m, 2 aryl-H), 7.18–7.04 (2H, m, 2 aryl-H), 6.44 (1H, s, H1), 5.80–5.71 (1H, m, H7), 5.48–5.46 (1H, m, H8), 4.84 (1H, dd, H5, $J_{5,6}$ = 7.2 Hz, $J_{5,7}$ = 2.5 Hz), 4.26–4.23 (2H, m, H6, C6-OH), 3.31–3.19 (2H, m, H9, H10b), 2.91–2.84 (1H, m, H14), 2.57 (1H, dd, H16b, $J_{16b,16a}$ = 14.3 Hz, $J_{16b,15b}$ = 3.7 Hz), 2.46 (3H, s, N-CH_3), 2.39–2.31 (2H, m, H10a, H16a), 2.20 (1H, td, H15a, $J_{15a,15b;15a,16a}$ = 12.8 Hz, $J_{15a,15b}$ = 5.7 Hz), 1.89–1.80 (1H, m, H15b) ppm; ^{13}C NMR (90.6 MHz, DMSO-d_6): δ = 162.73 (C2′), 157.29 (C4″), 138.52, 138.26 (C2, C4), 137.78 (C4), 134.62, 133.89, 132.52, 131.73, 129.03 (C3, C7, C8, C11, C12), 117.43, 117.36 (4 aryl-C), 106.92 (C1), 93.69 (C5), 68.61 (C9), 66.41 (C6), 46.79 (C16), 43.91, 43.66 (C13, NCH_3), 41.25 (C14), 38.60 (C15), 24.69 (C10) ppm; MALDI TOF: m/z = 425.1 (M + Na^+), calculated for $C_{24}H_{22}N_2O_4Na$ 425.1.

2′-(4-Nitrophenyl)-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxy-morphine dihydrochloride (**5i**, $C_{24}H_{23}Cl_2N_3O_5$)
Bright yellow solid, yield 587 mg (82%); m.p.: >250 °C; $[\alpha]_D^{25}$ = −2.6 (c = 0.1, methanol); IR (KBr): $\bar{\nu}$ = 3,550, 3,360, 2,970, 1,630, 1,570, 1,550, 1,410, 1,350, 1,340, 1,270, 1,140 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6): δ = 10.21–10.05 (2H, br s, 2 NH^+), 8.21–8.10 (4H, m, 4 aryl-H), 6.60 (1H, s, H1), 5.84–5.78 (1H, m, H7), 5.51–5.47 (1H, m, H8), 4.87 (1H, dd, H5, $J_{5,6}$ = 6.9 Hz, $J_{5,7}$ = 2.6 Hz), 4.30–4.23 (2H, m, H6, C6-OH), 3.39 (1H, dd, H9, $J_{9,10a}$ = 6.8 Hz, $J_{9,14}$ = 2.7 Hz), 3.28 (1H, d, H10b, J = 18.5 Hz), 2.90–2.84 (1H, m, H14), 2.63 (1H, dd, H16b, $J_{16b,16a}$ = 14.3 Hz, $J_{16b,15b}$ = 3.6 Hz), 2.46 (3H, s, N-CH_3), 2.32–2.24 (2H, m, H10a, H16a), 2.09 (1H, td, H15a,

$J_{15a,15b;15a,16a} = 12.7$ Hz, $J_{15a,15b} = 5.8$ Hz), 1.89–1.80 (1H, m, H15b) ppm; ^{13}C NMR (90.6 MHz, DMSO-d_6): $\delta = 163.12$ (C2′), 148.37 (C4″), 138.27, 137.66 (C2, C4), 136.48 (C1″), 134.92, 134.11, 133.60, 132.35, 131.18, 129.66, 128.41 (C3, C7, C8, C11, C12, 4 aryl-C), 106.61 (C1), 94.68 (C5), 67.94 (C9), 66.28 (C6), 46.74 (C16), 43.71, 43.48 (C13, NCH_3), 42.31 (C14), 39.53 (C15), 25.23 (C10) ppm; MALDI TOF: $m/z = 454.1$ ($M + Na^+$), calculated for $C_{24}H_{21}N_3O_5Na$ 454.1.

