DARK Classics in Chemical Neuroscience:

Aminorex analogs

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Abstract:

Aminorex (5-phenyl-4,5-dihydro-1,3-oxazol-2-amine) and 4-methylaminorex (4-methyl-5-phenyl-4,5-dihydro-1,3-oxazol-2-amine) are psychostimulants that have long been listed in Schedules IV and I of the UN Convention on Psychotropic Substances of 1971. However, a range of psychoactive analogs exist that are not internationally controlled and therefore often classified as new psychoactive substances (NPS). Aminorex analogs encompass failed pharmaceuticals that reemerged as drugs of abuse, and newly synthesized substances that were solely designed for recreational use by clandestine chemists. NPS, sometimes also referred to as "designer drugs" in alignment with a phenomenon arising in the early 1980s, serve as alternatives to controlled drugs. Aminorex and its derivatives interact with monoaminergic neurotransmission by interfering with the function of monoamine transporters. Hence, these compounds share pharmacological and neurochemical similarities with amphetamines and cocaine. The consumption of aminorex, 4-methylaminorex and 4,4'-dimethylaminorex (4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine) has been associated with adverse events including death, bestowing an inglorious fame on aminorex-derived drugs. In this review, a historical background is presented, as well as an account of the pharmacodynamic and pharmacokinetic properties of aminorex and various analogs. Light is shed on their misuse as drug adulterants of well-established drugs on the market. This review not only provides a detailed overview of an abused substance-class, but also emphasizes the darkest aspect of the NPS market, i.e. deleterious side effects that arise from the ingestion of certain NPS, as knowledge of the pharmacology, the potency or the identity of the active ingredients remains obscure to NPS users.

Keywords: Psychostimulants; designer drugs; new psychoactive substances; aminorex; monoamine transporters; drug abuse

Introduction

New psychoactive substances (NPS) are drugs that are not listed in the United Nations international drug control conventions of 1961 and 1971 but that may pose comparable threats to public health. The NPS term tends to be commonly applied to those substances that have emerged in the last decade.[1–3] The market is exceedingly dynamic - on a global level, 803 NPS have been reported to the United Nations Office on Drugs and Crime (UNODC) in the period between 2009–2017.[4] Within the European Union, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) is monitoring over 670 substances that have appeared over the last two decades[5]. The drugs encountered on the NPS market are quite diverse in nature but include synthetic cannabinoid receptor agonists affecting the endocannabinoid system, psychostimulants (largest group), hallucinogens, analgesics, central nervous system depressants and others[4].

The psychostimulants aminorex (5-phenyl-4,5-dihydro-1,3-oxazol-2-amine) and 4-methylaminorex (4-methyl-5-phenyl-4,5-dihydro-1,3-oxazol-2-amine, 4-MAR) (see Figure 1) have been listed (Schedules IV and I, respectively) in the UN Convention on Psychotropic Substances of 1971[6]. Aminorex was originally developed as an appetite suppressant with marketing authorization in Europe but was then removed from the market in the late 1960s due to pronounced adverse effects. In the 1980s, the aminorex analog 4-MAR appeared on the drug market and more recently, 4,4′-dimethylaminorex (4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine, 4,4'-DMAR) made its appearance (see below, Figure 1).

Aminorex and its analogs possess pronounced central nervous system (CNS) effects and, due to similarities in their pharmacological profile, might be classified as amphetamine-type stimulants. Studying the aminorex family of drugs is worthwhile because it highlights the multidisciplinary challenges faced by policymakers, clinicians, law enforcement, users and public health professionals. NPS mimic the effects of controlled drugs (including medicines) but are in many cases not controlled at the time when they are released onto the drug markets[7,8]. This has led to large-scale manufacturing of many analogs and derivatives in an effort to bypass these controls. As will be detailed below, even some minor changes to established structural templates can significantly change the pharmacological profile, which can result in severe adverse effects including deaths, thus, requiring the need for in-depth research. In addition, the NPS market often lacks control and regulation and consumers are prone to being sold mislabeled or heavily adulterated products, which has also been observed with aminorex analogs. This family of drugs has been around for over 50 years and even though some analogs have been banned, the opportunity for NPS entrepreneurs and organized crime groups to explore new analogs and derivatives has never been greater.

[Fig. 1]

Historical Context

Aminorex (Figure 1) was first described by Poos and colleagues in 1963 as one of several 2-amino-5-aryl-2-oxazolines with anorectic and CNS stimulating properties[9]. Their employer McNeil Laboratories consequently filed a patent claim, detailing various routes of synthesis and emphasizing the potent CNS activity of aminorex[10]. The patent claim also accentuates the importance of the introduction of new anorectic drugs to the market as an alternative to the, at the time, widely used amphetamine derivatives. To contextualize: From the year 1944

onwards, amphetamine derivatives, such as desoxyephedrine (methamphetamine), were used in the treatment of obesity in the U.S.A.[11] While other amphetamine derivatives were developed for the same indication, concerns with respect to their marked cardiovascular side effects and dependence-producing properties emerged. Aminorex was considered an alternative and, by the name of *Menocil* and *Apiquel*, sold over the counter between 1965 and 1968 in Austria, Germany and Switzerland[12,13]. Initial results suggested that aminorex appeared to be a safe and effective alternative to amphetamine derivatives as anorectic medication[14]. At the same time, Gurtner *et al*., amongst others, noticed an increase in the incidence of patients suffering from pulmonary hypertension in Bern, Switzerland[15]. In the preceding year, Kay and colleagues showed that oral ingestion of a substance can bring about the development of pulmonary hypertension in rats[16]. Soon, the connection was made that the ingestion of aminorex was responsible for the five- to twenty-fold increase in patients suffering from pulmonary hypertension[17–20]. The vascular lesions (plexogenic arteriopathy) found in patients who died from the ingestion of aminorex were consistent with those associated with idiopathic pulmonary arterial hypertension[12,21]. It was reported that, in Bern, 20% of those admitted to the hospital due to aminorex intake died at the time, with 50% dying in the following ten years[18,22,23]. Still, in general only between 0.2 and 3% of those who had, at the time, ingested aminorex suffered from symptomatic pulmonary arterial hypertension[19,24–26]. A more recent epidemiological study corroborated that the pulmonary hypertension epidemic had correctly been attributed to aminorex consumption[20]. Interestingly, the occurrence of pulmonary hypertension, following oral intake of aminorex could not be replicated in animal model studies[17,27–34]. These two observations suggests that individual genetic predisposition might have played a major role in the etiology of drug-induced pulmonary hypertension[19]. Current research suggests that the combination of genetic predisposition (mainly a mutation in the bone morphogenetic protein receptor type 2; BMPR2) and the presence of other risk factors (such as the oral intake of aminorex) increases the risk of developing pulmonary arterial hypertension[24,35,36]. The next steps in the discovery relating to mechanisms of action responsible for aminorex-induced pulmonary arterial hypertension were soon underway[37]. Weir and colleagues reported an aminorex-induced inhibition of K^+ channels in the lung, as well as increased pulmonary artery pressure[38,39]. Nevertheless, most explanations rather emphasize the drug's interaction with the serotonergic system and SERT (serotonin transporter; SLC6A4) in particular[40]. Seiler and colleagues have shown that aminorex causes release of serotonin (5-HT) at SERT, and that it inhibits 5-HT uptake, as well as monoamine oxidases[41,42]. Rothman *et al*. could confirm aminorex to be a substrate of SERT, accumulating intracellularly and causing the efflux of 5-HT[43]. SERT transactivates the platelet-derived growth factor receptor β (PDGFRβ) and SERT, 5-HT and 5-HT receptors (mostly 5-HT_{1B}) regulate the S100A4/Mts1 gene, inducing *c-fos* and cyclin D1 as well as Rho-kinase expression and activate tyrosine kinases, with each aspect being a contributing factor to pulmonary artery smooth muscle cell proliferation[35,40,44–47]. It is therefore likely that the interplay of individual genetic predisposition and oral intake of aminorex led to the pulmonary arterial hypertension epidemic, thus, ending the official, over the counter sale of aminorex in 1968[48]. The role of serotonergic mechanisms associated with the proliferation in pulmonary arterial hypertension has been reviewed[49].

