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A Concise Synthesis of Tetrabenazine and Its Crystal Structure

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*The title compound tetrabenazine was synthesized by reaction of 3-dimethylaminomethylheptan-2-one and 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride. This approach provides an efficient and concise way to the synthesis of the marketed drug tetrabenazine. The colorless single crystal of tetrabenazine suitable for X-ray analysis was obtained from saturated methanol solution. The X-ray results showed that tetrabenazine consists of (3*R*, 11b*R*) and (3*S*, 11b*S*) enantiomers. Two terminal methyl groups are disordered in the (3*R*, 11b*R*) enantiomer.*

Keywords Chiral center; configuration; enantiomer; Mannich reaction; tetrabenazine

Introduction

Tetrabenazine (TBZ) is a drug for the symptomatic treatment of hyperkinetic movement disorder and is marketed under the trade names Nitoman in Canada and Xenazine in New Zealand and some parts of Europe, and is also available in the USA as an orphan drug. The US Food and Drug Administration (FDA) first approved the use of TBZ to treat chorea associated with Huntington's disease in 2008. According to reports from countries where TBZ has been used for a longer period of time, 80% of patients show an improvement in chorea.

TBZ has been known since the 1950s. As a selective and reversible centrally acting monoamine depleting drug, its pharmacy mechanism is that TBZ is a high-affinity inhibitor of the vesicular monoamine transporter 2 (VMAT2) [1]. VMAT2 is an integral part of the mechanism for the vesicular storage of monoamine neurotransmitters in the mammalian brain neurons. TBZ, thus, inhibits the uptake of monoamines into synaptic vesicles and so diminishes their output at synapses between brain neurons. Therefore, imaging VMAT2 in the brain with radiolabeled TBZ or its derivatives provides a measurement reflecting the integrity of monoaminergic neurons, and so as to monitor or diagnose neurodegenerative disorders such as Parkinson's, Alzheimer's, Tourette's, and Huntington's disease [2]. In view of this, TBZ and its derivatives have recently been labeled with carbon-11 and fluorine-18

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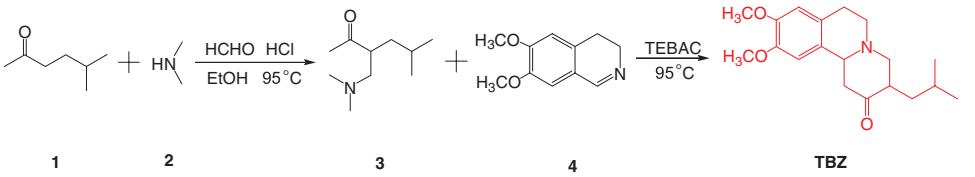
radioisotopes and used for in vitro and in vivo studies of the VMAT2 in animal and human brain. For example, ^{11}C-TBZ [3], ^{11}C-DTBZ [4–7], and ^{18}F-FP-DTBZ [8–10] have been prepared as positron emission tomography (PET) imaging agents targeting VMAT2. As part of an ongoing research program, our group is developing a new radiolabeled TBZ's derivative. For this reason, gram quantities of TBZ were required. Reported herein is the concise synthesis of TBZ as shown in Scheme 1.



Scheme 1. Synthesis of TBZ.

TBZ has two chiral centers at C-3 and C-11b as shown in Fig. 1. Therefore, in theory, there are four isomers of TBZ. In 1997, Kilbourn et al. suggested that TBZ itself may consist of (3*R*, 11b*R*) and (3*S*, 11b*S*) enantiomers [11]. By means of X-ray diffraction, we tried to use the most direct way to confirm this speculation.

Experimental

Materials and Physical Measurements

All solvents and reagents were of analytical grade and were used without further purification. IR spectra in the range 4000–400 cm^{-1} were obtained from samples in the form of KBr tablets using a Bruker Tensor 27 infrared spectrometer. MS spectra were recorded with a Waters Platform ZMD 4000 mass spectrometer. Proton NMR spectra were obtained on a Bruker Avance III 400 MHz Digital NMR Spectrometer in $CDCl_3$. A Bruker CCD APEX2 diffractometer was used for the X-ray structure study.

