Synthesis and Characterization of New Thebaine Derivatives as Potential Opioid Agonists and Antagonists: 2-[*N*-(1*H*-Tetrazol-5-yl)-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5-phenyl-1,3,4-oxadiazoles

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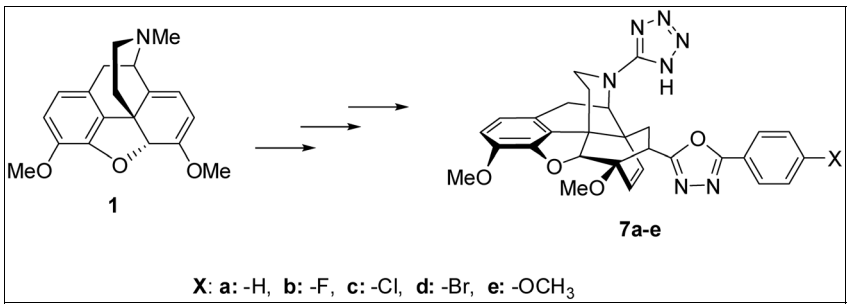

In this study, we report the synthesis a series of novel 2-[*N*-(1*H*-tetrazol-5-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5-phenyl-1,3,4-oxadiazole derivatives (**7a**–**e**) which have potential opioid antagonist and agonist. The substitution reaction of 6,14-*endo*-ethenotetrahydrothebaine-7α-carbohydrazide with corresponding benzoyl chlorides gave diacylhydrazine compounds **4a**–**e** in good yields. The treatment of compounds **4a**–**e** with $POCl_3$ caused the conversion of side-chain of compounds **5a**–**e** into 1,3,4-oxadiazole ring at C(7) position; thus, compounds **5a**–**e** were obtained. Subsequently, cyanamides (**6a**–**e**) were prepared from compounds **5a**–**e** and then compounds **7a**–**e** were synthesized by the azidation of **6a**–**e** with NaN_3. The structures of the compounds were established on the basis of their IR, ^{1}H NMR, ^{13}C APT, 2D-NMR (COSY, NOESY, HMQC, HMBC) and high-resolution mass spectral data.

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INTRODUCTION

There are at least three major types of opioid receptors which are widely distributed in mammalian systems [1]. It is generally thought that stimulation of μ receptors (MOR) leads to analgesic effects, respiratory depression, and physical dependence, κ receptors (KOR) produce analgesia and δ receptors (DOR) play a role in spinal analgesia but are involved in other biological processes, such as immune response [2–4]. Morphinan alkaloids and their semisynthetic derivatives are one of the most important groups of nonendogenous ligands for opioid receptor and exhibit properties of agonists and antagonists [5]. Thus, some of them are used as narcotic analgesics and pain-killer with opioid agonist properties; others are used as opioid antagonist for the treatment of narcotic overdosage and opioid addiction. These properties depend on substituents in different positions of the morphinan skeleton.

In our previous work, we successfully synthesized and characterized a series of (1,3,4-oxadiazol-2-yl)-*N*-arenamine derivates of 7α-substituted-6,14-*endo*-ethenotetrahydrothebaine [6]. It is well known that the 7α-substituted-6,14-*endo*-ethenotetrahydrothebaine derivates are very strong analgesic compounds that show high affinity for each of the μ, κ, and δ opioid receptor [7, 8]. Furthermore, the C rings in their structures essentially affect the pharmacological properties of these types of alkaloids [9, 10]. The reported pharmacological active compounds in the literature, such as etorphine **(I)** has a lipophilic substituent at position 7α of the C ring [11]. The introduction of additional heterocyclic fragments into the molecules of morphinan alkaloids leads to highly promising opioids. For example, nitrogen and sulphur containing morphinan alkaloids exhibit analgesic activity [12, 13]. 1,3,4-Oxadiazoles have attracted interest in medicinal chemistry as bioisosters of carboxylic acids, esters, and carboxamides. Because of their metabolic profile and ability to engage in hydrogen bonding, they are an important class of heterocyclic compounds that have a wide range of pharmaceutical and biological activities including analgesic, antimicrobial, antifungal, antinflammatory, and antihypertensive [14–16].

The nature of the substituent at the nitrogen atom in morphine alkaloids is a significant factor on their antagonist activity [17]. Through of *N*-demethylation of the tertiary amine in the opiate skeleton were pharmaceutically useful opiates, such as diprenorphine **(II)** and naloxone **(III)** obtained. They have been found that replacing cyclopropylmethyl and allyl groups with a methyl group greatly

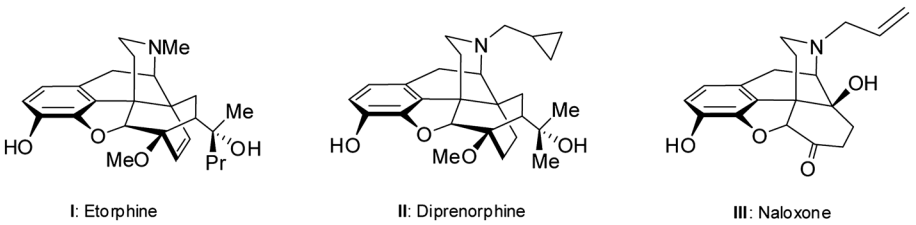


Figure 1. Structures of etorphine, diprenorphine, and naloxone.

increases efficacy antagonist effect particularly at MOR [18] (Fig. 1).

In the recent years, a lot of studies on tetrazole derivatives have been reported. Tetrazoles have become very popular because of their functionality and wide range of applications. Tetrazoles may be regarded as biological equivalents of the carboxyl group, and extensive studies on tetrazoles have been performed in the field of medicinal chemistry [19].

We report the synthesis a series of novel 6,14-*endo*-ethenotetrahydrothebaine derivatives including, tetrazole group at nitrogen atom and 5-substituted-phenyl-1,3,4-oxadiazole groups at C-7α position which have candidates to opioid agonist and antagonist agent.

RESULTS AND DISCUSSION

The target compound **2** was prepared from thebaine (**1**) by Diels–Alder reaction with methyl acrylate [10, 20]. We obtained compound **3** by the treatment of compound **2** with hydrazine hydrate [21]. Then, compound **3** reacted with benzoyl chlorid derivatives in toluene producing diacylhydrazine compounds **4a–e**. In 7α position oxadiazole ring substituted thebaine derivatives **5a–e** were obtained by the cyclodehydration of diacylhydrazines **4a–e** under the action of $POCl_3$ [22]. Further, 1,3,4-oxadiazole derivatives **5a–e** were refluxed with cyanogen bromide in dry $CHCl_3$ to obtain cyanamides **6a–e**. At least, the subsequent reaction of **6a–e** with NaN_3 and NH_4Cl in dry DMF furnished tetrazole compounds **7a–e** (Scheme 1).

The structures of the products were determined by analysis of their IR, ^{1}H NMR, ^{13}C APT, 2D-NMR (COSY, NOESY, HMQC, HMBC) and high resolution mass spectra for the molecular weights. In addition, the crystallographic structure of the compound **2** was previously reported by our group [20].

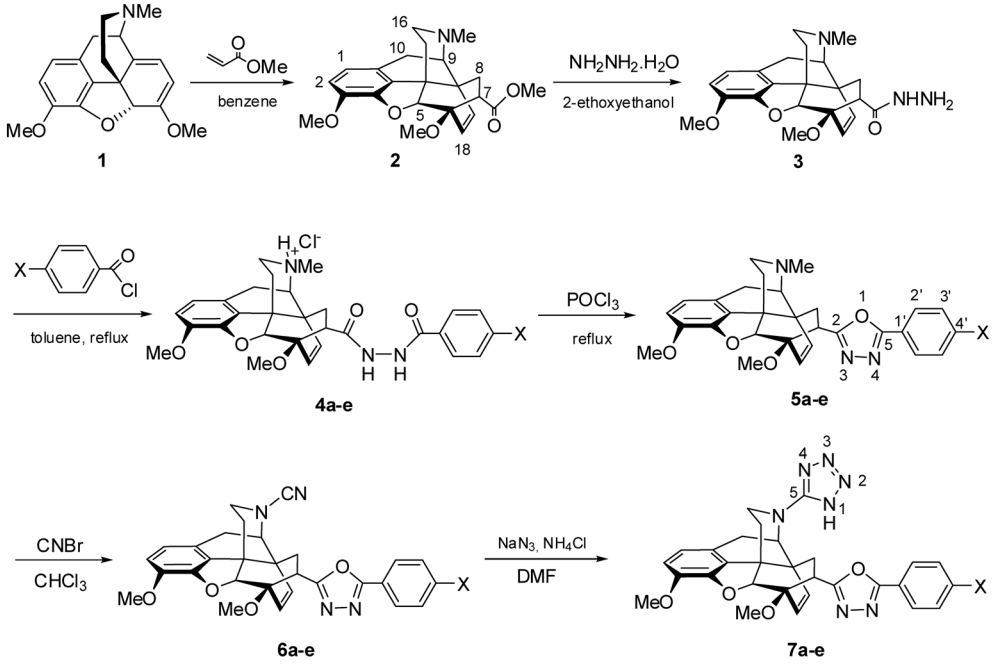
In the IR spectra of compound **4a–e**, characteristic bands of secondary amide in the regions 3200 cm^{-1}(N-H) were observed, and there were no absorption bands for -NH_2 belonging to compound **3**. After the cyclodehydration reactions of **4a–e** with $POCl_3$, N-H bands of amide groups disappeared in the spectra of 7α-1,3,4-oxadiazle rings substituted thebaine derivatives **5a–e**. A special feature of the IR spectra of the cyanamide products **6a–e** was the presence of absorption bands of cyanide groups at 2200–2225 cm^{-1}. *N*-Tetrazole compounds **7a–e** had the band at between 3535 and 3100 cm^{-1} revealing the formation of an intramolecular hydrogen bond with a nitrogen atom of tetrazole ring. In the ^{1}H-MNR spectra of compounds **4a–e** were confirmed through the loss of -NH_2 protons (broad at 4.07 ppm) signal belonging to compound **3**, when the hydrazinocarbonyl group converted to diacylhydrazine; instead of -NH_2 protons a new signal appeared originating from another -NH proton. In addition, one more N-H peak which was sourced from protonated *N*-Me group was shown of **4a–e.** The ^{13}C APT spectra of these compounds contained two carbonyl peaks at the weakest field. In the ^{1}H NMR spectra of compounds **5a–e** showed no signal belonging to the -NH groups due to the cyclodehydration reaction of **4a–e** with $POCl_3$. A singlet for methyl group on *N* atom disappeared by the replacement of **5a–e** with CNBr in the ^{1}H NMR spectra of **6a–e**. Significant structural information was provided by two-dimensional COSY, NOESY, HMQC, and HMBC experiments for compound **7d**. A NOESY experiment showing NOE effect of the H-5β proton at 5.07 ppm to H-7β proton at 4.07 enabled the determination as the *S* configuration of the C-7. The C-3 methoxy group (proton at 3.78 ppm / carbon at 56.44 ppm from HMQC) showed NOE to the H-2 proton at 6.77 ppm; moreover other methoxy group (proton at 3.54 ppm / carbon at 51.66 ppm) showed NOE to the H-18 proton at 5.57 ppm. An HMBC correlation from the H-17 proton at 5.86 ppm to the carbon at 31.19 ppm, allowed assignment of C-8, on which the two germinal protons were assigned based on HMQC correlation 1.84 ppm (H-8α)/31.19 ppm and 2.72 ppm (H-8β)/31.19 ppm. An HMBC correlation from the H-16eq proton at 3.82–3.85 ppm to the carbon at 131.50 ppm, allowed its assignment of terazole rings carbon. A tree-band HMBC correlation between the H-2′ proton at 7.90 ppm to the carbon at 167.41 ppm allowed its assignments as C-5 of oxadiazole ring.

