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Structure-Activity Studies on Amphetamine Analogs Using Drug Discrimination Methodology

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GLENNON, R. A., R. YOUNG, A. E. HAUCK AND J. D. McKENNEY. *Structure-activity studies on amphetamine analogs using drug discrimination methodology.* PHARMACOL BIOCHEM BEHAV 21(6)895–901, 1984.—Animals (rats) trained to discriminate 1.0 mg/kg of S(+)-amphetamine sulfate from saline, using a standard operant training procedure, were administered doses of various amphetamine analogs in tests of stimulus generalization in order to study structure-activity relationships (SAR). The types of structural variation of the amphetamine molecule that were investigated included (a) benz-fusion of the aromatic nucleus, (b) α-demethylation of the alkyl side chain, (c) conversion of the benzylic methylene to a carbonyl group, and (d) conformational restriction of the side chain. Benz-fusion and α-demethylation appear to have a detrimental effect on activity in that none of these analogs produced amphetamine-appropriate responding. However, the carbonylated analog, i.e., cathinone, was found to be equipotent with amphetamine. Furthermore, as with amphetamine, the S-isomer of cathinone was found to be more active than its enantiomer. With respect to the conformationally-restricted analogs, the most potent compound was 2-aminotetralin which was about half as active as racemic amphetamine.

Amphetamine Drug discrimination Structure-activity studies Cathinone 2-Aminotetralin 2-Aminoindane

DRUG discrimination is rapidly gaining acceptance as a research tool for investigations of the stimulus properties of drugs [4,24]. Basically, this method consists of training animals to distinguish or discriminate a given training drug from another agent (or vehicle); once trained, these animals can be employed to study the temporal and dose effects of the training drug, as well as the effects of various neurochemical and neuropharmacological manipulations. In addition, these animals can be challenged by the administration of metabolites of the training drug, or by other agents suspected of producing effects similar to those of the training drug, and/or by the administration of suspected antagonists. Such studies can be useful for investigations of mechanisms of action and/or for the identification of novel agents with similar stimulus properties. One application of drug discrimination methodology that has received relatively little attention is the formulation of structure-activity relationships (SAR). This method, because it affords results that are both quantitative and qualitative in nature, would appear to be ideally suited for such studies. For example, employing animals trained to discriminate 1.0 mg/kg of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) from saline, we have been able to investigate the SAR for the DOM-like stimulus properties of a large series of agents [13]. The basic structural skeleton of DOM is comprised of a phenylisopropylamine (*i.e.*, amphetamine) backbone, and yet the discriminative stimulus properties (as well as the effects in humans) of DOM and amphetamine are quite different [16]. We now wish to turn our attention to the investigation of the SAR for amphetamine-like stimulus effects.

Various investigators have employed racemic, S(+)- or R(−)-amphetamine as a training drug in tests of discriminative control of responding in animals (see [16] and [28] for a review). The amphetamine-stimulus has been attenuated by pretreatment of the animals with haloperidol [5, 19, 26, 29] and pimozide [15] suggesting involvement of a dopaminergic mechanism; likewise, amphetamine-stimulus generalization has been demonstrated to occur with the dopamine agonist apomorphine [16,26]. Amphetamine-stimulus generalization also occurs with other central stimulants such as N-monomethylamphetamine (methamphetamine) [17,20] and cocaine [5, 6, 17, 19].

With respect to the effects of structural modification, enantiomeric potency comparisons have been made, and several ring-substituted derivatives have been evaluated. As a discriminative stimulus, S(+)-amphetamine is more potent than its racemate or R(−)-enantiomer [16]. Ho and coworkers have also demonstrated that the 4-methoxy derivative of racemic amphetamine produces amphetamine-like stimulus effects, while certain structurally-related agents such as DOM and its homolog 1-(2,5-dimethoxy-4-ethylphenyl)-2-aminopropane (DOET) do not share this property [17,29]. Several other derivatives have also been examined [16], however, to date, there has not been a systematic study

of the SAR of amphetamine analogs with respect to amphetamine-like stimulus effects. We have recently undertaken this task. Using rats trained to discriminate 1.0 mg/kg of (+)-amphetamine sulfate from saline, the goal of this initial study was to explore the effect of four basic types of gross structural modification of the amphetamine molecule: (a) benz-fusion of the aromatic nucleus, (b) removal of the α-methyl group, (c) conversion of the benzylic methylene to a carbonyl group, and (d) conformational restriction of the alkyl side chain (see Fig. 1). Evaluation of the two possible benz-fused analogs of amphetamine might be expected to identify regions of bulk tolerance, while the conformationally-restricted or conformationally-defined analogs might provide information with respect to the necessary conformational requirements. Finally, the naturally-occurring carbonyl derivative cathinone has already been demonstrated to be a central stimulant and its evaluation in the present study seemed warranted because of its close structural similarity to amphetamine.

