Asymmetric synthesis, crystal structure, and antidepressant activity of 2-aryl-3-alkyl-5-methyl-2-morpholinol hydrochlorides

Gao Cao, Ai-Xi Hu, and Xin-Rong Xiao

Abstract: 2-Aryl-3-alkyl-5-methyl-2-morpholinols were synthesized from the reactions of chiral 2-aminopropan-1-ol with 2-bromo-1-phenylpropan-1-one, 2-bromo-1-(3-chlorophenyl)propan-1-one, 1-(4-(benzyloxy)phenyl)-2-bromopropan-1-one, 2-bromo-1-(6-methoxy- naphthalen-2-yl)propan-1-one, and 1-(4-(benzyloxy)phenyl)pentan-1-one in *N*-methyl-2-pyrrolidone (NMP), respectively. The 2-aryl-3-alkyl-5-methyl-2-morpholinols were reacted with hydrogen chloride to give the hydrochloride salts with yields of 56%–77%. The structures of the products were proven by means of their ^{1}H NMR, IR, and MS spectroscopic data. The stereochemical properties of representative products were established unambiguously by the X-ray single crystal analysis. The antidepressant activities of the title compounds were assayed by the mouse forced swimming test (FST). The FST results confirm the antidepressant properties of our products.

Key words: morpholinol hydrochloride, hemiacetal, chiral synthesis, X-ray diffraction, absolute configuration, antidepressant activity.

Résumé : Opérant dans la *N*-méthylpyrrolid-2-one (NMP), on a réalisé la synthèse de 2-aryl-3-alkyl-5-méthylmorpholin-2-ols par les réactions du 2-aminopropan-1-ol avec respectivement de la 2-bromo-1-phénylpropan-2-one, de la 2-bromo-1-(3-chlorophényl)propan-1-one, de la 1-[4-(benzyloxy)phényl]-2-bromopropan-2-one, de la 2-bromo-1-(6-méthoxynaphtalén-2-yl)propan-1-one et de la 1-[4-(benzyloxy)phényl]pentan-1-one. Les réactions des 2-aryl-3-alkyl-5-méthylmorpholin-2-ols avec de l'acide chlorhydrique conduit à la formation des chlorhydrates avec des rendements allant de 56 % à 77 %. On a confirmé l'identité des structures des produits à l'aide de données de résonance magnétique nucléaire du ^{1}H, de spectroscopie IR et de spectrométrie de masse. Les propriétés stéréochimiques de produits représentatifs ont été établies sans ambiguïté à l'aide de la diffraction de rayons X par des cristaux uniques. On a évalué les propriétés antidépressives des composés mentionnés dans le titre en les administrant à des souris impliquées dans un test où elles sont forcées de nager. Les résultats de ces études permettent de confirmer les propriétés antidépressives de ces produits.

Mots-clés : chlorhydrates de morpholinols, hémiacétal, synthèse chirale, diffraction des rayons X, configuration absolue, activité antidépressive.

[Traduit par la Rédaction]

Introduction

2-Aryl-2-morpholinol derivatives have been utilized extensively by chemists because of their pharmaceutical importance in drug design and extensive application in organic synthesis. The biological utility of 2-aryl-2-morpholinol derivatives is wide-ranging, including analeptic, antioxidant, hypocholesterolemic, anorectic, adrenergic blocking, and antifungal properties, and they are especially widely described for their antidepressant activities. 2-Aryl-2-morpholinol derivatives also have been used to treat human diseases such as tardive dyskinesia, minimal brain dysfunction, obesity, migraine, sexual dysfunction, chronic fatigue, restless legs syndrome, Parkinson's disease (1–9).

Research on phenylmorpholinols has led to the discovery of (3,5-difluorophenyl)morpholinol, a novel antidepressant agent and selective inhibitor of norepinephrine uptake, which is active in animal behavioral models that respond to effective clinical antidepressant drugs (10). The racemate compound 2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol has been synthesized and the (+) and (–) enantiomers of the racemate have been subsequently separated via chromatography (11, 12) or dynamic kinetic resolutions (13–15). This product is useful in prophylaxis or therapy, especially as a stimulant and antidepressant for the central nervous system. Musso (16) designed and synthesized a chiral hapten for radioimmunoassay of the antidepressant (2*S*,3*S*,5*R*)-2-(3,5-difluorophenyl)-3,5-dimethyl-2-morpholinol hydrochloride. However, the problem of the synthesis of 2-aryl-2-morpholinol derivatives is that the preparation requires a

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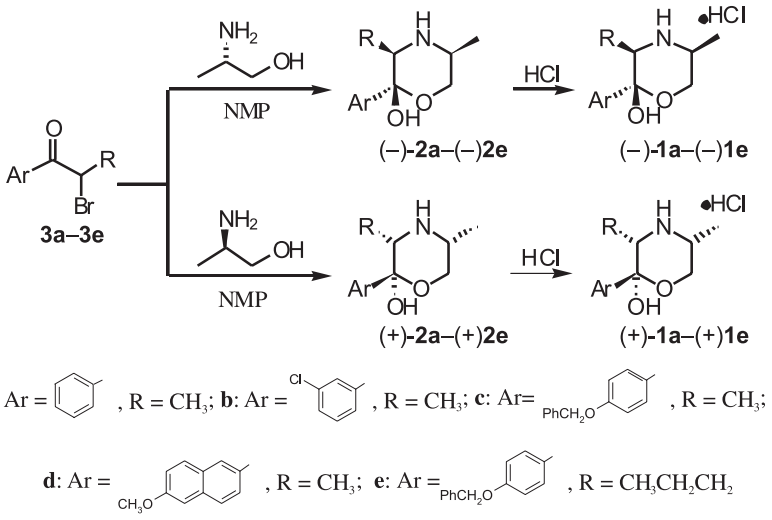
Scheme 1. Synthesis of 2-aryl-3-alkyl-5-methyl-2-morpholinol hydrochlorides.



long reaction time and that the solvent is volatile and poisonous (17–20).