In conclusion, we have synthesized new 2-[*N*-(1*H*-Tetrazol-5-yl)-6,14-*endo*-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5-phenyl-1,3,4-oxadiazole (**7a–e**) which are potential analgesic and evaluated their structures with spectroscopic methods.

EXPERIMENTAL

All the reagents for synthesis were commercially available and used without further purification or purified by standard methods before use. Melting points were determined using an Electrothermal

Scheme 1. Synthesize of 2-[*N*-(1*H*-Tetrazol-5-yl)-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5-phenyl-1,3,4-oxadiazoles.



X: **a:** -H, **b:** -F, **c:** -Cl, **d:** -Br, **e:** -OCH_3

9100 apparatus, uncorrected. All NMR spectra were recorded on a Bruker 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) NMR spectrometer, DMSO-d_6. Chemical shift values were reported in ppm relative to that for TMS used as an internal reference standard, *J* in Hz. MS were obtained from Waters LCT Premier XE LTOF (EI TOF MS) instruments. FTIR spectra were recorded on a Mattson 1000 spectrometer using KBr pellets. The progress of reactions was monitored by TLC using Silufol UV-254 plates. The products were isolated by column chromatography (CC) on silica gel. The compounds **2** and **3** were synthesized using a published method. All the physical and spectral data were in line with the previously reported results [20, 21].

General procedure for the synthesis of compounds 4a–e. A solution of 7α-(hydrazinocarbonyl)-6,14-*endo* ethenotetrahydrothebaine **3** (0.79 g, 2 mmol in 10 mL toluene) was added 2 mmol of a corresponding benzoyl chloride compound. The reaction mixture was boiled for 1 h and monitored with TLC. The white crystals of adducts **4a–e** after cooling were filtered. The corresponding diacylhydrazine solid substance was recrystallized from an appropriate solvent.

1-[(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-carbonyl]-2-benzoylhydrazine hydrochloride (4a, $C_{29}H_{31}N_3O_5$.HCl). Recrystallized from methanol-chloroform. Yield 79%; dp 247–248°C; IR (KBr): 3200 (-N-H); 3023 (=C-H); 2971 (C-H); 1657, 1695 (-C=O); 1600, 1628 (N-C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.35 (s, 1H, N-H); 9.85 (s, 1H, N-H); 9.54 (b, 1H, N-H); 7.79 (d, $J_{2',3'}$ = 7.4 Hz, 2H, H-2′); 7.48 (t, $J_{3',4'}$ = 7.4 Hz; 1H, H-4′); 7.39 (t, $J_{2',3'}$ = 7.3 Hz; 2H, H-3′); 6.66 (d, $J_{1,2}$ =8.2 Hz, 1H, H-2); 6.53 (d, $J_{1,2}$ =8.2 Hz, 1H, H-1); 5.61 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-18); 5.44 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-17); 4.66 (s, 1H, H-5β); 4.09 (d, $J_{9\alpha,\ 10\alpha}$ = 6.4 Hz, 1H, H-9α); 3.64 (s, 3H, 3-OCH_3); 3.43 (s, 3H, 6-OCH_3); 3.38 (d, $J_{10\alpha,\ 10\beta}$ = 18 Hz, 1H, H-10β); 3.08–3.16 (m, 2H, H-8β, H-15ax); 2.78–2.97 (m, 6H, H-7β, H-10α, H-16eq, *N*-CH_3); 2.00–2.07 (m, 2H, H-15eq, H-16ax); 1.40 (dd, $J_{8\alpha,8\beta}$ = 12.7 Hz, $J_{8\alpha,7\beta}$ = 6.5 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 24.66 C(10); 30.30 C(8); 30.82 C(15); 40.84 C(7); 42.11 CH_3-*N*; 42.53 C(14); 45.82 C(16); 46.69 C(13); 52.18 CH_3O-C(6); 56.56 CH_3O-C(3); 61.18 C(9); 80.38 C(6); 91.35 C(5); 114.79 C(2); 120.41 C(1); 125.71 C(11); 125.75 C(4′) 128.35 C(18); 129.025 C(3′);132.21 C(2′); 132.37 C(12); 132.64 C(17); 132.92 C (1′); 143.31 C(3); 148.27 C(4); 165.66 (N-C=O); 170.42 (N-C=O) ppm; hrms (EI): 502.2317 ($[M - H]^+$, $C_{29}H_{32}N_3O_5^+$, calc. 502.2342).

1-[(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-carbonyl]-2-(4′-flourobenzoyl)hydrazine hydrochloride (4b, $C_{29}H_{30}FN_3O_5$.HCl). Recrystallized from methanol-chloroform. Yield 80%; dp 266–268°C; IR (KBr): 3290 (-N-H); 3066 (=C-H); 2961 (C-H); 1657,1695 (-C=O); 1604,1623 (N-C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.50 (s, 1H, N-H); 10.02 (s, 1H, N-H); 9.94 (b, 1H, N-H); 7.94–7.97 (m, 2H, H-2′); 7.30–7.37 (m, 2H, H-3′); 6.75 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.63 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.68 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-18); 5.53 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-17); 4.75 (s, 1H, H-5β); 4.18 (d, $J_{9\alpha,10\alpha}$ = 6.2 Hz, 1H, H-9α); 3.75(s, 3H, 3-OCH_3); 3.52 (s, 3H, 6-OCH_3); 3.46 (d, $J_{10\alpha,10\beta}$ =19.9 Hz, 1H, H-10β); 3.17–3.32 (m, 2H, H-8β, H-15ax); 2.86–3.05 (m, 6H, H-7β, H-10α, H-16eq, *N*-CH_3); 2.08–2.22 (m, 2H, H-15eq, H-16ax); 1.47 (dd, $J_{8\alpha,8\beta}$ = 12.2 Hz, $J_{8\alpha,7\beta}$ = 6.3 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 24.76 C(10); 30.72 C(8); 31.17 C(15); 42.09 C(7); 42.36 CH_3-*N*; 43.80 C(14); 45.83 C(16); 46.63 C(13); 52.12 CH_3O-C(6); 56.63 CH_3O-C(3); 61.11 C(9); 80.40 C(6); 91.92 C(5); 114.68 C(2); 115.77–115.99 ($J_{C(3')\text{-}F}$ = 22.0 Hz) C(3′);120.41 C(1); 125.91 C(11); 128.31 C(18); 129.45 C(1′); 130.59–130.68 ($J_{C(2')\text{-}F}$ = 9.0 Hz, C(2′)); 132.46 C (12); 132.75 C(17); 142.28 C(3); 148.22 C(4); 164.70 (N-C=O); 163.36–165.83 ($J_{C(4')\text{-}F}$ = 247.0 Hz, C(4′)); 171.67 (N-C=O) ppm; hrms (EI): 520.2250 ($[M - H]^+$, $C_{29}H_{31}FN_3O_5^+$, calc., 520.2248).

1-[(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-carbonyl]-2-(4′-chlorobenzoyl)hydrazine hydrochloride (4c,

$C_{29}H_{30}ClN_3O_5$.HCl). Recrystallized from ethanol-ethyl acetate. Yield 82%; dp 286–287 °C; IR (KBr): 3190 (-N-H); 3043 (=C-H); 2942 (C-H); 1657, 1690 (-C=O); 1595, 1620 (N-C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H, N-H); 9.99 (s, 1H, N-H); 9.42 (b, 1H, N-H); 7.90 (d, $J_{2',3'}$ = 8.5 Hz, 2H, H-2′); 7.58 (d, $J_{2',3'}$ = 8.5 Hz, 2H, H-3′); 6.75 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-2); 6.63 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1); 5.71 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-18); 5.54 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-17); 4.76 (s, 1H, H-5β); 4.19 (d, $J_{9\alpha,10\alpha}$ = 6.4 Hz, 1H, H-9α); 3.73 (s, 3H, 3-OCH_3); 3.51 (s, 3H, 3H, 6-OCH_3); 3.45–3.51 (m, 1H, H-10β); 3.23–3.26 (m, 2H, H-8β, H-15 ax); 2,99–3.16 (m, 6H, H-7β, H-10α, H-16eq, *N*-CH_3); 2.09–2.18 (m, 2H, H-15eq, H-16ax); 1.48 (dd, $J_{8\alpha,8\beta}$ = 12.6 Hz, $J_{8\alpha,7\beta}$ = 6.1 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 24.66 C(10); 30.29 C(8); 30.80 C(15); 40.79 C(7); 42.08 CH_3-*N*; 42.52 C(14); 45.81 C(16); 46.64 C(13); 52.15 CH_3O-C(6); 56.51 CH_3O-C(3); 61.13 C(9); 80.37 C(6); 91.28 C(5); 114.71 C(2); 120.41 C(1); 125.70 C(11); 137.06 C(4′); 128.31 C(18); 129.025 C (3′); 129.84 C(2′); 131.64 C(1′); 132.35 C(12); 132.70 C(17); 142.28 C(3); 148.22 C(4); 164.65 (N-C=O); 170.59 (N-C=O) ppm; hrms (EI): 536.1926 ([M − H]$^+$, $C_{29}H_{31}ClN_3O_5^+$, calc., 536.1952).

