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# Stereochemistry of tropane alkaloid of convolvine and their derivatives

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ABSTRACT

Structures of alkaloid convolvine (1) isolated from *Convolvulus subhirsutus* and its derivatives-convolamine(*N*-methylconvolvine) (2) and hydrochloride of *N*-benzylconvolvine (3) have been determined by single crystal X-ray diffraction technique. Compounds were crystallized in monoclinic space groups having four molecules in unit cell. All compounds contain a bicyclic ring system of tropane, where piperidine rings in all case adopt chair conformation. Hydrogen atom and methyl- and benzyl-substituents located in nitrogen atom of studied compounds occupy equatorial positions. The substituent of tropane core- the veratroyloxy group containing in all compound molecules is an α-axial oriented relative to the tropane core. In crystal structures of compound 1 and 2, the molecules are located in the distance of van der Waals interactions. The H-bond between the anion Cl and the proton of the N atom is observed in the crystal of *N*-benzylconvolvine hydrochloride (Cl···N 3.337 Å, Cl···H 2.42 Å and Cl-H-N 175°).

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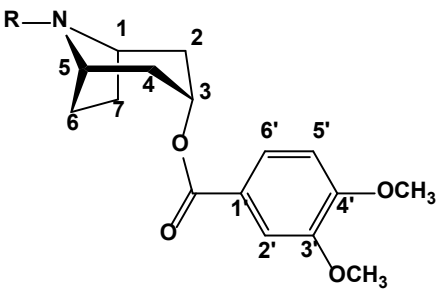
## 1. Introduction

It is known that some tropane alkaloids (atropine, scopolamine) have a quinolytic effect and are used in medicine as drugs [1]. In order to search for physiologically active substances among alkaloids of this class, modification is carried out on the basis of available substances. So plants of the *Convolvulus* genus are a source of convolvine alkaloids, which can be produced on an industrial scale. Based on this alkaloid, we previously synthesized a number of derivatives [2]. Convolamine (**2**) was obtained by methylation of convolvine (**1**) and *N*-benzylconvolvine (**3**) was obtained by reaction of convolvine with benzyl chloride (Scheme 1). Biological studies on some cultures of cancer cells have established a high anticancer activity of benzylconvolvine, superior to the activity of anticancer drugs used in medicine [3].

The issue of obtaining convolvine derivatives is based on natural compound and it is dependent on the structure of the starting natural product and the reactant. These factors govern not only the derivation of new products, but also chemical property of product molecule, manifestation of biological activity by the formation of intra- and inter-molecular H-bonds, as well as the stereochemistry of the veratroyloxy group. In this connection, the stereochemical behavior of the nitrogen atom and substituent in derivatives is of interest. To this end, for the consideration of structural issues, a X-ray analysis on single crystals of the obtained derivatives was performed.




R=H (**1**), R=$CH_3$ (**2**), $CH_2C_6H_5$ (**3**)

**Scheme 1**



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**Table 1.** Crystal data and details of the structure refinement for compounds **1**-**3**.