By structural modification of the drug, it is possible to obtain new compounds with comparable activity and lower toxicity. On the other hand, enantiomers of the same drug can have different pharmacodynamic and pharmacokinetic properties. Today, most new drugs and those under development consist of a single optically active isomer. The current trend in drug markets is a rapid increase in the sales of chiral drugs. Chiral drugs represent close to 40% of all drug sales worldwide in 2001 (21). Therefore, the synthesis of chiral 2-aryl-3-alkyl-5-methyl-2-morpholinol hydrochlorides was undertaken.

In this study, we report the synthesis of novel chiral 2-aryl-3-alkyl-5-methyl-2-morpholinols **2a**–**2e** and their hydrochloride salts **1a**–**1e** by the reactions of chiral 2-aminopropan-1-ol with α-bromo-aromatic ketones **3a**–**3e** in *N*-methyl-2-pyrrolidone (NMP) and their antidepressant activities. The synthesis of the title compounds was shown in Scheme 1.

Results and discussion[2]

Synthesis of optically active 2-aryl-3-alkyl-5-methyl-2-morpholinol hydrochlorides

The optical rotations of 2-aryl-3-alkyl-5-methyl-2-morpholinol hydrochlorides by the reactions of (*S*)-2-aminopropan-1-ol and (*R*)-2-aminopropan-1-ol with α-bromo-aromatic ketones are levorotatory and dextrotatory, respectively. The detailed data are tabulated in Table 1.

2-Aryl-3-alkyl-5-methyl-2-morpholinol hydrochlorides synthesized from opposite configuration 2-aminopropan-1-ol have the analogous melting points and the analogous numerical value, but the optical rotation is in the opposite direction. 2-Aryl-3-alkyl-5-methyl-2-morpholinol hydrochlorides synthesized from contrary configuration 2-aminopropan-1-ols should be a pair of enantiomers.

When 2-amino-2-methyl-1-propanol reacted with chiral α-ketotriflate, the enantiopure hydroxylbupropion products conformationally locked at (2*S*,3*S*) or (2*R*,3*R*). The (2*R*,3*S*) or (2*S*,3*R*) isomer was not observed (22). In our products, the ^{1}H NMR spectra show only one double singlet at δ: 0.90–1.10 for the 3-CH_3 group of the morpholine ring, which shows that the synthesized compounds are single enantiomers. If the products are diastereomeric [(2*R*,3*R*,5*S*)-**1a** to (2*R*,3*R*,5*S*)-**1e** and (2*R*,3*S*,5*S*)-**1a** to (2*R*,3*S*,5*S*)-**1e**] or [(2*S*,3*S*,5*R*)-**1a** to (2*S*,3*S*,5*R*)-**1e** and (2*S*,3*R*,5*R*)-**1a** to (2*S*,3*R*,5*R*)-**1e**], the methyl group at the axial position should be in the downfield position because the deshielding effect is stronger than at the equatorial position. So, the 3-CH_3 group of the morpholine ring should have two double singlets in the ^{1}H NMR spectrum.

Single crystal investigation of the representative products

The structure and stereochemical properties of (2*S*,3*S*,5*R*)-3,5-dimethyl-2-(3-chlorophenyl)-2-morpholinol hydrochloride and (2*R*,3*R*,5*S*)-3,5-dimethyl-2-(6-methoxy-2-naphthyl)-2-morpholinol hydrochloride were investigated by X-ray diffraction. Colorless crystals suitable for X-ray diffraction analysis were grown by slow evaporation of the mixture of ethanol and ether (1:1 *v*/*v*). X-ray data were collected on a Bruker AXS SMART 1000 CCD diffractometer equipped with graphite monochromated Mo K_α radiation (λ = 0.710 73 Å). The data set was recorded at RT in ω–ϕ scan mode. Preliminary orientation matrices were obtained from the first frames using SMART (23). The data were empirically corrected for absorption and other effects using

[2] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5120. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 292641 and 292642 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

Table 1. 2-Aryl-3-alkyl-5-methyl-2-morpholinol hydrochlorides.

			(+)-**1a** to (+)-**1e**			(–)-**1a** to (–)-**1e**		
	Ar	R	mp (°C)	$[\alpha]^{20}_D$ (°)[a]	yield (%)[b]	mp (°C)	$[\alpha]^{20}_D$ (°)[a]	yield (%)[b]
a	C_6H_5	Me	178–180	+30.8	59.6	176–178	–32.8	56.0
b	3-Cl-C_6H_4	Me	203 to 204	+40.6	59.6	200 to 201	–44.6	56.2
c	4-$PhCH_2O$-C_6H_4	Me	161–163	+10.8	77.0	159–162	–11.5	63.4
d	6-MeO-$C_{10}H_6$	Me	182–184	+13.7	69.4	181–183	–13.6	64.9
e	4-$PhCH_2O$-C_6H_4	n-Pr	169–171	+5.6	60.4	169–171	–5.2	60.8

[a]Solvent was EtOH, concn. = 1.0.
[b]Yields are based on the starting **3a**–**3e**.

Table 2. Crystallographic data and structure refinement for (+)-**1b** and (–)-**1d**.