Synthesis of 3-Dimethyl-Aminomethylheptan-2-One (3)

5-Methyl-2-hexanone (**1**) (35.2 mL), 40% dimethylamine aqueous solution (**2**) (8.6 mL), 40% formaldehyde solution (7.5 mL), and concentrated hydrochloric acid (7 mL) were dissolved in ethanol (130 mL). The mixture was stirred and heated under reflux at 95°C for

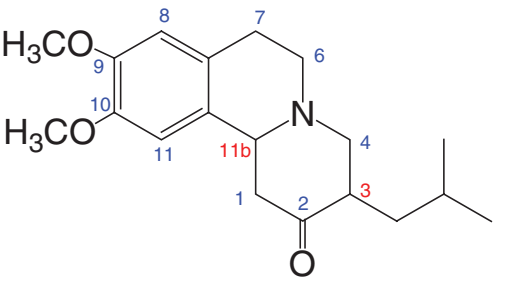


Figure 1. Structure of numbered TBZ.

5 h and the solvent was removed under reduced pressure. The residue was added to distilled water (100 mL) and then extracted several times with ether (30 mL × 3) to remove unreacted starting material. The aqueous phase was basified by 10% sodium hydroxide aqueous solution until the pH reached 9–10 and extracted with ether (50 mL × 3). Organic extracts were combined and concentrated in vacuum. The crude product was purified by chromatography (CH_2Cl_2/CH_3OH, 97/3) on silica gel, yielding 3-dimethyl-aminomethylheptan-2-one (**3**) (3.34 g). Yield: 39%. MS, *m/z*: 172.0 $[M+H]^+$; 194.0 $[M+Na]^+$. ^1H NMR($CDCl_3$, 400 MHz), δ: 2.82∼2.76(m, 1H), 2.67∼2.60(*t*, 1H), 2.21(m, 7H), 2.14(m, 3H), 1.55∼1.40(m, 2H), 1.23∼1.15(m, 1H), 0.89∼0.88(d, 3H), 0.87∼0.86(d, 3H).

Synthesis of Tetrabenazine (TBZ)

3-Dimethyl-aminomethylheptan-2-one (**3**) (3.34 g), 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (**4**) (4.80 g), and triethylbenzylammonium chloride (1.41 g) were dissolved in a mixed solution of water and ethanol with a one-to-one volume ratio (40 mL). The mixture was stirred and heated under reflux at 95°C for 6 h and the solvent was removed under reduced pressure. The residue was extracted thoroughly with ethyl ether. Organic extracts were combined and concentrated in vacuum. The crude product was purified by crystallization with methanol giving **TBZ** (3.50 g) as colorless crystals in a moderate yield (56%). MS, *m/z*: 318.2 $[M+H]^+$; 340.2 $[M+Na]^+$. IR (KBr, cm^{-1}): 2941; 2920; 1701; 1610; 1517; 1466. ^1H NMR($CDCl_3$, 400 MHz), δ: 6.62(s, 1H), 6.55(s, 1H), 3.86(s, 3H), 3.83(s, 3H), 3.52∼3.49(d, 1H), 3.31∼3.27(q, 1H), 3.16∼3.07(m, 2H), 2.92∼2.88(dd, 1H), 2.77∼2.71(m, 2H), 2.63∼2.51(m, 2H), 2.39∼2.33(*t*, 1H), 1.84∼1.78(m, 1H), 1.70∼1.63(m, 1H), 1.07∼1.00(m, 1H), 0.93∼0.92(d, 3H), 0.91∼0.90(d, 3H).

X-Ray Crystallography

A single crystal of the title compound with dimensions 0.50 × 0.38 × 0.13 mm was chosen for X-ray diffraction study. The data were collected on a Bruker APEX2 diffractometer equipped with graphite-monochromatic Mo-Kα radiation ($\lambda = 0.71073$ Å) by using ψ and ω scan mode at 296(2) K. In the range of $1.49^\circ < \theta < 25.00^\circ$, a total of 18,189 reflections were collected, of which 6288 were independent ($R_{int} = 0.0417$) and 3836 were observed with $I > 2\sigma(I)$.

