Research Article

Novel Aminopropiophenones as Potential Antidepressants

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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
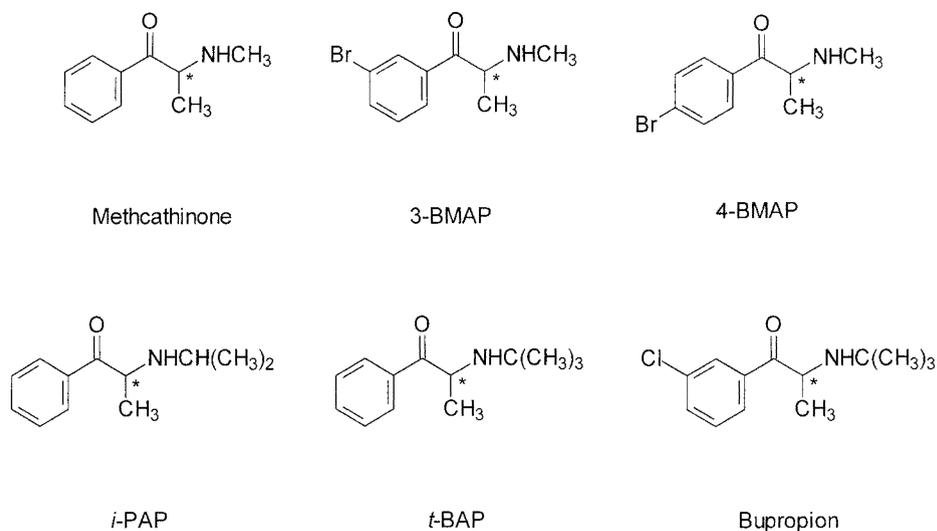
Fig. 1. Chemical structures of aminopropiophenones used in this study. Chiral center is indicated with an asterisk. All compounds were used as racemates.

contrast, methcathinone (Fig. 1), another aminopropiophenone, is a potent psychostimulant with cocaine- and amphetamine-like behavioral effects [Young and Glennon, 1993; Kaminski and Griffiths, 1994], no accepted medical uses, and a high potential for misuse in humans [Emerson and Cisek, 1993; Goldstone, 1993; Rosen, 1993].

An examination of the chemical structures of bupropion and methcathinone reveals that, while both drugs are aminopropiophenones, bupropion contains a chlorine atom on the phenyl ring and has a branched *tert*-butyl group instead of a methyl group on the side-chain amine (Fig. 1). This observation suggests that the psychopharmacology of these drugs can be shifted from stimulant activity to antidepressant activity by relatively small changes to the chemical structure, resulting in, for example, different affinities for monoamine transporters or receptors, altered pharmacokinetics, or a different mix of metabolic products. It is not known whether the antidepressant effect and the attenuated amphetamine-like properties of bupropion result from the presence of the phenyl ring substituent, the branched side-chain alkylamine, or both.

Earlier, we described the synthesis and in vitro investigation of several ring-substituted aminopropiophenones related to 3,4-methylenedioxymethamphetamine and methcathinone [Cozzi and Foley, 1999; Cozzi et al., 1999; Foley and Cozzi, 2002]. We reported that these compounds are inhibitors of plasma membrane monoamine uptake transporters and that molecules with phenyl ring substituents are more potent as serotonin uptake inhibitors relative to the unsubsti-

tuted compounds. Because the mechanism of action of some antidepressant and psychostimulant drugs involves the blockade of monoamine uptake, these in vitro studies suggested to us that the new compounds might have antidepressant or amphetamine-like effects in vivo.