Compound	(+)-**1b**	(–)-**1d**
CCDC No.	292641	292642
Empirical formula	$C_{12}H_{17}NO_2Cl_2$	$C_{17}H_{22}NO_3Cl$
Formula mass	278.17	323.81
Colour, habit	Colourless, block	Colourless, block
Crystal dimensions (mm^3)	0.26 × 0.22 × 0.20	0.50 × 0.38 × 0.18
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12$	$P2_12_12_1$
Z	4	4
a (Å)	8.718(2)	7.1093(4)
b (Å)	20.264(6)	7.6947(5)
c (Å)	7.882(2)	29.8868(19)
Collection ranges	$-10 \le h \le 9$, $-23 \le k \le 25$, $-9 \le l \le 9$	$-8 \le h \le 9$, $-9 \le k \le 7$, $-24 \le l \le 38$
T (K)	294(2)	292(2)
V ($Å^3$)	1392.5(6)	1634.93(17)
Calculated density (g/cm^3)	1.327	1.316
Mo K_α radiation (Å)	0.710 73	0.710 73
Absorption correction	Multiscan	Multiscan
F(000)	584	688
θ Range for data collection (°)	2.77–25.09	2.65–26.71
Measured reflections	7875	8797
Independent reflections	2836 (R_{int} = 0.0293)	3562 (R_{int} = 0.0185)
Data, restraints, parameters	2836, 0, 168	3562, 0, 203
Goodness-of-fit on F^2	1.029	1.055
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0350, $wR2$ = 0.0724	$R1$ = 0.0544, $wR2$ = 0.0964
R indices (all data)	$R1$ = 0.0541, $wR2$ = 0.0808	R1 = 0.0408, $wR2$ = 0.1092
Absolute structure parameter	–0.02(6)	0.07(8)
Largest diff. peak and hole (e $Å^{-3}$)	0.185 and –0.253	0.350 and –0.170

SADABS (24). The structure was solved by direct methods and refined by the full-matrix least-squares methods on F^2 with the program SHELXTL-97 (25). H atoms were positioned at geometrically possible positions and refined using the riding model with U_{eq} set equal to the U_{eq} of the parent atom multiplied by 1.2 (or 1.5 for the methyl groups). O–H and N–H of (+)-**1b** were freely refined. Further details of data collection and structure refinement are given in Table 2.

Absolute configuration of the representative compounds

According to the molecular structure of (–)-**1d** with atom labeling (Fig. 1), the naphthalene ring C(7)–C(16) is essentially planar with a mean deviation of 0.0242(3) Å. The morpholine ring is a distorted chair somewhat flattened at C(2) and sharpened at C(5), and the dihedral angles between the C(3)–C(2)–O(1) and C(1)–C(5)–N(1) planes and the N(1)–C(3)–O(1)–C(1) plane are 45.9(2)° and 52.4(2)°, respectively. The 3-methyl group and the 5-methyl group make dihedral angles of 39.8(3)° and 38.4(3)° with respect to the C(2)–C(3)–N(1) and C(1)–C(5)–N(1) planes; the 2-hydroxy group and the 2-(6-methoxy-2-naphthyl) group make dihedral angles of 38.9(2)° and 31.0(3)° with respect to the C(3)–C(2)–O(1) plane, respectively. The 3- and 5-methyl groups and the 2-hydroxy group are on the same side of the morpholine ring, but the 2-(6-methoxy-2-naphthyl) group is on the reverse side. The chiral carbon atoms of (–)-**1d**, C(2) and C(3) are (*R*)-configuration, and C(5) is (*S*)-configuration. The absolute configuration of (–)-**1d** is (2*R*,3*R*,5*S*).

Fig. 1. The ORTEP (26) plot of the X-ray crystal structure of compound (–)-**1d** with 30% probability displacement ellipsoids.

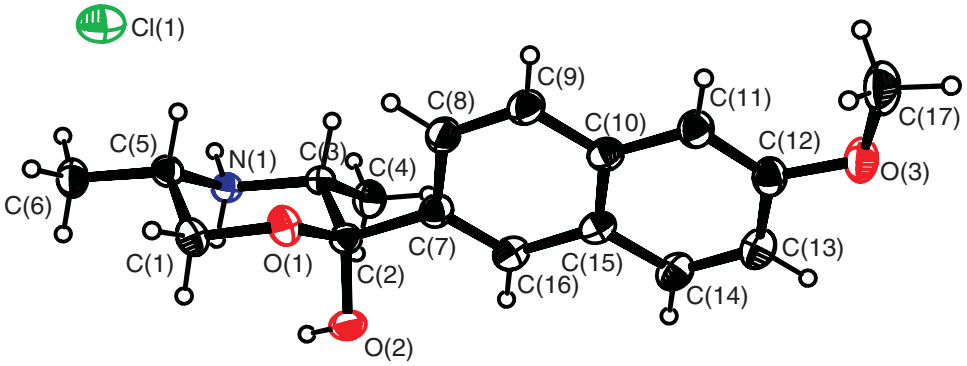
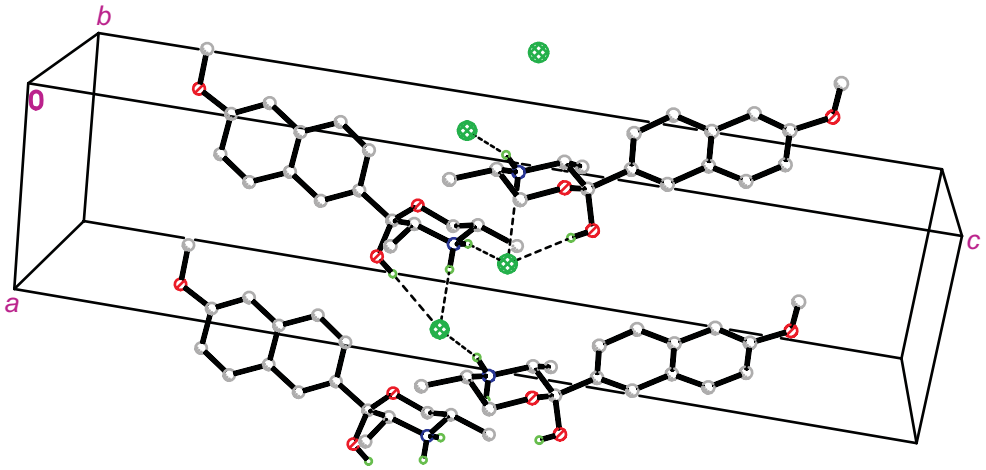


Fig. 2. The crystal packing of (–)-**1d**. For the sake of clarity, H atoms bonded to C atoms have been omitted. Hydrogen bonds have been shown as dashed lines.



