Review

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Aminoindanes – the next wave of 'legal highs'?

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Due to its closed ring system, 2-aminoindane is a conformationally rigid analogue of amphetamine. Internet websites offering synthetic compounds as 'research chemicals' have recently been advertising 5,6-methylenedioxy-2-aminoindane (MDAI), 5, 6-methylenedioxy-*N*-methyl-2-aminoindane (MDMAI), 5-iodo-2-aminoindane (5-IAI), and 5-methoxy-6-methyl-2-aminoindane (MMAI). The chemistry, pharmacology, and toxicological aspects of this new class of psychoactive substances are reviewed, as these could become the next wave of 'legal highs'. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: aminoindanes; legal highs; MDAI; MDMAI; 5-IAI; MMAI; serotonin.

Introduction

Historically, the terms 'legal highs' and 'herbal highs' referred to blends of psychoactive plants or fungi that could be smoked or ingested to induce dissociative effects and hallucinations. These terms, however, have more recently been widened to describe an extensive and growing range of entirely synthetic substances that have become popular as recreational drugs of abuse; this coincides with a period of intense media interest and legislative activity as governments across Europe and North America try to address the complex legal status of such substances. Recently popular legal highs, such as 4-methylmethcathinone (mephedrone) and related cathinones such as methylone and naphyrone have been placed under legal control in the UK[1] and some other countries. This control measure was urgently introduced in 2010 to deal with a cluster of alleged fatalities associated with the use of mephedrone. However, precise details of what role mephedrone played in these fatalities still remains unclear as there have been no systematic human or animal studies of the acute and chronic effects of this drug. Many new legal highs are analogues of substances that have been placed under legal control, presumably to give similar or new psychotropic experiences. Such a group of compounds are the aminoindanes (aminoindans).

Figure 1 illustrates that 2-aminoindane is a conformationally rigid analogue of amphetamine due to its closed ring system. The basic structure can be altered in a number of ways, such as substitution in the aromatic ring with a variety of functional groups, or the addition of a methylenedioxy bridge, and also *N*-alkylation. Internet websites offering synthetic compounds as 'research chemicals' have recently been advertising 5,6-methylenedioxy-2-aminoindane (MDAI), 5,6-methylenedioxy-*N*-methyl-2-aminoindane (MDMAI), 5-iodo-2-aminoindane (5-IAI), and 5-methoxy-6-methyl-2-aminoindane (MMAI), although some caution must always be exercised as to the chemical authenticity of the compounds supplied. It is possible that these, and other derivatives of 2-aminoindane could become the successors of mephedrone and other cathinone derivatives as a new wave of 'legal' designer drugs with unknown consequences.

Pharmacology

Although Solomons and Sam reported in 1973 that the aminoindanes possessed significant bronchodilating and analgesic properties,[2] more recent research points to the aminoindanes as having potent effects on serotonin release and re-uptake. A number of studies undertaken in the late 1980s and early 1990s concerning Ecstasy (3,4-methylenedioxymethamphetamine; MDMA) also included a comparison with a number of MDMA analogues that incorporated an indane ring. Johnson *et al*. drew attention to several rigid analogues that had been found to substitute for MDMA in drug discrimination studies.[3] They included 5, 6-methylenedioxy-2-aminoindane (MDAI) and 5-methoxy-6-methyl-2-aminoindane (MMAI). Nichols *et al*. also found this to be the case with 5-iodo-2-aminoindane (5-IAI) which substituted for MDMA in rats.[4]. Drug discrimination studies use animals that are trained to respond to certain drug effects and behaviour. By substituting for MDMA, the aminoindanes are likely to produce the empathogenic and entactogenic effects of serotonin releasing drugs. In fact Monte *et al*. showed that MMAI would be relatively selective in inducing the release of neuronal serotonin; also that MMAI was unlikely to have amphetamine or LSD-like properties and that the drug's overall behavioural profile would be related to its serotonergic effects.[5] Extensive investigations using animal models strongly indicate that MDMA is neurotoxic, particularly to the serotonergic system, but neurotoxicity in humans remains to be fully resolved.[6,7] By contrast, the aminoindanes seem to be relatively benign at recreational doses but this supposition is based on animal experiments and *in vitro* cell cultures, and thus it remains uncertain whether recreational users of aminoindanes would suffer from neurotoxicity. Johnson *et al*., Monte *et al*., and Marona-Lewicka *et al*. all conclude that whilst MMAI, MDAI, and