Two behavioral assays that are used to screen for antidepressants and amphetamine-like drugs are the Porsolt swim test for antidepressants and the locomotor activity assay for psychostimulants. In the Porsolt swim test, drugs that display antidepressant effects in humans have been shown to increase the swim times (i.e., decrease periods of immobility) of rats placed in an inescapable water chamber [Porsolt et al., 1977; Porsolt, 1979; Gorka and Wojtasik, 1980; Borsini and Meli, 1988]. Although the Porsolt swim test is an accepted method of screening compounds for antidepressant effects, it can produce false positives. For example, drugs such as antihistamines [Wallach and Hedley, 1979], anticholinergics [Sunal et al., 1994], and, in particular, psychostimulants [Shimazoe et al., 1987] can decrease periods of immobility in the swim test. Despite their positive effects in the Porsolt swim test, it seems clear that psychostimulant drugs elicit a different CNS response than do antidepressants like desipramine. Psychostimulant-induced decreases in immobility in the Porsolt test arise from one of the drugs' major behavioral effects in animals, namely, their ability to stimulate locomotor activity [Stolk and Rech, 1967; Zabik et al., 1978; Glennon et al., 1987; Riviere et al., 1999]. Furthermore, bupropion, though effective as an antidepressant and positive in the

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

UV-quenching spot with $R_f = 0.281$. This spot formed a coral-colored product when treated with 2% ninhydrin in acetone. ^{1}H NMR (300 MHz): δ 8.20 (s, 1H, ArH), 8.03 (d, 1H, ArH), 7.90 (d, 1H, ArH), 7.54 (t, 1H, ArH), 5.10 (q, 1H, CH), 2.78 (s, 3H, CH$_3$), 1.57 (d, 3H, CH$_3$).

2-(Methylamino)-1-(4-bromophenyl)propan-1-one (4-BMAP).

A solution of 2,4'-dibromopropiophenone (5 g, 17.1 mmol) in EtOH was added to 10.6 mL ice-cold 20% NH$_2$CH$_3$ to effect amination as described for 3-BMAP. Yield of the hydrochloride salt after recrystallization was 1.15 g (24.1% of ideal), mp = 186–189°C (dec.). TLC: $R_f = 0.230$. ^{1}H NMR (300 MHz): δ 8.00 (d, 2H, ArH), 7.80 (d, 2H, ArH), 5.13 (q, 1H, CH), 2.79 (s, 3H, CH$_3$), 1.58 (d, 3H, CH$_3$).

2-(iso-Propylamino)-1-phenylpropan-1-one (i-PAP).

The title compound was synthesized from 2-bromopropiophenone (2.6 mL, 17 mmol) and iso-propylamine (2.9 mL, 34 mmol) as described for the amination of 3-BMAP. Yield of the hydrochloride salt after recrystallization was 0.89 g (23.0% of ideal), mp = 203–206°C. TLC: $R_f = 0.375$. ^{1}H NMR (200 MHz): δ 8.13 (d, 2H, ArH), 7.76 (t, 1H, ArH), 7.62 (t, 2H, ArH), 5.31 (q, 1H, CH), 3.44 (m, 1H, CH), 1.60 (d, 3H, CH^3), 1.41 (d, 6H, CH^3).

2-(tert-Butylamino)-1-phenylpropan-1-one (t-BAP).

The title compound was synthesized from 2-bromopropiophenone (7.1 mL, 47 mmol) and tert-butylamine (4.9 mL, 47 mmol) as described for 3-BMAP. Yield of the hydrochloride salt after recrystallization was 1.14 g (10% of ideal), mp = 231–235°C. TLC: $R_f = 0.441$. ^{1}H NMR (200 MHz): δ 8.22 (d, 2H, ArH), 7.78 (t, 1H, ArH), 7.65 (t, 2H, ArH), 5.35 (q, 1H, CH), 1.62 (d, 3H, CH$_3$), 1.38 (s, 9H, CH$_3$).

Animals

Male Sprague-Dawley rats (150–175 g) were purchased from Harlan Labs, Indianapolis, IN. The animals were group-housed under a 12-hour light-dark cycle and received food and water ad libitum. The rats were housed in the Brody School of Medicine Animal Care Facilities, which have been accredited by the American Association for Laboratory Animal Care, Animal Welfare Assurance number A3469-01. Principles of laboratory animal care were followed in accordance with NIH guidelines.