The structure was solved by direct and difference Fourier map methods with SHELXS-97 [16]. Nonhydrogen atoms were refined by full-matrix least-squares techniques on F^2 with anisotropic thermal parameters, using SHELXL-97 [17]. All H atoms were allowed to ride on their parent atoms at distances of 0.93 Å (C–H aromatic), 0.96 Å (C–H methyl), 0.97 Å (C–H methylene), and 0.98 Å (C–H tert-methyl) with U_{iso}(H) values of 1.2–1.5 times U_{eq} of the parent atoms. The final full-matrix least-squares refinement gave $R = 0.0500$, $wR = 0.1284$ for 3836 reflections with $I > 2\sigma(I)$; the weighting scheme, $w = 1/[\sigma^2(F_O^2) + (0.0898P)^2 + 2.3218P]$, where $P = (F_O^2 + 2F_C^2)/3$. The maximum and minimum difference peaks and holes are 0.166 and –0.200 e·Å^{-3}, respectively. $S = 0.836$ and $(\Delta/\sigma)_{max} = 0.000$. The crystal data and refinement details are listed in Table 1. The selected bond lengths and bond angles are listed in Table 2.

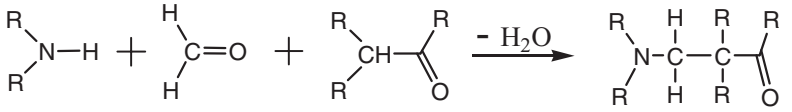
Table 1. Crystallographic data and structure refinement details

CCDC deposit number	819713
Empirical formula	$C_{19}H_{27}NO_3$
Formula weight	317.42
Temperature(K)	296(2)
Wavelength(Å)	0.71073
Crystal size(mm)	0.50 × 0.38 × 0.13
Crystal system	Monoclinic
Space group	$P2_1/c$
a(Å)	15.1494(15)
b(Å)	15.9159(15)
c(Å)	16.5924(16)
α(°)	90.00
β(°)	115.5930(10)
γ(°)	90.00
V(Å^3)	3608.2(6)
Z	8
$D_{ca.}$(g·cm^{-3})	1.169
F(000)	1376
Absorption coeff. (mm^{-1})	0.078
θ range(°)	1.49–25.00
Index ranges	$-18 \leq h \leq 16$; $-18 \leq k \leq 18$; $-19 \leq l \leq 19$
Reflections collected	18189
Independent reflections	6288 [$R_{int} = 0.0417$]
Observed reflections	3836
Data/restraints/parameters	6288/24/440
Goodness-of-fit on F^2	0.826
R, wR indices[$I > 2\sigma$ (I)]	0.0500, 0.1284
R, wR indices(all data)	0.0920, 0.1686
Largest diff. peak and hole(e·Å^{-3})	0.166, –0.200

Results and Discussion

Synthesis of 3-Dimethyl-Aminomethylheptan-2-One(3)

The Mannich reaction is an organic reaction which consists of an amino alkylation of an acidic proton placed next to a carbonyl functional group with formaldehyde and ammonia or any primary or secondary amine. The final product is a β-amino-carbonyl compound also known as a Mannich base. The reaction equation is shown in Scheme 2. The Mannich reaction is continuously causing widespread interest in chemical workers. The synthesis



Scheme 2. Mannich reaction.

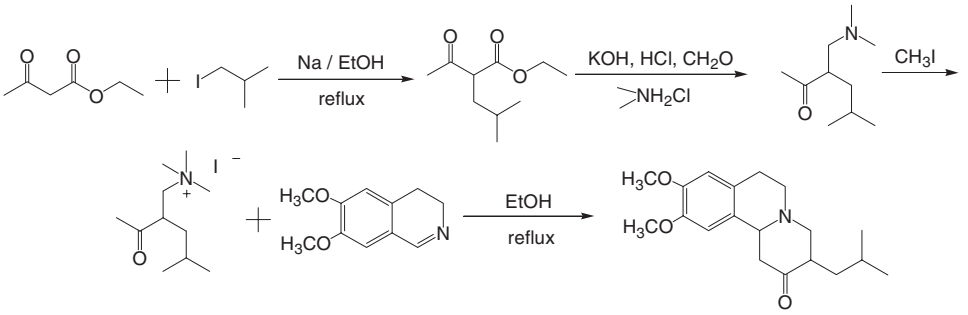
Table 2. Selected bond lengths (Å) and angles (°)

