Bromodimethylcathinone、BDMC[包含其異構物 4-Bromodimethylcathinone、2-Bromo、3-Bromo]

相關資料說明

資料整理：內政部警政署刑事警察局

一、名稱

(一)中文名稱：溴二甲基卡西酮（無俗名）

(二)英文名稱：Bromodimethylcathinone[包含其異構物 4-Bromodimethylcathinone、2-Bromo、3-Bromo]

(三)化學名：1-(Bromophenyl)-2-(dimethylamino)propan-1-one

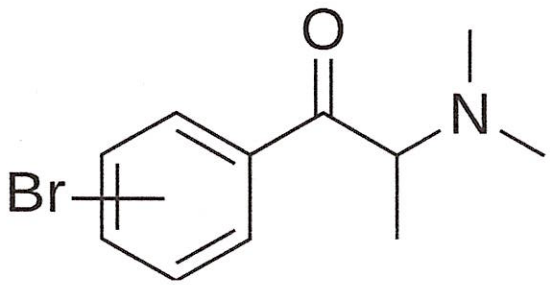
二、化學資料：

(一)分子式：$C_{11}H_{14}BrNO$

(二)分子量：256.14 g/mol

(三)化學結構：如圖

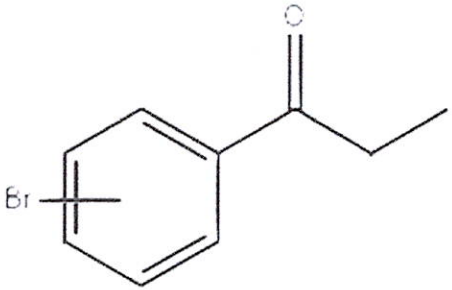
(四)CAS No.: 各異構物均無 CAS No.



三、藥理性質：

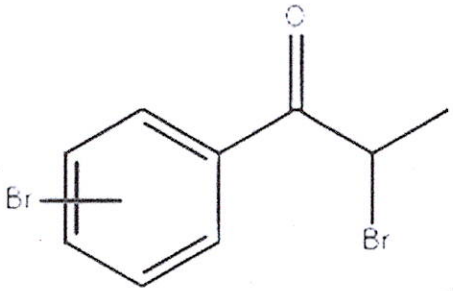
卡西酮類藥物結構類似安非他命類藥物，因此被認為具有相似的藥理作用，施用後會產生欣快感、興奮、活動力增加、多話、心情愉悅及增加性慾等作用，研究指出，在苯環上帶有取代基的卡西酮化合物，相較於未取代的化合物，對血清素再吸收的抑制效果更強，故更具有濫用毒品可能性及危險性之特質。

115年9月10日通過審議，列為第四級毒品先驅原料



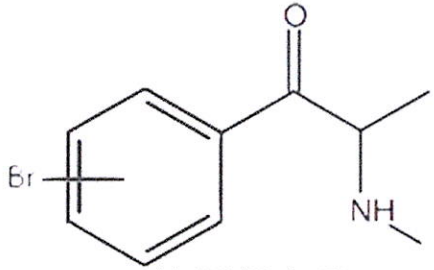
1-溴苯基-1-丙酮
(1-Bromophenyl-1-propanone 、Bromopropiophenone) [包含其異構物1-(4-Bromophenyl)-1-propanone、2-Bromo、3-Bromo]

含溴(Br)離子之強酸性物質，如氫溴酸或溴水 Br_2 (溴化) →



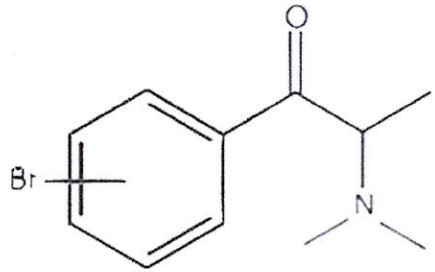
2-溴-溴苯丙酮
(2-Bromo-bromopropio-phenone) [包含其異構物4-Bromo、3-Bromo、2-Bromo]

甲胺(CH_3NH_2) (胺化) →



第三級毒品
#46項 溴甲基卡西酮
(Bromomethcathinone、BMC)