Locomotor Activity Assay

To test for drug effects on spontaneous locomotor activity, we used Automex 2S activity sensors (Columbus Instruments, Columbus, OH). The activity sensors detect changes in capacitance that occur as a result of an animal's movement within a cage placed atop the sensor. Movements trigger electrical impulses within the device that are recorded as activity counts. Rats were randomly assigned to control or drug groups with six animals/group. After the initial group of 6 control animals was tested, 2 new controls were always run along with the drug-treated animals such that 30 total control rats were tested over the course of the study. Rats were placed into the activity test cages for two separate periods. For the first period, each rat was placed into a test cage before injection with drug or vehicle to acquire baseline activity data. Movement activity was recorded for a total of 40 min. Activity counts during the first 10 min were discarded to exclude counts resulting from the initial exploratory behavior phase commonly seen when rats are introduced into a new environment. After the 40 min session, the rats were removed from the test cages and placed back into their home cages. After 2–3 hours, the rats were given intraperitoneal (i.p.) injections of vehicle (0.9% saline) or test compounds (dissolved in 0.9% saline) and then returned to the same locomotor activity cage that they had been in during the first session. In this way, we controlled for differences in the sensitivity of each activity monitor. Based on a published report [Glennon et al., 1987], 5 mg/kg methcathinone was used as a positive drug control for locomotor stimulation. Activity was monitored for another 40-min period and counts from the first 10 min were again excluded. The difference in activity counts between the first and second periods was calculated by subtraction. Data are expressed as the mean $\pm$ SEM of the change in activity between the two periods with each rat serving as its own control. Rats treated with various doses of test compounds were compared to rats that received vehicle only.

Porsolt Swim Test

To test the effectiveness of drugs as antidepressants, we used the Porsolt forced swim test. The method we used was essentially the procedure first described by Porsolt and colleagues [Porsolt et al., 1977]. Rats were randomly assigned to treatment groups with 6 animals/group, and as described above, after the initial group of 6 control animals was tested, 2 new controls were always run along with the drug-treated animals such that 32 total control rats were tested over the course of the Porsolt swim test study. Rats were placed into a 10-L glass beaker with a diameter of 22 cm and containing water to a depth of 17 cm. Water was used at 21–23°C and the water was changed after each rat. Rats were placed into the swim chamber for 15 min the day before the test. This