Bond lengths			
N(1)–C(5)	1.458(3)	N(2)–C(24)	1.463(3)
N(1)–C(6)	1.459(3)	N(2)–C(25)	1.457(3)
N(1)–C(10)	1.464(3)	N(2)–C(29)	1.465(3)
O(1)–C(14)	1.412(3)	O(4)–C(33)	1.425(3)
O(3)–C(8)	1.216(3)	O(6)–C(27)	1.215(3)
C(1)–C(2)	1.374(3)	C(20)–C(21)	1.370(3)
C(3)–C(4)	1.507(3)	C(22)–C(23)	1.506(3)
C(6)–C(7)	1.521(3)	C(25)–C(26)	1.534(3)
C(17)–C(18)	1.509(13)	C(36)–C(37)	1.498(5)
Bond angles			
C(5)–N(1)–C(6)	110.73(18)	C(24)–N(2)–C(25)	111.22(19)
C(5)–N(1)–C(10)	111.07(18)	C(24)–N(2)–C(29)	111.48(18)
C(6)–N(1)–C(10)	110.54(18)	C(25)–N(2)–C(29)	110.57(18)
C(1)–O(1)–C(14)	117.3(2)	C(20)–O(4)–C(33)	116.8(2)
O(3)–C(8)–C(9)	120.8(2)	O(6)–C(27)–C(28)	120.8(2)
O(3)–C(8)–C(7)	122.8(2)	O(6)–C(27)–C(26)	122.0(2)
C(1)–C(2)–C(3)	121.7(2)	C(20)–C(21)–C(22)	121.9(2)
C(3)–C(4)–C(5)	111.2(2)	C(22)–C(23)–C(24)	111.5(2)
C(6)–C(7)–C(8)	109.74(19)	C(25)–C(26)–C(27)	110.20(19)
C(7)–C(16)–C(17)	117.1(3)	C(26)–C(35)–C(36)	116.7(2)
C(18)–C(17)–C(19)	113.0(6)	C(37)–C(36)–C(38)	110.9(3)

methods of Mannich base are constantly improving. From the beginning of indirect synthesis, the method was developed into two-component way. In recent years, more and more attention has been paid in the three-component one-pot Mannich reaction of aldehyde, amine, and ketone. The three-component one-pot synthesis strategy enables the preparation of Mannich base to become more convenient and its applications become more and more extensive. In view of this, we designed the synthesis operation steps of 3-dimethyl-aminomethylheptan-2-one (**3**) using the Mannich reaction principle. Utilizing the concentrated hydrochloric acid and ethanol as a catalyst system, the Mannich reaction of 5-methyl-2-hexanone (**1**), dimethylamine (**2**), and formaldehyde solution occurred directly. This three-component one-pot preparation of compound **3** has not been reported. The method is simple, mild, and environmental friendly. It meets the requirements of green chemistry, and so it has potential applications.

Synthesis of TBZ

We found two preparation methods of **TBZ** in the literature [12,13]. In our practice, these two methods were summarized and improved. We got our own concise way in order to meet the growing needs of the marketed drug TBZ. In 1969, the method was as follows. Addition of 3-dimethyl-aminomethylheptan-2-one (**3**) to an aqueous solution of 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (**4**), after three days at room temperature, a quantitative yield of **TBZ** was obtained. Recently, the reported synthesis of TBZ is shown in Scheme 3. Our approach was that the mixed solution of 3-dimethyl-aminomethylheptan-2-one (**3**),



Scheme 3. The reported synthesis of TBZ.

6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (**4**), and triethylbenzylammonium chloride was stirred and heated under reflux at 95°C for 6 h. The final product was confirmed by ^{1}H NMR, MS, and IR. Compared with the former, significant savings in reaction time was achieved through the optimization of reaction conditions. In addition, the former method did not report the synthesis of 3-dimethyl-aminomethylheptan-2-one (**3**). It is very inconvenient to repeat the synthesis of TBZ using the former method. The latter method has four reaction steps. There are only two reaction steps in our approach. Our preparation method greatly reduces the operation steps, saving the cost of the preparation of **TBZ**, and reducing the pollution of the environment.