The data obtained from the NMR spectral analysis and X-ray investigation are in good agreement, giving evidence of similar conformational behavior in the crystal and in solution. In addition, the structure exhibits intermolecular hydrogen bonds of type N–H–Cl and O–H–Cl. The hydrogen bonds are N(1)–H(1C)–Cl(1)^{i} (2.27 Å, 162.1°) with symmetry codes x–1/2, 1/2–y, –z and N(1)–H(1D)–Cl(1)^{ii} (2.23 Å, 173.6°) and O(2)–H(2)–Cl(1)^{ii} (2.51 Å, 176.7°) with symmetry codes x–1, y–1, z. (Fig. 2).

The molecular structure of (–)-**1d** in crystal is stabilized by the intermolecular hydrogen bonds and the intermolecular electrostatic interactions between the positively charged atom N^+ and Cl^-; the chlorine atom is set apart from the hydroxyl oxygen atom (on the reverse side of the morpholine ring), and the hydroxyl oxygen atom of (–)-**1d** does not itself form a hydrogen bond with the chlorine atom. The structure of (+)-**1b** with atom numbering is shown in Fig. 3 (27).

Compared with (–)-**1d**, the chlorine atom of (+)-**1b** is closer to the hydroxyl oxygen atom and this is probably caused by the 2-Ar substitutes. Atom O(1) in the hydroxyl group acts as a hydrogen-bond donor via H(1) to atom Cl(2) forming the hydrogen bond O(1)–H(1)–Cl(2) (2.29 Å, 166°). Atom N(1) of the morpholine ring acts as a hydrogen-bond donor via H(1C) and H(1D) to two of the other chlorine atoms of the molecule forming the hydrogen bonds N(1)–H(1C)–Cl(2)^{i} (2.27 Å, 173.1°) and N(1)–H(1D)–Cl(2)^{ii} (2.34 Å, 151°) (Fig. 4).

Our synthesis of **1a**–**1e** produced a chair model of a six-membered ring, and the configuration is stable when the aryl and alkyl groups are at an equatorial position. Thus, the two formed chiral carbon atoms C(2) and C(3) in our products maintain "*Z*" shape and not "*E*" shape. The configuration of the products is determined by the chirality of 2-aminopropan-1-ol. The products were (2*R*,3*R*,5*S*)-**1a** to (2*R*,3*R*,5*S*)-**1e**, namely (–)-**1a** to (–)-**1e** when (*S*)-2-aminopropan-1-ol was used. The products were (2*S*,3*S*,5*R*)-**1a** to (2*S*,3*S*,5*R*)-**1e**, namely (+)-**1a** to (+)-**1e**) when (*R*)-2-aminopropan-1-ol was used. (Fig. 5).

When R was an H atom, we did not obtain 2-aryl-5-methyl-2-morpholinol hydrochloride products by the same procedure. α-Bromo-1-aromatic ethanones, such as 2-bromo-1-(4-methoxyphenyl)ethanone, 1-(4-(benzylo-xy) phenyl)-2-bromoethanone, or 2-bromo-1-(6-methoxynaphthalen-2-yl)ethanone, reacted with chiral 2-aminopropan-1-ol during the HCl acidification process initially obtaining a solid, which absorbed water from the environment to form a stagnant oil. The ^{1}H NMR spectra did not indicate cyclic (morpholine) structure, and the IR spectra showed a carbonyl group absorption band of the hydrochloride salt. The hemiketals with R = H are likely to exhibit ring-opening in aq. HCl.

