Tetrahedron 64 (2008) 10388–10394

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Formation of novel thiazolomorphinans and thiazoloaporphines

Levente Girán, Sándor Berényi, Attila Sipos *

Department of Organic Chemistry, University of Debrecen, PO Box 20, H-4010 Debrecen, Hungary

ARTICLE INFO

Article history:
Received 2 June 2008
Received in revised form 3 August 2008
Accepted 21 August 2008
Available online 28 August 2008

Keywords:
Morphinandiene
Aporphine
Acid-catalyzed rearrangement
Kaufmann-type thiazole formation
Microwave promotion
DFT calculations

ABSTRACT

A novel strategy has been developed for the synthesis of ring A fused thiazolomorphinans and ring D fused thiazoloaporphines offering the possibility of formation of regioisomeric products. The conventional thermal thiazole-forming reaction was replaced with microwave initiation and a detailed discussion has been presented on the proposed mechanism of the ring closure.

1. Introduction

Thiazole ring systems are widely used structural elements in medicinal chemistry. This structure, especially in the case of 2-amino substitution, has been applied in the development of the treatment of allergies, hypertension, inflammation, schizophrenia, bacterial and HIV infections.[1] Görlitzer and Schumann[2a] and our research group[2b] prepared thiazole-fused morphinans at their ring C in order to test the effect of this novel moiety on the affinity at opioid receptors (Fig. 1). Recently, Neumeyer's group[3] synthesized ring A fused 2′-aminothiazole derivatives of benzomorphans and morphinans to study their opioid agonist properties (Fig. 1). The affinity of these novel series was somewhat reduced from that of their phenol prototypes, one compound has been identified as possessing high affinity and selectivity at the κ receptor.

The 2-aminothiazole functionality has been successfully applied as a heterocyclic bioisostere of the phenol moiety also in dopamine agonists such as B-HT 920,[4a] PD 118440[1d] and pramipexole[4b] resulting in improved pharmacological properties (Fig. 1).

In the last two decades considerable amount of research activity was devoted to the synthesis and pharmacological evaluation of molecules possessing significant D-1 receptor activity with antagonistic character.[5] Regarding new aporphinoids developed for this neuropharmacological field two different approaches were applied for the formation of these compounds. One of them utilized and substituted natural origin aporphines, such as boldine and predicentrine.[6] The other procedure started with the acid-catalyzed rearrangement of the derivatives of natural morphine yielding *R*-aporphinoids and then applied a racemization/resolution sequence.[7] They found the presence of H-bond donor/acceptor 9-OH or H-bond acceptor 9-OCH_3 groups (substituted boldines/predicentrines) besides 8-halo/amino and 10/11-OCH_3 functions favourable. Generally, aporphine backbones with highly functionalized D-rings and substituents having the ability to form H-bonds are considered a promising starting point of the development of D1-active ligands.

Ring D fused thiazoloaporphines were also synthesized by our group targeting primarily the D2-receptor subtypes.[2b]

In the light of these studies on both thiazolomorphinans and dopaminergic thiazolo compounds we decided to form A- and D-ring fused (morphinan and aporphine backbone, respectively) derivatives retaining the free phenolic hydroxyl function of the alkaloid skeletons.

2. Results and discussion

Our attention turned to the formation of ring A fused thiazolomorphinans after the successful application of the Hantzsch-type thiazole synthesis for the introduction of this moiety to the ring C of morphinans.[2b] We aimed the development of a novel heteroring-forming methodology retaining the highly important pharmacophore 3-OH group[8] in order to obtain new, potentially opioid-active compounds with interesting substitution pattern on ring A. The structure of these compounds also offers the opportunity for the

* Corresponding author. Tel.: +36 52512900; fax: +36 52512836.
E-mail address: asipos@puma.unideb.hu (A. Sipos).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.08.069

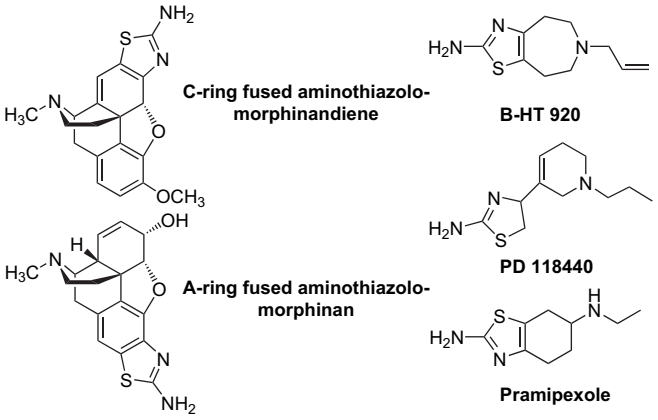


Figure 1. Opioid- and dopamine-active compounds bearing aminothiazole moiety.

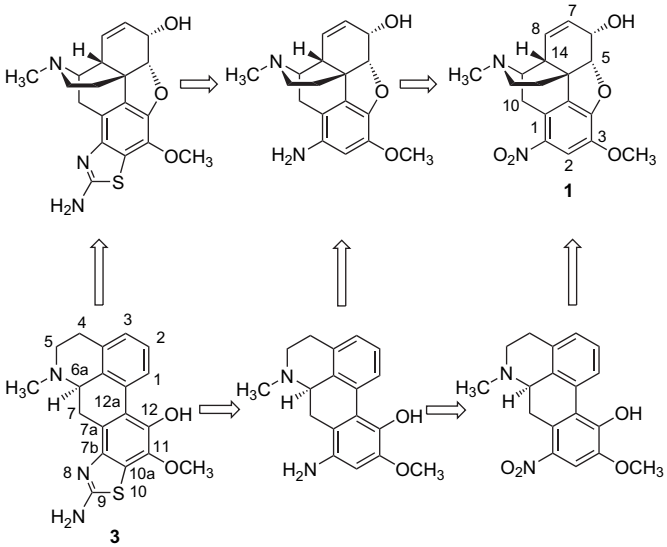
well-known acid-catalyzed rearrangement of the morphinan skeleton resulting in substituted aporphines with highly active pharmacophores at ring D according to recent findings on D1-active aporphines.[2c]

In the first stage we identified the Kaufmann-type aminothiazole formation[9] as a good choice to base the functionalization of ring D on. The reason for this was not only the fact that it was successfully applied on morphinan backbone earlier, but also the facile availability of the starting nitro-derivatives.