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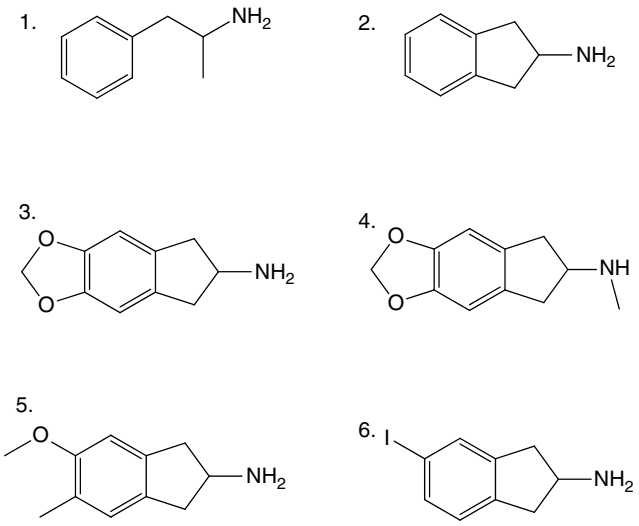

Figure 1. The structures of amphetamine (1) in comparison with 2-aminoindane (2) to show their similarity; 5,6-methylenedioxy-2-aminoindane (MDAI) (3), 5,6-methylenedioxy-*N*-methyl-2-aminoindane (MDMAI) (4), 5-methoxy-6-methyl-2-aminoindane (MMAI) (5) and 5-iodo-2-aminoindane (5-IAI) (6).

5-IAI (Figure 1) are highly potent selective serotonin releasing agents, they also report that these analogues did not show any long-term neurotoxicity in animal studies at the levels administered.[3,5,8] By examining rat-brain monoamine levels, it has been shown that MMAI caused an acute reduction in serotonin (and its metabolite 5-HIAA) in the frontal cortex or hippocampus, but no change in noradrenaline and an increase in dopamine.[3] These monoamines were no different to control values 1 to 2 weeks after dosing and, unlike some substituted amphetamines, there was no selective degeneration of serotonergic axons. Nichols *et al*. also reported a similar lack of neurotoxicity for MDAI in the rat frontal cortex and hippocampus brain region, their results indicating that no loss of serotonin uptake sites had occurred, presumably reflecting the absence of serotonin terminal degeneration.[9] In the study by Nichols on 5-IAI, only slight neurotoxicity was observed in rodents at very high doses and that significant serotonergic toxicity was only found at doses higher than 40 mg/kg, a dose that already approaches the lethal level for many amphetamine analogues in rodents.[4] However, extrapolation to likely human acute toxicity following abuse of very high doses is not possible.

MMAI, MDAI, and 5-IAI appear to affect the 5-HT system, but have an absence of action on dopamine and noradrenaline receptors. This would suggest stimulation of dopamine and/or noradrenaline levels in the brain plays a critical role in reported amphetamine analogue neurotoxicity. It has previously been shown that MDA and MDMA inhibit the synaptosomal uptake of serotonin, dopamine, and noradrenaline, and induce the release of serotonin from synaptosomes.[10] The pharmacological action of MDMA and MDA on these particular neurotransmitters is the key behind the extensive historical popularity of these drugs. Therefore, the purely serotonergic action of the aminoindanes is unlikely to produce the combination of desired effects, including stimulation, sought after by the drug taking community at large but this could lead to the taking of much larger doses, with unanticipated effects.