| Parameters | Compound 1 | Compound 2 | Compound 3 |
|---|---|---|---|
| Empirical formula | $C_{16}H_{21}NO_4$ | $C_{17}H_{23}NO_4$ | $C_{23}H_{28}NO_4$·Cl |
| Formula weight | 291.34 | 305.36 | 417.91 |
| Temperature (K) | 293 | 293 | 293 |
| Crystal system | Monoclinic | Monoclinic | Monoclinic |
| Space group | *Cc* | $P2_1/n$ | $P2_1/c$ |
| a, (Å) | 10.2405(7) | 8.8351(5) | 15.4528(4) |
| b, (Å) | 20.429 (2) | 19.6231(11) | 9.0258(2) |
| c, (Å) | 7.1993(7) | 9.2514(5) | 16.5962(5) |
| β (°) | 94.587(7) | 91.977(5) | 111.121(3) |
| Volume (Å$^3$) | 1501.3(2) | 1603.0(2) | 2159.2(1) |
| *Z* | 4 | 4 | 4 |
| $\rho_{calc}$ (g/cm$^3$) | 1.289 | 1.265 | 1.286 |
| μ (mm$^{-1}$) | 0.76 | 0.73 | 1.80 |
| F(000) | 624 | 656 | 888 |
| Crystal size (mm$^3$) | 0.60 × 0.45 × 0.40 | 0.55 × 0.45 × 0.25 | 0.25 × 0.30 × 0.40 |
| Radiation | CuKα (λ = 1.54184) | CuKα (λ = 1.54184) | CuKα (λ = 1.54184) |
| 2Θ range for data collection (°) | 9.6 to 152.6 | 9.0 to 152.6 | 10.8 to 176.4 |
| Index ranges | $-9 \le h \le 12$ | $-10 \le h \le 10$ | $-17 \le h \le 20$ |
| | $-22 \le k \le 25$ | $-17 \le k \le 24$ | $-11 \le k \le 8$ |
| | $-9 \le l \le 8$ | $-11 \le l \le 11$ | $-19 \le l \le 18$ |
| Reflections collected | 4762 | 6255 | 8728 |
| Independent reflections | 2197 [$R_{int}$ = 0.045] | 3228 [$R_{int}$ = 0.033] | 4317 [$R_{int}$ = 0.033] |
| Data/restraints/parameters | 2197/2/193 | 3228/0/199 | 4317/0/269 |
| Goodness-of-fit on $F^2$ | 1.067 | 0.996 | 1.022 |
| Final R indexes [I≥2σ (I)] | $R_1$ = 0.061, $wR_2$ = 0.135 | $R_1$ = 0.051, $wR_2$ = 0.119 | $R_1$ = 0.050, $wR_2$ = 0.133 |
| Final R indexes [all data] | $R_1$ = 0.105, $wR_2$ = 0.167 | $R_1$ = 0.078, $wR_2$ = 0.141 | $R_1$ = 0.070, $wR_2$ = 0.146 |
| Largest diff. peak/hole (e.Å$^{-3}$) | 0.19/-0.15 | 0.16/-0.20 | 0.31/-0.22 |

## 2. Experimental

### *2.1. Materials and apparatuses*

Convolvine (**1**) was isolated from *Convolvulus subhirsutus*. Reagents and solvents were purchased from commercial suppliers and used without further purifications. Single crystal X-ray diffraction (XRD) data was collected by using CuKα radiation (λ = 1.54184 Å) on a CCD Xcalibur Ruby diffractometer (Oxford Diffraction) at a room temperature. Data reduction including *multi-scan* absorption correction was done using *CrysAlisPRO* [4].

### *2.2. X-ray crystal structure determination of compounds 1-3*

Structures were solved by direct methods within the SHELXS-97 program [5] and refined with SHELXL-2014/7 refinement program [6]. All non-hydrogen atoms were refined by the least squares method ($F^2$) in the full-matrix anisotropic approximation. Hydrogen atoms at carbon atoms were positioned geometrically and refined according to a riding model with fixed isotropic displacement parameters $U_{iso}$ = $nU_{eq}$, where n = 1.5 for methyl groups and 1.2 for the others, ($U_{eq}$ is the equivalent isotropic parameter of displacement of the corresponding carbon atoms). The hydrogen atoms of the NH group are found from difference syntheses of electron density and refined isotropically.

### *2.3. Preparation of convolvine and its derivatives*

Isolation of convolvine (**1**) was performed according to the method [7]. The air-dried aerial part of *C. subhirsutus* (3 kg) was moistened with ammonia solution (10%), placed in a percolator, and after 2 h treated with $CHCl_3$ (six times). The combined $CHCl_3$ extracts were condensed to a volume of 2 L and worked up with $H_2SO_4$ solution (10%) to extract exhaustively the alkaloids. The combined acidic solutions were washed twice with a small quantity of $CHCl_3$ and made basic with ammonia solution (25%). The alkaloids were extracted with $CHCl_3$ to afford total bases (10.7 g). Total bases (10.7 g) were dissolved in $CHCl_3$ (2 L) and worked up with KOH solution (4%, 4 × 100 mL). The alkaline extracts were acidified with $H_2SO_4$ solution (20%), cooled, and made basic with ammonia solution (25%). Alkaloids were extracted exhaustively with $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous $Na_2SO_4$. Solvent was distilled off to produce phenolic alkaloids (2.5 g). After work up with base, the $CHCl_3$ solution was washed with distilled water and worked up successively with citrate-phosphate buffer at pH = 6.8 and 5.6 to extract completely the alkaloids. The buffer extracts were made basic with cooling using conc. $NH_4OH$ solution. Alkaloids were extracted with $CHCl_3$ to afford bases from the fractions with pH = 6.8 (5.5 g, convolvine) and 5.6 (2.2 g, convolamine with an impurity of convolvine).