Although little is known about illicit production and circulation of aminorex during the 1980s, it is interesting to note that this drug emerged decades later in a somewhat surreptitious form, which sparked new interest in the substance. A little backstory is necessary to understand this new development. The anthelmintic drug levamisole is mostly used for veterinary purposes

but was originally also intended for use in humans[50–52]. It is currently still being used for treatment in countries where the incidence of helminthiasis in humans is high across the population[51]. New indications, such as the treatment of the steroid-sensitive idiopathic nephrotic syndrome, treatment of colorectal cancer, various dermatologic conditions, pulmonary tuberculosis, recurrent aphthous stomatitis and severe aplastic anemia, have been explored[53–58]. Illicitly, levamisole is being used as an adulterant in street samples of cocaine. This practice has been increasingly reported from the onset of the new millennium onwards both in the U.S.A. and Europe[59,60]. In the beginning, the use of levamisole as an adulterant was considered enigmatic[59]. At the same time, a scandal occurred in the field of horseracing: the amphetamine-like drug aminorex was detected in the urine of dozens of horses, implicating the owners in illegal doping[61]. The common denominator in all the alleged doping cases was that the horses had been given the anthelmintic drug levamisole beforehand[61]. Barker *et al*., Bertol *et al*. and Ho *et al*. could show that aminorex was indeed formed as a metabolite of levamisole in both horses and humans[61–63]. This explained the detection of aminorex in drug screenings following the administration of levamisole, both as a drug and as an adulterant of cocaine. Interestingly, Ho *et al*. also detected the presence of 4-phenyl-4,5-dihydro-1,3-oxazol-2-amine (rexamino, Figure 1) in horses following subcutaneous administration of levamisole[63].

Cocaine is one of the most frequently consumed illicit substances and global cocaine production has been increasing during the last couple of years[4,64]. Common adulterants in cocaine include acetaminophen, acetylsalicylic acid, caffeine, lidocaine, (synthetic) cathinones, hydroxyzine and levamisole[65]. The latter is currently the most frequently found adulterant, with reports suggesting that between 60% and 80% of all investigated cocaine samples are adulterated with levamisole[65–69]. The abuse of levamisole-adulterated cocaine has been thoroughly documented and is associated with influenza-like symptoms, ANCA (anti-neutrophil cytoplasmic antibody) positive and negative vasculitis, causing retiform purpura, and glomerulonephritis, pyoderma gangrenosum, cutaneous necrosis (often of the ears, face and/or legs), neutropenia or agranulocytosis, leukocytopenia and multifocal inflammatory leukencephalopathy[70–105]. The media has picked up this story and reports about “flesh-eating cocaine” surface from time to time[106–108].

Two major hypotheses, aiming to explain the widespread use of levamisole as an adulterant in cocaine, are particularly noteworthy[70,109]. First of all, levamisole is widely used as a prophylactic anthelmintic drug in the livestock industry around the world and prominently so in agricultural societies[110]. Additionally, levamisole is economically highly viable and resembles cocaine in melting point, look and taste[70]. The second hypothesis is centered on the effects of cocaine and levamisole although it is unclear whether the decision of drug dealers to adulterate the street drug with levamisole deliberately considered its biological fate and its overall CNS effect on the user. Cocaine is an inhibitor of monoamine (re)uptake, binding to SERT, DAT (dopamine transporter; SLC6A3) and NET (norepinephrine transporter; SLC6A2)[111]. On the other hand, levamisole is a nicotinic acetylcholine receptor agonist, which can cause the release of monoamines and inhibits monoamine oxidases and catechol-*O*-methyl-transferase[112–116]. In itself, it is not a very potent inhibitor of monoamine uptake[117]. It appears that the levamisole metabolite aminorex plays an additional role in levamisole-mediated effects. As discussed later, aminorex is a potent releasing agent at SERT, DAT and NET, a quality it shares with amphetamine and many amphetamine-type stimulants[117]. Concerning the biological half-life of levamisole and aminorex, a certain synergism with

cocaine is noteworthy. Levamisole and aminorex have a longer half-life than cocaine and can therefore prolong the drug experience[117–119]. Additionally, levamisole has been shown to potentiate the rewarding and stimulating effects of cocaine in rats[68,109,120]. It might be the case that the hypotheses are complementary in nature and have both contributed to the fact that levamisole is, at this point in time, the most frequently used adulterant in cocaine. One question that remains to be answered is the role of the metabolite aminorex in the effects (and side-effects) of levamisole-adulterated cocaine. Hess and colleagues have shown in human plasma and urine samples collected from drivers (nota bene: under the influence of cocaine) that levamisole was present in approximately 40% of the plasma samples. In 10% of the samples, aminorex was detected, albeit the concentrations were near the detection limit[119]. In two post mortem urine samples with very high levamisole concentrations, aminorex quantification was also significant[119]. Eiden *et al*. found levamisole in 75% of all analyzed urine samples yet aminorex could not be detected[121]. In healthy individuals who ingested high doses of pure levamisole, comparatively small amounts of aminorex were found in plasma and urine[118,119]. It seems to be the case that the conversion rate from levamisole to aminorex might be quite low[121,122]. Still, Karch *et al*. describe the case of a deceased long-term poly-drug user with systemically detectable levamisole and aminorex levels who might have suffered from idiopathic pulmonary arterial hypertension and it has been shown that levamisole accumulates in lung tissue[123–126]. Deaths due to levamisole or aminorex toxicity associated with the consumption of cocaine have rarely been reported[126,127]. At this point, it is known that only a small fraction of levamisole is metabolized into aminorex and its (side-)effects seem negligible when compared to those observed with levamisole. Future studies should explore the prevalence of pulmonary arterial hypertension in long-term, high-dose users of levamisole-adulterated cocaine.