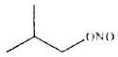
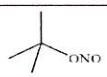
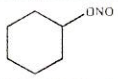
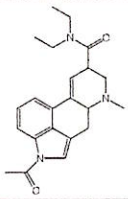
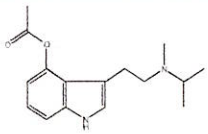
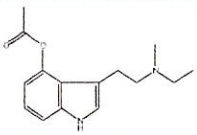
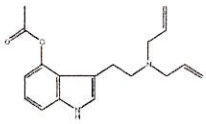
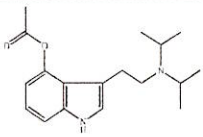
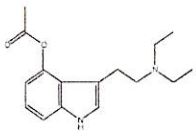
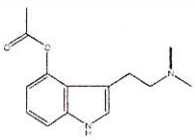
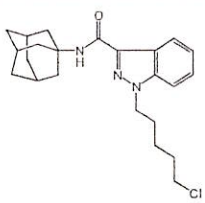
二甲胺(CH_3NH_2) (胺化) →



新興毒品---溴二甲基卡西酮
(Bromodimethylcathinone、BDMC)

List of "Designated Substances" in Japan (as of September 6, 2026)

Drug category, "Designated Substances (*)" was newly established in 2007 to control new psychoactive substances (NPS).
Their manufacture, import, sale, display, possession, use etc. are generally prohibited except for scietific purposes.
A total 2484 substances including 2 plants (*Salvia divinorum* and *Mitragina speciosa* (Kratom)) are currently controlled as "Designated Substances".
(Substances basis 359, Generic scheduling 2125)
95 substances, such as JWH-018, mephedrone, MDPV etc. have been already reclassified to be "Narcotics".
(*)They are controlled by "The Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices".

No.	Name	Other Name	Chemical Structure	Date of Enforcement
1	Isobutyl nitrite			April 1, 2007
2	Isopropyl nitrite			April 1, 2007
3	Isopentyl nitrite	Isoamyl nitrite		April 1, 2007
4	*tert*-Butyl nitrite			April 1, 2007
5	Cyclohexyl nitrite			April 1, 2007
6	Butyl nitrite			April 1, 2007
7	4-Acetyl-*N*,*N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline-9-carboxamide	ALD-52		February 28, 2020
8	4-Acetoxy-*N*-isopropyl-*N*-metyltryptamine	4-AcO-MIPT		April 4, 2015
9	4-Acetoxy-*N*-ethyl-*N*-methyltryptamine	4-AcO-MET		August 8, 2015
10	4-Acetoxy-*N*,*N*-diallyltryptamine	4-AcO-DALT		August 8, 2015
11	4-Acetoxy-*N*,*N*-diisopropyltryptamine	4-AcO-DIPT		April 1, 2007
12	4-Acetoxy-*N*,*N*-diethyltryptamine	4-AcO-DET		August 8, 2015
13	4-Acetoxy-*N*,*N*-dimethyltryptamine	4-AcO-DMT		August 8, 2015
14	*N*-(1-Adamantyl)-1-(5-chloropentyl)-1*H*-indazole-3-carboxamide	APINACA *N*-(5-chloropentyl) analog		April 18, 2016

DDR

DRUG DEVELOPMENT RESEARCH 60:252–260 (2003)

Research Article

Novel Aminopropiophenones as Potential Antidepressants

Kevin F. Foley and Nicholas V. Cozzi*

Department of Pharmacology and Toxicology, Brody School of Medicine, East Carolina University, Greenville, North Carolina

Strategy, Management and Health Policy				
Venture Capital Enabling Technology	Preclinical Research	Preclinical Development Toxicology, Formulation Drug Delivery, Pharmacokinetics	Clinical Development Phases I-III Regulatory, Quality, Manufacturing	Postmarketing Phase IV

ABSTRACT The atypical antidepressant drug bupropion and the psychostimulant drug methcathinone are both members of a chemical class known as aminopropiophenones. Differences in the psychoactive effects of these two drugs result from small variations in their chemical structures, but the relationship between chemical structure and psychoactivity has not been characterized. To investigate how structural modifications to aminopropiophenones affect antidepressant or stimulant activity, we synthesized several analogs of bupropion and methcathinone and tested the new compounds for antidepressant-like or psychostimulant effects. The synthesized compounds are 2-(methylamino)-1-(3-bromophenyl)propan-1-one (3-BMAP), 2-(methylamino)-1-(4-bromophenyl)propan-1-one (4-BMAP), 2-(*iso*-propylamino)-1-phenylpropan-1-one (*i*-PAP), and 2-(*tert*-butylamino)-1-phenylpropan-1-one (*t*-BAP). Bupropion, methcathinone, desipramine, and the newly-synthesized aminopropiophenones were administered to rats for behavioral testing. We used the Porsolt swim test to assess antidepressant-like activity and a locomotor activity assay to test for psychostimulant effects. All of the compounds displayed antidepressant-like effects in the Porsolt swim test. Some compounds, including bupropion, increased locomotor activity at moderate-to-high doses. A halogenated analog of methcathinone, 4-BMAP, increased swim time but did not stimulate locomotor activity, even at the highest dose tested. The data indicate that phenyl ring substitution or branched alkylamines can shift the psychopharmacological profile of aminopropiophenones from stimulant activity to antidepressant-like activity. Several of the new drugs may be effective antidepressants in humans with fewer stimulant-like side effects compared to bupropion. Drug Dev. Res. 60:252–260, 2003. © 2003 Wiley-Liss, Inc.