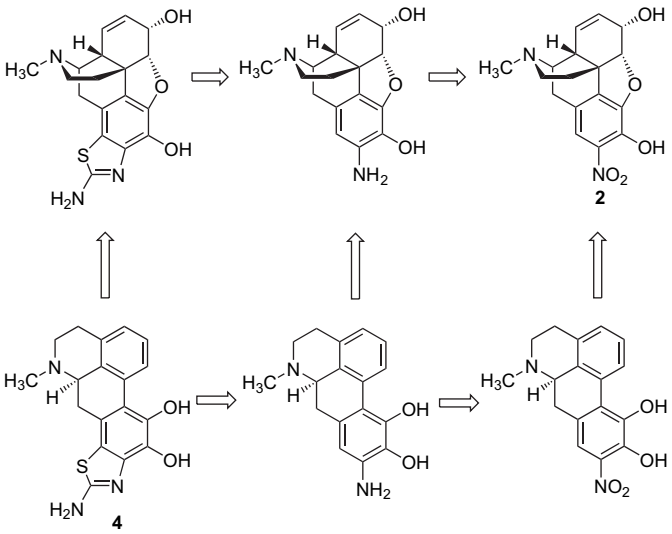
We found two alternative routes to form morphinan and aporphine backbones fused with aminothiazole moiety at rings A and D, respectively. One of them was initiated from 1-nitromorphinan yielding aminothiazoloapocodeine **3** as the final product (Scheme 1), whereas the second alternative was based on 2-nitromorphinan and led to aminothiazolo-apomorphine **4** (Scheme 2). The two main routes could be subdivided with respect to the target skeleton of the Kaufmann-type thiazole formation. It offered the chance of performing the heteroring formation in both cases on morphinans or aporphines.

The synthesis and structure elucidation of 1- and 2-nitromorphinans[10] were started in 1851 and were undoubtedly clarified in 1963.[11] We applied these historical methods for the synthesis of the 1-nitrocodeine (**1**)[10c] and 2-nitromorphine (**2**).[10d]

2-Nitromorphine (**2**) was found to be the only practicable choice as a starting product for the procedure initiated from 2-nitromorphinan. As a consequence of that, after performing the acid-



Scheme 1. Retrosynthesis of the procedure based on 1-nitrocodeine (**1**).



Scheme 2. Retrosynthesis of the procedure based on 2-nitromorphine (**2**).

catalyzed rearrangement, we had to work towards the aimed aminothiazole derivative on very sensitive catechol-containing aporphines. Although we finally resolved this problem with the application of immediate salt formation after each step, significantly lower overall yield was observed due to the oxidation sensitivity of the catechol motif. This fact particularly emphasized the importance of the alternative route building up the thiazole ring on the morphinan skeleton.

In order to develop an easy and reliable analytical procedure for verifying the actual position of the nitro-group of the starting compounds **1** and **2** instead of the complex and time-consuming procedures described in the literature,[11] we examined the possibilities offered by modern structural analysis and found the investigation of Nuclear Overhauser Effect (NOE) a good solution due to the easily identifiable 1-H, 2-H and 10-H protons (Fig. 2).

The observed NOEs were in accordance with the distances presented on the structures of **1** and **2** optimized at the B3LYP/6-31+G* level[12] in Figure 2 for 1-nitrocodeine (**1**) there was no NOE correlation between distant 2-H and 10β-H protons; however, for 2-nitromorphine (**2**) we found moderate correlation between 1-H and 10β-H nuclei.

2.1. Reductions and rearrangements

After obtaining and characterizing nitro-compounds **1** and **2** we looked for an appropriate reduction procedure to turn them into the corresponding amino-derivatives. The conventional procedure utilizes tin–hydrochloric acid reagents,[11] however, the product is formed in tin-salt form, from which the base could be liberated by

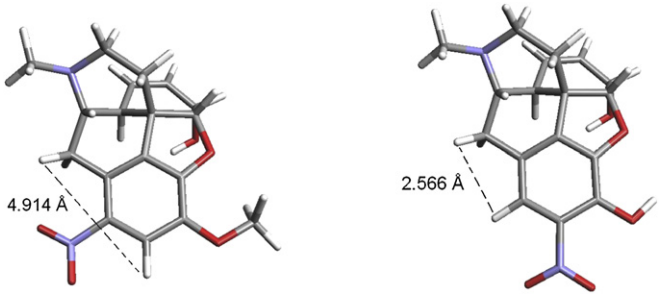


Figure 2. Important distances presented on the structures of **1** and **2** optimized at the B3LYP/6-31+G* level.

hydrogen sulfide gas. Owing to environmental and health issues regarding this procedure we started looking for an alternative method. After several unsuccessful runs with iron chips in hydrochloric acid, zinc in sodium hydroxide solution, ammonium formate and Raney-Ni catalyst in methanol[13] (poor conversion or difficulties during work-up procedure), the procedure applying formamidinesulfinic acid (FSA) in sodium hydroxide solution was adapted for both morphinan and aporphine backbones successfully (Scheme 3).[14]

As it was emphasized in the synthesis plans and Scheme 3, the acid-catalyzed rearrangement[15] is a determining procedure in the formation of the targeted aminothiazoloaporphines **3** and **4**. It was also presented in the retrosyntheses that these methodologies offer the opportunity of backbone-transformation in each step from morphinans to aporphines. Generally, in the acid-catalyzed rearrangements of 1-substituted codeines **1** and **5** we received the expected 8-nitro- and 8-aminoapocodeines (**7** and **9**) in excellent yields (Scheme 3, panel A). These apocodeines were found to be stable in free base form without any further transformation.

The rearrangement of 2-substituted morphines **2** and **6** (Scheme 3, panel B) gave 9-nitro- and 9-aminoapomorphines (**8** and **10**) in high yield, however, these compounds were found to be even more sensitive to oxidation in free base form than apomorphines without a substituent in positions 8 or 9, therefore immediate formation of the air-stable HCl salts was more significant.

2.2. Formation of the 2-aminothiazole ring

The optimization of the heteroring formation procedure was started on 1-aminocodeine (**5**) with the application of the conventional method of Kaufmann described in 1928[9] and adopted for morphinans by Neumeyer's group.[3] Amine **5** was treated with potassium thiocyanate and bromine in acetic acid and refluxed without protection from light. After several optimization steps including changes in the reaction time, the target temperature and the intensity of the lighting (application of outer exposition) there was no significant increase in the conversion, the isolated yield remained at a level of 20%. According to the literature, microwave induction (MW) has been applied successfully for the development of reactions taking place via a radical intermediate.[16] At this point it should be clarified that no mechanistic explanation is available for the Kaufmann-type reaction, however, all available experimental data point to the fact that the role of a radical intermediate is a reasonable assumption.