As mentioned above, there is no evidence of widespread consumption of aminorex in its own right, although Brewster and Davis reported in 1991 that aminorex has been, in at least one instance, misrepresented as 4-MAR to circumvent legal obstacles[128]. It appears that aminorex is mostly known for its use as an anorectic agent, associated with pulmonary arterial hypertension, and as a metabolite of the currently most widely used cocaine adulterant levamisole.

4-MAR (Figure 1) represents another anorectic substance first published by Poos and colleagues in 1963[9]. Yet, 4-methylaminorex was never marketed as an anorectic drug[11]. Approximately 25 years later, in the late 1980s, 4-MAR surfaced as a recreational drug and was sold by the street names “U4Euh” “ICE” or “4-MAX” in the United States and in Europe[129]. One fatality related to the ingestion of 4-MAR has been reported with the autopsy report suggestive of heart and lung failure, including pulmonary and brain edema[130]. In addition, a case study describes three family members, involved in the manufacturing and consumption of 4-MAR, who suffered from pulmonary hypertension[131]. This case report suggests that not only aminorex but also its derivative(s) might be appropriate stimuli to cause pulmonary hypertension in susceptible individuals. The substance was swiftly added to the list of controlled substance in the US and some European countries[129]. As mentioned above, both aminorex and 4-MAR are now controlled internationally and listed in Schedules IV and I of the United Nations Convention on Psychotropic Substances 1971[6].

Another twenty-five years later, a new aminorex analog appeared on the European drug market: 4,4'-DMAR (Figure 1) was introduced to the European NPS market originally offered for sale under the brand name “Serotoni”[132]. The compound was first encountered in

December 2012 in a customs seizure in the Netherlands[133]. Thirty-one deaths occurring between June 2013 and February 2014 in Europe were associated with the consumption of 4,4'-DMAR, with the substance claiming eight victims in Hungary, one in Poland and 22 in the United Kingdom[133]. Clinical notes and autopsy findings reported to the EMCDDA revealed hyperthermia, myoclonus, seizures, hallucinations, disorientation, agitation, internal bleeding and lung and brain edema, as well as lung and heart failure as the major clinical features[133]. The fatal outcomes were considered consistent with serotonin toxicity and norepinephrine-mediated cardiotoxicity[133–136]. In addition, the combination of 4,4'-DMAR with other drugs affecting the monoaminergic system might have contributed to the deaths[133]. 4,4'-DMAR tablets mimicked the style of MDMA (1-(2*H*-1,3-benzodioxol-5-yl)-*N*-methylpropan-2-amine, 3,4-methylendioxymethylamphetamine, "ecstasy"/"molly") tablets with respect to colors, shapes and logos[133]. Unfortunately, 4,4'-DMAR was seemingly misrepresented as MDMA and used as an adulterant and/or masking agent to hide the lack of the desired drug. It has been shown (see below) that 4,4'-DMAR acted as a 5-10 times more potent non-selective monoamine transporter releasing agent compared to MDMA. From this perspective, it seems likely that users who thought they had procured ecstasy died from acute overdoses as a consequence of norepinephrine, serotonin and dopamine toxicity[134,135]. These tragic events highlight one of the major problems of an unregulated, illicit NPS market – the misrepresentation of substances and the addition of under-researched adulterants that can lead to adverse effects including fatalities.

The identification of 4,4'-DMAR and its association with deaths occurring between June 2013 and February 2014 in Europe led to swift responses. In Europe, the EMCDDA launched a Joint Report to assess the available information in early 2014 followed by a risk assessment carried out by the EMCDDA's Scientific Committee in September 2014[133,137]. Upon reviewing the available information, a decision was made by the European Council to subject 4,4'-DMAR to Europe-wide control measures in 2015[138]. At a global level, and under the auspices of the World Health Organization, 4,4'-DMAR (amongst other substances) underwent the critical review stage at the thirty-seventh meeting of the Expert Committee on Drug Dependence in November 2015[139]. It was recommended to place 4,4'-DMAR in Schedule II of the UN 1971 Convention, which was subsequently confirmed by vote by the Commission on Narcotic Drugs in 18 March 2016, thus, placing it under international control[140,141]. Interestingly, 4,4'-DMAR still appears to be available for purchase from online vendors, mostly based in China[e.g.142], although it is unclear whether these vendors are able to supply it. In an Internet snapshot study published in 2014, it was reported that 4-MAR was advertised more frequently than 4,4'-DMAR[143].

The 4,4'-DMAR case demonstrated that the NPS market can employ mechanisms of self-correction and that when a substance is noticed to be dangerous, some Internet retailers abstain from selling this substance and shift their focus to other compounds. At the same time, the fact that 4,4'-DMAR was surreptitiously sold in mislabeled forms suggests the potential involvement of organized crime groups that sell NPS on the traditional illicit market as well. However, the discussions surrounding 4,4'-DMAR on user fora remains active to some extent.[144] Users seem to be hesitant to consume 4,4'-DMAR because of its association with the fatal intoxication cases but younger users who missed the opportunity to consume 4-MAR when it was uncontrolled in the 1980s, appear to express interest in a revival[145–147]. NPS users and clandestine chemists turn to various new substituents and derivatives of aminorex with

the hope to conserve the desired effects while simultaneously decreasing side-effects and toxicity (see Structural Features).

Structural Features

Aminorex and its derivatives are amphetamine-type (1-phenylpropan-2-amine) stimulants that contain one amino-oxazoline (4,5-dihydro-1,3-oxazol-2-amine) and one phenyl ring (Figure 1). One methyl group is added to the amino-oxazoline ring for 4-MAR (2-amino-4-methyl-5-phenyl-2-oxazoline) and MDMAR (5-(2*H*-1,3-benzodioxol-5-yl)-4-methyl-4,5-dihydro-1,3-oxazol-2-amine, Figure 1). Additionally, for 4,4′-DMAR (4-methyl-5-(4-methylphenyl)-4,5-dihydro-1,3-oxazol-2-amine), the phenyl ring is also methylated. Structurally, MDMAR constitutes an interesting MDMA and 4-MAR hybrid, containing the characteristic 1,3-dioxolane ring.[148]

Aminorex contains one chiral carbon and the available information indicates that it has only been evaluated as a racemic mixture. 4-MAR and other closely related analogs, for example disubstituted at C_4 and C_5, give rise to four stereoisomers, namely *trans*-(4*R*,5*R*), *trans*-(4*S*,5*S*), *cis*-(4*S*,5*R*) and *cis*-(4*R*,5*S*), and/or to two racemates, (±)-*trans* and (±)-*cis* forms. Marked differences in activity and potency between *cis*- and *trans* isomers have been reported for some of these compounds.[134,148–154] (see Pharmacodynamics & Pharmacokinetics). It has been shown for many amphetamine-type stimulants that isomers with an (*S*)-configured α-methyl group are more potent pharmacodynamically than the (*R*)-isomers[155–157].