1-[(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-carbonyl]-2-(4′-bromobenzoyl)hydrazine hydrochloride (4d, $C_{29}H_{30}BrN_3O_5$.HCl). Recrystallized from methanol-ethyl acetate. Yield 78%; dp 285–288°C**;** IR (KBr): 3358 (-N-H); 3035 (=C-H); 2957 (C-H); 1652, 1695 (-C=O); 1585, 1614 (N-C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.57 (s, 1H, N-H); 10.03 (s, 1H, N-H); 9.78 (b, 1H, N-H); 7.82 (d, $J_{2',3'}$ = 8.2 Hz, 2H, H-2′); 7.72 (d, $J_{2',3'}$ = 8.2 Hz, 2H, H-3′); 6.76 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-2); 6.62 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1); 5.68 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-18); 5.55 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-17); 4.75 (s, 1H, H-5β); 4,18 (d, $J_{9\alpha,10\alpha}$ = 6.2 Hz, 1H, H-9α); 3.73 (s, 3H, 3H, 3-OCH_3); 3.51 (s, 3H, 6-OCH_3); 3.43 (d, 1H, $J_{10\alpha,10\beta}$ =11.3 Hz, 1H, H-10β); 3.22–3.29 (m, 2H, H-8β, H-15 ax); 2.86 -3.05 (m, 6H, H-7β, H-10α, H-16eq, *N*-CH_3); 2.09–2.14 (m, 2H, H-15eq, H-16ax); 1.47 (dd, $J_{8\alpha,8\beta}$ = 12.8 Hz, $J_{8\alpha,7\beta}$ = 6.2 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 24.75 C (10); 30.27 C(8); 30.89 C(15); 40.77 C(7); 42.06 CH_3-*N*; 42.57 C (14); 45.83 C(16); 46.63 C(13); 52.14 CH_3O-C(6); 56.53 CH_3O-C (3); 61.13 C(9); 80.86 C(6); 91.23 C(5); 114.71 C(2); 120.42 C(1); 125.73 C(1′); 126.02 C(11); 128.29 C(18); 130.48 C(3′); 131.77 C (2′); 132.39 C(12);132.75 C(17); 142.29 C(3); 148.22 C(4); 164.89 (N-C=O); 170.59 (N-C=O); 171.61 C(4′) ppm; hrms (EI): 580.1460 ([M − H]$^+$, $C_{29}H_{31}BrN_3O_5^+$, calc., 580.1447).

1-[(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-carbonyl]-2-(4′-methoxybenzoyl)hydrazine hydrochloride (4e, $C_{30}H_{33}N_3O_6$.HCl). Recrystallized from methanol-ethyl acetate. Yield 89%; dp 285–288°C; IR (KBr): 3214 (-N-H); 3033 (=C-H); 2952 (C-H); 1652, 1695 (-C=O); 1604, 1614 (N-C=O) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.31 (s, 1H, N-H); 9.85 (s, 1H, N-H); 9.27 (b, 1H, N-H); 7.85 (d, $J_{2',3'}$ = 8.8 Hz, 2H, H-2′); 7.02 (d, $J_{2',3'}$ = 8.8 Hz, 2H, H-3′); 6.75 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.63 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.71 (d, $J_{17,18}$ = 8.9 Hz, 1H, H-18); 5.53 (d, $J_{17,18}$ = 8.9 Hz, 1H, H-17); 4.75 (s, 1H, H-5β); 4,19 (d, $J_{9\alpha,10\alpha}$ = 6.1 Hz, 1H, H-9α); 3.82 (s, 3H, 4′-OCH_3); 3.73 (s, 3H, 3-OCH_3); 3.51 (s, 3H, 6-OCH_3); 3.45–3.51 (m, 1H, H-10β); 3.23–3.27 (m, 1H, H-15ax); 2.88–3.09 (m, 7H, H-7β, H-8β, H-10α, H-16eq, *N*-CH_3); 2.11–2.13 (m, 2H, H-15eq, H-16ax); 1.48 (dd, $J_{8\alpha,8\beta}$ = 12.4 Hz, $J_{8\alpha,7\beta}$ = 5.8 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz DMSO-d_6): δ 24.71 C(10); 30.30 C (8); 30.86 C(15); 40.72 C(7); 42.10 CH_3-*N*; 42.55 C(14); 45.82 C(16); 46.66 C(13); 52.13 CH_3O-C(6); 55.84 CH_3O-C(3); 56.67 CH_3O-C(4′); 61.15 C(9); 80.39 C(6); 91.29 C(5); 114.08 C(3′); 114.75 C(2); 114.80 C(2′); 120.40 C(1); 125.07 C(1′); 125.74 C(11); 128.36 C(18); 132.40 C(12); 132.66 C(17); 142.30 C(3); 148.26 C(4); 162.38 (N-C=O); 165.15 (N-C=O); 170.64 C(4′) ppm; hrms (EI): 532.2430 ([M − H]$^+$, $C_{30}H_{34}N_3O_6^+$, calc., 532.2448).

General procedure for the synthesis of compounds 5a–e. The compounds **5a–e** was synthesized using with improving of published method [22]. A solution of corresponding compound **4a–e** (1 mmol) in 5 mL $POCl_3$ was refluxed in an oil bath for 3 h. The mixture was cooled to room temperature, poured slowly onto about 20 g of ice and stirred for 20 min. (Caution! When the mixture is poured onto ice, a very high exothermic reaction occurs). The resulting suspension was basified to pH 9 with a saturated solution of NaOH, and the precipitate was extracted into ethyl acetate (2 × 30 mL). The extract was dried over $MgSO_4$ and evaporated. The residue was recrystallized from an appropriate solvent.

2-(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-phenyl-1,3,4-oxadiazole (5a, $C_{29}H_{29}N_3O_4$). Recrystallized from ethyl acetate-hexane. Yield 66%; mp 208–209°C; (ref. 22, 210–212°C); IR (KBr): 3057(=C-H), 2971 (C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62–7.92 (m, 5H, H-2′, H-3′, H-4′); 6.64 (d, $J_{1,2}$ =8.2 Hz, 1H, H-2); 6.53 (d, $J_{1,2}$ =8.2 Hz, 1H, H-1); 5.70 (d, $J_{17,18}$ =8.7 Hz, 1H, H-17); 5.58 (d, $J_{17,18}$ =8.7 Hz, 1H, H-18); 4.94 (s, 1H, H-5β); 3.93 (dd, $J_{7\beta,8\beta}$ = 9.3 Hz, $J_{7\beta,8\alpha}$ = 6.1 Hz, 1H, H-7β); 3.70 (s, 3H, 3-OCH_3); 3.47 (s, 3H, 6-OCH_3); 3.26 (d, $J_{9\alpha,\ 10\alpha}$ = 6.5 Hz, 1H, H-9α); 3.14–3.17 (m, 1H, H-8β); 3.10 (d, $J_{10\alpha,10\beta}$ = 17.4 Hz, 1H, H-10β); 2.45–2.47 (m, 1H, H-16eq); 2.30 (s, 3H, *N*-CH_3); 2.17–2.25 (m, 3H, 16ax, H-10α, H-15 ax); 1.73–1.74 (m, 1H, H-15eq); 1.63 (dd, $J_{8\alpha,8\beta}$ = 12.8 Hz, $J_{8\alpha,7\beta}$ = 6.1 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 22.20 C(10); 33.01 C(8); 31.58 C(15); 33.92 C(7); 42.95 C(14); 43.58 CH_3-*N*; 45.53 C(16); 47.00 C(13); 51.53 CH_3O-C(6); 56.45 CH_3O-C(3); 59.59 C(9); 81.40 C(6); 90.90 C(5); 113.90 C(2); 119.98 C(1); 123.99 C(1′); 126.74 C(17); 128.08 C(11); 128.65 C(3′); 129.95 C(2′); 134.42 C(12); 134.44 C (4′); 137.24C(18); 141.77 C(3); 147.80 C(4); 164.55 (C=N); 167.56 (C=N) ppm; hrms (EI): 484.2188 ([M − H]$^+$, $C_{29}H_{30}N_3O_4^+$, calc., 484.2236).

2-(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-(4′-flourophenyl)-1,3,4-oxadiazole (5b, $C_{29}H_{28}FN_3O_4$). Recrystallized from methanol-chloroform. Yield 60%; mp 263–265°C; IR (KBr): 3057 (-C=H), 2962 (-C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96–7.99 (m, 2H, H-2′); 7.43–7.47 (m, 2H, H-3′); 6.65 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.55 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.69 (d, $J_{17,18}$ = 8.9 Hz, 1H, H-17); 5.56 (d, $J_{17,18}$ = 8.7 Hz, 1H, H-18); 4.94 (s, 1H, H-5β); 3.95 (dd, $J_{7\beta,8\beta}$ = 9.2 Hz, $J_{7\beta,8\alpha}$ =6.7, 1H, H-7β); 3.70 (s, 3H, 3-OCH_3); 3.48 (s, 3H, 6-OCH_3); 3.26 (d, $J_{9\alpha,10\alpha}$ = 6.2 Hz, 1H, H-9α); 3.11 (d, $J_{10\alpha,10\beta}$ = 18.5 Hz; 1H, H-10β); 3.11–3.13 (m, 1H, H-8β); 2.45–2.50 (m, 1H, H-16eq); 2.33 (s, 3H, *N*-CH_3); 2.31–2.18 (m, 3H, H-16ax, H-10α, 15ax); 1.71–1.73 (m, 1H, 15eq); 1.65 (dd, $J_{8\alpha.8\beta}$ = 12.4 Hz, $J_{8\alpha.7\beta}$ = 6.7 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 21.67 C(10); 31.04 C(8); 32.47 C(15); 33.34 C(7); 42.43 C (14); 43.08 CH_3-*N*; 45.02 C(16); 46.48 C(13); 50.99 CH_3O-C(6); 56.01 CH_3O-C(3); 59.07 C(9); 80.88 C(6); 90.29 C(5); 113.29 C (2); 116.62–116.84 ($J_{C(3')\text{-}F}$ = 22.0 Hz) C(3′));119.49 C(1); 120.13 C(1′); 126.79 C(17); 128.12 C(11); 128.89–128.98 ($J_{C(2')\text{-}F}$ = 9.0 Hz, C(2′));133.88 C(12); 137.77 C(18);

141.24 C(3); 147.25 C(4); 165.21–162.72 ($J_{C(4')\text{-}F}$ = 249.0 Hz, C(4′)); 163.32 (C═N); 167.09 (C═N) ppm; hrms (EI): 502.2071 ([M − H]$^+$, $C_{29}H_{29}FN_3O_4^+$, calc., 502.2142).