A mixture of 0.1 g of convolvine alkaloid, 1 mL of methyl iodide and 0.4 g of potassium iodide in 30 mL of dry acetone was heated in a water bath for 1 hour. When the cooled filtrate was concentrated, a crystalline precipitate (**2**) was formed with M.p.: 114-115 ° (acetone) in the amount of 0.11 g and not giving melting point depression with a convolamine sample.

Synthesis of *N*-benzylconvolvine (**3**) was carried out according to the method [2]. A mixture of convolvine (0.15 g) and benzylchloride (0.1 mL) was left at room temperature for 2 d. After this time the product was separated by treatment with acetone and purified over a column of $Al_2O_3$ to afford crystals (0.15 g, 78.9%) with M.p.: 88-89 °C.

## 3. Results and discussion

The molecular structures of convolvine **1** and its derivatives **2** and **3** are shown in Figure 1. Crystallographic data are presented in Table 1. The tropane alkaloid and derivatives are crystallized in the Cc space groups (containing glade plane) and $P2_1/n$, $P2_1/c$ (with elements of the center of symmetry and glade plane), respectively. Consequently, the crystals contain both enantiomers of the molecules of the alkaloid **1** and its derivatives **2** and **3**.

XRD analysis result allows to set the relative configuration of the center C3. The substituent the veratroyloxy group in position C3 has an α-axial orientation relative to the tropane core. The orientation and location of the substituents of the N and C3 atoms in compounds **1**, **2** and **3** coincides with those observed in convolinine [8] and *o*-benzoyltropine hydrochloride [9]. In molecules **1**-**3**, the veratroyloxy group is planar with an accuracy of ±0.040, ±0.039 and ±0.036 Å, respectively, and the benzyl group at N1 in **3** is ±0.008 Å.

**Table 2**. Selected bond lengths and bond angles of molecule **1**.

| Atom-Atom | Bond length (Å) | Atom-Atom | Bond length (Å) | Atom-Atom | Bond length (Å) |
|---|---|---|---|---|---|
| O1-C16 | 1.348 (8) | N1-C5 | 1.468 (10) | C6-C7 | 1.539 (11) |
| O1-C3 | 1.465 (7) | N1-H1A | 0.85 (8) | C1'-C6' | 1.379 (9) |
| O2-C16 | 1.205 (7) | C1-C2 | 1.517 (10) | C1'-C2' | 1.398 (8) |
| O3-C4' | 1.364 (7) | C1-C7 | 1.539 (9) | C1'-C16 | 1.486 (8) |
| O3-C17 | 1.427 (8) | C2-C3 | 1.513 (9) | C2'-C3' | 1.378 (8) |
| O4-C3' | 1.361 (7) | C3-C4 | 1.521 (10) | C3'-C4' | 1.413 (8) |
| O4-C18 | 1.424 (8) | C4-C5 | 1.534 (10) | C4'-C5' | 1.383 (8) |
| N1-C1 | 1.466 (10) | C5-C6 | 1.545 (10) | C5'-C6' | 1.379 (9) |
| **Atom-Atom-Atom** | **Bond angles (°)** | **Atom-Atom-Atom** | **Bond angles (°)** | **Atom-Atom-Atom** | **Bond angles (°)** |
| C16-O1-C3 | 117.4 (5) | N1-C5-C4 | 106.6 (6) | O4-C3'-C4' | 114.6 (5) |
| C4'-O3-C17 | 117.7 (5) | N1-C5-C6 | 106.3 (6) | C2'-C3'-C4' | 120.1 (5) |
| C3'-O4-C18 | 116.8 (5) | C4-C5-C6 | 112.4 (6) | O3-C4'-C5' | 126.0 (5) |
| C1-N1-C5 | 100.9 (5) | C7-C6-C5 | 102.7 (6) | O3-C4'-C3' | 115.5 (5) |
| N1-C1-C2 | 106.8 (6) | C6-C7-C1 | 104.5 (6) | C5'-C4'-C3' | 118.5 (5) |
| N1-C1-C7 | 105.7 (6) | C6'-C1'-C2' | 120.5 (6) | C6'-C5'-C4' | 121.8 (6) |
| C2-C1-C7 | 112.7 (6) | C6'-C1'-C16 | 117.8 (5) | C5'-C6'-C1' | 119.3 (6) |
| C3-C2-C1 | 113.4 (6) | C2'-C1'-C16 | 121.7 (5) | O2-C16-O1 | 122.9 (6) |
| O1-C3-C2 | 109.2 (5) | C3'-C2'-C1' | 119.8 (6) | O2-C16-C1' | 124.5 (6) |
| O1-C3-C4 | 106.9 (5) | O4-C3'-C2' | 125.3 (6) | O1-C16-C1' | 112.6 (5) |