In accordance with this conclusion further optimization of the reaction was performed with the application of MW initiation instead of conventional thermal effect. Obtained results were in line with our expectations; the isolated yields were higher in this pressurized vessel method. Exploiting the freedom of choice of parameters offered by CEM Discover apparatus, we kept the maximal power permitted by the system for such an ionic-polar solution and applied 130 °C as target temperature with 15 min hold time. It was found that high temperature was favourable for thiazole formation. In Figure 3 a typical run is presented showing consistent controlled temperature and non-controlled pressure.

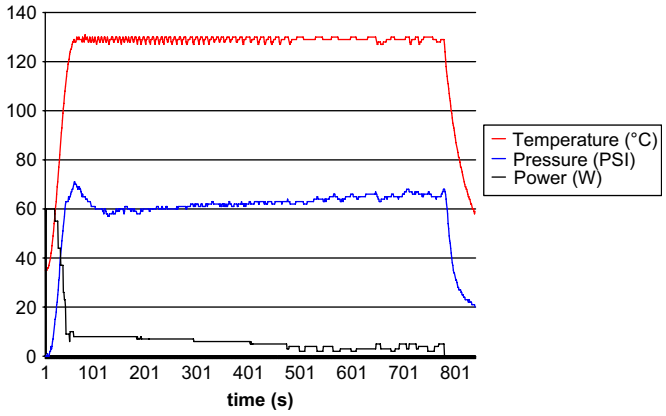


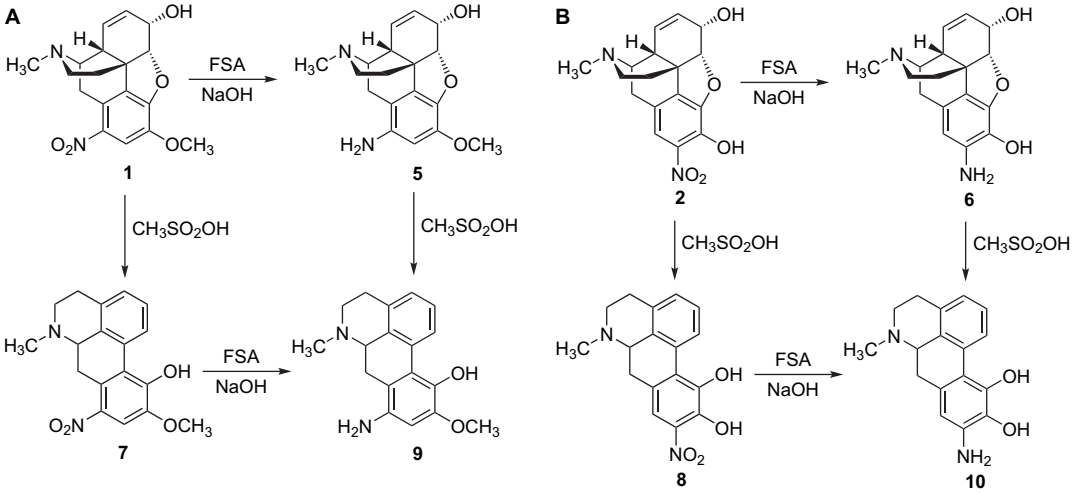
Figure 3. Typical run for the MW-assisted thiazole formation.

As it was mentioned, the optimization of the formation of 2-aminothiazole ring was performed on 1-aminocodeine (**5**, Scheme 3, panel A). The developed methodology was found to be applicable and practicable for 2-aminomorphine (**6**) and corresponding aporphines **9** and **10** without major modification (Scheme 4).

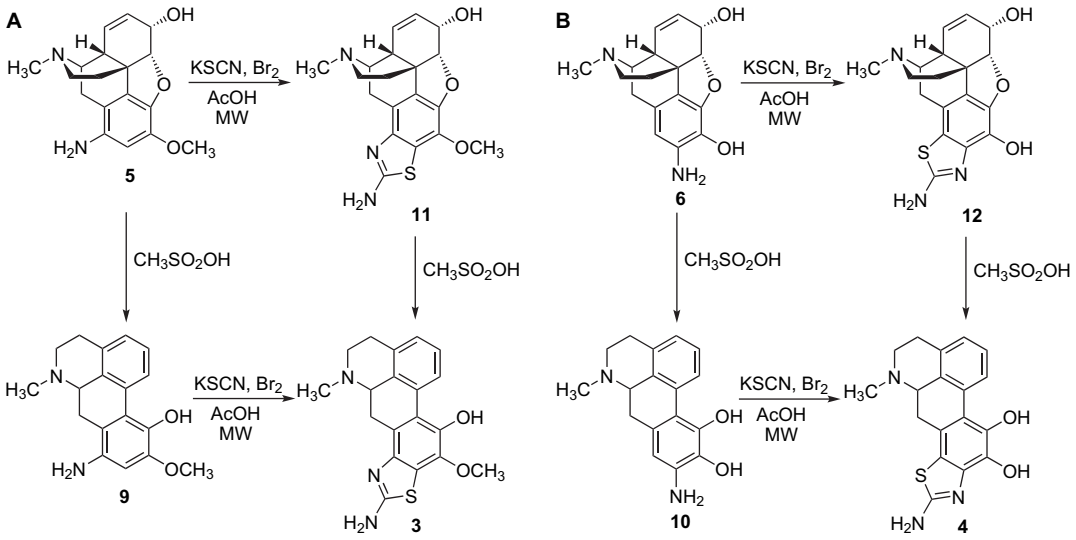
2.3. Study on the mechanism of the thiazole formation

The above-presented thiazole formation has been applied frequently for the synthesis of pharmacologically active compounds.[17] After an extensive literature search it was found that there is no unambiguous explanation available for the mechanism of this important heteroring-forming reaction. Maggiolo presumed the *ortho*-thiocyanation of the ring as a starting step,[18] while Trapani et al. state that the main step is the reaction between in situ formed $(SCN)_2$ and substituted anilines.[19]

We have carried out a detailed study based on DFT (Density Functional Theory) calculations using the Gaussian 98 program



Scheme 3. Reduction and rearrangement sequences **A** and **B** starting from nitromorphinans **1** and **2**, respectively.



Scheme 4. Heteroring formation and rearrangement sequences **A** and **B** starting from aminomorphinans **5** and **6**, respectively.

with the standard 6-31+G* basis set, as the electron correlation was expected to be critical in order to evaluate the reaction profile properly.[12] The hybrid functional B3LYP developed by Becke and also Lee, Yang and Parr was applied throughout this study as we received satisfactory control data at this level.[20] Stationary points were characterised by frequency calculations.[21] All intermediates and products have positive Hessian matrices. Transition structures show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration. Several reaction paths were checked by intrinsic reaction coordinate (IRC) calculations.[22]

Maggiolo's interpretation was interpreted in the form of a nucleophile radical substitution on aromatic system, however, our calculations do not support this alternative as the energetic and steric parameters of the involved intermediates were found to be highly unfavourable.