2-(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-(4′-chlorophenyl)-1,3,4-oxadiazole (5c, $C_{29}H_{28}ClN_3O_4$). Recrystallized from methanol-chloroform. Yield 66%; mp 278–280°C; IR (KBr): 3040(═C-H), 2928 (C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, $J_{2',3'}$ = 8.6 Hz, 2H, H-2′); 7.68 (d, $J_{2',3'}$ = 8.6 Hz, 2H, H-3′); 6.65 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.56 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.70 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-17); 5.56 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-18); 4.94 (s, 1H, H-5β); 3.95 (dd, $J_{7\beta,8\beta}$ = 9.4 Hz, $J_{7\beta,8\alpha}$ = 6.1 Hz, 1H, H-7β); 3.70 (s, 3H, 3-OCH_3); 3.47 (s, 3H, 6-OCH_3); 3.25 (d, $J_{9\alpha,\ 10\alpha}$ = 6.3 Hz, 1H, H-9α); 3.16 (d, $J_{10\alpha,10\beta}$ = 17.9 Hz, 1H, H-10β); 3.13–3.15 (m, 1H, H-8β); 2.17–2.31 (m, 4H, H-16eq, H-16ax, H-10α, H-15ax); 2.09 (s, 3H, *N*-CH_3); 1.71–1.74 (m, 1H, H-15eq); 1,65 (dd, $J_{8\alpha,8\beta}$ = 12.8 Hz, $J_{8\alpha,7\beta}$ = 6.1 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 22.30 C (10); 30.68 C(8); 31.04 C(15); 33.38 C(7); 42.43 C(14);43.08 CH_3-*N*; 45.02 C(16); 46.49 C(13); 51.01 CH_3O-C(6);. 55.90 CH_3O-C(3); 59.07 C(9); 81.88 C(6); 90.29 C(5); 113.31 C(2); 119.49 C(1); 122.32 C(1′); 126.79 C(17); 128.05 C(3′); 128.08 C(11); 129.65 C(2′); 133.88 C(12); 136.54 C(4′) 136.79 C(18); 141.25 C(3); 147.26 C(4); 163.32 (-C═N); 167.27 (-C═N) ppm; hrms (EI): 518.1886 ([M − H]$^+$, $C_{29}H_{29}ClN_3O_4^+$, calc., 518.1847).

2-(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-(4′-bromophenyl)-1,3,4-oxadiazole (5d, $C_{29}H_{28}BrN_3O_4$). Recrystallized from methanol-ethyl acetate. Yield 65%, mp 275–278°C; IR (KBr): 3061 (═C-H), 2952 (C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (d, $J_{2',3'}$ = 8.7 Hz, 2H, H-2′); 7.82 (d, $J_{2',3'}$ = 8.7 Hz, 2H, H-3′); 6.65 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.55 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.69 (d, 1H, $J_{17,18}$ = 8.8 Hz, H-17); 5.56 (d, 1H, $J_{17,18}$ = 8.8 Hz, H-18); 4.94 (s, 1H, H-5β); 3.95 (dd, $J_{7\beta,8\beta}$ = 9.4 Hz, $J_{7\beta,8\alpha}$ = 6.3 Hz, 1H, H-7β); 3.70 (s, 3H, 3-OCH_3); 3.46 (s, 3H, 6-OCH_3); 3.26 (d, $J_{9\alpha,\ 10\alpha}$ = 6.2 Hz, 1H, H-9α); 3.14 (d, $J_{10\alpha,10\beta}$ = 16.8 Hz, 1H, H-10β); 3.12–3.11 (m, 1H, H-8β); 2.45–2.47 (m, 1H, H-16eq); 2.31 (s, 3H, *N*-CH_3); 2.17–2.28 (m, 3H, H-16ax, H-10α, H-15ax,); 1.72–1.70 (m, 1H, H-15eq); 1,63 (dd, $J_{8\alpha,8\beta}$ = 12.8 Hz, $J_{8\alpha,7\beta}$ = 6.3 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 22.68 C(10); 31.03 C(8); 32.47 C(15); 33.37 C(7); 42.42 C(14); 43.07 CH_3-*N*; 45.02 C(16); 46.48 C(13); 51.00 CH_3O-C(6); 55.90 CH_3O-C(3); 59.06 C(9); 80.88 C(6); 90.28 C(5); 113.30 C(2); 119.50 C(1); 122.64 C(1′); 125.43 C(11); 126.78 C (17); 128.12 C(12); 128.25 C(3′); 132.58 C(2′); 133.87 C(4′) 136.81 C(18); 141.25 C(3); 147.25 C(4); 163.45 (-C═N); 167.49 (-C═N) ppm; hrms (EI): 562.1343 ([M − H]$^+$, $C_{29}H_{29}BrN_3O_4^+$, calc., 562.1341).

2-(6,14-endo-Etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-(4′-methoxyphenyl)-1,3,4-oxadiazole (5e, $C_{30}H_{31}N_3O_5$). Recrystallized from methanol-ethyl acetate, Yield: 60%; mp 168–170°C; IR (KBr): 3033 (═C-H), 2966 (C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (d, $J_{2',3'}$ = 8.8 Hz, 2H, H-2′); 7.15 (d, $J_{2',3'}$ = 8.8 Hz, 2H, H-3′); 6.65 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-2); 6.55 (d, $J_{1,2}$ = 8.1 Hz, 1H, H-1); 5.69 (d, 1H, $J_{17,18}$ = 8.6 Hz, H-17); 5.67 (d, 1H, $J_{17,18}$ = 8.6 Hz, H-18); 4.99 (s, 1H, H-5β); 3.92 (dd, $J_{7\beta,8\beta}$ = 9.2 Hz, $J_{7\beta,8\alpha}$ = 6.1 Hz, 1H, H-7β); 3.85 (s, 3H, 4′-OCH_3); 3.71 (s, 3H, 3-OCH_3); 3.46 (s, 3H, 6-OCH_3); 3.25 (d, $J_{9\alpha,\ 10\alpha}$ = 6.3 Hz, 1H, H-9α); 3.15 (d, $J_{10\alpha,10\beta}$ = 17.8 Hz 1H, H-10β); 3.11–3.13 (m, 1H, H-8β); 2.46–2.45 (m, 1H, H-16eq); 2.34 (s, 3H, *N*-CH_3); 2.14–2.31 (m, 3H, H-16ax, H-10α, H-15ax,); 1.74–1.71 (m, 1H, H-15eq); 1,64 (dd, $J_{8\alpha,8\beta}$ = 12.8 Hz, $J_{8\alpha,7\beta}$ = 6.1 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 22.71 C(10); 31.57 C(8); 33.02 C(15); 33.38 C(7); 43.57 CH_3-*N*; 43.59 C(14); 45.53 C(16); 46.98 C(13); 51.48 CH_3O-C(6); 55.96 CH_3O-C(3); 56.55 CH_3-O-C(4′); 59.59 C(9); 81.38 C(6); 90.90 C(5); 113.87 C(2); 115.36 C (3′); 119.96 C(1); 125.07 C(1′); 127.31 C(17); 128.64 C(11); 128.66 C(2′); 134.43 C(12); 137.17 C(18); 141.76 C(3); 147.81 C (4); 162.34 C(4′); 164.46 (-C═N); 166.94 (-C═N) ppm; hrms (EI): 514.2319 ([M − H]$^+$, $C_{30}H_{32}N_3O_5^+$, calc., 514.2342).

General procedure for the synthesis of compounds 6a–e. A solution of corresponding compound **5a–e** (0.5 mmol) and cyanogen bromide (0.1 g, 1 mmol, Caution! cyanogen bromide is a poison, may be fatal if inhaled or swallowed; causes burns and severe irritation.) in 10 mL of dry chloroform were refluxed for 24 h to obtain *N*-CN compounds and reaction was monitored with TLC. The cooled reaction mixture was evaporated, and the residue was purified by column chromatography on silica gel using ethyl acetate/petrol ether (2:1) as eluent. The residue was recrystallized from an appropriate solvent.

2-(N-Cyano-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-phenyl-1,3,4-oxadiazole (6a, $C_{29}H_{26}N_4O_4$). Recrystallized from methanol-chloroform. Yield 54%; mp 283–285°C; IR (KBr): 3047(═C-H), 2976 (C-H), 2200 (-CN) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.60–7.94 (m, 5H, H-2′, H-3′, H-4′); 6.73 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.62 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.70 (d, $J_{17,18}$ = 8.6 Hz, 1H, H-17); 5.68 (d, $J_{17,18}$ = 8.6 Hz, 1H, H-18); 5.00 (s, 1H, H-5β); 4.13 (d, $J_{9\alpha,10\alpha}$ = 6.6 Hz, 1H, H-9α); 4.06 (dd, $J_{7\beta,8\beta}$ = 9.5 Hz, $J_{7\beta,8\alpha}$ = 6.0 Hz, 1H, H-7β); 3.79 (s, 3H, 3-OCH_3); 3.48 (s, 3H, 6-OCH_3); 3.15-3.39 (m, 3H, H-16eq, H-16ax, H-10α); 3.13 (d, $J_{10\alpha,10\beta}$ = 19.2 Hz, 1H, H-10β); 2.95 (dd, $J_{8\alpha,8\beta}$ = 11.8 Hz, $J_{7\beta,8\beta}$ = 9.5 Hz 1H, H-8β); 2.30–2.33 (m, 1H, H-15ax); 1.82–1.89 (m, 2H, H-8α, H-15eq) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 30.87 C(15); 31.15 C(8); 31.73 C (10); 33.87 C(7); 40.81 C(14); 41.86 C(16); 46.60 C(13); 51.67 CH_3O-C(6); 56.42 CH_3O-C(3); 57.64 C(9); 81.13 C(6); 90.70 C (5); 114.42 C(2); 118.41 (*N*-CN); 120.43 C(1); 126.77 C(4′), 123.92 C(1′); 126.56 C(12); 128.13 C(17); 128.16 C(2′); 132.37 C(3′); 132.86 C(11); 135.35 C(18); 142.19 C(3); 148.04 C(4); 164.64 (-C═N); 167.09 (-C═N) ppm; hrms (EI): 495.2023 ([M − H]$^+$, $C_{29}H_{27}N_4O_4^+$, calc., 495.2032).