If aminoindanes such as MDAI and MMAI are to enjoy the relative popularity with drugs users as previous legal highs such as the cathinones, it is possible they will be taken as a 'cocktail' with well-established stimulants such as cocaine, amphetamine, or methamphetamine. However, this could be associated with an unexpected toxicity. Studies reported by Johnson *et al*. and Monte *et al*. have indicated that serotonin-releasing agents generally potentiate the effects of indirectly acting dopaminergic drugs and point out the involvement of dopamine in both neuro- and cardiotoxicity.[3,5,10] Other aminoindanes that have been sold online as legal highs include the indane analogues of the anorectic type drugs such as that of fenfluramine, *N*-ethyl-5-trifluoromethyl-2-aminoindane ETAI), and that of norfenfluramine, 5-trifluoromethyl-2-aminoindane (TAI)(Figure 2). Studies carried out on rats reported by Cozz *et al*. showed that these indanes are capable of causing an indirect serotonergic effect.[11] It should be noted that there is some evidence that long-term use of fenfluramine for weight loss (withdrawn some years ago due to cardiotoxicity) may cause deficiencies in serotonin transporters that might be associated with possible signs of neurotoxicity and may be a useful population (ex-fenfluramine users) for further investigation, where the confounding variable of multiple drug abuse is less problematic.[7]

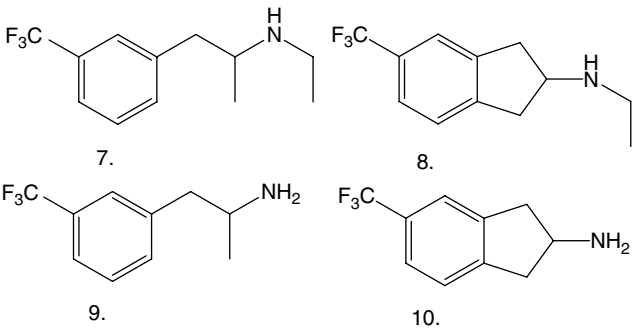

Figure 2. Fenfluramine (7) and ETAI ((8); norfenfluramine (9) and TAI (10).

Synthesis of aminoindanes

Analogues of 2-aminoindanes have historically been prepared using indanone, indene or after intramolecular cyclization of the acyl chloride derivative of 3-phenyl-2-propanoic acid also known as dihydrocinnamic acid. Nichols *et al*. described the procedure for synthesising aminoindanes such as MDAI shown in Scheme 1.[9] The method utilises the intramolecular cyclisation of 3-(3,4-methylenedioxyphenyl)propionyl chloride (a) to form an indanone (b), followed by treatment with amyl nitrite in methanol and HCl to yield an oxime (c). A catalytic hydrogenation reaction using palladium produces the 2-aminoindan analogue (d), which is isolated as the HCl salt.

The initial step for creating an aminoindane from a dihydrocinnamic acid requires conversion of the carboxylic acid to an acid chloride using a chlorinating reagent such as phosphorus pentachloride. Intramolecular cyclisation of the dihydrocinnamoyl chloride produces an indanone. Treatment of the indanone with an alkyl nitrite under acidic conditions yields the hydroxyimino ketone. The final stage of the synthesis involves a reduction of the oxime to the aminoindane *via* hydrogenation. Both Nichols *et al*. and Monte *et al*. successfully used palladium supported on carbon as the catalyst.[5,9]

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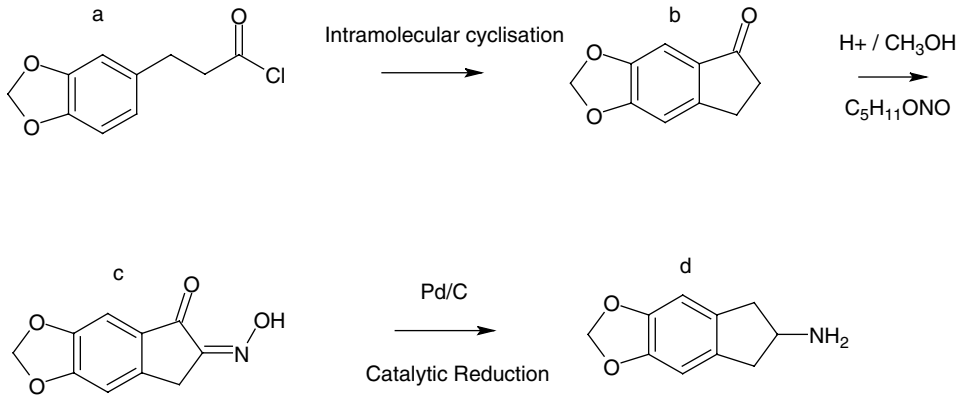

Scheme 1. The Nichols *et al*[9] procedure for synthesising 5,6-methylenedioxy-2-aminoindane (MDAI).