The 4,4′-DMAR isomer 3,4-dimethylaminorex (3,4-MAR, Figure 1) has been considered structurally similar to methamphetamine[155]. It has first been described by Poos and colleagues[9]. The analog seems to be a compound that has rarely been reported as a street drug but has rather been experimented with in scientific laboratories[153,155,158]. However, similar to *N*-methylaminorex (Figure 1), it has been detected in the European Union in 2015[159]. Various other, seemingly lesser known derivatives of aminorex have been mentioned in publications or the Internet but have not been investigated in a systematic manner[160]. Poos *et al*. have characterized various other locations (on the phenyl and oxazoline ring) and substituents and an overview of aminorex analogs has been published by Trachsel *et al.*[9,161] (Figure 2).

[Fig. 2]

Since the discovery of 4-MAR on the street market in the 1980s it is not surprising that this has caught the attention of law enforcement officials. In a reflective piece on future drugs of abuse published by Cooper as part of an international symposium held in 1988, the author lists aminorex, 4-MAR and six other analogs of particular interest (anorectic potency in rats comparable to amphetamine) (Figure 2) that were based on the work on Poos and colleagues from McNeil Laboratories[9]. Although not specifically mentioned in this personal communication between Poos and Cooper, the author also suspected the 4-fluoro- and 4-chlorophenyl analogs of 4-MAR and *N*,*N*-dimethyl-4-MAR to have “psychotomimetic” properties[10,162,163]. Other examples disclosed in a patent published by Poos included 4-alkyl analogs of aminorex (Figure 3) and methoxyphenyl-substituted analogs, although detailed

information was not provided[10]. Information about their occurrence on the streets is currently unavailable.

[Fig. 3]

Similarly, the literature based on the work carried out at McNeil Laboratories sparked interest among individuals interested in the chemistry and psychopharmacological exploration of psychoactive substances, collectively interacting through an online discussion forum called *The Hive* that was in operation between 1997–2004. Many of the posts are still available in archived form online[164]. The idea of preparing 4,4′-DMAR following established aminorex-type chemistry was proposed in 2003 (the idea apparently emerged during the synthesis of 4-methylmethcathinone that several years later became known as the NPS mephedrone), although it is unclear whether this was taken further by any other *Hive* member[165].

More recently, a user of another online drug forum shared information on a method of synthesis and effects related to 5-(2-fluorophenyl)-4,5-dihydro-1,3-oxazol-2-amine, i.e. the *ortho*-fluoro analog of 4-MAR (Figure 3)[166,167]. It was stated that the fluorinated analog was believed to be safer and less cardiotoxic,[166] which illustrates the persistent interest of the NPS community in aminorex derivatives while expressing a cautious approach toward minimizing possible side-effects and toxicity. Still, there seems to be a scientific basis for such an assumption because Rickli and colleagues have shown that 4-methyl and 4-bromo substitutions lead to more potent serotonergic properties than 4-fluoro groups[168]. It appears that users expressed an interest in the fluoro-substituted analog[169] and it was also mentioned that it might be already available for purchase[170]. A recent report from an online test purchase conducted by the Slovenian National Forensic Laboratory, suggests that the *para*-fluoro analog of 4-MAR (5-(4-fluorophenyl)-4-methyl-4,5-dihydro-1,3-oxazol-2-amine, 4'F,4-MAR) is also available for purchase from Internet vendors[171] (Figure 1). This substance has been offered for sale under the label "4-FPO" and mostly consists of the *trans*-isomer[171]. The mislabeled substance is currently being discussed in various user fora and sometimes described as a phenmetrazine derivative, which highlights the potential for confusion[172–175]. Its synthesis has even been described in detail by a clandestine chemist[176]. These new developments illustrate the abiding relevance of and interest in aminorex and its analogs in the NPS scene.

Synthesis

The procedure reported by Poos and co-workers for the preparation of 4-MAR analogs involved the reaction of 2-amino-1-phenylpropan-1-ol precursors with cyanogen bromide followed by cyclization. Correspondingly, the use of 2-amino-1-phenylethanol has been described to provide aminorex[9]. Furthermore, Poos et al.[9] and Klein et al.[129] showed that the reaction of cyanogen bromide with the norephedrine led to the formation of the *cis*-racemate whereas the employment of norpseudoephedrine gave the *trans*-form of 4-MAR. Interestingly, when investigating a case related to the clandestine synthesis of 4-MAR, it was found that norephedrine could be converted predominantly to the *trans*-product by reaction with potassium cyanate[177], an idea that has been discussed on *The Hive* forum[178]. The recent characterization of a 4'F-4-MAR sample obtained from a test purchase revealed the presence of the *trans*-form and the detection of the *cis*-form as a minor component[171]. In analogy to what has been described during the forensic investigation of the *trans*-4-MAR synthesis[177], it would be interesting to consider that the conversion of the 2-amino-1-(4-fluorophenyl)propan-1-ol precursor might have involved potassium cyanate as well. Interestingly, the procedure

described for the synthesis of 4'F-4-MAR on the Internet also involved the use of this same reagent although the described procedure did not reveal whether the resulting aminorex analog represented the *trans*- or *cis*-form[176]. The synthesis of racemic *cis*- and *trans*-4,4'-DMAR is shown in Figure 4, which was based on the reaction of 2-amino-1-(4-methylphenyl)propan-1-ol with either cyanogen bromide or potassium cyanate. 1-(4-Methylphenyl)propan-1-one served as the starting material for the preparation of the alcohol intermediate (Figure 4)[134]. Correspondingly, *cis*- and *trans*-MDMAR have been prepared *via* the norepinephrine-type precursor 2-amino-1-(2*H*-1,3-benzodioxol-5-yl)propan-1-ol[148]. An interesting observation reported for MDMAR (and not for 4,4'-DMAR) was that the racemic *cis*-form converted to the *trans*-form when exposed to water-containing solutions but not when exposed to acetonitrile, which suggested a potential role of water in this conversion process[148].

[Fig. 4]

Pharmacodynamics & Mechanisms of Action

It was known to Poos and colleagues that aminorex was not only an anorectic drug but also a drug with CNS stimulating properties[9]. Another study from the same laboratory revealed that aminorex was a releasing agent of catecholamines[179]. Rothman and colleagues later confirmed that aminorex was not a mere non-transported uptake inhibitor of monoamine transporters (like cocaine) but rather a releasing agent similar to amphetamine and that its main effects derived from its interaction with the monoamine transporters NET, DAT and SERT[180]. Since then, various groups have also performed transporter release assays, classifying aminorex and its derivatives as monoamine transporter substrates and releasing agents of monoamines[134,135,148].

Brandt *et al*. and McLaughlin and colleagues have demonstrated that aminorex, 4-MAR, 4,4'-DMAR and MDMAR were potent releasing agents in rat brain synaptosomal preparations at DAT, SERT and NET, with the lowest EC_{50} (half maximal effective concentration) at DAT, followed closely by NET and SERT[134,148] (see Table 1). Furthermore, it has been shown that the presence of additional methyl groups added onto aminorex to form 4-MAR and 4,4'-DMAR have barely changed its potency to cause efflux of monoamines at DAT and NET but have immensely increased its releasing potency at SERT[134]. The DAT/SERT ratio, with higher values indicating greater selectivity for DAT over SERT, was 45 for aminorex, 31 for 4-MAR and only 2 for 4,4'-DMAR[134]. In closely related substances, it has been established that substitution of the *para*-position led to decreased selectivity for DAT over SERT[168,181,182]. In comparison, MDMA's DAT/SERT ratio is 0.6 but its EC_{50} was five to ten times higher than that reported for 4,4'-DMAR[148]. MDMAR's potency was slightly lower than that of 4,4'-DMAR but higher than MDMA's[148].