2-(N-Cyano-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-(4′-flourophenyl)-1,3,4-oxadiazole (6b, $C_{29}H_{25}FN_4O_4$). Recrystallized from ethylacetate-hexan. Yield 50%; mp 296–298° C; IR (KBr): 3050 (-C═H), 2938 (-C-H), 2200 (-CN) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.94–7.98 (m, 2H, H-2′); 7,43–7.49 (m, 2H, H-3′); 6.72 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.62 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.69 (d, $J_{17,18}$ = 8.9 Hz, 1H, H-17); 5.65 (d, $J_{17,18}$ = 8.9 Hz, 1H, H-18); 4.99 (s, 1H, H-5β); 4.14 (d, $J_{9\alpha,\ 10\alpha}$ = 5.9 Hz, 1H, H-9α); 4.06 (dd, $J_{7\beta,8\beta}$ = 9.4 Hz, $J_{7\beta,8\alpha}$= 5.9 Hz, 1H, H-7β); 3.71 (s, 3H, 3-OCH_3); 3,47 (s, 3H, 6-OCH_3); 3.37-3.20 (m, 3H, H-16eq, H-16ax, H-10α); 3.12 (d, $J_{10\alpha,10\beta}$ = 18.6 Hz, 1H, H-10β); 2.94 (dd, $J_{8\alpha,8\beta}$ = 12.6 Hz, $J_{7\beta,8\beta}$ = 9.4 Hz, 1H, H-8β); 2.29–2.37 (m, 1H, H-15ax); 1.81–1.88 (m, 2H, H-15eq, H-8α) ppm ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 30.38 C(15); 30.63 C(8); 31.23 C(10); 33.38 C (7); 41.37 C(14); 41.40 C(16); 46.11 C(13); 51.17 CH_3O-C(6); 55.93 CH_3O-C(3); 57.16 C(9); 80.61 C(6); 90.19 C(5); 113.95 C(2); 116.84–116.61 ($J_{C3'\text{-}F}$ = 23.0 Hz, C(3′)); 117.93 (CN); 119.96 C(1); 120.10 C(1′); 126.06 C(12); 126.61 C(17); 128.94–129.03 ($J_{C(2')\text{-}F}$ = 9.0 Hz, C(2′)); 132.35 C(11); 141.70 C(3); 134.87 C(18); 147.52 C(4); 162.76–165.25

($J_{C4'\text{-}F}$ = 249.0 Hz, C(4′)); 163.43 (C═N);166.63 (C═N) ppm; hrms (EI): 513.1958 ([M – H]$^+$, $C_{29}H_{26}FN_4O_4^+$, calc., 513.1938).

2-(N-Cyano-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-(4-chlorophenyl)-1,3,4-oxadiazole (6c, $C_{29}H_{25}ClN_4O_4$). Recrystallized from methanol-ethyl acetate. Yield 54%; mp 297–299°C; IR (KBr): 3057(═C-H), 2942 (C-H), 2209 (-CN) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.93 (d, $J_{2',3'}$ = 8.5 Hz, 2H, H-2′); 7.70 (d, $J_{2',3'}$ = 8.5 Hz, 2H, H-3′); 6.72 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.62 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.70 (d, $J_{17,18}$ = 8.7 Hz, 1H, H-17); 5.67 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-18); 4,99 (s, 1H, H-5β); 4.14 (d, $J_{9\alpha,10\alpha}$ = 6.2 Hz, 1H, H-9α); 4.07 (dd, $J_{7\beta,8\beta}$ = 9.3 Hz, $J_{7\beta,8\alpha}$ = 6.1 Hz, 1H, H-7β); 3.72 (s, 3H, 3-OCH_3); 3.47 (s, 3H, 6-OCH_3); 3.28–3.35 (m, 3H, H-16eq, H-16ax, H-10α); 3.12 (d, $J_{10\alpha,10\beta}$ = 18.9 Hz, 1H, H-10β); 2.93 (dd, $J_{8\alpha,8\beta}$ = 12.6 Hz, $J_{7\beta,8\beta}$ = 9.3 Hz 1H, H-8β); 2.30–2.33 (m, 1H, H-15ax); 1.81–1.88 (m, 2H, H-15eq, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 30.88 C(15); 31.73 C(8); 31.14 C(10); 33.91 C(7); 40.38 C(14); 41.87 C(16); 46.61 C(13); 51.68 CH_3O-C(6); 56.43 CH_3O-C(3); 57.65 C(9); 81.13 C(6); 90.69 C(5); 114.46 C(2); 118.42 (CN); 120.46 C(1); 122.77 C(1′); 126.57 C(12); 128.10 C(17); 128.60 C(3′); 130.15 C (2′); 132.85 C(11); 135.41 C(18); 137.11 C(4′), 142.20 C(3); 148.03 C(4); 163.93 (C═N); 167.32 (C═N) ppm; hrms (EI): 529.1669 ([M – H]$^+$, $C_{29}H_{26}ClN_4O_4^+$, calc., 529.1643).

2-(N-Cyano-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl-5-(4′-bromophenyl)-1,3,4-oxadiazole (6d, $C_{29}H_{25}BrN_4O_4$). Recrystallized from ethylacetate-hexane, Yield 56%; mp 316–317°C; IR (KBr): 3059(═C-H), 2978 (C-H), 2122 (-CN) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.92 (d, $J_{2',3'}$ = 8.9 Hz, 2H, H-2′); 7.87 (d, $J_{2',3'}$ = 8.9 Hz, 2H, H-3′); 6.78 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.68 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.75 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-17); 5.71 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-18); 5.05 (s, 1H, H-5β); 4.19 (d, $J_{9\alpha,10\alpha}$ = 5.9 Hz, 1H, H-9α); 4.13 (dd, $J_{7\beta,8\beta}$ = 9.5 Hz, $J_{7\beta,8\alpha}$ = 6.3 Hz, 1H, H-7β); 3.78 (s, 3H, 3-OCH_3); 3.53 (s, 3H, 6-OCH_3); 3.20–3.48 (m, 3H, H-16eq, H-16ax, H-10α); 3.17 (d, $J_{10\alpha,10\beta}$ = 18.8 Hz, 1H, H-10β); 2.98 (dd, $J_{8\alpha,8\beta}$ = 12.5 Hz, $J_{7\beta,8\beta}$ = 9.5 Hz 1H, H-8β); 2.39–2.43 (m, 1H, H-15ax); 1.87–1.94 (m, 2H, H-15eq, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 30.38 C (15); 30.64 C(8); 31.23 C(10); 33.42 C(7); 40.33 C(14); 41.37 C(16); 46.11 C(13); 51.18 CH_3O-C (6); 55.94 CH_3O-C (3); 57.15 C(9); 80.62 C(6); 90.19 C(5); 113.95 C(2); 117.92 (CN); 119.96 C(1); 122.60 C(1′); 125.48 C(4′), 126.07 C(12); 127.59 C(17); 128.21 C(3′); 132.35 C(11); 132.57 C(2′); 134.91 C(18); 141.70 C(3); 147.53 C(4); 163.54 (C═N); 166.83 (C═N) ppm; hrms (EI): 573.1136 ([M – H]$^+$, $C_{29}H_{26}BrN_4O_4^+$, calc., 573.1137).

2-(N-Cyano-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl)-5-(4′-methoxyphenyl)-1,3,4-oxadiazole (6e, $C_{30}H_{29}N_4O_5$). Recrystallized from ethyl acetate-hexane, Yield: 50%; mp 175–177°C; IR (KBr): 3057 (═C-H), 2942 (C-H), 2209 (-CN) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.86 (d, $J_{2',3'}$ = 8.8 Hz, 2H, H-2′); 7.15 (d, $J_{2',3'}$ = 8.8 Hz, 2H, H-3′); 6.73 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.62 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.68 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-17); 5.65 (d, $J_{17,18}$ = 8.8 Hz, 1H, H-18); 4,99 (s, 1H, H-5β); 4.14 (d, $J_{9\alpha,10\alpha}$ = 6.0 Hz, 1H, H-9α); 4.01 (dd, $J_{7\beta,8\beta}$ = 9.5 Hz, $J_{7\beta,8\alpha}$ = 6.1 Hz, 1H, H-7β); 3.85 (s, 3H, 4′-OCH_3); 3.79 (s, 3H, 3-OCH_3); 3.47 (s, 3H, 6-OCH_3); 3.19–3.39 (m, 3H, H-16eq, H-16ax, H-10α); 3.12 (d, $J_{10\alpha,10\beta}$ = 18.9 Hz, 1H, H-10β); 2.92 (dd, $J_{8\alpha,8\beta}$ = 12.6 Hz, $J_{7\beta,8\beta}$ = 9.5 Hz 1H, H-8β); 2.29–2.37 (m, 1H, H-15ax); 1.82–1.87 (m, 2H, H-15eq, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 30.90 C(15); 31.16 C(8); 31.73 C(10); 33.83 C(7); 41.86 C(14); 41.92 C (16); 46.60 C(13); 51.64 CH_3O-C(6); 55.98 CH_3O-C(3); 56.44 CH_3O-C(4′); 57.65 C(9); 81.11 C(6); 90.73 C(5); 114.45 C(2); 115.38 C(3′); 116.32 (CN); 118.42 C(1′); 120.43 C(1); 126.57 C(12); 128.16 C(17); 128.60 C(2′); 132.89 C(11); 135.30 C(18); 142.20 C (3); 148.06 C(4); 162.39 (C═N); 164.56 (C═N); 166.50 C(4′) ppm; hrms (EI): 525.2125 ([M – H]$^+$, $C_{30}H_{30}N_4O_5^+$, calc., 525.2138).

General procedure for the synthesis of compounds 7a–e. A solution of corresponding compound **6a–e** (0.3 mmol) in 5 mL DMF were added NaN_3 (0.19 g, 3 mmol) and NH_4Cl (0.15 g, 3 mmol). The mixture was heated for 4 h under reflux, and the reaction completion was checked by TLC. After refluxing, the reaction mixture was cooled to room temperature and evaporated under reduced pressure. The residue product was extracted with ethyl acetate-water (30:10 mL). The organic layer was dried over $MgSO_4$ and the solvent evaporated. The crude product was recrystallized from an appropriate solvent.