General procedure for Pd-catalyzed vinylation

The direct (hetero)vinylation reactions were carried out in a sealed tube at 110 °C for 18 h under nitrogen. A solution of oxazolomorphinan **5a** (0.35 mmol) was allowed to react with vinyl bromide (2 equiv.) with 4 mg palladium acetate (0.017 mmol), 144 mg potassium phosphate (0.70 mmol), and 12 mg 2-(dicyclohexylphosphino)biphenyl (10 mol%) in 3 cm^3 1,4-dioxane/water (95:5). After filtration on Celite and concentration in vacuo, the crude product was purified by column chromatography on silica gel using a chloroform/methanol (8:2) as the eluent to afford the 2′-vinyloxazole derivatives **5j**–**5l**.

2′-(2-Methylprop-1-enyl)-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxymorphine (**5j**, $C_{22}H_{24}N_2O_3$)
Pale yellow solid, yield 80 mg (63%); m.p.: 232–234 °C; $[\alpha]_D^{25} = -21.4$ ($c = 0.1$, chloroform); $R_f = 0.56$ ($CHCl_3$/MeOH = 8:2); IR (KBr): $\bar{\nu} = 3{,}530, 3{,}310, 3{,}030, 2{,}990, 1{,}620, 1{,}330, 1{,}300, 1{,}240, 680\,cm^{-1}$; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 6.53$ (1H, s, H1), 6.21 (1H, s, H1″), 5.81–5.77 (1H, m, H7), 5.34–5.30 (1H, m, H8), 4.79 (1H, dd, H5, $J_{5,6} = 6.3$ Hz, $J_{5,7} = 1.7$ Hz), 4.31–4.29 (1H, m, H6), 3.33–3.26 (2H, m, H9, H10b), 2.89–2.84 (1H, m, H14), 2.50 (1H, dd, H16b, $J_{16b,16a} = 14.4$ Hz, $J_{16b,15b} = 4.6$ Hz), 2.39 (3H, s, N-CH_3), 2.29–2.22 (2H, m, H10a, H16a), 2.01 (1H, td, H15a, $J_{15a,15b;15a,16a} = 12.4$ Hz, $J_{15a,15b} = 5.4$ Hz), 1.95–1.88 (1H, m, H15b), 1.80 (3H, s, C2″-CH_3), 1.78–1.68 (4H, m, C2″-CH_3, C6-OH) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 152.15$ (C2′), 144.54 (C2″), 139.22 (C2), 138.16 (C4), 133.63, 133.26, 132.43, 128.72, 128.33, (C3, C7, C8, C11, C12), 121.72 (C1″), 106.84 (C1), 94.27 (C5), 68.23 (C9), 65.98 (C6), 47.13 (C16), 43.91, 43.46 (C13, NCH_3), 41.66 (C14), 35.81 (C15), 25.65, 25.09 (C10, C2″-CH_3), 21.70 (C2″-CH_3) ppm; HRMS: m/z (%) = 387.1690 ($M + Na^+$, 100), calculated for $C_{22}H_{24}N_2O_3Na$ 387.1685.