Spectroscopic Characterization

The infrared spectra of TBZ show strong absorption bands at 2941 and 2920 cm^{-1}, with a shoulder at approximately 2900 cm^{-1} mainly due to the C–H stretching vibration of the methyl and methylene groups present in the title compound molecule.

TBZ exhibits a sharp band of large intensity at 1701 cm^{-1}, which is attributed to the C=O stretching vibration of the carbonyl group. The C=C skeletal vibration of the benzene ring in the TBZ molecule appears at 1610, 1517, and 1466 cm^{-1}.

The ^{1}H NMR spectrum of the TBZ in $CDCl_3$ solution shows two singlet peaks for the benzene ring hydrogen atoms (-PhH) at δ 6.62 and 6.55 ppm. The hydrogen atoms of the methoxyl groups (-OCH_3) bonded to the aromatic ring in the TBZ are observed in the ^{1}H NMR spectrum as two singlets, exhibiting at δ 3.86 and 3.83 ppm. The two doublets at δ 0.93∼0.92 and 0.91∼0.90 ppm are assigned to the hydrogen atoms of the methyl groups (-CH_3). On the other hand, the signals referred to the hydrogen atoms of the methylene and tert-methyl groups (-CH_2R; -CHR_2) appear at δ 3.52∼3.49, 3.31∼3.27, 3.16∼3.07, 2.92∼2.88, 2.77∼2.71, 2.63∼2.51, 2.39∼2.33, 1.84∼1.78, 1.70∼1.63, and 1.07∼1.00 ppm, respectively.

Crystal Structure

The colorless single crystal of TBZ was grown from methanol solution by slow evaporation at room temperature. The single crystal is a polyhedron, and we used an Olympus IX51 microscope camera to capture its pictures. The front and side images are shown in Fig. 2, and the single crystals are magnified by one hundred times.

The title compound crystallized in the monoclinic system, space group $P2_1/c$ with unit cell parameters: a = 15.1494(15) Å, b = 15.9159(15) Å, c = 16.5924(16) Å,

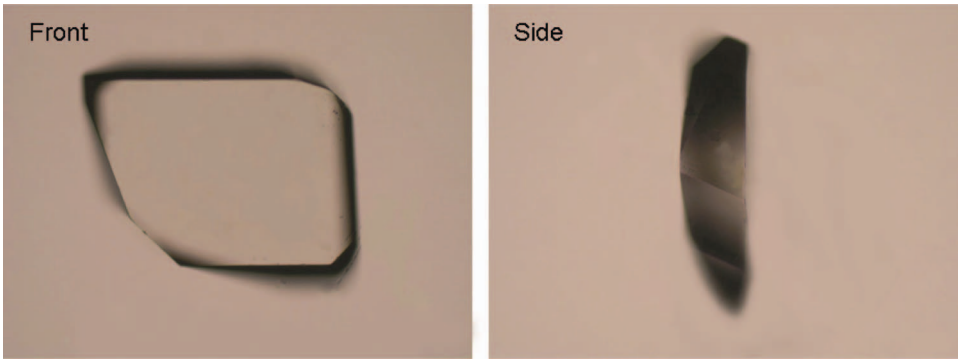


Figure 2. Front and side views of the single crystal of TBZ.

$\beta = 115.5930(10)^{\circ}$, $\mu = 0.078$ mm^{-1}, $V = 3608.2(6)$ Å^3, $Z = 8$, $Dc = 1.169$ g cm^{-3}, $F(000) = 1376$, $T = 296(2)$ K. The molecular structure of TBZ is shown in Fig. 3 and a perspective view of the crystal packing in the unit cell is shown in Fig. 4.

There are three rings in the structure of TBZ, namely benzene ring, nitrogen-containing six-membered ring, and nitrogen-containing six-membered ketone ring. They do not share a common plane. The benzene ring is a plane conformation, the other two rings are chair conformations.