2-[N-(1H-Tetrazol-5-yl)-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5-phenyl-1,3,4-oxadiazole (7a, $C_{29}H_{27}N_7O_4$). Recrystallized from ethyl acetate-hexane, Yield: 50%; mp 195–198°C; IR (KBr): 3395–3171 (-N-H); 3043 (═C-H), 2928 (C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.62–7.94 (m, 5H, H-2′, H-3′, H-4′); 6.74 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.63 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.81 (d, 1H, $J_{17,18}$ = 8.6 Hz, H-17); 5.68 (d, 1H, $J_{17,18}$ = 8.6 Hz, H-18); 5.02 (s, 1H, H-5β); 4.68 (d, $J_{9\alpha,10\alpha}$ = 6.5 Hz, 1H, H-9α); 3.99 (dd, $J_{7\beta,8\beta}$ = 9.2 Hz, $J_{7\beta,8\alpha}$ = 6.6 Hz, 1H, H-7β); 3.70–3.79 (m, 4H, H-16eq, 3-O-CH_3); 3.40 (s, 3H, 6-OCH_3); 3.04–3.20 (m, 2H, H-16ax, H-10α); 2.93 (d, $J_{10\alpha,10\beta}$ = 20.3 Hz, 1H, H-10β); 2.82 (dd, $J_{8\alpha,8\beta}$ = 12.5 Hz, $J_{7\beta,8\beta}$ = 7.7 Hz, 1H, H-8β); 2.30–2.37 (m, 1H, H-15ax,); 1.95–1.98 (m, 1H, H-15eq); 1,80 (dd, $J_{8\alpha,8\beta}$ = 12.5 Hz, $J_{8\alpha,7\beta}$ = 6.6 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 30.30 C(10); 31.24 C(8); 32.18 C(15); 33.48 C(7); 42.05 C(14); 44.05 C(16); 46.60 C(13); 51.67 CH_3O-C(6); 54.87 CH_3O-C(3); 56.42 C(9); 81.13 C(6); 90.88 C(5); 113.06 C(4′); 114.87 C(2); 114.90 C(3′); 118.27 C(1′); 120.43 C(1); 127.14 C (11); 128.13 C(18); 128.86 C(2′); 132.36 (N═C-N); 133.58 C(12); 135.60 C(17); 140.04 C(3); 148.06 C(4); 164.38 (-C═N); 168.89 (-C═N) ppm; hrms (EI): 538.2211 ([M – H]$^+$, $C_{29}H_{28}N_7O_4^+$, calc., 538.2203).

2-[N-(Tetrazol-1H-5-yl)-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5-(4′-flourophenyl)-1,3,4-oxadiazole (7b, $C_{29}H_{26}FN_7O_4$). Recrystallized from methanol. Yield 55%; mp 263–266°C; IR (KBr): 3328–3223 (-N-H), 3066 (-C═H), 2947 (-C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96–8.04 (m, 2H, H-2′); 7.43 -7.48 (m, 2H, H-3′); 6.72 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-2); 6.58 (d, $J_{1,2}$ = 8.3 Hz, 1H, H-1); 5.80 (d, 1H, $J_{17,18}$ = 8.7 Hz, H-17); 5.67 (d, 1H, $J_{17,18}$ = 8.7 Hz, H-18); 5.02 (s, 1H, H-5β); 4.67 (d, $J_{9\alpha,10\alpha}$ = 5.9 Hz, 1H, H-9α); 4.01 (dd, $J_{7\beta,8\beta}$ = 8.8 Hz, $J_{7\beta,8\alpha}$ = 5.9 Hz, 1H, H-7β); 3.71–3.79 (m, 4H, H-16eq, 3-OCH_3); 3.45 (s, 3H, 6-OCH_3); 3.15–3.23 (m, 2H, H-16ax, H-10α); 2.85 (d, $J_{10\alpha,10\beta}$ = 15.2 Hz, 1H, H-10β); 2.69 (dd, $J_{8\alpha,8\beta}$ = 10.0 Hz, $J_{7\beta,8\beta}$ = 7.4 Hz, 1H, H-8β); 2.41–2.50 (m, 1H, H-15ax,); 1.91–1.95 (m, 1H, H-15eq); 1,78 (dd, $J_{8\alpha,8\beta}$ = 12.9 Hz, $J_{8\alpha,7\beta}$ = 6.1 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 31.12 C(10); 31.20 C(8); 31.27 C(15); 33.90 C(7); 42.06 C(14); 45.43 C(16); 47.35 C (13); 51.65 CH_3O-C(6); 55.38 CH_3O-C(3); 56.44 C(9); 81.30 C(6); 90.77 C(5); 114.32 C(2); 117.03 C(11); 117.12–117.34 ($J_{C3'\text{-}F}$ = 22.0 Hz, C(3′)); 120.42 C(1); 120.63 C(1′); 128.17 C (18); 129.41–129.59 ($J_{C2'\text{-}F}$ = 9.0 Hz, C(2′)); 130.15 (N═C-N); 133.32 C(12); 135.90 C(17); 142.09 C(3); 148.00 C(4); 165.73–163.24 ($J_{C4'\text{-}F}$ = 249.0 Hz, C(4′)); 166.89 (C═N);

167.22 (C=N) ppm; hrms (EI): 556.2103 ([M – H]$^+$, $C_{29}H_{27}FN_7O_4^+$, calc., 556.2109).

2-[N-(Tetrazol-1H-5-yl)-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5-(4′-cholorophenyl)-1,3,4-oxadiazole (7c, $C_{29}H_{26}ClN_7O_4$). Recrystallized from methanol-chlorofom Yield: 58%; mp 268–270°C; IR (KBr): 3471–3200 (-N-H), 3057 (=C-H), 2942 (C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.00 (d, $J_{2',3'}$ = 8.5 Hz, 2H, H-2′); 7.75 (d, $J_{2',3'}$ = 8.5 Hz, 2H, H-3′); 6.78 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.65 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.86 (d, 1H, $J_{17,18}$ = 8.8 Hz, H-17); 5.74 (d, 1H, $J_{17,18}$ = 8.8 Hz, H-18); 5.08 (s, 1H, H-5β); 4.78 (d, $J_{9\alpha,\ 10\alpha}$ = 5.6 Hz, 1H, H-9α); 4.05 (dd, $J_{7\beta,8\beta}$ = 9.3 Hz, $J_{7\beta,8\alpha}$ = 6.1 Hz, 1H, H-7β); 3.72–3.83 (m, 4H, H-16eq, 3-OCH$_3$); 3.49 (s, 3H, 6-OCH$_3$); 3.22–3.30 (m, 2H, H-16ax, H-10α); 2.90 (d, $J_{10\alpha,10\beta}$ = 17.1 Hz, 1H, H-10β); 2.82 (dd, $J_{8\alpha,8\beta}$ = 12.7 Hz, $J_{7\beta,8\beta}$ = 9.3 Hz 1H, H-8β); 2.40–2.45 (m, 1H, H-15ax); 1.99–2.02 (m, 1H, H-15eq); 1,85 (dd, $J_{8\alpha,8\beta}$ = 12.7 Hz, $J_{8\alpha,7\beta}$ = 6.1 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 28.96 C(10); 30.68 C(8); 30.76 C(15); 33.41 C(7); 40.07 C(14); 41.55 C(16); 46.85 C(13); 51.14 CH$_3$-O-C(6); 54.87 CH$_3$-O-C(3); 55.92 C(9); 80.80 C(6); 90.23 C(5); 113.79 C(2); 114.23 (N=C-N); 119.92 C(1); 122.27 C (1′);126.51 C(11); 127.66 C(18); 128.06 C(3′);129.64 C (2′);132.79 C(12); 135.43 C(17); 136.56 C(4′); 141.58 C(3); 147.48 C(4); 163.38 (-C=N); 166.89 (-C=N) ppm; hrms (EI): 572.1801 ([M – H]$^+$, $C_{29}H_{27}ClN_7O_4^+$, calc., 572.1813).

2-[N-(Tetrazol-1H-5-yl)-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5-(4′-bromophenyl)-1,3,4-oxadiazole (7d, $C_{29}H_{26}BrN_7O_4$). Recrystallized from methanol. Yield: 60%; mp 261–264°C; IR (KBr): 3385–3138(N-H), 3052(=C-H), 2961 (-C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.90 (d, $J_{2',\ 3'}$ = 8.8 Hz, 2H, H-2′); 7.84 (d, $J_{2',\ 3'}$ = 8.8 Hz, 2H, H-3′); 6.77 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-2); 6.63 (d, $J_{1,2}$ = 8.0 Hz, 1H, H-1); 5.86 (d, 1H, $J_{17,18}$ = 8.7 Hz, H-17); 5.73 (d, 1H, $J_{17,18}$ = 8.7 Hz, H-18); 5.07 (s, 1H, H-5β); 4.73 (d, $J_{9\alpha,\ 10\alpha}$ = 6.3 Hz, 1H, H-9α); 4.07 (dd, $J_{7\beta,8\beta}$ = 6.4 Hz, $J_{7\beta,8\alpha}$ = 7.1 Hz, 1H, H-7β); 3.70–3,85 (m, 4H, H-16eq, 3-OCH$_3$); 3.54 (s, 3H, 6-OCH$_3$); 3.22–3,28 (m, 2H, H-16ax, H-10α); 2.93 (d, $J_{10\alpha,10\beta}$ = 16.7 Hz, 1H, H-10β); 2.72 (dd, 1H, $J_{8\alpha,8\beta}$ = 12.5 Hz, $J_{7\beta,8\beta}$ = 6.4 Hz, 1H, H-8β); 2.39–2.43 (m, 1H, H-15ax); 1.97–1.99 (m, 1H, H-15eq); 1,84 (dd, $J_{8\alpha,8\beta}$ = 12.5 Hz, $J_{7\beta,8\alpha}$ = 7.1 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 31.13 C(10); 31.19 C(8); 31.27 C(15); 33.89 C(7); 40.07 C(14); 45.44 C(16); 47.35 C(13); 51.66 CH$_3$O-C(6); 56.44 CH$_3$O-C(3); 56.48 C(9); 81.30 C(6); 90.85 C(5); 114.31 C(2); 120.40 C(1); 123.12 C(1′); 127.23 C(11); 128.14 C(18); 128.68 C (3′); 131.50 (N=C-N); 133.07 C(2′); 133.32 C(4′); 135.96 C(17); 135.98 C(12); 142.18 C(3); 147.99 C(4); 164.00 (-C=N); 167.41 (-C=N) ppm; hrms (EI): 616.1323 ([M – H]$^+$, $C_{29}H_{27}BrN_7O_4^+$, calc., 616.1308).