2′-(Prop-1-en-2-yl)-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxymorphine (**5k**, $C_{21}H_{22}N_2O_3$)
Off-white solid, yield 66 mg (54%); m.p.: 220–222 °C; $[\alpha]_D^{25} = -23.2$ ($c = 0.1$, chloroform); $R_f = 0.60$ ($CHCl_3$/MeOH = 8:2); IR (KBr): $\bar{\nu} = 3{,}530, 3{,}320, 3{,}040, 2{,}990, 1{,}630, 1{,}310, 670\,cm^{-1}$; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 6.48$ (1H, s, H1), 5.87–5.81 (1H, m, H7), 5.57 (1H, d, H2″, $J = 2.3$ Hz), 5.38–5.27 (2H, m, H8, H2″), 4.71 (1H, dd, H5, $J_{5,6} = 6.4$ Hz, $J_{5,7} = 1.9$ Hz), 4.31–4.26 (1H, m, H6), 3.35–3.23 (2H, m, H9, H10b), 2.89–2.85 (1H, m, H14), 2.60 (1H, dd, H16b, $J_{16b,16a} = 14.2$ Hz, $J_{16b,15b} = 4.2$ Hz), 2.48 (3H, s, N-CH_3), 2.33–2.29 (2H, m, H10a, H16a), 2.20 (3H, s, C1″-CH_3), 1.97 (1H, td, H15a, $J_{15a,15b;15a,16a} = 12.4$ Hz, $J_{15a,15b} = 5.4$ Hz), 1.91–1.85 (1H, m, H15b, C6-OH) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 151.95$ (C2′), 138.47 (C2), 137.62 (C4), 133.35, 133.06, 132.72, 130.18, 128.71, 128.10 (C3, C7, C8, C11, C12, C1″), 118.70 (C2″), 107.20 (C1), 95.25 (C5), 69.01 (C9), 65.27 (C6), 47.30 (C16), 44.04, 43.87 (C13, NCH_3), 41.23 (C14), 35.73 (C15), 28.44 (C2″-CH_3), 25.55 (C10) ppm; HRMS: m/z (%) = 373.1535 ($M + Na^+$, 100), calculated for $C_{21}H_{22}N_2O_3Na$ 373.1528.

2′-(E-2-Phenylethenyl)-1′,3′-oxazolo-(4′,5′:2,3)-3-deoxymorphine (**5l**, $C_{26}H_{24}N_2O_3$)
Yellow solid, yield 108 mg (75%); m.p.: 212–214 °C; $[\alpha]_D^{25} = -18.5$ ($c = 0.1$, chloroform); $R_f = 0.62$ ($CHCl_3$/MeOH = 8:2); IR (KBr): $\bar{\nu} = 3{,}530, 3{,}320, 3{,}080, 3{,}030, 2{,}980, 1{,}620, 1{,}440, 1{,}330, 1{,}250, 670\,cm^{-1}$; ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 7.37$–7.12 (5H, m, aryl-H), 6.91 (1H, d, H2″, $J = 14.6$ Hz), 6.79 (1H, d, H1″, $J = 14.5$ Hz), 6.51 (1H, s, H1), 5.87–5.80 (1H, m, H7), 5.36–5.33 (1H, m, H8), 4.81 (1H, dd, H5, $J_{5,6} = 6.4$ Hz, $J_{5,7} = 1.9$ Hz), 4.34–4.30 (1H, m, H6), 3.34–3.28 (2H, m, H9, H10b), 2.90–2.86 (1H, m, H14), 2.54 (1H, dd, H16b, $J_{16b,16a} = 14.1$ Hz, $J_{16b,15b} = 4.4$ Hz), 2.44 (3H, s, N-CH_3), 2.29–2.23 (2H, m, H10a, H16a), 2.05 (1H, td, H15a, $J_{15a,15b;15a,16a} = 12.2$ Hz, $J_{15a,15b} = 5.2$ Hz), 1.99–1.90 (2H, m, H15b, C6-OH) ppm; ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = 154.66$ (C2′), 138.61 (C2), 137.68, 137.30 (C4, C1‴), 133.62, 133.49, 133.11, 132.81, 129.30, 128.92, 128.81, 128.58, 128.31, 127.53, 127.11 (C3, C7, C8, C11, C12, C2″, 5 aryl-C), 109.50 (C1″), 107.32 (C1), 93.91 (C5), 68.62 (C9), 66.22 (C6), 47.48 (C16), 44.03, 43.62 (C13, NCH_3), 41.66 (C14), 35.81 (C15), 25.59 (C10) ppm; HRMS: m/z (%) = 435.1671 ($M + Na^+$, 100), calculated for $C_{26}H_{24}N_2O_3Na$ 435.1685.

Computational procedure

We carried out the geometry optimization at Becke's three-parameter hybrid (B3LYP) levels [35–38] in the DFT with the basis set 6-31G(d,p) using Gaussian 03 [39]. The solvent effect was not considered. The models for morphine and codeine obtained at the B3LYP/6-31G(d,p) level were very much in accordance with X-ray data [40, 41].

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