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
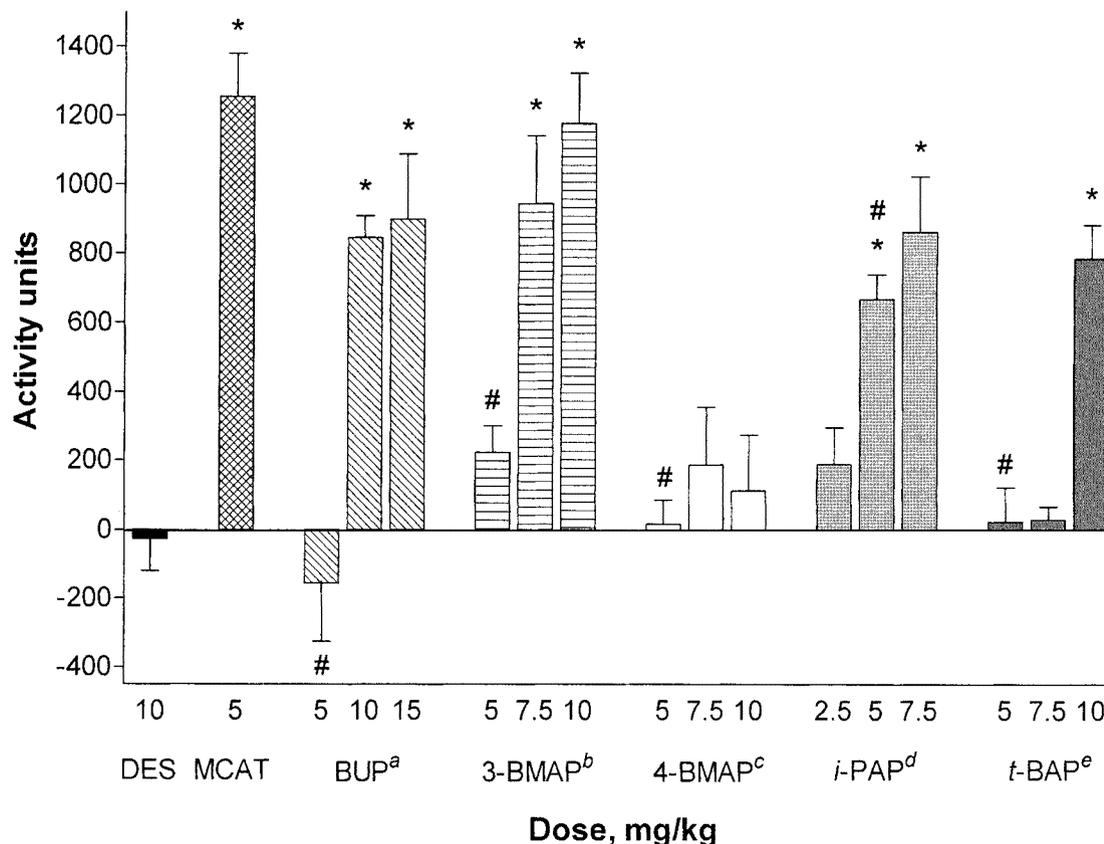
Fig. 2. Effect of test compounds on spontaneous locomotor activity. Rats were placed into an activity monitor for a 40-min acclimatization session. After this session, animals were injected with vehicle or various doses of test compounds then returned to the activity cages for a second 40-min session. Counts occurring during the first 10 min of each session were excluded. Vehicle served as baseline; data are expressed as the change in spontaneous activity counts ("activity units") between the first and second monitoring period compared to vehicle controls. ANOVA of various treatments revealed significant effects of dose on locomotor activity. *$P<0.05$ vs. vehicle. #$P<0.05$ vs. methcathinone at the same dose. [a]$F_{(3,41)}=34.11$, $P<0.0001$. [b]$F_{(3,44)}=52.19$, $P<0.0001$. [c]$F_{(3,44)}=1.305$, $P=NS$. [d]$F_{(3,44)}=36.75$, $P<0.0001$. [e]$F_{(3,43)}=32.34$, $P<0.001$. DES = desipramine, MCAT = methcathinone, BUP = bupropion; other compound abbreviations as noted in text.

4-BMAP are less potent as locomotor stimulants in part because they cannot undergo para-hydroxylation to yield a behaviorally active metabolite similar to para-hydroxyamphetamine. Another example of a potential metabolic difference among these drugs involves the N-alkyl groups. The size and branching of N-alkyl groups influence psychoactivity among amphetamine-like compounds, with larger alkyl substituents resulting in reduced activity [Dal Cason et al., 1997]. Apparently, the rates of N-dealkylation and deamination increase with the size of the alkyl group [Beckett and Shenoy, 1973; Caldwell, 1976; Yamada et al., 1997], leading to more rapid inactivation. If the metabolism of our test compounds parallels that of these other drugs, we would predict that i-PAP and t-BAP, incorporating iso-propylamine or a tert-butylamine groups, respectively, would be more rapidly deactivated than methcathinone

and that i-PAP and t-BAP would, therefore, have reduced amphetamine-like locomotor stimulant activity. This is in fact what was observed.

Bupropion, as reported previously [Cooper et al., 1980, 1994], decreased immobility in the swim test (Fig. 3). This effect is thought to be predictive of its antidepressant effects in humans. Although bupropion did decrease swim test immobility, it also caused significant locomotor stimulation at doses of 10 and 15 mg/kg. Locomotor stimulation was also reported by another group with a bupropion dose of 12.5 mg/kg [Zarrindast and Hosseini-Nia, 1988]. These stimulant effects may account for some of the side effects associated with bupropion use in humans.