The molecular ellipsoid graph of TBZ in Fig. 3 reveals that there are four chiral carbons in the two molecules. The configurations of four chiral carbons are *R, R, S,* and *S*, corresponding to the C-7, C-10, C-26, and C-29 (namely the C-3 and C-11b positions of the

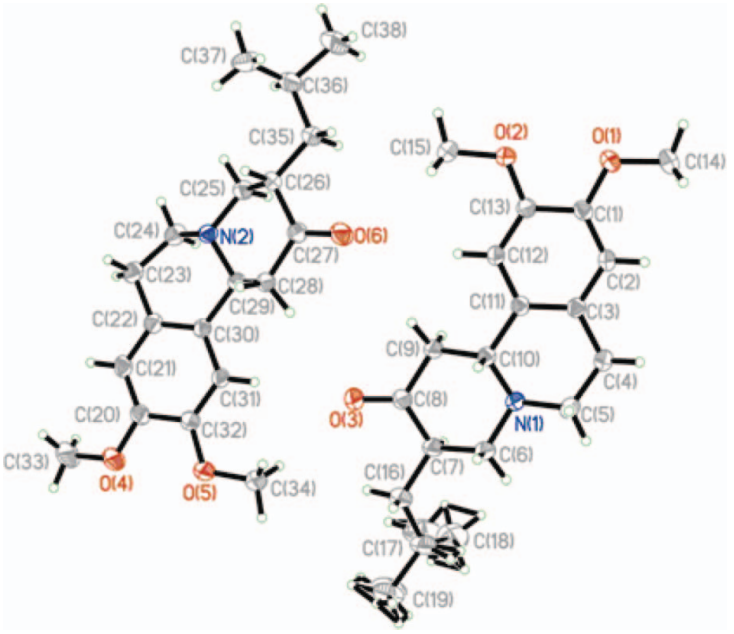


Figure 3. The molecular structures of TBZ's enantiomers; 30% probability ellipsoids are shown.

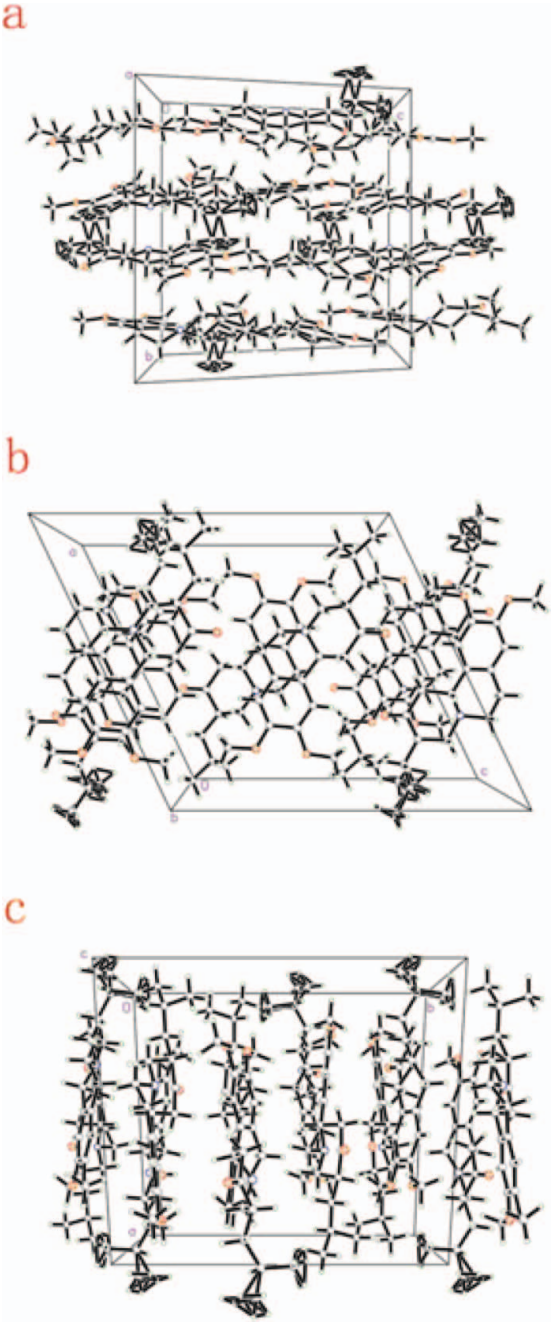


Figure 4. Packing of the TBZ molecules viewed along the a, b and, c axis, respectively.