Fig. 3. The ORTEP plot of the X-ray crystal structure of compound (+)-**1b.**

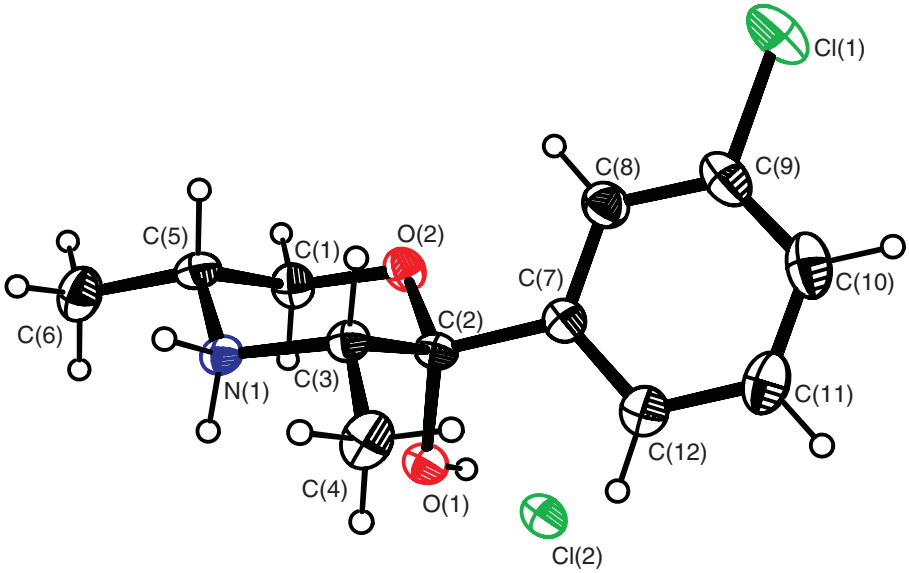
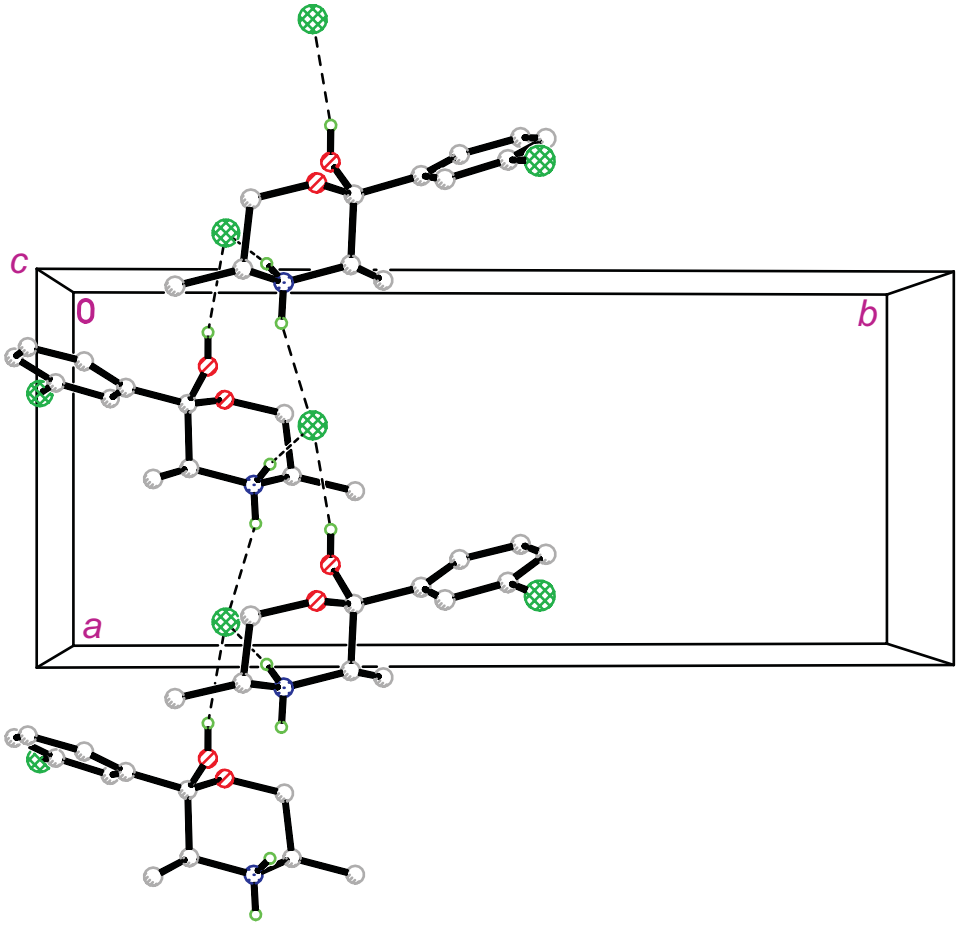


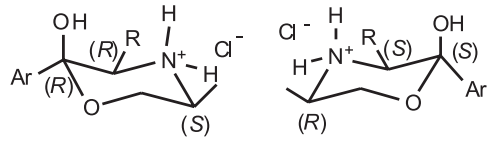
Fig. 4. Autostereogram of the crystal structure of (+)-**1b** with hydrogen bonds.



Antidepressant activities of 2-Aryl-3-alkyl-5-methyl-2-morpholinols hydrochloride

Clinical depression is one of the most complex human diseases. It has an unequivocally strong hereditary component and affects about 15% of the population at some point during their lives. The present study was undertaken to investigate the effect of 2-aryl-3-alkyl-5-methyl-2-morpholinols hydrochloride on depression in the mouse

Fig. 5. Absolute configuration of the title compound.



(2*R*,3*R*,5*S*)-(–)-**1a** to (2*R*,3*R*,5*S*)-(–)-**1e** (2*S*,3*S*,5*R*)-(+)-**1a** to (2*S*,3*S*,5*R*)-(+)-**1e**

forced swimming test (FST), an animal model of depression that is widely used to predict the antidepressant action of drugs in humans (28).

Male KM mice (the KM mouse strain is one of the outbred strains of mice introduced from Swiss mice to Kunming City, Yunnan Province, China) weighing 20–30 g were used in this study. The animals were housed in plastic cages under standard light (light on from 0700 to 2100 hours) and temperature (22 ± 1 °C) conditions for at least three days before experimentation with free access to standard laboratory food and tap water. Compounds **1d** and **1e** were chosen as title compounds and were suspended in a CMC solution (1%) with a concentration of 4 mg/mL in a dose volume of 0.1 mL per 10 g body weight in mice. Behavioral observations took place between 0800 and 1500 and each animal was used only once. A standard antidepressant drug amitriptyline was employed to standardize the animal models of depression and to compare the antidepressant efficacy of the title compounds.

Thirty minutes after intraperitoneal (IP) injection of the drugs, the mice were individually placed in a vertical glass cylinder (height of 25 cm, diameter of 12 cm) containing water (depth of 15 cm at 22 °C) and forced to swim. After an initial 2 min period of vigorous activity, each animal assumed a typical immobile posture. A mouse was considered to be immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water. The total duration of immobility was recorded during the next 4 min of a total 6 min test. The changes in immobility duration were studied after administering drugs in separate groups of animals. (Table 3).

According to the results in Table 3, the title compounds showed potent antidepressant activity, where the title compounds (+)-**1d** and (+)-**1e** show better activity than (–)-**1d** and (–)-**1e**, which shows that the configuration of (2*S*,3*S*,5*R*) compounds have greater antidepressant activity than the (2*R*,3*R*,5*S*) configuration.

Following the test, animals were allowed to dry and returned to their home cage. Adverse drug reactions were not observed in the 24 h period after the FST test. These results confirm the antidepressant properties of our products, suggesting the possible use of this drug in depressive patients that may be resistant to classical antidepressant therapy.