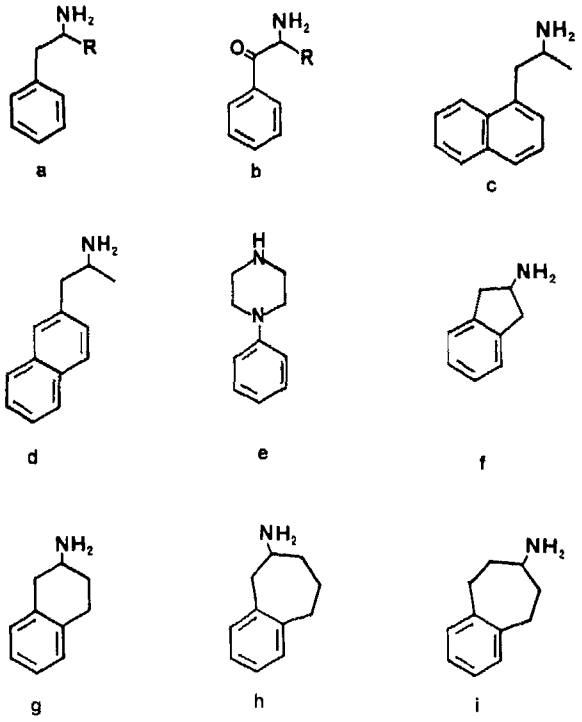

FIG. 1. Structures of (a) amphetamine (R=CH_3), (a) phenethylamine (R=H), (b) cathinone (R=CH_3), (b) α-demethylcathinone (R=H), (c) 1-NAP, (d) 2-NAP, (e) 1-PP, (f) 2-AI, (g) 2-AT, (h) 6-AB, and (i) 7-AB.

METHOD

Subjects

The animals used in this study were ten male Sprague-Dawley rats. They weighed between 250–300 g at the beginning of the experiment. The rats were housed individually and were gradually food-deprived to approximately 80% of their free-feeding weights.

Apparatus

Behavioral testing was conducted in standard operant chambers (Model E10-10, Coulbourn Instruments, Lehigh Valley, PA) housed within light- and sound-attenuating outer chambers. One wall of the chamber contained the intelligence panel, which consisted of two levers with a dipper for delivery of reinforcement (0.01 ml of sweetened milk) centered between the levers. The recessed area in which the dipper was located was illuminated with a white light when the dipper was activated. Illumination of the operant chamber was provided by a 28 V houselight. Solid-state and electromechanical programming and recording equipment were used.

Discrimination Procedure

Rats were trained to lever-respond on both the right and left levers for sweetened milk under a variable interval 15-second (VI-15s) schedule of reinforcement. After lever responding was established, each daily session was preceded by an injection of either *S*(+)-amphetamine sulfate (1.0 mg/kg) or saline (1.0 ml/kg). All rats received their injection of (+)-amphetamine or saline 15 min before each session. Training sessions were 15 min long. Responding on one of the levers was reinforced after the administration of (+)-amphetamine, while responses on the opposite lever were reinforced following saline administration; all conditions were counterbalanced. Saline or (+)-amphetamine was administered on a double alternation schedule (i.e., 2 days saline, 2 days (+)-amphetamine). On every fifth day the rats discrimination learning was assessed during an initial 2.5 min non-reinforced (extinction) period followed by a 12.5 min training session. Data that were collected during the 2.5 min extinction periods included total responses (expressed as mean responses/min) and percent drug appropriate responding (i.e., responses on the drug designated lever/total number of responses). After 50 training sessions the rats discrimination performance was stable under each treatment condition. AMPH-appropriate responding (of total responses) was greater than 80% (mean=93%, mean responses/min=14.5) after drug administration and less than 20% (mean=7.3%, mean responses/min=14.9) after saline administration.