Kaufmann examined the potential reactive species of the thiazole formation and presented proofs on the presence of in situ formed $(SCN)_2$ and HSCN.[9] Our calculations pointed to the fact that in acetic acid medium it is HSCN that performs the thiourea formation of substituted anilines (Scheme 5).

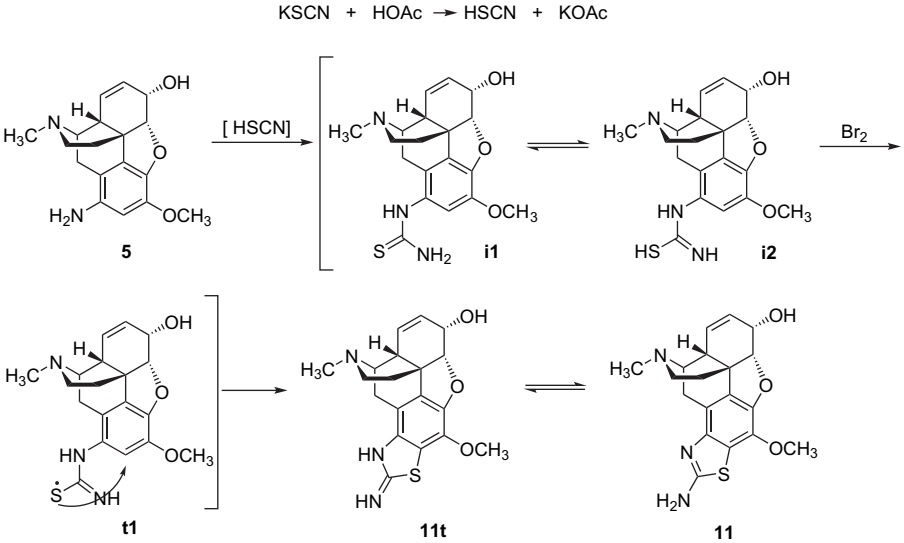
The formation of HSCN from KSCN was also described by Klason.[23] In order to confirm the general presumption on the role of radical species we performed the MW-promoted heteroring formation of **5** in the absence of bromine and in the presence of bromine and α-tocopherol, a free radical scavenger. The analysis of both product mixtures showed the absence of product **11**, furthermore we were able to identify the similar side-products.

The **t1**→**11t** conversion was submitted for further study to identify the energetic and steric character of the participating species (Fig. 4 and Table 1).

In accordance with the calculated geometry data the radical-containing thiourea moiety migrates from the energetically favourable **t1** conformation to the σ-complex structure. Simultaneously the electron distribution of the aromatic ring changes and the C2–H bond elongates.

3. Conclusions

We have presented a novel strategy for the synthesis of ring A fused thiazolomorphinans and ring D fused thiazoloaporphines offering the possibility of formation of regioisomeric products. In the key step of the synthesis routes the conventional thermal



Scheme 5. Proposed mechanism for the thiazole formation on compound **5**.

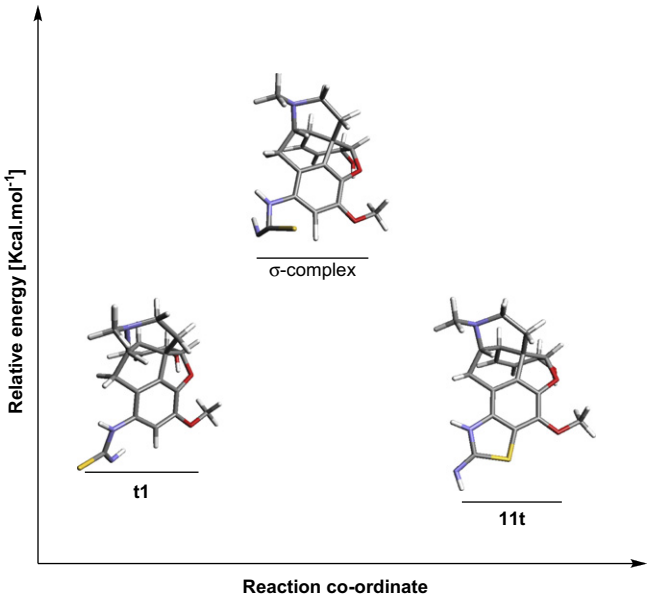


Figure 4. Calculated relative energies and structures of participating species optimized at the B3LYP/6-31+G* level.

thiazole-forming reaction was replaced with microwave initiation. A detailed study has been presented on the proposed mechanism of the ring closure including experimental proofs and DFT calculations.

4. Experimental part

4.1. General details

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Thin layer chromatography was performed on pre-coated Merck 5554 Kieselgel 60 F_{254} 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 AM 360 spectrometer, chemical shifts are reported in parts per million (δ) from internal TMS and coupling constants (J) are measured in hertz. High resolution mass spectral measurements were performed with a Bruker micrOTOF-Q instrument in the ESI mode. Optical rotation was determined with a Perkin–Elmer Model 241 polarimeter. IR spectra were recorded on Perkin–Elmer 283 B spectrometer.

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.

For test reactions regarding mechanistic studies we used (±)α-tocopherol, Ph. Eur. grade.

4.2. Synthesis route starting from 1-nitrocodeine (1)

Method A for reduction of nitro-compounds. The nitro-derivative (3.2 mmol) was suspended in a mixture of EtOH (15 mL) and water (5 mL). A solution of NaOH (0.72 g, 18 mmol) in H_2O (10 mL) was made up and 5 mL portion of this was added to the suspension. FSA (0.97 g, 8.7 mmol) was dissolved in the remaining 5 mL of NaOH solution and transferred to the alkaline solution of the nitro-derivative. The reaction mixture was heated with stirring on an oil bath at 90 °C under N_2 for 1 h. After a few minutes the nitro-compound completely dissolved. The product mixture was allowed to cool to room temperature, the organic solvent was evaporated in vacuo, the aqueous solution was extracted with $CHCl_3$/MeOH=2/1 mixture, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to afford the amino-compound.

Table 1
Important parameters of involved species

Species	Distance (Å)			Dihedral angle (°)		Rel energy (kcal mol^{-1})
	N3′···C2	S···C2	C2–H	C1–N–C–N	C1–N–C–S	
t1	3.143	5.414	1.123	27.61	156.28	0
σ-Complex	4.324	2.359	1.475	58.55	84.31	34
11t	3.812	1.705	—	−177.96	6.06	−4

Method B for thiazole ring closure. Aminomorphinan (0.32 mmol) and KSCN (130 mg, 1.34 mmol) were dissolved in glacial acetic acid (3 mL) in a 10 mL glass tube and one drop of bromine was added. The reaction was carried out in MW reactor for 15 min at 130 °C with 60 W of maximum power, under pressure in a sealed vial. After cooling, the reaction mixture was poured on to ice water and the pH was adjusted to 9 by adding concentrated ammonia solution in the presence of ice. The mixture was extracted with ethylacetate, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford the appropriate aminothiazole derivative.