Conclusions

In summary, we report herein a rapid and efficient synthesis of some novel 2-aryl-3-alkyl-5- methyl-2-morpholinol hydrochlorides by the reaction of chiral 2-aminopropan-1-ol with α-bromo-aromatic ketones in NMP. Advantages of this approach include short reaction time, ease of operation, and excellent overall yields. The title compounds exhibited potent antidepressant activity in the FST test.

Table 3. Effects of target compounds on the time in mice forced swimming test.

Treatment	No. of mice	IP dose (mg/kg)	Immobility[a]
CMC (1%)	10	—	138.0±21.7
Amitriptyline	8	20	18.5±4.4[b]
(–)-**1d**	8	40	40.3±10.3[b]
(+)-**1d**	8	40	8.4±6.8[b]
(–)-**1e**	8	40	62.1±13.7
(+)-**1e**	8	40	24.8±7.3

[a]Results are expressed as mean ± S.E.M.
[b]$P < 0.05$ *vs.* CMC (1%).

Materials and methods

Instrumentation

All melting points were measured on an X-4 electrothermal digital melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian Inova-400 instrument with TMS as internal standard operating at 399.970 MHz. IR spectra were recorded on Avatar 360FT infrared spectrometer, using KBr discs. ESI-MS measurements were recorded on a Finngan LCQ LC-MS spectrometer. Optical rotations were measured on a WZZ-3 polarimeter. TLC analysis was carried out on glass plates, kept in iodine, using silica gel. X-ray data were collected on a Bruker AXS Smart 1000 CCD diffractometer.

General experimental procedure for the preparation of α-bromo-aromatic ketones

α-Aromatic ketone (0.1 mol) was dissolved in anhydrous ethanol (200 mL) and the mixture was stirred and heated to reflux. Cupric bromide (0.2 mol) was added to the reaction mixture in batches and the course of the reaction was followed by TLC analysis. After the reaction finished, the mixture was filtered and concentrated in vacuo. The resulting residue was taken up in dichloromethane, washed with 10% hydrochloric acid, washed with water until neutral, dried over anhydrous sodium sulfate, and concentrated in vacuo to give racemic α-bromo-aromatic ketones **3a**–**3e** (29).

Preparation of 2-aryl-3-alkyl-5-methyl-2-morpholinols hydrochloride

The general experimental procedure was as follows. α-Bromo-aromatic ketones **3a**–**3e** (0.01 mol) were added to a solution of (*S*)-2-aminopropan-1-ol (0.04 mol) in NMP (10 mL), and stirred for 1 h at RT. When no trace of starting material remained (by TLC analysis), an excess of water (30 mL) was added to the mixture, then extracted with diethyl ether (30 mL). The aqueous layer was extracted further with diethyl ether (15 mL) three times. The organic extracts were combined, washed (10 mL water), and dried by anhydrous sodium sulfate. After filtering, the filtrate was stirred in an ice bath, the pH adjusted to acidity by passing anhyd. HCl through it slowly, yielding a white crystalline substance, which was filtered and washed with acetone, and dried to give (–)-**1a** to (–)-**1e**. Compounds (+)-**1a** to (+)-**1e**) were synthesized using (*R*)-2-aminopropan-1-ol by the same pro-

cedure. Selected characterization data of the products follows.

(2*R*,3*R*,5*S*)-3,5-Dimethyl-2-phenyl-2-morpholinol hydrochloride (–)-1a

^{1}H NMR (CD_3SOCD_3, 400 MHz) δ: 0.94 (d, *J* = 6.4 Hz, 3H, CH_3), 1.22 (d, *J* = 6.4 Hz, 3H, CH_3), 3.28–3.50 (br m, 2H, morpholine ring 3,5-H), 3.79–3.93 (m, 2H, morpholine ring 6-H), 7.36–7.54 (m, 6H, C_6H_5, OH), 8.75, 10.34 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3244, 3037, 2937, 2787, 2738, 2681, 2532, 2438, 1560, 1452, 1388, 1350, 1261, 1178, 1138, 1090, 1057, 1001, 764, 702. ESI-MS *m*/*z*: 209 (M^+ + 2 – HCl), 208 (M^+ + 1 – HCl), 190 (M^+ + 1 – HCl – H_2O).

(2*R*,3*R*,5*S*)-3,5-Dimethyl-2-(3-chlorophenyl)-2-morpholinol hydrochloride (–)-1b

^{1}H NMR (CD_3SOCD_3, 400 MHz) δ: 0.98 (d, *J* = 6.4 Hz, 3H, CH_3), 1.24 (d, *J* = 6.4 Hz, 3H, CH_3), 3.36–3.56 (br m, 2H, morpholine ring 3,5-H), 3.81–3.94 (m, 2H, morpholine ring 6-H), 7.45–7.59 (m, 4H, C_6H_4), 7.89 (s, 1H, OH), 8.78, 10.39 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3211, 2976, 2947, 2898, 2790, 2681, 2551, 2515, 2459, 1572, 1450, 1373, 1250, 1184, 1142, 1093, 1059, 997, 906, 800, 708. ESI-MS *m*/*z*: 244 (M^+ + 2 – HCl), 243 (M^+ + 1 – HCl), 242 (M^+ – HCl), 226 (M^+ + 2 – HCl – H_2O), 224 (M^+ – HCl – H_2O).