Generalization Tests

Maintenance of the (+)-amphetamine-saline discrimination was insured by continuation of training sessions throughout generalization testing period. Discrimination training sessions were conducted with (+)-amphetamine or saline during the two days prior to any generalization test. Animals not discriminating amphetamine (i.e., less than 80% amphetamine-appropriate responding when given drug) from saline (i.e., more than 20% amphetamine-appropriate responding when given saline) were excluded from the subsequent test session. During generalization investigations, test sessions were interposed among discrimination training sessions. During these test sessions the animals were allowed 2.5 min with no reinforcement for lever responding, and were then removed from the operant chambers. An odd number of training sessions (not less than three) separated any 2 test sessions. Generalization tests investigated the ability of the (+)-amphetamine-stimulus to generalize (substitute) to the various amphetamine analogs. Doses of the amphetamine analogs were administered in a random sequence with a 15 min injection-time interval prior to the ex-

tinction test period. Stimulus generalization was defined, in this study, as being greater than 80% amphetamine-appropriate responding. That is, stimulus generalization was said to occur when the animals, after administration of a given dose of challenge drug, made greater than 80% of the total responses on the amphetamine-designated lever. Animals making less than five total responses during the 2.5-min extinction session were reported as being disrupted.

For those compounds where generalization occurred, ED_{50} values were determined from the dose-response data by the method of Finney [9].

Drugs

1-(1-Naphthyl)-2-aminopropane hydrochloride (1-NAP) was prepared according to a published procedure [10]; 1-(2-naphthyl)-2-aminopropane hydrochloride (2-NAP) (m.p. 203–204°C) was prepared in a similar manner, i.e., by lithium aluminum hydride reduction of the corresponding nitrostyrene (m.p. 83–84°C). 1-Phenyl-piperazine (subsequently converted to its hydrochloride salt) (1-PP) and 2-aminoindane hydrochloride (2-AI) were purchased from Aldrich Chemical Co., (+)-amphetamine sulfate from Sigma Chemical Co., and racemic, S(−)-, and R(+)-cathinone were gifts from NIDA (via Dr. E. May, MCV/VCU). α-Demethylcathinone hydrochloride was synthesized as previously reported [7], and racemic 2-aminotetralin hydrochloride was a gift from the Psychopharmacology Research Branch of NIMH (Dr. A. Manian). Both 6-amino- and 7-amino-6,7,8,9-tetrahydro-5H-benzocycloheptene, 6-AB and 7-AB, respectively, were synthesized in our laboratory. A small amount of 6-AB was prepared by the method of Cannon *et al.* [3]; a larger quantity of this compound was prepared by a second method: 1-Tetralone was ring-expanded to the corresponding tetrahydrobenzocycloheptene-6-one via a Wittig/thalium trinitrate rearrangement reaction as described by Taylor *et al.* [30]. This product was converted to its oxime (m.p. 101–102°C) by treatment with hydroxylamine hydrochloride, and an ethanolic solution of this oxime was catalytically (10% Pd/C) reduced to afford 6-AB after treatment of the product with hydrochloric acid; m.p. 238–242°C (lit. [3] m.p. 237–239°C). 7-AB was prepared in several steps from *o*-xylene. Photolytic bromination of *o*-xylene afforded α,α′-dibromoxylene which was reacted, according to the method of Ewing and Paquette [8] with *n*-butyl-lithium followed by treatment with *t*-butyl acetate. This diester was cyclized, hydrolyzed, and decarboxylated to yield the known tetrahydrobenzocycloheptene-7-one. Amination was achieved by treatment of this ketone with sodium cyanoborohydride and ammonium acetate, the hydrochloride salt (m.p. 278–280°C) was prepared by treating the amine with hydrochloric acid; results of microanalysis (Atlantic Microlabs, Atlanta, GA) of this new compound are as follows: calculated (found) for $C_{11}H_{16}NCl$, C: 66.81 (66.56), H: 8.17 (8.23), N: 7.09 (6.96)%. The spectral data (infrared, proton nmr) for all compounds were consistent with their assigned structures. The structures of these agents are shown in Fig. 1.

Solutions of all agents in sterile saline were prepared fresh daily and were administered via intraperitoneal injection.