Method C for acid-catalyzed rearrangement. A mixture of the morphinan (0.32 mmol) and methanesulfonic acid (5 mL) was stirred for 25 min at 90 °C. Then the reaction mixture was poured on to ice water and the pH was adjusted to 9 by adding concentrated ammonia solution with constant ice cooling. The mixture was extracted with ethylacetate, the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to yield the appropriate aporphine.

4.2.1. 1-Nitrocodeine (*1*)

Compound **1** was prepared according to the previously described method.[10c] All the physical properties are in line with reported data.[10] HRMS (ESI) m/z (%) found: 345.1456 (M^++H, 43), calculated for $C_{18}H_{21}N_2O_5^+$: 345.1445 (M^++H); ν_{max} (KBr disc) broad band 3200 (OH), 1520 (NO_2) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ=7.30 (s, 1H, H2), 5.63, 5.47 (2d, 2H, H7–H8, J_{7-8} 5.2), 4.25–4.05 (m, 2H, $H5_a$, $H6_a$), 3.89 (s, 3H, OCH_3), 3.22–2.62 (m, 4H, $H9_b$, $H10_a$, $H10_b$, $H14_b$), 2.46–2.12 (m, 6H, NCH_3, $H15_b$, $H16_a$, $H16_b$), 2.04 (dt, 1H, $H15_a$, $J_{15a-15b;16a-16b}$ 11.6, $J_{15a-15b}$ 4.7); ^{13}C NMR (360 MHz, $CDCl_3$) δ=149.14 (C4), 146.27 (C3), 140.43 (C1), 133.21, 131.69, 128.01, 114.82, 108.12 (5C), 93.11 (C5), 70.72 (C6), 58.84 (C9), 56.34 (OCH_3), 53.11 (C16), 43.11, 41.55, 38.77 (C13, C14, NCH_3), 35.74 (C15), 29.18 (C10).

4.2.2. 1-Aminocodeine (*5*)

Compound **5** was prepared according to general method A. All the physical properties are in line with reported data.[10] Yield: 620 mg (68%); HRMS (ESI) m/z (%) found: 315.1712 (M^++H, 100), calculated for $C_{18}H_{23}N_2O_3^+$: 315.1703 (M^++H); ν_{max} (KBr disc) 3450, 3350 (NH_2), broad band 3200 (OH) cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ=6.23 (s, 1H, H2), 5.71, 5.54 (2d, 2H, H7–H8, J_{7-8} 5.7), 5.10 (br s, 2H, NH_2), 4.40 (d, 1H, $H5_a$, J_{5a-6a} 7.6), 4.14–4.07 (m, 1H, $H6_a$), 3.73 (s, 3H, OCH_3), 3.34–2.48 (m, 4H, $H9_b$, $H10_a$, $H10_b$, $H14_b$), 2.39–2.01 (m, 7H, NCH_3, $H15_a$, $H15_b$, $H16_a$, $H16_b$); ^{13}C NMR (360 MHz, $CDCl_3$) δ=147.24 (C3), 138.19 (C1), 134.58, 131.29, 128.63, 127.77, 111.93, 109.66 (6C), 92.87 (C5), 70.34 (C6), 58.08 (C9), 56.31 (OCH_3), 53.28 (C16), 43.19, 40.93, 39.48 (C13, C14, NCH_3), 35.63 (C15), 27.11 (C10).

4.2.3. 2′-Aminothiazole-(4,5:2,1)-codeine (*11*)

Compound **11** was prepared according to general method B. Yield: 62 mg (54%). Colourless crystals; R_f (chloroform/methanol=1/1) 0.33; mp: 164–166 °C; $[\alpha]_D^{25}$ −83 (c 0.10, methanol); HRMS (ESI) m/z (%) found: 372.1388 (M^++H, 100), calculated for

$C_{19}H_{22}N_3O_3S^+$: 372.1376 (M^++H); ν_{max} (KBr disc) 3450, 3350 (NH_2), broad band 3200 (OH) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ=5.61, 5.55 (m, 2H, H7–H8), 5.11 (br s, 2H, NH_2), 4.11–3.89 (m, 5H, $H5_a$, $H6_a$, OCH_3), 3.32–2.57 (m, 4H, $H9_b$, $H10_a$, $H10_b$, $H14_b$), 2.41–1.69 (m, 7H, NCH_3, $H15_a$, $H15_b$, $H16_a$, $H16_b$); ^{13}C NMR (90 MHz, $CDCl_3$) δ=168.25 (C2′), 139.25, 136.29, 131.47, 126.38, 126.11, 119.72, 113.48, 105.62 (8C), 94.41 (C5), 74.23 (C6), 60.11 (C9), 56.17 (OCH_3), 49.49 (C16), 43.28, 41.64, 39.94 (C13, C14, NCH_3), 38.87 (C15), 27.21 (C10).

4.2.4. 9-Amino-12-hydroxy-6-methyl-11-methoxythiazolo[4,5-k]5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline (**3**)

Compound **3** was prepared according to general method B in a yield of 72 mg (60%) and was prepared according to general method C in a yield of 465 mg (49%). Colourless crystals; R_f (chloroform/methanol=4/1) 0.38; mp: 163–165 °C; $[\alpha]_D^{25}$ −209 (*c* 0.10, methanol); HRMS (ESI) *m*/*z* (%) found: 354.1271 (M^++H, 100), calculated for $C_{19}H_{20}N_3O_2S^+$: 354.1249 (M^++H); ν_{max} (KBr disc) 3450, 3350 (NH_2), broad band 3200 (OH) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ=7.21–6.92 (m, 3H, H1, H2, H3), 5.48 (br s, 2H, NH_2), 4.11–3.83 (m, 4H, $H6_a$, 10-OCH_3), 3.21–2.42 (m, 9H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, NCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ=169.71 (C9), 143.21, 138.45, 135.48, 133.39, 128.68, 124.54, 119.90, 117.72, 112.82, 110.02, 109.56, 108.75 (12C), 64.48 (C6), 56.12 (OCH_3), 49.82 (C5), 41.12 (NCH_3), 33.31 (C7), 25.74 (C4).