numbered TBZ shown in Fig. 1), respectively. Therefore, the single crystal of TBZ consists of (3*R*, 11b*R*) and (3*S*, 11b*S*) enantiomers. Terminal methyl groups at C-18 and C-19 are disordered in the (3*R*, 11b*R*) enantiomer. In the two enantiomers, various bond lengths and bond angles are all basically the same, and only small differences exist between them. The

interatomic distances of conjugated C–C bonds in the benzene ring vary from 1.370(3) Å to 1.406(3) Å. That of other C–C bonds range from 1.499(3) Å to 1.596(14) Å. The bond lengths of C–N and C–O single bonds vary in the range of 1.457(3)~1.465(3) Å and 1.367(3)~1.425(3) Å, respectively. That of C=O double bonds are 1.215(3) and 1.216(3), and they are obviously shorter than C–O single bonds, suggesting that they have substantial double bond character. These data are in accordance with the typical bond lengths in organic compounds [14].

There are two different patterns of the stacked arrangements in general aromatic systems for $\pi\cdots\pi$ interactions: offset face-to-face and edge-to-face packing. The distance between aromatic ring centroids with the range of 3.3–3.8 Å is the valid value of $\pi\cdots\pi$ interactions both in the two patterns [15]. The shortest distance between two benzene ring centroids is 5.161 Å in the crystal stacking of TBZ as shown in Fig. 5. Obviously, in the crystal packing, there is no $\pi\cdots\pi$ interaction, and the molecules of TBZ are mainly stabilized by Van der Waals forces.