It has recently been shown that 4,4'-DMAR binds to monoamine transporters with higher affinities compared to monoamine receptors, albeit it has also been shown to bind to hDAT, hNET, hSERT and 5-HT_{2A} and 5-HT_{2C} receptors with relatively low affinities[135] (see Table 1). Due to the lack of interaction with the trace amine-associated receptor 1 (TAAR1), 4,4'-DMAR is suspected to be unable to trigger the auto-inhibitory pathway that, for example, MDMA possesses at least in rodents[135,183,184].

Aminorex										
DAT			**NET**			**SERT**			**Reference**	**Cell system**
Inhibition IC_{50} in nM	**Release EC_{50} in nM**	**Affinity K_i in nM**	**Inhibition IC_{50} in nM**	**Release EC_{50} in nM**	**Affinity K_i in nM**	**Inhibition IC_{50} in nM**	**Release EC_{50} in nM**	**Affinity K_i in nM**		
--	9.1±0.9	--	--	15.1±3.5	--	--	414±78	--	Brandt et al.[134]	Rat brain synaptosomes
710±1050	--	--	1970±1200	--	--	26,290 ±1,030	--	--	Hofmaier et al.[117]	HEK293 cells
[K_i = 216±7]	--	784±16	--	--	--	[K_i = 1,244±106]	--	27,700±990	Rothman et al.[43]	Rat brain synaptosomes
[K_i = 216±7]	49.4±7.5	--	[K_i = 54.5±4.8]	26.4±2.8	--	[K_i = 1,244±106]	193±23	--	Rothman et al.[111,180,185,186]	Rat brain synaptosomes
--	--	--	--	--	--	[K_i = 1,380]	[% above basal flow: 51-116]	--	Tao et al.[187]	Rat brain tissue
4-methylaminorex										
--	1.7±0.2	--	--	4.8±0.9	--	--	53.2±6.8	--	Brandt et al.[134]	Rat brain synaptosomes ((±)-*cis*-4-MAR)
4,4'-dimethylaminorex										
--	8.6±1.1	--	--	26.9±5.9	--	--	18.5±2.8	--	Brandt et al.[134]	Rat brain synaptosomes ((±)-*cis*-4,4'-DMAR)
1040 (95% CI: 848 to 1282)	--	533.8±44.2	500 (95% CI: 447 to 553)	--	266.8±57	1750 (95% CI: 1446 to 2126)	--	1881±183.1	Maier et al.[135]	HEK293 cells ((±)-*cis*-4,4'-DMAR)
--	10.9±0.7	--	--	11.8±2.0	--	--	17.7±2.3	--	McLaughlin	Rat brain

									et al.[148]	synaptosomes ((±)-*cis*-4,4'-DMAR)
--	24.4±2.7	--	--	31.6±4.6	--	--	59.9±17.2	--	McLaughlin et al.[148]	Rat brain synaptosomes ((±)-*trans*-4,4'-DMAR)

Table 1: In vitro uptake inhibition, release and affinity data for aminorex and its analogs.

Poos and colleagues could not notice differences in potency between *cis* and *trans*-4-MAR as far as the ability to reduce food intake in rats was concerned[9]. As previously mentioned, amphetamine-type stimulants that possess an (*S*)-configured α-methyl group are generally more potent in producing effects in the central nervous system than the respective (*R*)-isomers[188]. Correspondingly, it has been shown for 4-MAR that *trans*-(4*S*,5*S*) is more potent than *cis*-(4*S*,5*R*) and *cis*-(4*R*,5*S*) at increasing extracellular dopamine concentrations and thus causing dopamine-related, dose-dependent locomotor activation [149,150,152] (see Table 2). Concerning the compounds' 5-HT release, it has been shown that *cis*-(4*S*,5*R*) is more potent than *trans*-(4*S*,5*S*) and *cis*-(4*R*,5*S*)[149]. Glennon and Misenheimer have shown that the *trans*-(4*S*,5*S*) isomer is the most potent isomer at the generalization of (*S*)-(+)-amphetamine stimuli, followed by the two *cis*-isomers[151]. All these studies showed the *trans*-(4*R*,5*R*) isomer have the, by far, weakest potency. Whether a direct relationship between the substance's potency and its number of (*S*)-configured methyl groups exists, similar to (*S*)-amphetamine, remains to be established. While it has been shown for 4-MAR that the (±)-*trans* racemate is more potent than the (±)-*cis* racemate to induce stimulus generalization in rats, a study comparing the potency of 4,4'-DMAR and MDMAR racemates in rat brain synaptosomes paints a different picture[148,151] (see Table 2). McLaughlin and colleagues point out that the (±)-*cis* racemates of 4,4'-DMAR and MDMAR seem to be slightly more potent than the respective (±)-*trans* racemates at evoking efflux at monoamine transporters[148].

Aminorex		
Model organism	**Results**	**Study**
Humans	Toxic doses for humans were determined to be located between 1-2 mg/kg. Symptoms occur between 15 and 120 mins after consumption and are characterised by seizures, respiratory depression, mydriasis, tachycardia, hypertension and hyperpnea.	Borbély et al.[189]
Hereford calves	An increase in arterial blood pressure but no pulmonary side-effects after daily i.v. injections (0.25 mg/kg) for one month were reported.	Byrne-Quinn & Grover[28]
Sprague-Dawley rats	A dose of 1.5 µmol/kg, administered i.v., elicited increased motor activity. Stereotypical behaviour was not detected in doses up to 112 µmol/kg.	Costa et al.[37]
Wistar rats	After administration of 6.5 to 22mg/kg aminorex daily for 118 consecutive days, no anatomical differences of the pulmonary vessels were detectable.	Engelhardt & Hort[32]
Humans	This retrospective study highlighted that anticoagulant therapy with warfarin in aminorex-caused pulmonary hypertension had beneficial effects on their survival time.	Frank et al.[190]
Rabbits	Aminorex was found to be an efficient 5-HT releaser in platelets, similar in potency to amphetamine.	Friström et al.[191]
Human subjects	Two studies (79 and 60 subjects) have proven aminorex (7.5 mg) to be an effective anorectic agent, similar to dextroamphetamine and diethylpropion but more effective than phenmetrazine. Side-effects concerning the CNS, the GI tract and the renal system, as well as leukopenia were reported.	Hadler[14]
Mongrel cats	1.0 mg/kg i.p. caused a 90 % decrease in food intake and lead to 81.5 % of a 12 hour session being spent awake, 16.5 % in slow-wave sleep and 2.0 % in paradoxical sleep.	Johnson et al.[192]
Baboons	Self-injection experiments showed for doses of 0.1 and 0.32 mg/kg/injection cyclical patterns of self-injection, with numbers of injections per day similar to cocaine, suggesting abuse potential. Food intake was decreased significantly at the highest concentration.	Kaminski et al.[193]
Wistar albino rats; beagle dogs	Treatment with aminorex for 43 (rats) and 20 weeks (dogs) did not	Kay et al.[17]