4.2.5. 8-Nitroapocodeine (**7**)

Compound **7** was prepared according to general method C. Yield: 831 mg (87%). Orange crystals; mp: 128–130 °C; $[\alpha]_D^{25}$ −704 (*c* 0.10, chloroform); HRMS (ESI) *m*/*z* (%) found: 327.1344 (M^++H, 13), calculated for $C_{19}H_{20}N_3O_2S^+$: 327.1339 (M^++H); ν_{max} (KBr disc) broad band 3200 (OH), 1540 (NO_2) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ=7.52 (s, 1H, H9), 7.11–6.84 (m, 3H, H1, H2, H3), 6.13 (s, 1H, 11-OH), 4.01–3.89 (m, 4H, $H6_a$, 10-OCH_3), 3.18–2.44 (m, 9H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, NCH_3); ^{13}C NMR (90 MHz, $CDCl_3$) δ=151.48 (C10), 146.78 (C11), 141.23 (C8), 137.45, 134.71, 132.29, 130.88, 127.76, 123.40, 113.71, 111.65, 109.35 (9C), 60.48 (C6), 56.34 (OCH_3), 52.82 (C5), 41.12 (NCH_3), 33.24 (C7), 25.22 (C4).

4.2.6. 8-Aminoapocodeine hydrochloride (**9**·HCl)

Compound **9**·HCl was prepared according to general method A in a yield of 510 mg (56%) and was prepared according to general method C in a yield of 360 mg (34%). Grey crystals; mp: 178–180 °C; $[\alpha]_D^{25}$ −421 (*c* 0.10, methanol); HRMS (ESI) *m*/*z* (%) found: 297.1584 (M^++H, 100), calculated for $C_{18}H_{21}N_2O_2^+$: 297.1598 (M^++H); ν_{max} (KBr disc) 3450, 3350 (NH_2), broad band 3200 (OH) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$ from free base) δ=6.99–6.74 (m, 4H, H1, H2, H3, H9), 6.31 (s, 1H, 11-OH), 5.24 (br s, 2H, NH_2), 4.08–3.92 (m, 4H, $H6_a$, 10-OCH_3), 3.37–2.57 (m, 9H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, NCH_3); ^{13}C NMR (90 MHz, $CDCl_3$ from free base) δ=149.72 (C11), 137.87, 135.61, 134.67, 131.01, 127.08, 126.83, 123.29, 123.11, 118.70, 115.44, 113.35 (11C), 60.34 (C6), 56.32 (OCH_3), 54.11 (C5), 41.17 (NCH_3), 33.78 (C7), 27.24 (C4).

4.3. Synthesis route starting from 2-nitromorphine (2)

4.3.1. 2-Nitromorphine (**2**)

Compound **2** was prepared according to the previously described method.[11] All the physical properties are in line with reported data.[11] HRMS (ESI) *m*/*z* (%) found: 331.1303 (M^++H, 26), calculated for $C_{18}H_{21}N_2O_5^+$: 331.1288 (M^++H); ν_{max} (KBr disc) broad band 3200 (OH), 1510 (NO_2) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ=7.33 (s, 1H, H1), 6.14 (br s, 1H, 3-OH), 5.68, 5.65 (2d, 2H, H7, H8, J_{7-8} 5.8), 4.28–4.16 (m, 2H, $H5_a$, $H6_a$), 3.27–2.61 (m, 4H, $H9_b$, $H10_a$, $H10_b$, $H14_b$), 2.44–2.19 (m, 6H, NCH_3, $H15_b$, $H16_a$, $H16_b$), 1.99 (dt, 1H, $H15_a$, $J_{15a-15b;16a-16b}$ 10.1, $J_{15a-15b}$ 4.9); ^{13}C NMR (360 MHz, $CDCl_3$) δ=145.63 (C4), 137.78, 134.80, 130.09, 126.47, 123.78, 119.81, 118.12 (7C), 93.31 (C5), 70.56 (C6), 59.81 (C9), 53.39 (C16), 43.56, 40.99, 39.79 (C13, C14, NCH_3), 35.19 (C15), 32.18 (C10).

4.3.2. 2-Aminomorphine (**6**)

Compound **6** was prepared according to general method A. Yield: 510 mg (55%). All the physical and spectral data were in line with previously published data.[14] Mp: >250 °C; $[\alpha]_D^{25}$ −187 (*c* 0.10, methanol); HRMS (ESI) *m*/*z* (%) found: 301.1561 (M^++H, 100), calculated for $C_{17}H_{21}N_2O_3^+$: 301.1547 (M^++H); ν_{max} (KBr disc) 3350 (NH_2), broad band 3200 (OH) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ=7.11 (s, 1H, H1), 6.04 (br s, 1H, 3-OH), 5.74, 5.69 (2d, 2H, H7, H8, J_{7-8} 6.2), 5.56 (br s, 2H, NH_2), 4.11–4.03 (m, 2H, $H5_a$, $H6_a$), 3.45–2.65 (m, 4H, $H9_b$, $H10_a$, $H10_b$, $H14_b$), 2.38–2.09 (m, 6H, NCH_3, $H15_b$, $H16_a$, $H16_b$), 2.01 (dt, 1H, $H15_a$, $J_{15a-15b;16a-16b}$ 10.0, $J_{15a-15b}$ 5.4); ^{13}C NMR (360 MHz, $CDCl_3$) δ=145.11 (C4), 136.11, 131.85, 131.09, 128.60, 126.27, 120.86, 114.67 (7C), 94.69 (C5), 71.16 (C6), 60.38 (C9), 52.88 (C16), 44.01, 42.38, 40.23 (C13, C14, NCH_3), 35.39 (C15), 31.80 (C10).

4.3.3. 2′-Aminohtiazole-(4,5:1,2)-morphine hydrochloride (**12**·HCl)

Compound **12**·HCl was prepared according to general method B. Yield: 64 mg (51%). Colourless crystals; R_f (chloroform/methanol=4/1) 0.41; mp: >250 °C; $[\alpha]_D^{25}$ −35 (*c* 0.10, methanol); HRMS (ESI) *m*/*z* (%) found: 358.1243 (M^++H, 100), calculated for $C_{19}H_{20}N_3O_2S^+$: 358.1220 (M^++H); ν_{max} (KBr disc) 3450, 3350 (NH_2), broad band 3200 (OH) cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ=6.64 (br s, 1H, 3-OH), 6.11–5.92 (m, 2H, H7, H8), 5.33 (s, 2H, NH_2), 4.27–4.01 (m, 2H, $H5_a$, $H6_a$), 3.27–2.52 (m, 4H, $H9_b$, $H10_a$, $H10_b$, $H14_b$), 2.39–1.68 (m, 7H, NCH_3, $H15_a$, $H15_b$, $H16_a$, $H16_b$); ^{13}C NMR (90 MHz, DMSO-d_6) δ=168.44 (C2′), 142.21, 135.70, 129.44, 126.71, 122.10, 115.34, 114.97, 113.12 (8C), 93.37 (C5), 67.72 (C6), 59.21 (C9), 51.11 (C16), 43.11, 41.65, 38.77 (C13, C14, NCH_3), 32.77 (C15), 29.18 (C10).