(2*R*,3*R*,5*S*)-3,5-Dimethyl-2-(4-benzyloxyphenyl)-2-morpholinol hydrochloride (–)-1c

^{1}H NMR (CD_3SOCD_3, 400 MHz) δ: 0.95 (d, *J* = 6.4 Hz, 3H, CH_3), 1.20 (d, *J* = 6.4 Hz, 3H, CH_3), 3.26–3.49 (br m, 2H, morpholine ring 3,5-H), 3.78–3.91 (m, 2H, morpholine ring 6-H), 5.10 (s, 2H, OCH_2), 7.01–7.45 (m, 10H, C_6H_4, C_6H_5, OH), 8.71, 10.20 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3286, 2941, 2792, 2679, 2553, 2455, 1604, 1510, 1456, 1387, 1240, 1173, 1057, 1005, 831, 41, 698. ESI-MS *m*/*z*: 315 (M^+ + 2 – HCl), 314 (M^+ + 1 – HCl), 296 (M^+ + 1 – HCl – H_2O).

(2*R*,3*R*,5*S*)-3,5-Dimethyl-2-(6-methoxy-2-naphthyl)-2-morpholinol hydrochloride (–)-1d

^{1}H NMR (CD_3SOCD_3, 400 MHz) δ: 0.97 (d, *J* = 6.4 Hz, 3H, CH_3), 1.23 (d, *J* = 6.4 Hz, 3H, CH_3), 3.57 (br m, 2H, morpholine ring 3,5-H), 3.87 (s, 3H, OCH_3), 3.92–3.97 (m, 2H, morpholine ring 6-H), 7.16–8.05 (m, 7H, $C_{10}H_6$, OH), 8.81, 10.17 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3404, 2951, 2893, 2800, 2740, 2682, 2596, 2490, 1610, 1485, 1387, 1269, 1198, 1063, 1001, 854. ESI-MS *m*/*z*: 289 (M^+ +2 – HCl), 288 (M^+ + 1 – HCl), 270 (M^+ + 1 – HCl – H_2O).

(2*R*,3*R*,5*S*)-3-Propyl-5-methyl-2-(4-benzyloxyphenyl)-2-morpholinol hydrochloride (–)-1e

^{1}H NMR (CD_3SOCD_3, 400 MHz) δ: 0.57–1.38 (m, 10H, CH_3, $CH_2CH_2CH_3$), 3.21–3.53 (br m, 2H, morpholine ring3,5-H), 3.75–3.91 (m, 2H, morpholine ring 6-H), 5.11 (s, 2H, OCH_2), 7.01–7.45 (m, 10H, C_6H_4, C_6H_5, OH), 8.78, 9.67 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3198, 2968, 1630, 1565, 1508, 1455, 1330, 1254, 1080, 1010. ESI-MS *m*/*z*: 342 (M^+ + 1 – HCl).

(2*S*,3*S*,5*R*)-3,5-Dimethyl-2-phenyl-2-morpholinol hydrochloride (+)-1a

^{1}H NMR (CD_3SOCD_3, 400MHz) δ: 0.96 (d, *J* = 6.4 Hz, 3H, CH_3), 1.23 (d, *J* = 6.4 Hz, 3H, CH_3), 3.54–3.60 (br m, H, morpholine ring3, 5-H), 3.83–3.97 (m, 2H, morpholine ring 6-H), 7.41–7.56 (m, 5H, C_6H_5), 8.02 (s, 1H, OH), 8.75, 10.17 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3244, 3037, 2936, 2787, 2738, 2681, 2532, 1560, 1541, 1452, 1388, 1350, 1261, 1092, 1057, 1001, 764, 702. ESI-MS *m*/*z*: 209 (M^+ + 2 – HCl), 208 (M^+ + 1 – HCl), 190 (M^+ + 1 – HCl – H_2O).

(2*S*,3*S*,5*R*)-3,5-Dimethyl-2-(3-chlorophenyl)-2-morpholinol hydrochloride (+)-1b

^{1}H NMR (CD_3SOCD_3 + D_2O, 400MHz) δ: 0.97 (d, *J* = 6.4 Hz, 3H, CH_3), 1.23 (d, *J* = 6.4 Hz, 3H, CH_3), 3.40–3.60 (br m, 2H, morpholine ring 3, 5-H), 3.85–3.95 (m, 2H, morpholine ring 6-H), 7.47–7.58 (m, 4H, C_6H_4), 7.890 (s, 1H, OH), 8.78, 10.39 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3209, 2942, 2790, 2458, 1572, 1551, 1454, 1254, 1201, 1145, 1090, 1002. ESI-MS *m*/*z*: 244 (M^+ + 2 – HCl), 243 (M^+ + 1 – HCl), 242 (M^+ – HCl), 226 (M^+ + 2 – HCl – H_2O), 224 (M^+ – HCl – H_2O).

(2*S*,3*S*,5*R*)-3,5-Dimethyl-2-(4-benzyloxyphenyl)-2-morpholinol hydrochloride (+)-1c

^{1}H NMR (CD_3SOCD_3, 400MHz) δ: 0.96 (d, *J* = 6.4 Hz, 3H, CH_3), 1.22 (d, *J* = 6.4 Hz, 3H, CH_3), 3.29–3.51 (br m, 2H, morpholine ring 3, 5-H), 3.79–3.93 (m, 2H, morpholine ring 6-H), 5.12 (s, H, OCH_2), 7.03–7.47 (m, 10H, C_6H_4, C_6H_5, OH), 8.70, 10.01 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3286, 2941, 2792, 2679, 2455, 1604, 1575, 1508, 1456, 1387, 1240, 1173, 1057, 1005, 831, 741, 698. ESI-MS *m*/*z*: 315 (M^+ + 2 – HCl), 314 (M^+ + 1 – HCl), 296 (M^+ + 1 – HCl – H_2O).