Key words: bupropion; methcathinone; Porsolt; locomotor; psychostimulant; depression

INTRODUCTION

The aminopropiophenone bupropion (Fig. 1), a drug prescribed under the brand names Wellutrin® and Zyban®, is used clinically to treat several psychological conditions. Bupropion has been used successfully in the treatment of attention deficit hyperactivity disorder (ADHD), as an antidepressant, and as an adjunct in smoking cessation programs [Daviss et al., 2001; Gonzales et al., 2001]. In some patients, bupropion produces stimulant-like side effects such as insomnia, anxiety, tremors, and agitation. Bupropion is self-administered by nonhuman primates [Bergman et al., 1989; Lamb and Griffiths, 1990], but it appears that the drug has a low potential for misuse in humans [Griffith et al., 1983], with only one report of recreational use [McCormick, 2002]. In

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Porsolt test, can itself produce locomotor stimulation [Cooper et al., 1980; Zarrindast and Hosseini-Nia, 1988]. Thus, a drug that stimulates locomotor activity and, therefore, tests positive in the Porsolt test may or may not be an effective antidepressant. The most promising antidepressant candidates would seem to be compounds that decrease swim test immobility times without causing significant locomotor stimulation. Drugs like desipramine fit this profile. However, even if they did not show significant antidepressant effects, the identification of new compounds possessing psychostimulant properties would also be valuable. For example, the psychostimulant amphetamine is a useful drug for the treatment of ADHD and narcolepsy [Shindler et al., 1985; James et al., 2001].

To help elucidate the relationship between chemical structure and behavioral effects of aminopropiophenones, we synthesized several novel compounds for in vivo testing (Fig. 1). We examined two ring-brominated methcathinone analogs that we had previously synthesized and reported as monoamine uptake inhibitors. These compounds are 2-(methylamino)-1-(3-bromophenyl)propan-1-one (3-BMAP) and 2-(methylamino)-1-(4-bromophenyl)propan-1-one (4-BMAP). These compounds both inhibit serotonin uptake with an IC_{50} value of 2 μM and they inhibit norepinephrine uptake with IC_{50} values of 158 and 453 nM, respectively [Cozzi and Foley, 1999; Foley and Cozzi, 2002] We also synthesized two new compounds with *N*-alkyl substituents: 2-(*iso*-propylamino)-1-phenylpropan-1-one (*i*-PAP), and 2-(*tert*-butylamino)-1-phenylpropan-1-one (*t*-BAP). We compared these molecules to bupropion, methcathinone, and desipramine for their behavioral effects using both the Porsolt swim test and locomotor activity assays. Through these studies, we were able to identify several compounds as potential new antidepressants.

METHODS AND MATERIALS

Drugs and Reagents

Desipramine hydrochloride and racemic bupropion hydrochloride were purchased from Sigma-Aldrich Chemical Company, Milwaukee, WI. Methcathinone hydrochloride was synthesized in racemic form with a 50% yield as described by Zhingel and colleagues [Zhingel et al., 1991]. The test compounds 3-BMAP, 4-BMAP, *i*-PAP, and *t*-BAP were synthesized as racemates in our laboratory and were isolated as the hydrochloride salts. Chemical structures and purities for all synthetic compounds were confirmed with proton nuclear magnetic resonance spectroscopy (NMR), thin-layer chromatography (TLC), and melting point determination (Mel-Temp device; melting points are uncorrected). TLC was performed on glass-backed silica gel plates (250 μm thick, particle size 5–17 μm, pore size 60 Å) with fluorescent indicator using a CH_2Cl_2:hexane:MeOH 45:45:10 mobile phase. NMR spectra were acquired on either a Varian Inova (200 MHz) or Brüker AM 300 (300 MHz) instrument in CD_3OD with 0.03% tetramethylsilane (TMS) as internal standard; chemical shifts are reported in parts per million (δ) relative to TMS. The following abbreviations are used to designate NMR signal patterns: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

2-(Methylamino)-1-(3-bromophenyl)propan-1-one (3-BMAP).