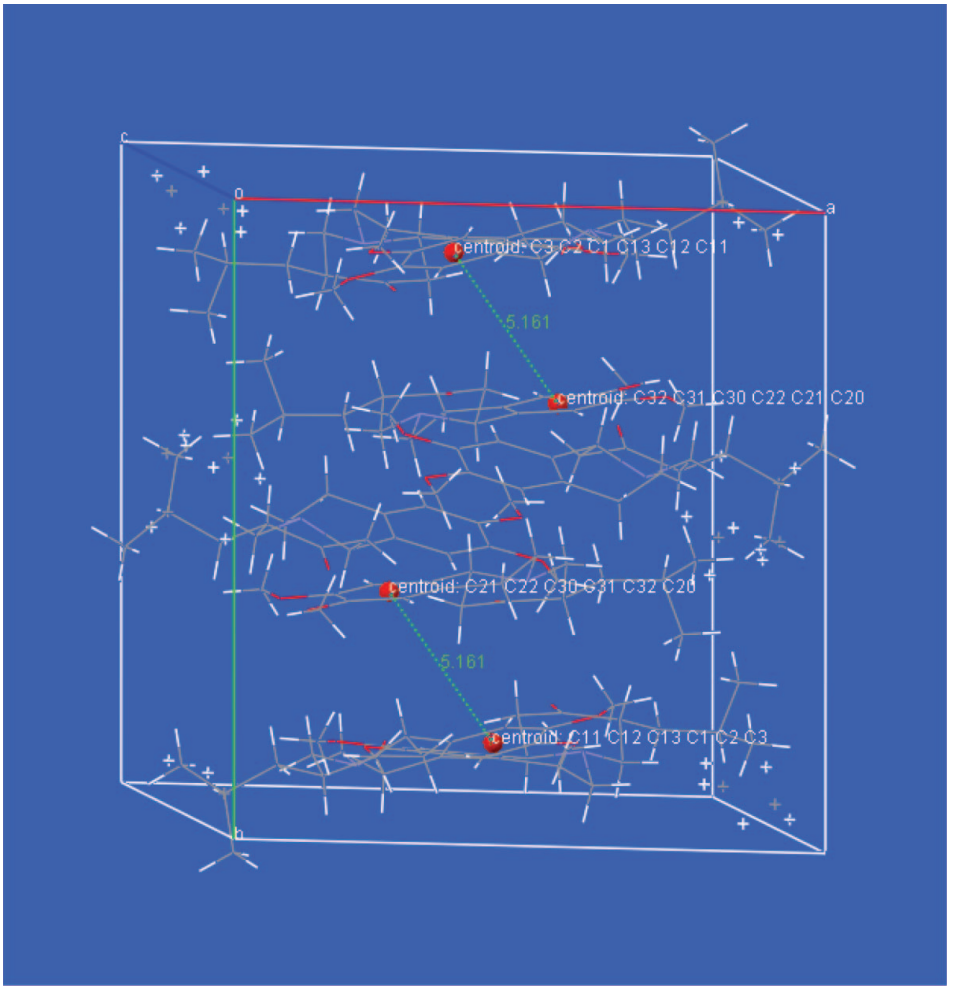


Figure 5. The shortest distance between two benzene ring centroids in the crystal stacking of TBZ.

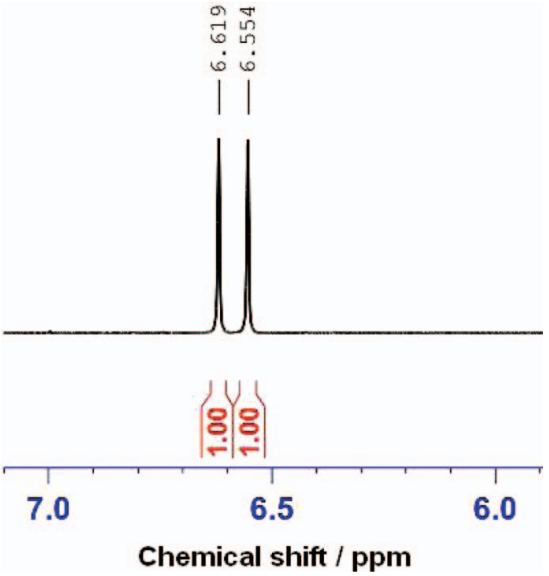


Figure 6. Chemical shifts of the benzene ring hydrogen atoms in the ^{1}H NMR spectrum of the TBZ.

Configuration of Tetrabenazine

It is well known that enantiomers are mirror-image isomers, which are nonsuperimposable. They only differ in the way the atoms are oriented in space. Enantiomers in principle do not differ in their physical properties unless they are placed in a chiral environment. For this reason, in the ^{1}H NMR spectroscopy, the hydrogen atoms inside different enantiomers have the same chemical shift, and that of diastereomers have differences in chemical shift. In theory, there are four isomers of the TBZ, namely (3*R*, 11b*R*), (3*S*, 11b*S*), (3*R*, 11b*S*), and (3*S*, 11b*R*) isomers. The TBZ synthesized by our team is a racemic form. If it consists of diastereomers, in the ^{1}H NMR spectrum of TBZ, the two benzene ring proton resonances at C-8 and C-11, as shown in Fig. 1, will split into multiple peaks, rather than two singlet peaks. This can be indirectly confirmed from the literature [10]. The two benzene ring proton resonances in TBZ synthesized by our team are shown in Fig. 6. There are two singlet peaks. By this means, we can determine that our TBZ consists of (3*R*, 11b*R*) and (3*S*, 11b*S*) enantiomers or (3*R*, 11b*S*) and (3*S*, 11b*R*) enantiomers. The X-ray diffraction of the single crystal chosen from TBZ's saturated methanol solution indicated that the precipitated crystal contains (3*R*, 11b*R*) and (3*S*, 11b*S*) enantiomers. Finally, we can infer that TBZ obtained from our method consists of (3*R*, 11b*R*) and (3*S*, 11b*S*) enantiomers. This conclusion is consistent with the speculation in the literature [11]. The configuration of TBZ is determined directly, which may provide some help for the further study of structure–activity relationship for the binding of the enantiomers of TBZ to the VMAT2.

Conclusions

By means of X-ray diffraction, we used the most direct way to confirm that the TBZ consists of (3*R*, 11b*R*) and (3*S*, 11b*S*) enantiomers. In addition, our method provides an efficient and concise way to the synthesis of the marketed drug TBZ.

Supporting Information

CCDC-819713 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, 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.

Acknowledgments

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