Analytical and other aspects

Recently Wohlfarth and Weinman[12] and also Elliott[13] have discussed the ongoing challenges presented to analytical toxicologists in the detection and measurement of new psychoactive substances. For materials obtained in illicit drug seizures, structural characterization is largely reliant on spectroscopy, where useful comparison of data can also be made to analogous substances that have already been characterized, as well as an increasing reliance on high resolution mass spectrometry for elemental analysis. NMR, infra-red and Raman spectroscopy, however, are not suitable, for the subsequent identification of such drugs in biological matrices, where there is a specificity problem, primarily due to the domination of matrix effects (even after extraction), as well as a concentration issue (analyte concentrations are much less than 1 mg/ml). The clinical and forensic toxicologist is, therefore, heavily reliant on chromatography-mass spectrometry for identification of new substances, given current limitations concerning cross-reactivity in established immunoassay drug screens. Even so, there is an inevitable delay before these substances are added to mass spectral libraries, as well as the problems associated with the lack of availability of reference standards (including major metabolites of drugs, once identified). With respect to the reference standards for the aminoindanes, it is advantageous that 1-aminoindane, 2-aminoindane and MDAI are already available, for example, from LGC Standards (UK), 5-IAI is to be imminently launched, MDMAI is under current development, and MMAI has been added to their target list of materials for production. As an aside, tetralins that are structurally similar to aminoindanes, are now being supplied (methylenedioxyaminotetraline; MDAT) and prepared (6,7-methylenedioxy-N-methyl-2-aminotetralin).

Numerous legal highs are widely available on the Internet as suppliers attempt to replace and emulate the popularity of the recently banned cathinone analogues. Many of these drugs are made for the market based on research from animal studies, or analogues of compounds first synthesized and documented by Alexander Shulgin.[14] Relying solely on existing drugs misuse legislation may not be enough to control the supply of these new compounds and a more intelligent and pragmatic approach to recreational drug use needs to be urgently sought, which is established more on public health warnings supported by evidence-based risk assessment of new substances of abuse.

Although this review suggests the aminoindanes may be set to replace the cathinones as the next legal high, it is by no means a foregone conclusion. Any new drug will have to produce a required set of effects that creates or enhances a pleasurable recreational experience if it is to reach the same dramatic levels of use seen with mephedrone. If the aminoindanes, taken by themselves, or in 'cocktails', do not give users the high they are seeking, then they are unlikely to make a significant impact on the drug scene. This has already been encountered with a phenylethylamine; 4-methylthioamphetamine being a poor substitute for MDMA, causing a number of fatalities in users whom most likely took repeated doses to seek a desired effect, a slow onset of action possibly increasing the risk of overdose due to the perception that the initial dose was too low.[15,16] Toxicological studies need to be undertaken in order to assess the potential damage that the aminoindanes may have on potential users; this could be based on a better understanding of drug structure–pharmacological activity relationships, *in vitro* studies on cell cultures, as well as animal studies using selected compounds for more detailed evaluation. Further research should also investigate the dangers of polypharmacy with novel compounds. The combination of 2-aminoindane analogues with dopamine releasing agents and/or reuptake inhibitors has the potential to significantly alter the toxicity profile of these chemicals following acute or chronic ingestion, particularly in naive users.

The rapid creation of analytical profiles on the researched aminoindanes, using the major spectroscopic, chromatographic and mass spectrometric techniques, would provide valuable cost-effective assistance in drug identification for relevant law enforcement agencies, as well as the more rapid investigation of unexpected or suspicious deaths. What is clear is that legal highs will continue to present significant challenges and problems for scientists and politicians as a sizable proportion of the younger population continue to look for new ways of intoxication.

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