A solution of 3-bromopropiophenone (5.0 g, 23.5 mmol) dissolved in 25 mL CH_2Cl_2 was added to a 125-mL Erlenmeyer flask. The flask was cooled on ice and 10 drops of AcOH were added. A 20% solution of Br_2 in CH_2Cl_2 was added in portions with stirring until the color of bromine persisted; a total of ~5 mL was added. The reaction was transferred to a separatory funnel and washed with 2 × 25 mL H_2O. The methylene chloride was removed by evaporation on the hot plate, leaving the α-bromo ketone product as a light yellow oil. Fifteen mL 95% EtOH was added and the solution was heated to boiling; the solution became colorless. The alcoholic solution of the α-bromo ketone was cooled to ambient temperature then added dropwise with stirring to an ice-cold 20% solution of NH_2CH_3 in 1:1 EtOH:H_2O (7.3 mL, 47 mmol) over a 20-min period. Stirring was continued for about 2 h during which time the solution became cloudy and colored yellow-orange. After transferring to a separatory funnel, the aqueous layer was discarded and the organic layer was washed with 3 × 25 mL H_2O. Twenty-five mL H_2O was added and the mixture was acidified to pH ~2.0 with 1M HCl to effect solution of the free base amine. The aqueous solution was washed with 3 × 30 mL CH_2Cl_2. The solution was then made basic (pH ~ 12.0) with 5M NaOH and extracted with 3 × 30 mL diethyl ether. The ether extracts were combined and dried over $MgSO_4$. After filtering, 1M HCl in ether was added dropwise to the free base amine-ether solution with stirring. The white solids of 3-BMAP HCl that precipitated were vacuum filtered and washed liberally with fresh ether and dried under vacuum. The solids were recrystallized by dissolving in 20 mL boiling *i*-PrOH, filtering the alcohol solution, then flooding with 100 mL diethyl ether. The solution was stored at −20°C overnight to allow crystal formation. The white crystals that formed were vacuum filtered, washed with ether, and dried under vacuum. Yield: 1.02 g (15.6% of ideal), mp = 178–181°C (dec.). TLC revealed one

treatment will produce periods of immobility of 8–12 min total duration, during which the rat will assume a characteristic floating posture. After the initial 15-min exposure, the rat was removed from the water, dried with a towel, and returned to its home cage. The rats were then given i.p. injections of vehicle (0.9% saline) or test drug (dissolved in 0.9% saline) at 24 h, again at 5 h, and again at 1 h prior to a second exposure to the swim chamber, for a total of three injections. As a positive antidepressant drug control, we used 10 mg/kg desipramine [Detke et al., 1995]. One hour after the last injection, the rats were placed back into the water chamber for 5 min. During the second exposure, rats will again become immobile and the total period of immobility in vehicle-treated rats serves as a baseline against which to compare antidepressant drugs. The animals' behavior during the 5-min test period was recorded on videotape and the duration of immobility was scored extemporaneously by an observer blinded to the treatments. Data are expressed as the mean ± SEM of the time spent immobile. The floating times of rats given test compounds were compared to those of rats that received vehicle.

Statistics

Outliers were identified using Grubbs' test [Grubbs 1969]. Treatment effects in the locomotor activity assay and in the Porsolt swim test were compared to vehicle controls using one-way ANOVA with dose as the main effect. Post hoc analyses were conducted using Dunnett's multiple comparisons test. Comparisons between different drugs and methcathinone at the same dose or between desipramine, methcathinone, and vehicle were made using the Tukey-Kramer multiple comparisons test. $P<0.05$ was considered significant.

RESULTS

The chemical syntheses of the new aminopropiophenones were performed as described and all analytical data were consistent with the assigned structures. All the aminopropiophenones were used as racemates in the behavioral assays.