2-[N-(Tetrazol-1H-5-yl)-6,14-endo-etheno-6,7,8,14-tetrahydrothebaine-7α-yl]-5(4′-methoxyphenyl)-1,3,4-oxadiazole (7e, $C_{30}H_{29}N_7O_5$). Recrystallized from methanol-ethyl acetate, Yield: 65%; mp 228–230°C; IR (KBr): 3385–3138 (N-H), 3052 (=C-H), 2961(-C-H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): δ 7.85 (d, $J_{2',3'}$ = 8.8 Hz, 2H, H-2′); 7.14 (d, $J_{2',3'}$ = 8.8 Hz, 2H, H-3′); 6.71 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-2); 6.58 (d, $J_{1,2}$ = 8.2 Hz, 1H, H-1); 5.80 (d, 1H, $J_{17,18}$ = 8.7 Hz, H-17); 5.67 (d, 1H, $J_{17,18}$ = 8.7 Hz, H-18); 5.00 (s, 1H, H-5β); 4.66 (d, $J_{9\alpha,\ 10\alpha}$ = 6.4 Hz, 1H, H-9α); 3.97 (dd, $J_{7\beta,8\beta}$ = 9.2 Hz, $J_{7\beta,8\alpha}$ = 6.1 Hz, 1H, H-7β); 3.84 (s, 3H, 4′-OCH$_3$); 3.71–3.79 (m, 4H, H-16eq, 3-OCH$_3$); 3.48 (s, 3H, 6-OCH$_3$); 3.15–3.24 (m, 2H, H-16ax, H-10α); 2.87 (d, $J_{10\alpha,10\beta}$ = 18.8 Hz, 1H, H-10β); 2.72 (dd, $J_{8\alpha,8\beta}$ = 12.7 Hz, $J_{7\beta,8\beta}$ = 9.2 Hz, 1H, H-8β); 2.29–2,33 (m, 1H, H-15ax,); 1.91–1.94 (m, 1H, H-15eq); 1,77 (dd, $J_{8\alpha,8\beta}$ = 12.7 Hz, $J_{7\beta,8\alpha}$ = 6.1 Hz, 1H, H-8α) ppm; ^{13}C-APT NMR (100 MHz, DMSO-d_6): δ 31.13 C(10); 31.19 C(8); 31,28 C(15); 33.89 C(7); 40,62 C(14); 42,07 C(16); 47,35 C (13); 51.63 CH$_3$O-C(6); 55.40 CH$_3$O-C(3); 55.97 CH$_3$O-C(4′);56.48 C(9); 81.30 C(6); 90.85 C(5); 112.10 (N=C-N); 114.38 C(2); 115.83 C(3′); 116.43 C(1′); 120.40 C(1); 127.06 C(11); 128,19 C (18); 128.57 C(2′); 133.36 C(12); 135.83 C(17); 142,10 C(3); 148.04 C(4); 162.38 (-C=N); 164.53 (-C=N); 166.59 C(4′) ppm; hrms (EI): 568.2296 ([M – H]$^+$, $C_{30}H_{30}N_7O_5^+$, calc., 568.2308).

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REFERENCES AND NOTES

[1] Dhawan, B. N.; Cesselin, F.; Raghubir, T.; Reisine, T.; Bradley, P. B.; Portoghesse, P. S.; Hamon, M. Pharmacol Rev 1996, 48, 567.

[2] Sporer, K. A. Ann Int Med 1999, 130, 584.

[3] Nutt, D. J. Lancet 1996, 347, 31.

[4] Spanagel, R.; Herz, A.; Shippenberg, T. S. J Neurochem 1990, 55, 1734.

[5] Kalinin, V. N.; Shishkov, I. V.; Moiseev, S. K.; Shults, E. E.; Tolstikov, G. A.; Sosnina, N. I.; Petrovskii, P. V.; Lyssenko, K. A. Helv Chim Acta 2006, 89, 861.

[6] Yavuz, S.; Yildirir, Y. Helv Chim Acta 2010, 93, 2406.

[7] Lewis, J. W.; Husbands, S. M. J Med Chem 2004, 43, 139.

[8] Lewis, J. W.; Husbands, S. M. Curr Pharm Design 2004, 10, 717.

[9] Maat, L.; Woudenberg, R. H.; Meuzelaar, G. J.; Linders, J. T. M. Bioorg Med Chem 1999, 7, 529.

[10] Bentley, K. W.; Hardy, D. G. J Am Chem Soc 1967, 89, 3267.

[11] Takemori, A. E.; Hayashi, G.; Smits, S. E. Eur J Pharmacol 1972, 20, 85.

[12] Zhang, A.; Li, F.; Ding, C.; Yao, Q.; Bidlack, J. M.; Hilbert, J. E.; Knapp, B. I.; Neumeyer, J. L. J Med Chem 2007, 50, 2747.

[13] Liu, C. H.; Zhong, B.; Liu, C.; Wu, B.; Gong, Z. Acta Chim Slov 2005, 52, 80.

[14] Dolman, S. J.; Gosselin, F.; O′Shea, P. D.; Davies, I. W. J Org Chem 2006, 71, 9584.

[15] Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. J Med Chem 1991, 34, 2060.

[16] Holla, B. S.; Gonsalves, R.; Shenoy, S. Eur J Med Chem 2000, 35, 267.

[17] Lenz, G. R.; Evans, S. M.; Walters, D. E.; Hopfinger, A. J. Opiates; Academic Press: Orlando, 1986.

[18] Nogrady, T. Medicinal Chemistry–A Biochemical Approach; Oxford University Press: Oxford, UK, 1988.

[19] Jin, T.; Kamijo, S.; Yamamoto, Y. Tetrahedron Lett 2004, 45, 9435.

[20] Odabasoglu, M.; Yavuz, S.; Pamir, Ö.; Yildirir, Y.; Büyükgüngör, O. Acta Crystalogr 2009, 65, o864.

[21] Bentley, K. W.; Hardy, D. G.; Smith, A. C. B. J Chem Soc C 1969, 2235.

[22] Bentley, K. W.; Burton, M.; Uff, B. C. J Med Chem 1984, 27, 1276.

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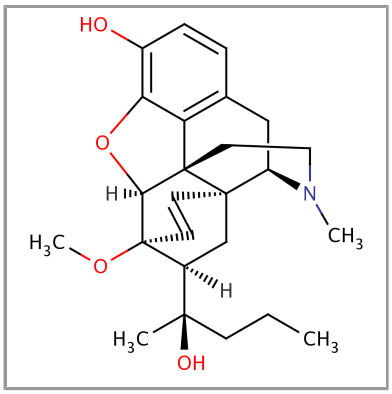

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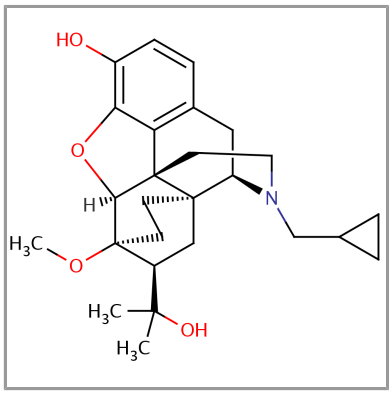

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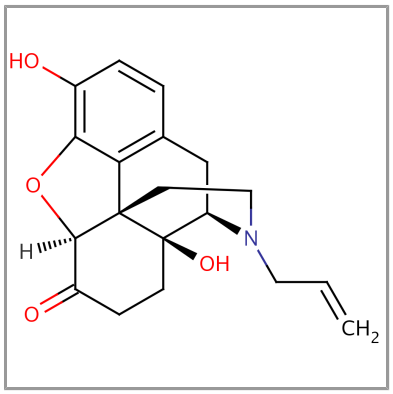

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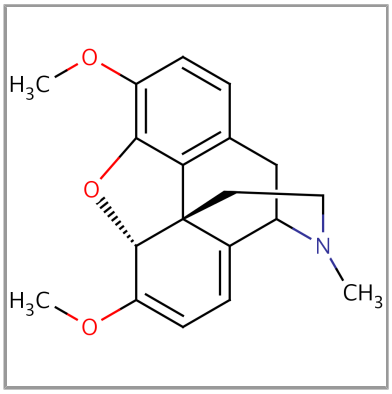

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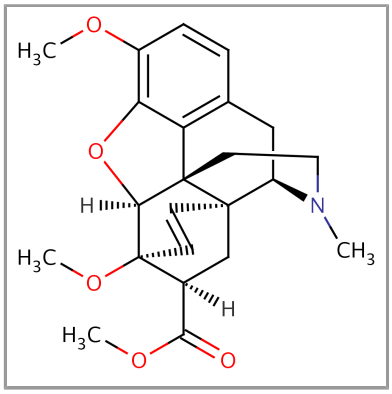

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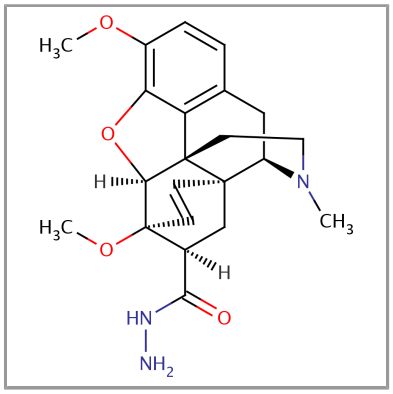

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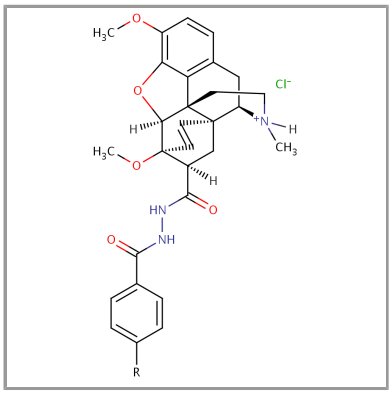

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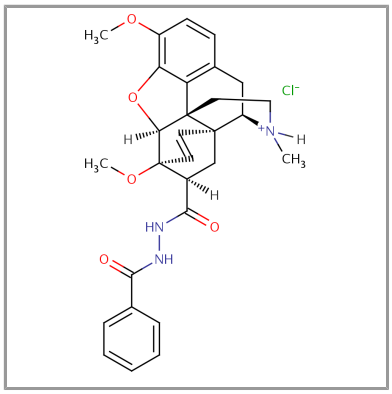

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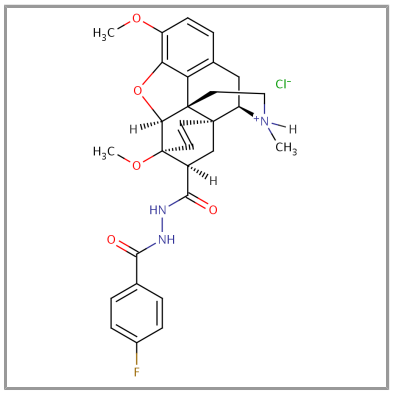

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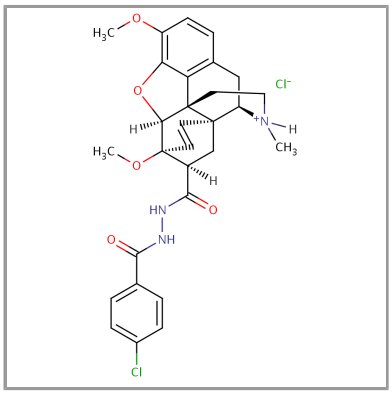