4.3.4. 9-Amino-11,12-dihydroxy-6-methylthiazolo[5,4-k]5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline hydrochloride (**4**·HCl)

Compound **4**·HCl was prepared according to general method B in a yield of 88 mg (72%) and was prepared according to general method C in a yield of 96 mg (68%). Colourless crystals; R_f (chloroform/methanol=1/3) 0.22; mp: >250 °C; $[\alpha]_D^{25}$ −68 (*c* 0.10, methanol); HRMS (ESI) *m*/*z* (%) found: 340.1128 (M^++H, 100), calculated for $C_{18}H_{18}N_3O_2S^+$: 340.1114 (M^++H); ν_{max} (KBr disc) 3450, 3350 (NH_2), broad band 3200 (OH) cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ=7.42–7.02 (m, 3H, H1, H2, H3), 6.58–6.39 (br s, 2H, 2-OH), 5.22 (s, 2H, NH_2), 4.14 (dd, 1H, $H6_a$, J_{6a-7a} 9.2, J_{6a-7b} 3.1), 3.21–2.48 (m, 9H, $H4_a$, $H4_b$,$H5_a$, $H5_b$, $H7_a$, $H7_b$, NCH_3); ^{13}C NMR (90 MHz, DMSO-d_6) δ=171.17 (C2′), 142.61, 139.70, 136.33, 131.27, 128.18, 126.61, 122.10, 119.76, 115.44, 113.69, 111.07, 110.88 (12C), 60.88 (C6), 53.17 (C5), 40.88 (NCH_3), 30.44 (C7), 28.12 (C4).

4.3.5. 9-Nitroapomorphine hydrochloride (**8**·HCl)

Compound **8**·HCl was prepared according to general method C. Yield: 520 mg (49%). Yellow crystals; mp: >250 °C; $[\alpha]_D^{25}$ −221 (*c* 0.10, methanol); HRMS (ESI) *m*/*z* (%) found: 313.1189 (M^++H, 56), calculated for $C_{17}H_{17}N_3O_4^+$: 313.1183 (M^++H); ν_{max} (KBr disc) broad band 3200 (OH), 1540 (NO_2) cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ=7.40 (s, 1H, H8), 7.21–7.01 (m, 3H, H1, H2, H3), 6.42 (br s, 2H, 10-OH, 11-OH), 4.14, 4.08 (2d, 1H, $H6_a$, J_{6a-7a} 11.0, J_{6a-7b} 3.2), 3.18–2.27 (m, 9H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, NCH_3); ^{13}C NMR (90 MHz, DMSO-d_6) δ=145.75 (C11), 136.35, 132.22, 130.08, 127.73, 125.21, 119.40, 117.69, 116.18, 115.33, 115.01, 113.78 (11C), 60.34 (C6), 52.33 (C5), 43.13 (NCH_3), 33.72 (C7), 26.45 (C4).

4.3.6. 9-Aminoapomorphine hydrochloride (**10**·HCl)

Compound **10**·HCl was prepared according to general method A in a yield of 575 mg (59%) and was prepared according to general method C in a yield of 480 mg (49%). All the physical properties are in line with previously reported data.[10e] HRMS (ESI) *m*/*z* (%) found:

283.1457 (M^++H, 100), calculated for $C_{17}H_{19}N_2O_2^+$: 283.1441 (M^++H); ν_{max} (KBr disc) 3450, 3350 (NH_2), broad band 3200 (OH) cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ=7.03–6.88 (m, 4H, H1, H2, H3, H9), 6.31 (br s, 2H, 2× –OH), 5.22 (br s, 2H, NH_2), 4.08 (dd, 1H, $H6_a$, J_{6a-7a} 9.1, J_{6a-7b} 3.1), 3.37–2.59 (m, 9H, $H4_a$, $H4_b$, $H5_a$, $H5_b$, $H7_a$, $H7_b$, NCH_3); ^{13}C NMR (90 MHz, DMSO-d_6) δ=145.53 (C11), 134.39, 131.56, 130.45, 127.48, 123.30, 121.67, 120.93, 117.63, 116.49, 115.91, 115.78 (11C), 63.28 (C6), 52.92 (C5), 43.43 (NCH_3), 33.28 (C7), 25.79 (C4).

4.4. Computational procedure

We have carried out the geometry optimization at Becke's three-parameter hybrid (B3LYP)[20] levels in the DFT with the basis set 6-31G* using Gaussian 98.[12] The solvent effect was not considered.

Acknowledgements

The authors are grateful to the National Science Foundation (Grant OTKA reg. nos. T049436 and NI61336) for the financial support. We thank Péter Pázmány Programme (NKTH, RET006/2004) to allow us the use of microwave reactor and Szabolcs Fekete for the valuable technical help.