Drug-induced changes in the spontaneous locomotor activity of rats are shown in Figure 2. Vehicle control animals were less active during the second time period in the locomotor activity monitor than they were during the first period, presumably because of acclimatization. During this period, vehicle control animals often went to sleep. Rats treated with 10 mg/kg desipramine, 5 mg/kg bupropion, 3-BMAP, or *t*-BAP, 2.5 mg/kg *i*-PAP, and all doses of 4-BMAP were similar to control rats. At higher doses, bupropion, 3-BMAP, *i*-PAP, and *t*-BAP all produced hyperactivity (Fig. 2). The positive control methcathinone was the most potent stimulator of locomotor activity in this assay and even produced stereotypic stimulant behavior at the 5 mg/kg test dose. The stereotypy was manifested by extensive sniffing and repetitive head bobbing. This behavior was not seen with any of the other compounds. The results of the Porsolt swim tests are shown in Figure 3. Every drug decreased immobility in the Porsolt test at some dose; bupropion and *i*-PAP decreased immobility at all doses tested.

DISCUSSION

In previous studies, we reported the synthesis and in vitro evaluation of some novel aminopropiophenones as monoamine uptake inhibitors. To test whether these drugs were active in vivo and to investigate how changes to the chemical structure of aminopropiophenones affect psychoactivity, we examined the previously synthesized drugs and two newly synthesized compounds for their behavioral effects in rats. We compared these drugs to methcathinone for amphetamine-like effects and we compared them to bupropion and desipramine for antidepressant potential.

In the locomotor assay, the positive control drug methcathinone was the most potent stimulator of hyperactivity and even produced stereotypy at the single test dose of 5 mg/kg. Desipramine, as expected, did not stimulate motor activity. Of the other aminopropiophenones tested, only *i*-PAP caused hyperactivity at the 5 mg/kg dose, albeit not to the same degree as methcathinone (Fig. 2). As the dose was raised, however, all of the compounds except 4-BMAP did eventually produce increases in locomotor activity (Fig. 2). Attenuation of the amphetamine-like motor response in these drugs could occur for several reasons including altered pharmacokinetics and metabolism. An example of a potential metabolic difference involves the blockade of 4-hydroxylation by phenyl ring substituents. Cytochrome P450-catalyzed hydroxylation of the aromatic ring 4-position is the major pathway of phenylalkylamine metabolism in the rat [Caldwell, 1976]. The product of the hydroxylation of amphetamine, *para*-hydroxyamphetamine, is an inhibitor of norepinephrine, dopamine, and serotonin uptake [Wenger and Rutledge, 1974; Kaminskas et al., 2002], is twice as potent as amphetamine itself as a sympathomimetic agent [Simpson, 1979, 1980], and is a powerful locomotor stimulant when given intracerebrally [Taylor and Sulser, 1973]. In 3-BMAP and 4-BMAP, there is a bromine atom on the aromatic ring at the 3- or 4-positions, respectively. Ring substitution at these positions seems to prevent aromatic hydroxylation [Bruce and Maynard, 1968; Caldwell et al., 1975]. It is therefore possible that 3-BMAP and