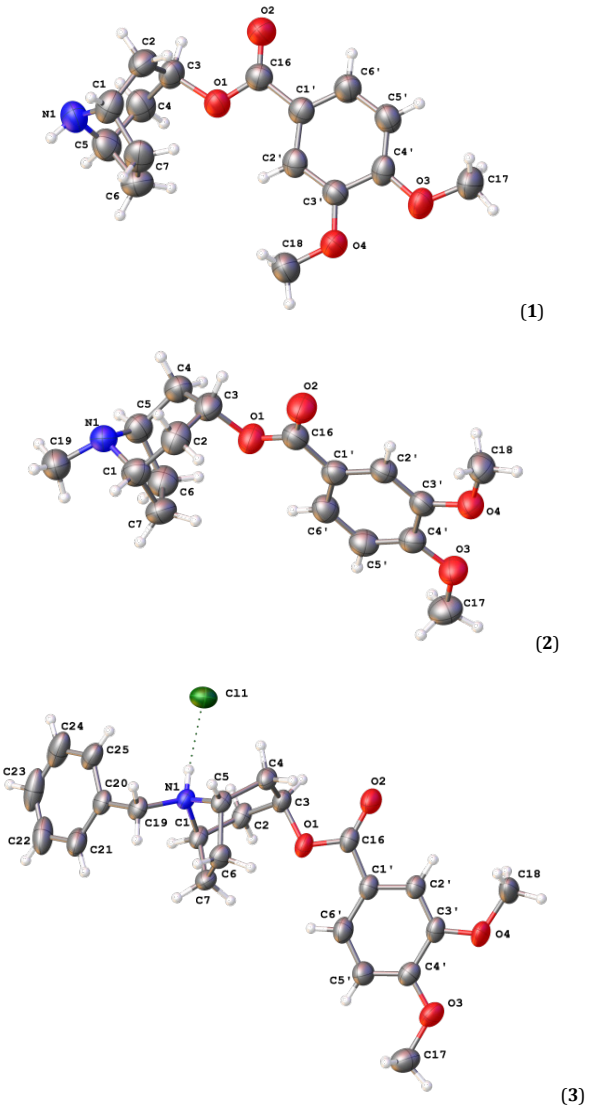


**Figure 1.** The molecular structures of compounds **1**-**3**.

The veratroyloxy group is distorted from the plane of symmetry of the tropane core, which is characterized by the torsion angle H3-C3-O1-C1', whose values for compound **1**-**3** are 33, 29 and 33°, respectively. It should be noted that the carbonyl group in these compounds and analogues known in the literature [8-12] is always *syn*-directed relative to the β-axially located hydrogen atom at C3. But the methoxyl group in the *ortho* position of the C3' veratroyloxy fragment in these compounds is located differently relative to the tropine core (Figure 1), which indicates a free rotation around the C16-C1' bond forming different rotamers.