RESULTS

Using animals (rats) trained to discriminate 1.0 mg/kg of S(+)-amphetamine sulfate from saline, amphetamine-stimulus generalization was found to occur to 2-AI (ED_{50}=2.12 mg/kg), 2-AT (ED_{50}=1.20 mg/kg), (±)-cathinone ED_{50}=0.72 mg/kg), R(+)-cathinone (ED_{50}=4.41 mg/kg), and S(−)-cathinone (ED_{50}=0.34 mg/kg) (Table 1). Stimulus generalization was not observed to occur with phenethylamine, 1-NAP, 2-NAP, 1-PP, 6-AB, 7-AB, or α-demethylcathinone (Table 1). The latter compound produced saline-appropriate responding and a depression in response rate at the highest dose (i.e., 3 mg/kg) tested. Similar results were obtained with 2-NAP at 3.35 mg/kg. Phenethylamine, 1-PP and 1-NAP produced saline-appropriate responding at 5.75, 1.0 and 2.75 mg/kg, respectively, while administration of higher doses resulted in disruption of behavior (i.e., no responding in a majority of the animals tested). 6-AB produced saline-appropriate responding at doses of up to 20 mg/kg, whereas 7-AB produced similar responding at 17.5 mg/kg and disruption of behavior at 20 and 25 mg/kg. All four animals treated with 25 mg/kg of 7-AB died within 24 hours of administration of drug. Where stimulus generalization occurred, the animals' response rates were not significantly different than those observed after administration of saline, or the training dose of S(+)-amphetamine. The structures of all the agents used in this study are shown in Fig. 1.

DISCUSSION

Most of the agents employed in this study have been previously examined for amphetamine-like properties. For example, 2-AI and 2-AT produce anorectic effects in animals, with 2-AI apparently being the more active [23]. Phenethylamine, 1-NAP and 2-NAP are inactive as locomotor stimulants in rodents; while 2-AI and 2-AT produce locomotor stimulation, both are less active than amphetamine [23,31]. At high doses, 6-AB produces a biphasic effect, an initial locomotor depressant action followed, after approximately two to three hours, by weak locomotor stimulation [32]. Racemic and S(−)-cathinone also produce locomotor stimulation in mice; R(+)-cathinone is less active in this regard [11,31]. 2-AT is more active than 2-AI in producing rotational behavior in 6-hydroxydopamine-lesioned rats, while 6-AB is inactive at 10 mg/kg [3]. No previously reported study has examined this entire series of agents and, as a consequence, it is difficult to make potency comparisons within this series. Nevertheless, there do appear to be some qualitative similarities between these results and the amphetamine-like stimulus properties of these same agents.

Fusion of the b(e)-face or the c(d)-face of racemic amphetamine to a benzene ring results (at least) in a dramatic decrease in potency; at approximately five-times the ED_{50} dose of amphetamine, 1-NAP and 2-NAP produce saline-like responding. These results suggest that the large hydrophobic surfaces introduced by benz-fusion are not well tolerated. On the other hand, conversion of the benzylic methylene to a carbonyl group (i.e., cathinone) appears to have little effect on activity or potency. The S(−)-isomer of cathinone is essentially equiactive (on a molar basis) with the S(+)-isomer of amphetamine; similar results are seen upon comparison of the potencies of their racemic mixtures. Furthermore, in both cases, the R-isomers are less potent than their respective S-enantiomers. These results are consistent with the recent finding that cathinone-stimulus generalization occurs to amphetamine [27], and with the results of an earlier preliminary study in which it was reported that an amphetamine-stimulus generalized to cathinone [25]. The α-methyl groups of amphetamine and cathinone, particularly of their S-isomers, appear to make a positive contribution toward