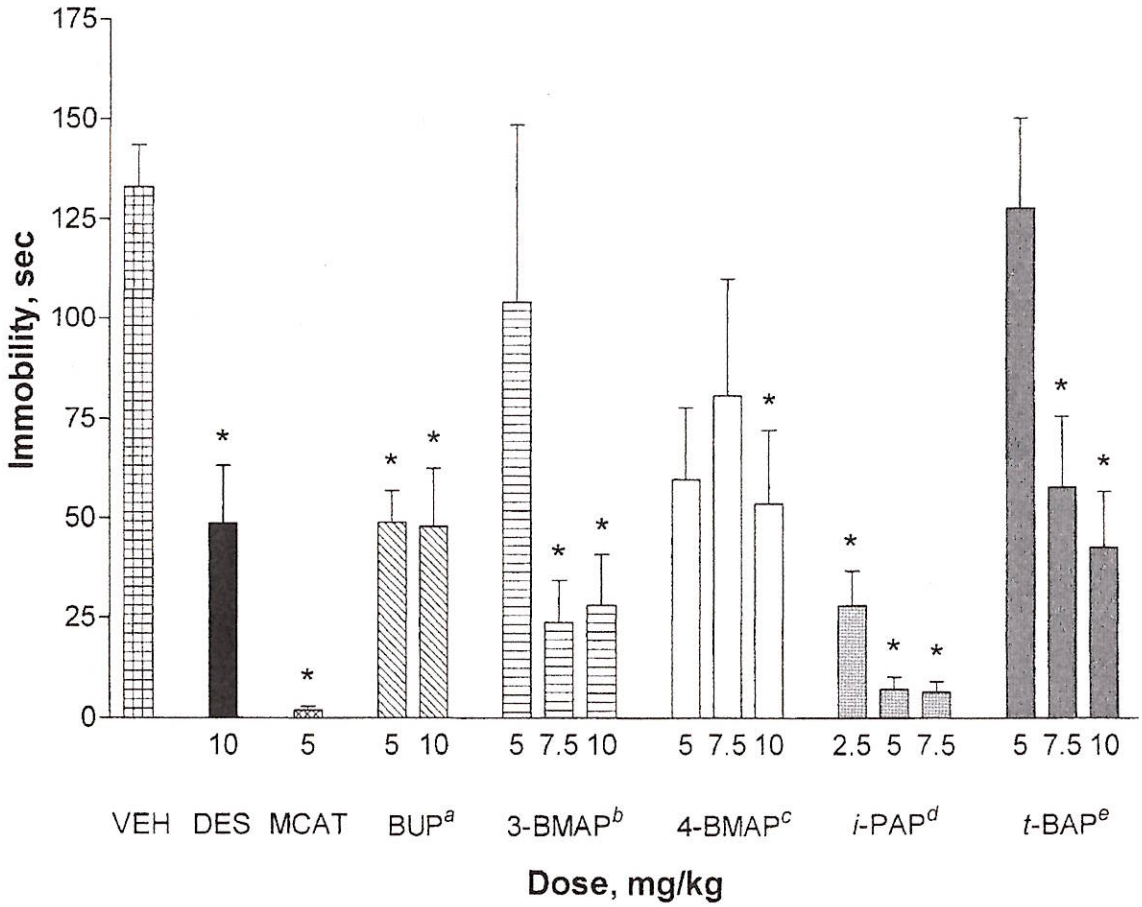

Fig. 3. Effect of test compounds on immobility in the Porsolt swim test. Rats were exposed to an inescapable water chamber for 15 min as described under Methods and Materials. Twenty-four hours later, after a three-dose drug or vehicle regimen, rats were returned to the swim chamber for 5 min and floating times were recorded and compared to vehicle. ANOVA of various treatments revealed significant effects of dose on immobility. $^{*}P<0.05$ vs. vehicle. $^{a}F(2,39)=9.211$, $P=0.0005$. $^{b}F(3,46)=8.654$, $P=0.0001$. $^{c}F(3,46)=5.535$, $P=0.0025$. $^{d}F(3,45)=21.55$, $P<0.0001$. $^{e}F(3,45)=6.176$, $P=0.0013$. VEH = vehicle, DES = desipramine, MCAT = methcathinone, BUP = bupropion; other compound abbreviations as noted in text.

methcathinone significantly reduced immobility. However, the antidepressant desipramine also reduced immobility and yet was inert as a locomotor stimulant. Likewise, bupropion, 4-BMAP, *i*-PAP, and *t*-BAP all reduced immobility in the Porsolt swim test at doses that did not produce hyperactivity (Figs. 2 and 3). Thus, by combining these two assays, we are able to discriminate putative antidepressant activity from locomotor stimulation. It should be noted that drugs that produce hyperactivity might nevertheless be excellent antidepressant agents.

In summary, we synthesized aminopropiophenone drugs that are as effective as bupropion in the Porsolt swim test and yet exhibit fewer locomotor stimulant effects at similar doses. It is clear that small changes to the chemical structures of methcathinone or bupropion elicit significant changes in behavioral activity. Of the drugs tested, most were locomotor stimulants at some dose, including the antidepressant bupropion. All of the compounds decreased immobility in the forced swim test and three compounds did so with fewer locomotor stimulant effects than bupropion. The results indicate that either phenyl ring substitution or a branched side-chain alkylamine are sufficient to attenuate psychostimulant effects in aminopropiophenones. This research also suggests that 4-BMAP, *i*-PAP, and *t*-BAP may be effective antidepressants in humans with a more favorable side effect profile compared to bupropion.

ACKNOWLEDGMENTS

We thank Jacqueline McKeel for excellent technical assistance. This work was supported, in part, with a grant from the National Alliance for Research on

Sunal R, Gumusel B, Kayaalp SO. 1994. Effect of changes in swimming area on results of "behavioral despair test". Pharmacol Biochem Behav 49:891–896.

Taylor WA, Sulser F. 1973. Effects of amphetamine and its hydroxylated metabolites on central noradrenergic mechanisms. J Pharmacol Exp Ther 185:620–632.

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