(2*S*,3*S*,5*R*)-3,5-Dimethyl-2-(6-methoxy-2-naphthyl)-2-morpholinol hydrochloride (+)-1d

^{1}H NMR (CD_3SOCD_3, 400MHz) δ: 1.00 (d, *J* = 6.4 Hz, 3H, CH_3), 1.26 (d, *J* = 6.4 Hz, 3H, CH_3), 3.59–3.65 (br m, 2H, morpholine ring 3, 5-H), 3.88 (s, 3H, OCH_3), 3.88–4.03 (m, 2H, morpholine ring 6-H), 7.19–8.03 (m, 6H, $C_{10}H_6$), 8.03 (s,1H, OH), 8.81, 10.29 (2 × bs, 2H, NH, HCl). IR (KBr, cm^{-1}) ν: 3401, 2951, 2893, 2800, 2740, 2682, 2596, 2490, 1610, 1485, 1387, 1269, 1198, 1063, 1001, 854. ESI-MS *m*/*z*: 289 (M^+ + 2 – HCl), 288 (M^+ + 1 – HCl), 270 (M^+ + 1 – HCl – H_2O).

(2*S*,3*S*,5*R*)-3-Propyl-5-methyl-2-(4-benzyloxyphenyl)-2-morpholinol hydrochloride (+)-1e

^{1}H NMR (CD_3SOCD_3, 400MHz) δ: 0.81 (t, *J* = 6.8Hz, 3H, 5-CH_3), 1.16–1.33 (m, 5H, CH_2CH_3), 1.84–1.89 (m, 2H, CH_2), 3.23–3.96 (br m, 4H, morpholine ring 3,5-H, 6-H), 5.25 (s, 2H, OCH_2), 7.02–7.48 (m, 9H, C_6H_4, C_6H_5), 8.06 (s, 1H, OH). IR (KBr, cm^{-1}) ν: 3164, 2956, 2798, 1613, 1587, 1513, 1467, 1402, 1312, 1249, 1098, 1011. ESI-MS *m*/*z*: 342 (M^+ + 1 – HCl).

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References

1. J. Bartroli, E. Turmo, M. Alguero, E. Boncompte, M.L. Vericat, J. Garcia-Rafanell, and J. Forn. J. Med. Chem. **38**, 3918 (1995).
2. T. Mancilla, L.S. Zamudio-Rivera, H.I. Beltrán, L. Carrillo, and N. Farfán. Synthetic Communications, **35**, 357 (2005).
3. A.X. Hu, H.Y. Wu, K. Chen, L.T. Yang, and B. Zhou. Chin. J. Appl. Chem. **22**, 343 (2005).
4. J.E. Matthews and D.L. Musso. PCT Int. Appl. WO 2001-026641, 19 April 2001.
5. A. Feriani, G. Gaviraghi, G. Toson, B. Valsecchi, P. Caldirola, M. Ravasi, L. Merlini, C. Redaelli, E. Grana, and F. Zonta. Farmaco, **47**, 3 (1992).
6. J.C. Barland. PCT Int. Appl. WO 2005-053700, 16 June 2005.
7. P.F. Morgan, D.L. Musso, and J.J. Partridge. US Patent Appl. 2003064988, 3 April 2003.
8. M.C. Chrysselis, E.A. Rekka, and P.N. Kourounakis. J. Med. Chem. **43**, 609 (2000).
9. L.K. James, L.M. David, G.E. Boswell, E.S. Francis, and R.C. Barrett. J. Med. Chem. **39**, 347 (1996).
10. J.L. Kelley, D.L. Musso, and G.E. Boswell. US Patent 5-104-870, 14 April 1992.
11. J.A. Asche, J.A. Johnston, S.M. Learned-Coughlin, and A. Bye. US Patent Appl. 2003032643, 13 February 2003.
12. P. Adam, O. Ludemann-Hombourger, E. Ndzie, D.S. Ross, M. Schaeffer, and C. Suteu. PCT Int. Appl. WO 2005-040140, 6 May 2005.
13. J.J. Partridge. PCT Int. Appl. WO 2005-042503, 12 May 2005.
14. M.A. Harris and A. Negus. PCT Int. Appl. WO 2005-040141, 6 May 2005.
15. J.J. Partridge. PCT Int. Appl. WO 2005-044809, 19 May 2005.
16. D.L. Musso and J.L. Kelley. Tetrahedron: Asymmetry, **6**, 841 (1995).
17. J.L. Kelley, D.L. Musso, G.E. Boswell, and B.R. Cooper. Eur. Patent Appl. EP 0426416, 8 May 1991.
18. F. Berrée, A. Debache, Y. Marsac, B. Collet, P.G. Bleiz, and B. Carboni. Tetrahedron, **62**, 4027 (2006).
19. F. Berrée, A. Debache, Y. Marsac, and B. Carboni. Tetrahedron Lett. **42**, 3591 (2001).
20. A.A. Asselin and L.G. Humber. U. S. Patent 4-044-131, 23 August 1977.
21. H. Caner, E. Groner, L. Levy, and I. Agranat. Drug Discovery Today, **9**, 105 (2004).
22. Q.K. Fang, Z. Han, P. Grover, D. Kessler, C.H. Senanayake, and S.A. Wald. Tetrahedron: Asymmetry, **11**, 3659 (2000).
23. SMART [computer program]. Bruker AXS Inc., Madison, Wisconsin, USA. 2001.
24. G.M. Sheldrick. SADABS [computer program]. University of Göttingen, Göttingen, Germany. 1996.
25. SHELXTL [computer program]. Bruker AXS Inc., Madison, Wisconsin, USA. 1997.
26. L.J. Farrugia. J. Appl. Cryst. **30**, 565 (1997).
27. A.X. Hu, G. Cao, X.R. Xiao, and H.Y. Wu. Acta Crystallogr. Sect. E: Struct. Rep. Online, **62**, o1584 (2006).
28. R.D. Porsolt, M. Le-Pichon, and M. Jalfre. Nature (London), **266**, 730 (1977).
29. A.X. Hu, P. Chen, Z. Yang, X.Y. Wu, and K. Chen. Chin. J. Med. Chem. **12**, 340 (2002).