References and notes

1. (a) Hargrave, K. D.; Hess, F. K.; Oliver, J. T. *J. Med. Chem.* **1983**, *26*, 1158; (b) Patt, W. C.; Hamilton, H. W.; Taylor, M. D.; Ryan, M. J.; Taylor, D. G., Jr.; Connolly, C. J. C.; Doharty, A. M.; Klutchko, S. R.; Sircar, I.; Steinbaugh, B. A.; Bately, B. L.; Painchand, C. A.; Rapundalo, S. T.; Michniewicz, B. M.; Olzon, S. C. J. *J. Med. Chem.* **1992**, *35*, 2562; (c) Haviv, F.; Ratajczyk, J. D.; DeNet, R. W.; Kerdesky, F. A.; Walters, R. L.; Schmidt, S. P.; Holms, J. H.; Young, P. R.; Carter, G. W. *J. Med. Chem.* **1988**, *31*, 1719; Clemence, F.; Marter, O. L.; Delevalle, F.; Benzoni, J.; Jouanen, A.; Jouquey, S.; Mouren, M.; Deraedt, R. *J. Med. Chem.* **1988**, *31*, 1453; (d) Jaen, J. C.; Wise, L. D.; Caprathe, B. W.; Tecle, H.; Bergmeier, S.; Humblet, C. C.; Heffner, T. G.; Meltzner, L. T.; Pugsley, T. A. *J. Med. Chem.* **1990**, *33*, 311; (e) Tsuji, K.; Ishikawa, H. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1601; Bailey, N.; Dean, A. W.; Judd, D. B.; Middlemiss, D.; Storer, R.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1409; (f) Bell, F. W.; Cantrell, A. S.; Hoberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordon, C. L.; Kinnick, M. D.; Lind, P.; Morin, J. M., Jr.; Noreen, R.; Oberg, B.; Palkowitz, J. A.; Parrish, C. A.; Pranc, J.; Zhang, H.; Zhou, X.-X. *J. Med. Chem.* **1995**, *38*, 4929.
2. (a) Görlitzer, K.; Schumann, R. *Pharmazie* **1992**, *47*, 893; Görlitzer, K.; Schumann, R. *Pharmazie* **1993**, *48*, 31; (b) Tóth, M.; Gyulai, Z. S.; Berényi, S.; Sipos, A. *Lett. Org. Chem.* **2007**, *4*, 444; Sipos, A.; Mueller, F. K. U.; Lehmann, J.; Berényi, S. *Monatsh. Chem.* 2008, DOI: 10.1007/s00706-008-0044-z. (c) Loghin, F.; Chagraoui, A.; Asencio, M.; Comoy, E.; Speisky, H.; Cassels, B. K.; Protais, P. *Eur. J. Pharm. Sci.* **2003**, *18*, 133.
3. Zhang, A.; van Vilet, S.; Neumeyer, J. L. *Tetrahedron Lett.* **2003**, *44*, 6459; Zhang, A.; Xiong, W.; Hilbert, J. E.; DeVita, E. K.; Bidlack, J. M.; Neumeyer, J. L. *J. Med. Chem.* **2004**, *47*, 1886; Zhang, A.; Li, F.; Ding, C.; Yao, Q.; Knapp, B. I.; Bidlack, J. M.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 2747.
4. (a) Andén, N. E.; Nilsson, H.; Ros, E.; Thornström, U. *Acta Pharmacol. Toxicol. (Copenh.)* **1983**, *52*, 51; (b) Mierau, J.; Schneider, F. J.; Ensinger, H. A.; Chio, C. L.; Lajiness, M. E.; Huff, R. M. *Eur. J. Pharmacol.* **1995**, *290*, 29; Schneider, C. S.; Mierau, J. *J. Med. Chem.* **1987**, *30*, 494; van Vliet, A. L.; Rodenhuis, N.; Wikström, H. *J. Med. Chem.* **2000**, *43*, 3549.
5. (a) Zhang, A.; Zhang, Y.; Branfman, A. R.; Baldessarini, R. J.; Neumeyer, J. L. *J. Med. Chem.* **2007**, *50*, 171; (b) Zhang, A.; Neumeyer, J. L.; Baldessarini, R. *J. Chem. Rev.* **2007**, *107*, 274.
6. (a) Sobarzo-Sánchez, E. M.; Arbaoui, J.; Protais, P.; Cassels, B. K. *J. Nat. Prod.* **2000**, *63*, 480; (b) Asencio, M.; Hurtado-Guzmán, C.; López, J. J.; Cassels, B. K.; Protais, P.; Chagraoui, A. *Bioorg. Med. Chem.* **2005**, *13*, 3699.
7. Schaus, J. M.; Titus, R. D.; Foreman, M. M.; Mason, N. R.; Truex, L. T. *J. Med. Chem.* **1990**, *33*, 600.
8. Shiotani, S.; Kometani, T.; Iitaka, Y.; Itai, A. *J. Med. Chem.* **1978**, *21*, 153; Portoghese, P. S. *J. Med. Chem.* **1965**, *8*, 609.
9. Kaufmann, H. P. *Arch. Pharm.* **1928**, *266*, 197.
10. (a) Anderson, T. *Liebigs Ann.* **1851**, *77*, 358; (b) Wieland, H.; Kappelmeier, P. *Ann.* **1911**, *382*, 306; (c) Ochiai, E.; Nakamura, T. *Proced. Imp. Acad.* **1938**, *14*, 13; (d) Ach, F.; Knorr, L.; Lingenbrink, H.; Hörlein, H. *Chem. Ber.* **1909**, *42*, 3503; (e) Wieland, H.; Kappelmeier, P. *Ann.* **1911**, *382*, 357.
11. Ochiai, E.; Nakamura, T. *Chem. Ber.* **1939**, *72*, 684; Bognár, R.; Gaál, D. *Gy. Magy. Kém. Foly.* **1963**, *69*, 17; *Chem. Abstr.* **1963**, *59*, 1969b.
12. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J.- L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98, Revision A.3*; Gaussian: Pittsburgh, PA, 1998; The models for morphine and codeine obtained at the B3LYP/6-31+G* level were very much in accord with X-ray data (ref.: Lutz, M.; Speck, A. L. *Acta Crystallogr., C* **1998**, *54*, 1477; Canfield, D. V.; Barrick, J.; Giessen, B. C. *Acta Crystallogr., C* **1987**, *43*, 977 , respectively).
13. Rosenström, U.; Sköld, C.; Lindeberg, G.; Botros, M.; Nydberg, F.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **2004**, *47*, 859.
14. Chatterjie, N.; Minar, A.; Clarke, D. D. *Synth. Commun.* **1979**, *9*, 647.
15. Granchelli, F. E.; Filer, C. N.; Soloway, A. H.; Neumeyer, J. L. *J. Org. Chem.* **1980**, *45*, 2275; Berényi, S.; Hosztafi, S.; Makleit, S.; Szeifert, I. *Acta Chim. Acad. Sci. Hung.* **1982**, *110*, 363; Csutorás, C. S.; Berényi, S.; Makleit, S. *Synth. Commun.* **1996**, *26*, 2251; Sipos, A.; Debreceni, S. Z.; Szabó, R.; Gyulai, Z. S.; Berényi, S. *Synth. Commun.* **2007**, *37*, 2549; Sipos, A.; Kiss, B.; Schmidt, É.; Greiner, I.; Berényi, S. *Bioorg. Med. Chem.* **2008**, *16*, 3773.
16. Bansal, V.; Kanodia, S.; Thapliyal, P. C.; Khanna, R. N. *Synth. Commun.* **1996**, *26*, 887; Olofsson, K.; Kim, S. Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539; Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
17. Erian, A. W.; Sherif, S. M. *Tetrahedron* **1999**, *55*, 7957.
18. Maggiolo, A. *J. Am. Chem. Soc.* **1951**, *73*, 5815.
19. Trapani, G.; Franco, M.; Latrofa, A.; Reho, A.; Liso, G. *Eur. J. Pharm. Sci.* **2001**, *14*, 209.
20. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648; (b) Becke, A. D. *Phys. Rev. A* **1998**, *38*, 3098; (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785; (d) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200.
21. McIver, J. W.; Komornicki, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 2625.
22. (a) González, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154; (b) González, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523; (c) Fukui, K. *Acc. Chem. Res.* **1981**, *14*, 363.
23. Klason, T. *J. Prakt. Chem.* **1887**, *35*, 406.