**Table 3**. Selected bond lengths and bond angles of molecule **2**.

| Atom-Atom | Bond length (Å) | Atom-Atom | Bond length (Å) | Atom-Atom | Bond length (Å) |
|---|---|---|---|---|---|
| O1-C16 | 1.340 (3) | N1-C5 | 1.469 (3) | C6-C7 | 1.536 (3) |
| O1-C3 | 1.468 (3) | N1-C1 | 1.474 (3) | C1'-C6' | 1.381 (3) |
| O2-C16 | 1.208 (3) | C1-C2 | 1.530 (3) | C1'-C2' | 1.403 (3) |
| O3-C4' | 1.357 (2) | C1-C7 | 1.547 (3) | C1'-C16 | 1.478 (3) |
| O3-C17 | 1.426 (3) | C2-C3 | 1.516 (3) | C2'-C3' | 1.370 (3) |
| O4-C3' | 1.366 (2) | C3-C4 | 1.517 (3) | C3'-C4' | 1.412 (3) |
| O4-C18 | 1.419 (3) | C4-C5 | 1.524 (3) | C4'-C5' | 1.384 (3) |
| N1-C19 | 1.466 (3) | C5-C6 | 1.545 (3) | C5'-C6' | 1.386 (3) |
| **Atom-Atom-Atom** | **Bond angles (°)** | **Atom-Atom-Atom** | **Bond angles (°)** | **Atom-Atom-Atom** | **Bond angles (°)** |
| C16-O1-C3 | 117.03 (17) | O1-C3-C4 | 107.46 (19) | O4-C3'-C2' | 124.95 (18) |
| C4'-O3-C17 | 117.67 (18) | C3-C4-C5 | 113.36 (19) | O4-C3'-C4' | 115.34 (17) |
| C3'-O4-C18 | 116.52 (17) | N1-C5-C4 | 107.22 (19) | C2'-C3'-C4' | 119.71 (18) |
| C19-N1-C5 | 112.2 (2) | N1-C5-C6 | 105.72 (18) | O3-C4'-C5' | 125.61 (18) |
| C19-N1-C1 | 111.92 (18) | C4-C5-C6 | 112.61 (19) | O3-C4'-C3' | 114.90 (18) |
| C5-N1-C1 | 100.67 (17) | C7-C6-C5 | 103.54 (19) | C5'-C4'-C3' | 119.49 (18) |
| N1-C1-C2 | 107.47 (18) | C6-C7-C1 | 103.76 (18) | C4'-C5'-C6' | 120.33 (19) |
| N1-C1-C7 | 105.22 (19) | C6'-C1'-C2' | 119.40 (19) | C1'-C6'-C5' | 120.4 (2) |
| C2-C1-C7 | 112.9 (2) | C6'-C1'-C16 | 123.69 (19) | O2-C16-O1 | 123.1 (2) |
| C3-C2-C1 | 113.02 (19) | C2'-C1'-C16 | 116.87 (18) | O2-C16-C1' | 124.3 (2) |
| O1-C3-C2 | 109.29 (19) | C3'-C2'-C1' | 120.62 (19) | O1-C16-C1' | 112.59 (18) |

**Table 4**. Selected bond lengths and bond angles of molecule **3**.

| Atom-Atom | Bond length (Å) | Atom-Atom | Bond length (Å) | Atom-Atom | Bond length (Å) |
|---|---|---|---|---|---|
| O1-C16 | 1.306 (2) | N1-H1 | 0.92 (3) | C3'-C4' | 1.478 (3) |
| O1-C3 | 1.426 (2) | C1-C2 | 1.606 (3) | C4'-C5' | 1.320 (3) |
| O2-C16 | 1.270 (3) | C2-C3 | 1.526 (3) | C5'-C6' | 1.358 (3) |
| O3-C4' | 1.322 (3) | C3-C4 | 1.467 (3) | C19-C20 | 1.396 (3) |
| O3-C17 | 1.511 (3) | C1-C7 | 1.584 (3) | C20-C25 | 1.391 (3) |
| O4-C3' | 1.295 (2) | C6-C7 | 1.522 (3) | C20-C21 | 1.422 (4) |
| O4-C18 | 1.490 (3) | C1'-C2' | 1.341 (3) | C21-C22 | 1.300 (4) |
| N1-C1 | 1.422 (2) | C1'-C6' | 1.443 (3) | C22-C23 | 1.375 (5) |
| N1-C5 | 1.507 (3) | C1'-C16 | 1.460 (3) | C23-C24 | 1.428 (5) |
| N1-C19 | 1.550 (2) | C2'-C3' | 1.344 (3) | C24-C25 | 1.277 (4) |
| **Atom-Atom-Atom** | **Bond angles (°)** | **Atom-Atom-Atom** | **Bond angles (°)** | **Atom-Atom-Atom** | **Bond angles (°)** |
| C16-O1-C3 | 110.32 (17) | C4-C3-C2 | 112.88 (17) | O3-C4'-C3' | 119.99 (19) |
| C4'-O3-C17 | 121.10 (19) | C3-C4-C5 | 113.89 (18) | C4'-C5'-C6' | 115.0 (2) |
| C3'-O4-C18 | 118.22 (18) | N1-C5-C6 | 102.29 (17) | C5'-C6'-C1' | 124.22 (19) |
| C1-N1-C5 | 103.74 (15) | N1-C5-C4 | 104.55 (16) | O2-C16-O1 | 126.0 (2) |
| C1-N1-C19 | 108.16 (16) | C6-C5-C4 | 121.10 (16) | O2-C16-C1' | 128.48 (18) |
| C5-N1-C19 | 112.08 (15) | C7-C6-C5 | 102.05 (17) | O1-C16-C1' | 105.46 (18) |
| C1-N1-H1 | 107.2 (15) | C6-C7-C1 | 106.92 (17) | C20-C19-N1 | 109.10 (18) |
| C5-N1-H1 | 109.4 (16) | C2'-C1'-C16 | 111.9 (2) | C25-C20-C19 | 116.3 (2) |
| C19-N1-H1 | 115.4 (15) | C6'-C1'-C16 | 126.77 (18) | C25-C20-C21 | 124.2 (2) |
| N1-C1-C7 | 99.06 (16) | C1'-C2'-C3' | 114.6 (2) | C19-C20-C21 | 119.4 (2) |
| N1-C1-C2 | 105.04 (17) | O4-C3'-C2' | 119.9 (2) | C22-C21-C20 | 118.6 (3) |
| C7-C1-C2 | 119.44 (17) | O4-C3'-C4' | 116.3 (2) | C21-C22-C23 | 116.1 (3) |
| C3-C2-C1 | 114.75 (17) | C2'-C3'-C4' | 123.85 (18) | C22-C23-C24 | 125.7 (3) |
| O1-C3-C2 | 111.96 (18) | C5'-C4'-O3 | 119.1 (2) | C25-C24-C23 | 117.8 (3) |
| O1-C3-C4 | 99.66 (18) | C5'-C4'-C3' | 120.9 (2) | C24-C25-C20 | 117.6 (3) |