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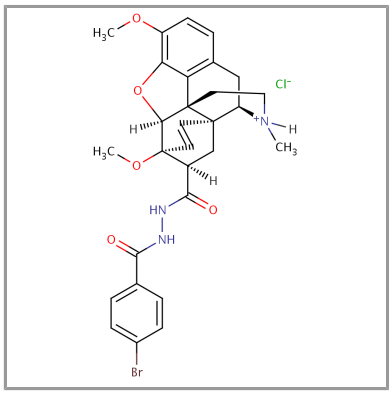

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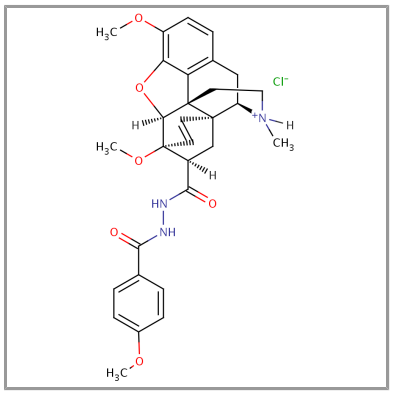

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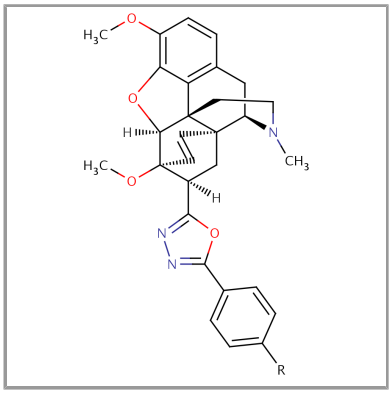

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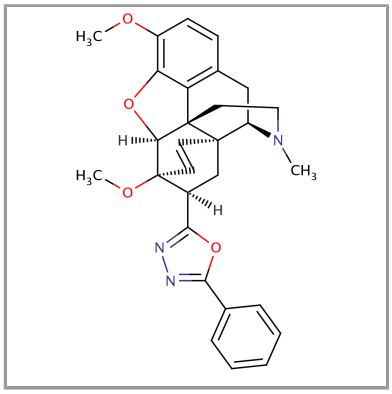

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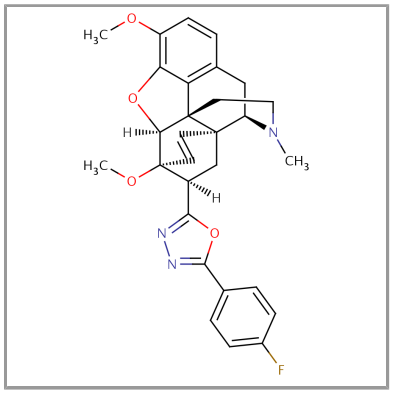

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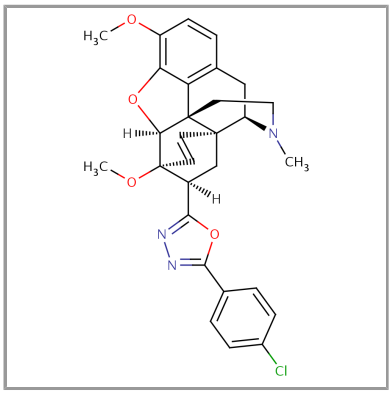

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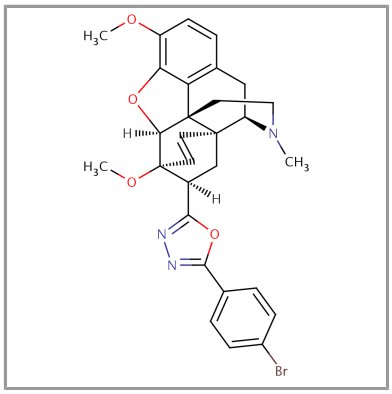

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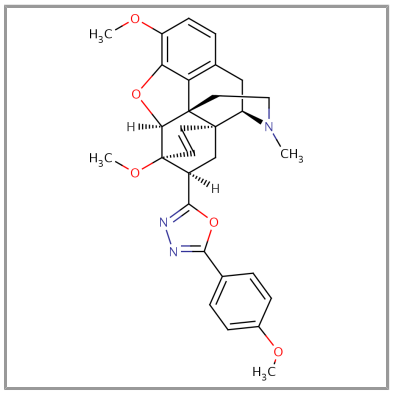

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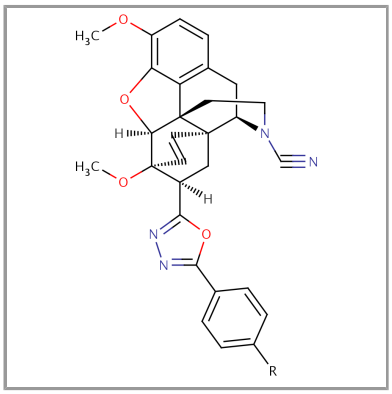

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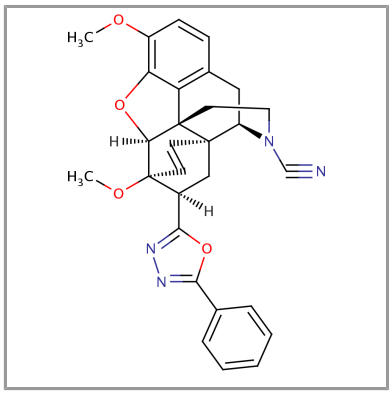

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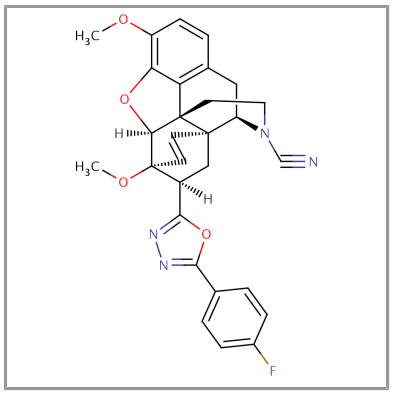

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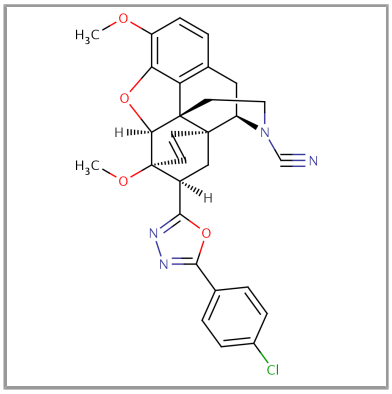

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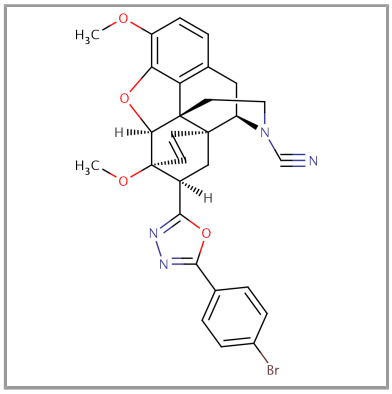

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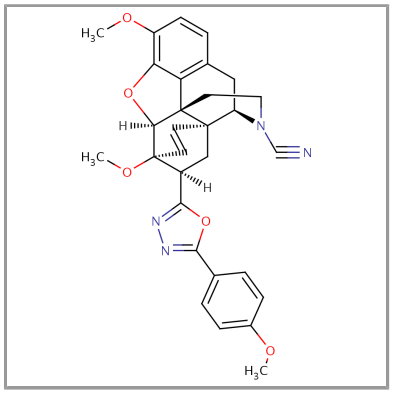

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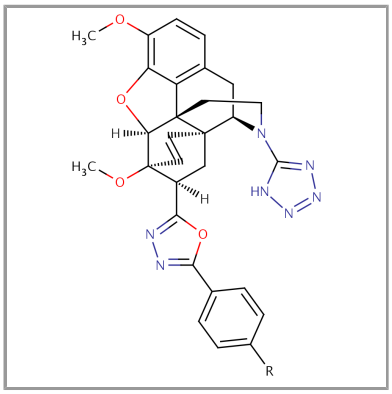

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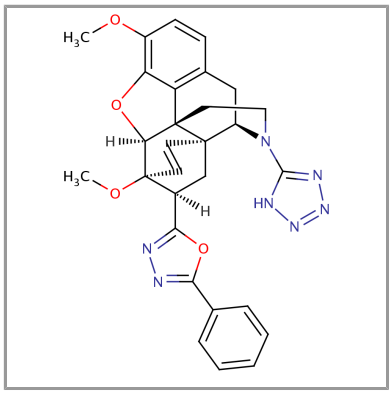

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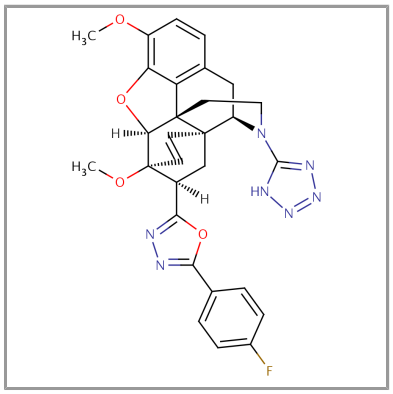

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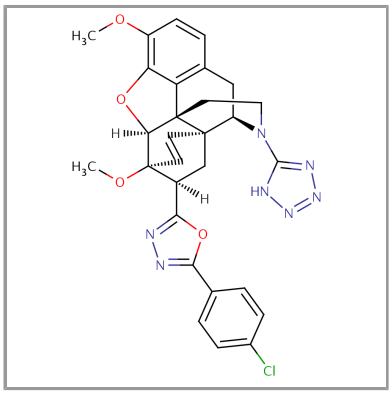

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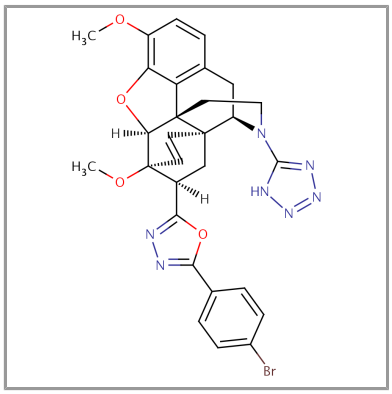

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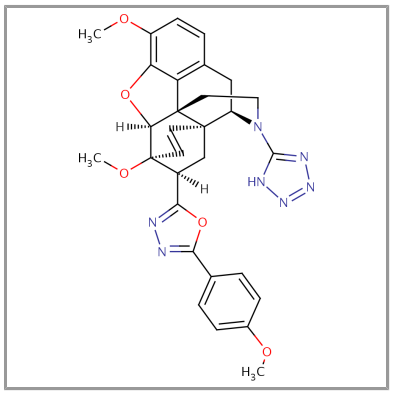

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