	reveal evidence of pulmonary vascular disease.	
Human subjects	Aminorex was shown to be an effective anorectic drug and no relevant side-effects were reported after a daily intake of 10 mg for 120 days (20 patients).	Kew[194]
Beagle dogs	Treatment of dogs with high doses of aminorex for 13 weeks led to no significant pulmonary and cardiac abnormalities.	Leuschner et al.[33]
Swine (young)	Aminorex was given for three months but no significant cardiovascular and pulmonary side-effects could be detected.	Mlczoch et al.[195]
Swine	Up to 15 mg/kg of aminorex per day was fed to swine for four months. No signs of pulmonary arterial hypertension could be detected but a slight decrease in cardiac and pulmonary function was noticeable.	Orr et al.[31]
Sprague-Dawley rats	Aminorex was shown to be amongst the most potent amphetamine-type stimulants concerning its ability to evoke anorexia and stimulant activity.	Paul et al.[196]
CHO cells	Aminorex inhibits hKv1.5 channels with a $K_D > 300$ µM.	Perchenet et al.[39]
Rats	Aminorex was shown to have an ED_{50} of 5.8 mg/kg.	Poos et al.[9]
Rats	3 and 6 mg/kg were administered orally and motor activity was evaluated. Aminorex, when compared to 4-MAR and amphetamine, was shown to reach peak motor activity levels earlier (after 40 minutes) than the other compounds (4-MAR after 80 minutes and amphetamine after 130 minutes).	Poos et al.[197]
Sprague-Dawley rats	Aminorex was shown to generalise for amphetamine and to have an ED_{50} of 3.0 µmol/kg. No stimulus generalisation could be obtained with rexamino.	Russell et al.[153]
Wistar rats	Aminorex induced stereotyped behaviour, lasting three hours at 5.0 mg/kg, administered s.c. in rats pre-treated with α-methyl-p-tyrosine.	Sayers & Handley[198]
Patas monkeys	Up to 4 mg/kg of aminorex was administered for 347 consecutive days and cardiac catheterization and autopsy results revealed no significant pulmonal and cardiac pathologies.	Smith et al.[29]
Mongrel dogs	Administration of 1.0 to 1.5 mg/kg aminorex five times per week over two years lead to histologically detectable changes in the pulmonary arteries of 60% of the dogs. The changes were not as severe as those	Stepanek & Zak[34]

	detected in humans suffering from pulmonary arterial hypertension.	
Chinese hamsters, V79 Chinese hamster cells, Saccharomyces cerevisiae, Escherichia coli, Salmonella typhimurium	In contrast to other amino-oxazoline derivatives, mutagenic effects of aminorex could not be shown in vitro and vivo. Most of the other tested compounds were mutagenic but methylation of the oxazoline ring reduced the detrimental effects.	Suter et al.[199]
Sprague-Dawley rats	Aminorex caused 5-HT release in rat hypothalamus in a dose-dependent manner.	Tao et al.[187]
Beagle dogs	1.5 mg/kg aminorex was orally administered and transient increases of pulmonary and systemic arterial blood pressure but no formation of pulmonary hypertension were noted.	Will & Bisgard[30]
Rhesus monkeys, CF-1 mice, Sprague-Dawley rats	Aminorex substituted for amphetamine in generalisation tests, served as a positive enforcer (both in monkeys), caused stimulant-mediated locomotor effects at 1.25 mg/kg (mice) and worsened signs of withdrawal (rats).	Woolverton et al.[200]
Sprague-Dawley rats	Stimulus-generalisation tests revealed that aminorex is recognised by rats as an amphetamine-type stimulant (starting from doses of 0.5 mg/kg).	Young[201]
Sprague-Dawley rats	4-MAR (ED_{50}=1.11) was six times less potent than aminorex (ED_{50}=0.22) in cocaine stimulus generalisation experiments.	Young & Glennon[202]
Sprague-Dawley rats	Aminorex (1 µmol/kg) substituted for *S*-methcathinone in stimulus generalisation experiments with an ED_{50} of 0.27 mg/kg.	Young & Glennon[203]
CBA mice	Between 25 mg/kg were injected intraperitoneally for three times in 24 hours. No significant changes in DOPAC or 5-HIAA, as well as no long-lasting depletion of monoamines could be detected.	Zheng et al.[155]
	4-methylaminorex	
Sprague-Dawley rats	The *trans*-4*S*,5*S*-isomer was the most potent isomer concerning a suppression of the basal firing rate of spontaneously active dopaminergic neurons (*trans*-4*S*,5*S* > *cis*-4*R*,5*S* = *cis*-4*S*,5*R* >>*trans*-4*R*,5*R*). This effect could be reversed by the addition of haloperidol and the D_2 and D_3 receptor antagonists eticlopride and sulpiride. The (pre-)treatment with pindolol, fluoxetine, granisetron and phentolamine (amongst others) did not change the effects, while pre-treatment with	Ashby et al.[150]

	α-methyl-p-tyrosine and reserpine did.	
Sprague-Dawley rats	The isomers of 4-MAR were ranked according to their ability to induce stereotyped behaviour at various doses: *trans*-4*S*,5*S* > *cis*-4*R*,5*S* = *cis*-4*S*,5*R* >*trans*-4*R*,5*R*. This effect could be attenuated by administration of dopamine receptor antagonists, suggesting a dopaminergic neural causation of 4-MAR's behavioural effects.	Batsche et al.[152]
Humans	A case is described where aminorex was misrepresented as 4-MAR.	Brewster & Davis[128]
Sprague-Dawley rats	Acute changes after administration of a single dose were determined. Between 5 and 20 mg/kg were administered. Tryptophan hydroxylase activity declined in a dose-dependent manner. Locomotor activity was dose-dependent and 20 mg/kg led to clonic seizures, oftentimes fatal.	Bunker et al.[204]
Humans	A fatality involving 4-MAR is described (blood levels: 21.3 mg/L and urine levels: 12.3 mg/L).	Davis & Brewster[130]
Humans	A case study is presented where three members of a family that produced and consumed 4-MAR, developed pulmonary hypertension.	Gaine et al.[131]
Sprague-Dawley rats	Administration of the *cis*- and *trans*-racemate led to amphetamine stimulus generalisation with the *trans*-racemate being three times more potent than the *cis*-racemate (ED_{50}: *trans*-4*S*,5*S*, 0.25 mg/kg > *cis*-4*S*,5*R*, 1.22 mg/kg = *cis*-4*R*,5*S*, 1.52 mg/kg > *trans*-4*R*,5*R*).	Glennon & Misenheimer[151]
CF-1 mice	The seizure-causing properties of 4-MAR were evaluated. Its CD_{50} was determined to be 90µg and its CD_{97} 110 µg, following intracerebroventricular injection. Thus, 4-MAR has a very steep dose-seizure curve. Onset of the seizures was intermediate (between 60-300 sec) and clonus duration was between 30 and 300 sec. After the termination of clonic activity, a second seizure episode followed after a short period of behavioural arrest. Flunarizine and valproate could be shown to be effective in preventing 4-MAR-caused seizures.	Hanson et al.[205]
Wistar rats	The rank order of potency for elevating extracellular dopamine levels was *trans*-4*S*,5*S* > *cis*-4S,5R = *cis*-4R,5S >*trans*-4*R*,5*R* 4-MAR and for elevating 5-HT *cis*-4*S*,5*R* >*trans*-4S,5S = *cis*-4*R*,5*S* > *trans*-4*R*,5*R*. All isomers caused a decrease of extracellular concentrations of DOPAC and HVA. At lower doses (2.5 and 5.0 mg/kg), the isomers (except for	Kankaanpää et al.[149]