All of the other test compounds were effective in reducing immobility in the Porsolt swim test at some dose (Fig. 3). As expected of a locomotor stimulant,
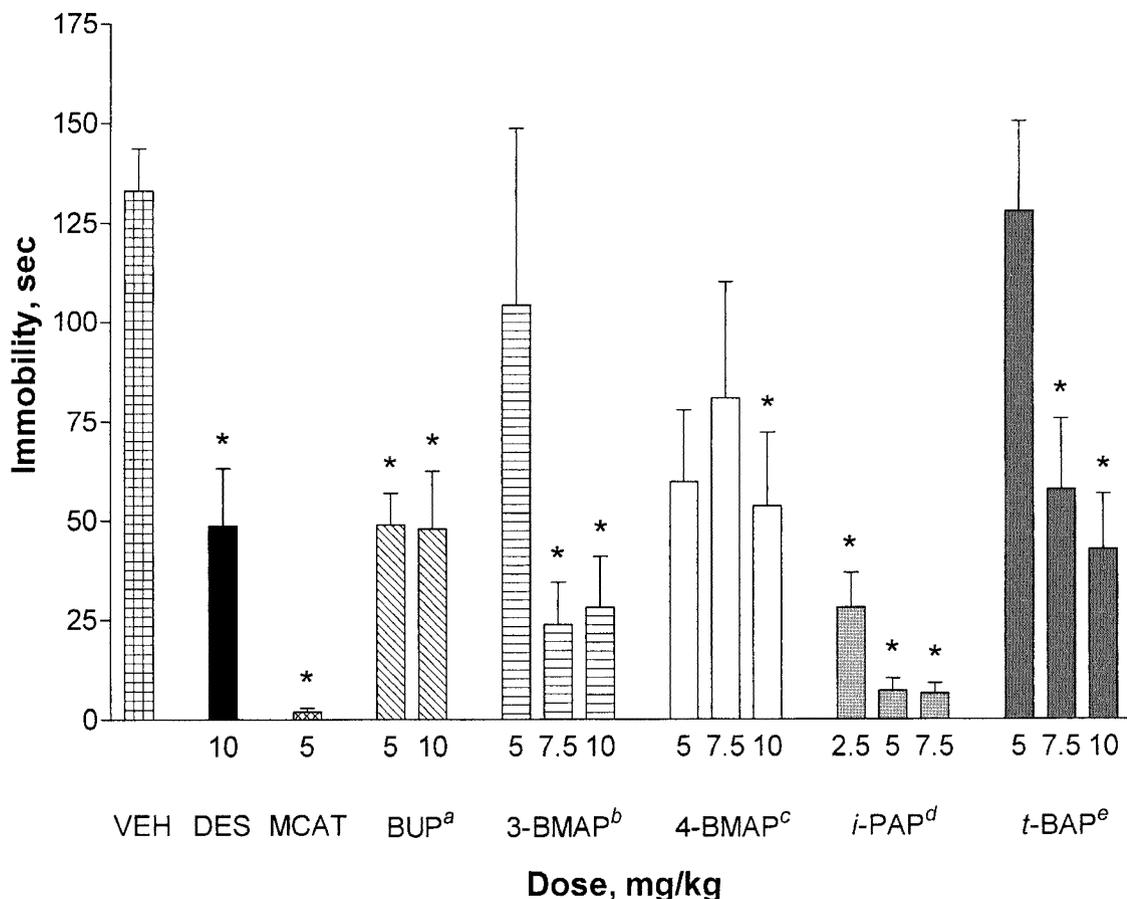
Fig. 3. Effect of test compounds on immobility in the Porsolt swim test. Rats were exposed to an inescapable water chamber for 15 min as described under Methods and Materials. Twenty-four hours later, after a three-dose drug or vehicle regimen, rats were returned to the swim chamber for 5 min and floating 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

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