TABLE 1

RESULTS OF GENERALIZATION STUDIES USING (+)-AMPHETAMINE AS TRAINING DRUG

Agent	Dose (mg/kg)	N*	Amphetamine Appropriate Responding† (±SEM)	Mean Resp Per Min† (±SEM)
(±)-Amphetamine§		ED_{50}=0.62 mg/kg		
S(+)-Amphetamine§		ED_{50}=0.42 mg/kg		
R(−)-Amphetamine§		ED_{50}=1.23 mg/kg		
(±)-1-NAP	0.75	4/4	8% (7.7)	11.7 (1.0)
	1.50	4/4	7% (4.2)	11.6 (1.4)
	2.75	3/4	15% (3.5)	10.0 (1.0)
	3.35	1/4	—¶	
	4.0	1/4	—¶	
(±)-2-NAP	0.75	4/4	3% (2.3)	12.0 (1.5)
	1.50	4/4	20% (5.8)	10.9 (1.3)
	2.75	3/4	18% (4.3)	8.6 (2.3)
	3.35	3/4	14% (9.9)	6.3 (1.0)
(±)-Cathinone	0.5	4/4	21% (8.7)	13.2 (1.8)
	0.75	4/4	54% (15.7)	12.3 (1.2)
	1.0	4/4	78% (9.8)	12.0 (1.9)
	1.5	4/4	93% (3.1)	12.8 (1.5)
		ED_{50}=0.72 (0.49–1.07) mg/kg‡		
S(−)-Cathinone	0.25	4/4	32% (5.6)	12.1 (1.3)
	0.50	5/5	65% (11.4)	11.5 (1.3)
	0.75	4/4	95% (3.0)	11.3 (1.1)
		ED_{50}=0.34 (0.20–0.58) mg/kg		
R(+)-Cathinone	1.5	4/4	3% (2.6)	14.3 (2.3)
	3.0	4/4	32% (4.8)	13.7 (1.0)
	6.0	4/4	59% (16.0)	12.0 (2.2)
	8.0	3/3	79% (14.4)	11.5 (1.7)
	9.0	4/4	89% (6.3)	12.1 (1.4)
		ED_{50}=4.41 (2.46–7.94) mg/kg		
α-Demethylcathinone	1.5	4/4	29% (25.6)	10.0 (2.9)
	2.25	3/4	13% (4.3)	7.1 (2.5)
	3.0	3/4	9% (8.3)	6.2 (2.3)
I-PP	0.5	6/6	24% (7.8)	12.5 (1.8)
	0.75	6/6	26% (6.6)	8.0 (2.5)
	1.0	4/4	12% (6.4)	7.3 (1.2)
	1.25	1/5	—¶	
	1.5	2/5	—	
	2.0	1/4	—	
Phenethylamine	1.0	4/4	3% (2.3)	10.3 (1.5)
	3.0	4/4	8% (7.7)	9.0 (1.8)
	4.5	3/4	0%	10.0 (2.1)
	5.25	3/4	15% (5.5)	7.5 (2.5)
	5.50	3/4	10% (8.6)	8.7 (1.3)
	5.75	3/4	6% (5.6)	8.1 (2.1)
	6.0	1/4	—¶	
2-AI	1.0	4/4	11% (5.5)	12.3 (2.9)
	2.0	4/4	49% (15.6)	11.9 (1.4)
	3.0	4/4	72% (14.1)	12.4 (2.1)
	4.0	4/4	83% (9.5)	12.6 (2.5)
		ED_{50}=2.12 (1.28–3.53) mg/kg		

Continued on next page

TABLE 1

RESULTS OF GENERALIZATION STUDIES USING (+)-AMPHETAMINE AS TRAINING DRUG (Continued)

Agent	Dose (mg/kg)	N*	Amphetamine Appropriate Responding† (±SEM)	Mean Resp Per Min† (±SEM)
2-AT	0.5	5/5	18% (7.0)	11.5 (1.8)
	1.0	5/5	46% (13.6)	12.8 (1.1)
	1.5	5/5	32% (14.4)	12.3 (2.1)
	2.0	5/5	80% (12.0)	10.3 (1.3)
	2.3	4/5	83% (10.5)	12.3 (1.8)
	2.75	5/5	88% (5.4)	14.5 (2.1)
		ED_{50}=1.20 (0.71–2.02) mg/kg		
6-AB	2.0	4/4	23% (10.3)	15.3 (1.9)
	5.0	4/4	24% (8.1)	14.7 (2.3)
	10.0	4/4	17% (4.5)	10.5 (1.8)
	12.5	4/4	15% (5.8)	12.5 (1.5)
	15.0	3/4	17% (16.7)	10.3 (1.5)
	20.0	3/4	14% (3.3)	8.3 (2.1)
7-AB	5.0	4/4	9% (5.1)	10.5 (2.2)
	10.0	4/4	29% (20.0)	12.3 (1.8)
	15.0	4/4	33% (15.8)	14.3 (1.0)
	17.5	3/4	9% (4.1)	6.8 (2.3)
	20.0	1/4	—¶	
	25.0	0/4	—¶	
Saline (1 ml/kg)		10/10	7.3% (2.8)	14.9 (2.0)

*Number of animals responding/number of animals to receive drug.
†Data obtained during 2.5-min extinction session.
‡ED_{50} with 95% confidence limits in parenthesis.
§Data previously reported [12]; included for comparative purposes.
¶Disruption of behavior; i.e., no responding.