	trans-4*R*,5*R*) caused rises in locomotor activity and high doses (10 mg/kg) caused biphasic behaviour patterns, with initial rises in locomotor activity being followed by rapid declines and engagement in stereotyped behaviour, ataxia or catatonia.	
Baboons, rhesus monkeys	Self-administration experiments highlighted cyclical patterns of self-injection, where days with many injections (0.32 mg/kg/injection) were followed by low-rate days (in baboons). This behaviour lead to agitation, stereotypic movements, hypersensitivity and hallucinations. Rhesus monkeys had unlimited access to the compound for one hour and administered up to 100 injections (0.003 to 0.03 mg/kg/injection). The results were interpreted as 4-MAR having strong potential for abuse.	Mansbach et al.[206]
Wistar rats	Conditioned place preference tests revealed that all isomers equipotently induced preference. This effect was, for some isomers, attenuated by the administration of dopamine receptor antagonists and lesions in the nucleus accumbens. Rewarding properties of 4-MAR consumption were revealed to be connected to the dopaminergic system.	Meririnne et al.[207]
Rats	The ED_{50} of *cis*-4-MAR was determined to be 8.8 mg/kg.	Poos et al.[9]
Rats	3 and 6 mg/kg were administered orally and motor activity was evaluated. 4-MAR caused peak motor activity levels earlier (after 80 minutes) than amphetamine (130 minutes) but later than aminorex (40 minutes).	Poos et al.[197]
Sprague-Dawley rats	4*S*,5*S*-4-MAR was shown to generalise for amphetamine and to have an ED_{50} of 1.7 μmol/kg.	Russell et al.[153]
Mongrel dogs	Sympathomimetic effects of the compound can be attributed to an increased release of catecholamines (published in 1963).	Yelnosky & Katz[179]
Sprague-Dawley rats	4-MAR (ED_{50}=1.11) was six times less potent than aminorex (ED_{50}=0.22) in cocaine stimulus generalisation experiments.	Young & Glennon[202]
Sprague-Dawley rats	*Cis*-4-MAR (2.3 μmol/kg) substituted for *S*-methcathinone in stimulus generalisation experiments with an ED_{50} of 0.49 mg/kg.	Young & Glennon[203]
CBA mice	Between 5 and 30 mg/kg (depending on the stereoisomer) were	Zheng et al.[155]

	injected intraperitoneally for three times in 24 hours. DOPAC levels were increased but no long-lasting depletion of monoamines could be detected.	
4,4'-dimethylaminorex		
Sprague-Dawley rats	An extensive chemical analysis of 4,4'-DMAR was conducted (crystal structure analysis, mass spectrometry, chromatography and spectroscopy). Monoamine transporter assay results are mentioned in Table 1.	Brandt et al.[134]
--	A mini-review of 4,4'-DMAR.	Coppola & Mondola[208]
Humans	4,4'-DMAR-caused fatalities were examined. Post-mortem concentrations of 4,4'-DMAR were between 0.20 to 3.75 mg/L. Liquid chromatography and mass spectrometry approaches of screening for 4,4'-DMAR were described.	Cosbey et al.[209]
--	A mini-review of 4,4'-DMAR.	Glanville et al.[210]
--	Drug fora were analysed to paint a picture of the way users discussed 4,4'-DMAR.	Loi et al.[144]
HEK293 cells, rPC12 cells, human striatal synaptic vesicles	4,4'-DMAR was classified as a non-selective monoamine releasing agent and binding data was provided. Inhibition of VMAT2 hints at long-term neurotoxic effects in chronic abusers of the substance.	Maier et al.[135]
Sprague-Dawley rats	An in-depth chemical analysis of MDMAR was provided. In addition, monoamine transporter assays comparing *cis*-MDMAR, *trans*-MDMAR, *cis*-4,4′-DMAR and *trans*-4,4′-DMAR are portrayed in Table 1.	McLaughlin et al.[148]
--	An internet snapshot survey was conducted to analyse the availability of 4,4'-DMAR and 4-MAR in April 2014.	Nizar et al.[143]

Table 2: A summary of pharmacodynamic and toxicological studies on aminorex and its analogs.

Pharmacokinetics

Aminorex, when available as an anorectic drug, existed in the form of 7.5 to 20 mg aminorex fumarate, base or pamoate tablets, to be consumed orally[211]. 4-MAR seems to mostly have been ingested orally, insufflated or smoked in doses ranging from 5 to >25 mg depending on the routes of administration[212]. 4,4'-DMAR has mostly been consumed orally or insufflated but has also been inhaled and administered i.v. with doses ranging from 10 to 200 milligrams[133,208,210].

Cressman and colleagues have tested the change of aminorex fumarate plasma concentration over time in human participants.[211] They have shown that aminorex fumarate has a relatively long half-life of 8 hours and effects can even be prolonged and high concentrations maintained by utilizing sustained-release tablets. It has been determined in horses that aminorex is rapidly absorbed (with a half-life of 30 minutes) and that it is eliminated in various steps with a half-life of 24 hours in the slow, extended terminal elimination phase[213]. This can be pharmacokinetically modelled via a multi-compartment model where the compound is quickly eliminated from plasma and accumulates in deeper compartments and is then slowly metabolized (see Table 3). The accumulation of aminorex and its derivatives might explain the reported cyclical patterns of 4-MAR self-administration in baboons with high rate of self-injection across days alternating with low rates across days[206]. For (±)-*cis*-4,4'-DMAR, Lucchetti and colleagues have shown that the compound is rapidly distributed into peripheral tissue, easily passes the blood-brain-barrier and is slowly eliminated with a half-life of five hours[214]. The compound has been shown to be lipophilic with a brain-to-plasma ratio three times that of (±)-*cis*-4-MAR[154,215].