**Table 5**. Intra- and inter-molecular interactions in the crystals **1-3**.

| D-H...A | d(D-H), Å | d(H...A), Å | d(D...A), Å | ∠(DHA), ° | Symmetry |
|---|---|---|---|---|---|
| **Compound 1** | | | | | |
| C17-H17a...O2 | 0.96 | 2.47 | 3.405(9) | 164 | 1+*x*, *y*, *z* |
| **Compound 2** | | | | | |
| C18-H18c...O2 | 0.96 | 2.53 | 3.268(3) | 134 | 1-*x*, 1-*y*, 2-*z* |
| **Compound 3** | | | | | |
| N1-H...Cl1 | 0.93(3) | 2.42(3) | 3.337(2) | 174(2) | - |
| C2-H2a...Cl1 | 0.97 | 2.76 | 3.499(2) | 133 | - |
| C4-H4b...Cl1 | 0.97 | 2.82 | 3.552(3) | 133 | - |
| C7-H7a...O4 | 0.97 | 2.20 | 3.106(3) | 155 | -*x*, -*y*, -*z* |
| C19-H19b...Cl1 | 0.97 | 2.64 | 3.577(2) | 162 | 1-*x*, -1-*y*, -*z* |

Bond length in the molecules **1**-**3** closely comparable with only small variations around the N1 nitrogen atom. N1-C1 (1.466(10) Å), N1-C5 (1.468(10) Å) bonds in molecule **1** and N1-C1 (1.466(10) Å), N1-C5 (1.468(10) Å) and N1-C19 1.466(3) Å bonds in molecule **2** are almost the same. In case molecule **3** with protonation of N1 atom those bond lengths equals to 1.422(2), 1.507(3), 1.550(2) Å, respectively (Tables 2-4).

In crystal structures **1** and **2**, the molecules are located in the distance of van der Waals interactions. However, the crystal structure indicates that the molecules in the crystals are associated by intermolecular weak C-H...O interactions (Table 5). Crystal **3** is the hydrochloride salt. The H-bond between the anion Cl and the proton of the N atom is observed in the crystal, the H-bond parameters are the following: Cl1···N1 3.337(2) Å, Cl1···H 2.42(3) Å, Cl1···HN1 174(2)°. A weak H-bond of C7-H···O4 type is observed, and also π-π interactions between the aromatic sites of the veratroyloxy group of molecules transformed by the center of symmetry.

## 4. Conclusion

Crystal structures of convolvine alkaloid and its two derivatives were deduced by single crystal XRD analysis. Piperidine rings in compounds adopt chair conformation. Hydrogen atom and methyl- and benzyl-substituents located

in nitrogen atom of **1**-**3** occupy equatorial positions. The veratroyloxy group containing in all compound molecules is an α-axial oriented relative to the tropane core. Free rotation of dimethoxyphenyl- group around the C16-C1' bond leads different rotamers in crystals of compound **1**-**3**.

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**Supporting information**

CCDC 1935317 (**1**), CCDC 1935318 (**2**) and CCDC 1935324 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

**Disclosure statement**

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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