activity in that removal of these α-methyl groups results in agents (i.e., phenethylamine and α-demethylcathinone, respectively) that produce saline-like responding at ten (or more) times the ED_{50} dose of amphetamine and cathinone. These results are consistent with the observation that α-demethylcathinone does not produce (±)-cathinone-appropriate responding at several times the ED_{50} dose of (±)-cathinone in animals trained to discriminate racemic cathinone from saline [14], and support an early observation by Huang and Ho [18] that, in the absence of a monoamine oxidase inhibitor, phenethylamine does not produce amphetamine-appropriate responding in rats. Based on the results of the latter study, it appears that certain α-demethyl derivatives may be incapable of producing amphetamine-like stimulus effects because of their rapid metabolism by monoamine oxidase.

The conformation of the alkyl side chain of amphetamine can be restricted in several different ways. The results of nuclear magnetic resonance studies suggest that, in solution, the preferred side chain conformation of various phenylisopropylamines is an extended trans-phenylamino arrangement [2,22]; this conformation can be mimicked, to some extent, by the semi-rigid structure of 2-AT. In addition, 2-AI and 6-AB represent other conformational possibilities worthy of consideration [3]. Examination of Dreiding models of amphetamine and 7-AB reveals that the latter, though not necessarily in a preferred conformation, can orient itself in such a fashion that the distance between the aromatic nucleus and the terminal amine is similar to that which can be achieved by amphetamine. As a consequence, all four conformationally-restricted analogs were examined in the present study. With the finding that, of the four different possibilities, 2-AT is most similar in potency to racemic amphetamine, it may be that 2-AT best mimics the conformation of amphetamine necessary for producing amphetamine-like stimulus effects.

The possibility exists that 1-PP may also represent a reasonable conformational mimic of amphetamine. Piperazine itself is a conformationally flexible molecule in which ring inversion and pyramidal atomic inversion can occur. Of the three possible invertomers, the one in which the lone pair of electrons on nitrogen are both equatorial is of low population [21]; in fact the preferred conformation of 1-phenyl substituted piperazines is that in which the phenyl substituent is equatorial [1]. Thus, a likely conformation of 1-PP would be that shown in Fig. 2; as such, the distance between the aromatic ring and terminal amine is a close approximation of that found in amphetamine. That 1-PP is inactive can not be

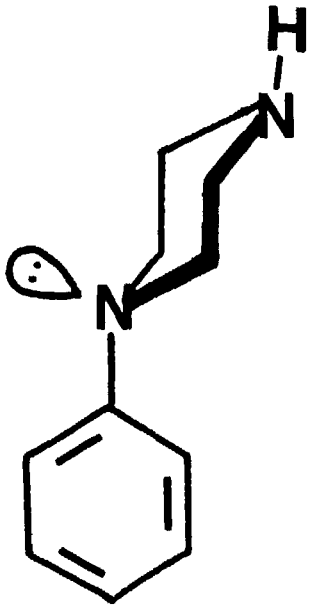

FIG. 2. Structure of 1-PP in a conformationally reasonable form.

explained on the basis of its being a secondary amine; a secondary amine derivative of amphetamine (i.e., methamphetamine) has been demonstrated to be equiactive in tests of stimulus control of behavior [12]. There are several possible explanations for the inactivity of 1-PP; these include (a) the electronic effect of the piperazine ring on the aromatic nucleus, (b) skewing of the phenyl-piperazine orientation as a result of pi-overlap involving the lone pair electrons (see Fig. 2), and (c) other steric and electronic considerations imposed by the piperazine ring on features necessary for producing amphetamine-like effects.

This initial study on the effect that structural modification of the amphetamine molecule has on its discriminative stimulus properties reveals that none of the structural variants investigated was significantly more potent than amphetamine itself. Both benz-fusion of the aromatic ring, and removal of the α-methyl group of amphetamine result in derivatives that produce saline-like effects at doses of five-times the ED_{50} dose of racemic amphetamine. Of the conformationally-restricted analogs, only the five- and six-membered ring derivatives, 2-AI and 2-AT, respectively, produced amphetamine-like effects; however, both agents were less active than amphetamine. The only structural change that appears to have no effect on amphetamine-appropriate responding is replacement of the benzylic methylene of amphetamine with a carbonyl group to afford cathinone. Furthermore, with both compounds, it is the S-isomer that is the more potent. Because of the above results, further SAR studies will focus on the effect of aromatic substitution on the discriminative stimulus properties of amphetamine and cathinone.

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