Concerning the metabolic fate of aminorex, unpublished data from McNeil Laboratories seems to suggest that 31% are excreted non-metabolized and that the amino-oxazoline ring is being hydrolysed to hydroxyphenylurea[216]. Previously, another study identified hydroxyaminorex as one major metabolite in horses[213]. Henderson and colleagues have found three metabolites of 4-MAR: (i) the active metabolite norephedrine, caused by the hydrolysis of 4-MAR; (ii) 4-(2-amino-4-methyl-4,5-dihydro-1,3-oxazol-5-yl)phenol, emerging through hydroxylation; and (iii) 4-methyl-5-phenyl-1,3-oxazolidin-2-one, caused by the deamination of 4-MAR[216]. It was also hypothesized that the methyl group might inhibit the hydrolysis of the amino-oxazoline ring. Lucchetti and colleagues could produce similar results for (±)-*cis*-4,4'-DMAR[215]. They discovered four metabolites, caused by hydrolysis, hydroxylation, deamination (which has already been shown for 4-MAR) and oxidation of the compound. The main metabolite located in plasma and brain was the one not detected in 4-MAR, caused by oxidation of 4,4'-DMAR's *para*-methyl group[215]. It has been demonstrated that aminorex is mostly eliminated renally over the course of 72 hours[211].

It has been revealed that the concentration of the two *trans* isomers of 4-MAR in rat brain tissue, 30 minutes after i.p. injection, is significantly higher than that of the *cis* isomers[217]. Similarly, the concentration of *trans* isomers is also increased in dialysate and plasma[149]. Additionally, the elimination of the *trans*-(4*R*,5*R*) isomer is three times slower than that of the others[154]. The bioavailability of the *trans*-(4*R*,5*R*) isomer is significantly higher than the other isomers', indicating protection from pre-systemic metabolic degradation. It has been shown to accumulate in tissue, i.e. mostly in the kidney, liver, brain and muscles, significantly more than the other isomers of 4-MAR. There is a remarkable difference in pharmacokinetic properties between *trans*-(4S,5S)-, *cis*-(4S,5R)- and *cis*-(4R,5S)-isomers, which resemble

each other, and the *trans*-(4*R*,5*R*) isomer. It is remarkable that, even though the brain concentration of *trans*-(4*R*,5*R*)-4-MAR is by far the highest, the substance is less potent than the other isomers[154].

Aminorex			
Model organism	**ADME**	**Results**	**Study**
In vivo: human subjects; in vitro dissolution	A	Aminorex fumarate, as sustained-release tablets in doses of 15 and 20 mg/tablet, was determined to have good absorption rates and allow for prolonged effects.	Cressman et al.[211]
In vivo: Standardbred gelding horses; in vitro: horse liver microsomes	M	Aminorex and rexamino were discovered to be metabolites of levamisole in horse urine and plasma.	Ho et al.[63]
In vivo: Thoroughbred horses	A, D, E	Aminorex was administered orally and i.v. Distribution could be described by a three-compartment (with half-lives of 0.04, 2.30 and 18.82 hours) and a two-compartment model, respectively. The substance was renally eliminated and urinary excretion peaked after two hours for the i.v. group and six hours for the p.o. group.	Soma et al.[213]
4-methylaminorex			
In vivo: Sprague-Dawley rats	M, E	4-MAR is mostly eliminated renally (and secondly via the GIT) in its unchanged form (60%). Three metabolites could be identified: 4-MAR is hydrolysed to norephedrine, the phenyl ring can be hydroxylated to form 2-amino-5-[p-hydroxyphenyl]-4-methyl-2-oxazoline and deamination leads to metabolite 5-phenyl-4-methyl-2-oxazolidinone.	Henderson et al.[216]
In vivo: Wistar rats	E	4-MAR isomers could be detected by more than half of the tested on-site immunoassays, mostly as (meth-)amphetamine or cocaine. How to detect and quantify 4-MAR in urine using TLC and GC/MS is described in detail.	Kankaanpää et al.[217]
In vitro	A	Chemical properties of the stereoisomers are described in detail.	Klein et al.[129]
In vivo: Wistar rats	A, D, M, E	Oral bioavailability of 4-MAR was significantly lower than after i.v. or intraperitoneal administration.	Meririnne et al.[154]

		Marked differences between the isomers concerning their half-lives were found (for details see main text). Elimination of the *trans*-4R,5R-isomer was 3 times slower than that of the others. The highest concentrations of 4-MAR were located in the kidney, liver, brain and muscles, suggesting a significant ability to cross the blood-brain-barrier. The metabolites norephedrine (from the *cis*-isomers) and norpseudoephedrine (from the *trans*-isomers) were detected in blood and brain.	
4,4'-dimethylaminorex			
In vivo: Wistar rats	A, D, E	1 mg/kg *cis*-4,4′-DMAR was given i.v. The compound was more rapidly and extensively distributed than 4-MAR and more slowly eliminated (plasma $t_{1/2}$ of 5.14 ± 0.65 h). I.p. doses of *cis*-4,4′-DMAR (1, 3 and 10 mg/kg) show a dose-dependent AUC. Data was quantified with HPLC-MS/MS.	Lucchetti et al.[214]
In vivo: Wistar rats	A, D, M	I.p. injections lead to fast brain absorption (t_{max} = 30-60 minutes) and high brain concentrations with a brain-to-plasma ratio of 24. The $t_{1/2}$ was determined to be approximately 50 minutes. Four metabolites, caused by hydroxylation, oxidation, hydrolysis and oxidative deamination of *cis*-4,4′-DMAR were identified in plasma and in low concentrations also in the brain. Behavioural experiments highlight the rewarding and addictive properties of *cis*-4,4′-DMAR.	Lucchetti et al.[215]

Table 3: A summary of pharmacokinetic studies on aminorex and its analogs.

Behavioral Effects and Dependence Potential

Stimulus generalization tests conducted with rats revealed that aminorex is similar to amphetamine in its effects, albeit slightly less potent[151,201]. Similar results are available for 4-methylaminorex[153,204]. Rexamino, detected as a levamisole metabolite in horses, on the other hand, was determined to be inactive in a drug discrimination study in rats trained to discriminate (*S*)-amphetamine from saline, which was consistent with comments made by Poos who disclosed that rexamino was devoid of CNS stimulant activity[10,63,153]. Interestingly, derivatives of rexamino have been discovered to be highly potent TAAR1 agonists[218]. Further investigations have revealed that aminorex and 4-methylaminorex substitute for cocaine stimuli[188]. These results have been corroborated in experiments with rhesus monkeys, suggesting that aminorex seems to have an abuse liability similar to amphetamine[200]. Using self-administration paradigms in baboons and rhesus monkeys, Mansbach *et al.* have shown that 4-MAR displayed reinforcing effects in primates[206]. The conditioned place preference test has been utilized in rats to assess the rewarding, dopamine-dependent effects of 4-MAR and 4,4'-DMAR consumption[207,215].

It has been hypothesized that the psychomotoric effects associated with aminorex involved interactions with brain receptors or releasing dopamine[37]. The attribution of effects to extracellular dopamine could be confirmed for 4-MAR (for enantiomeric differences see above), even though the cited studies did not include measures of extracellular norepinephrine, that might also be implicated in the behavioral effects in rats[149,150,219,220]. Batsche and colleagues have considered this option and administered D_1 and D_2 receptor antagonists in conjunction with 4-MAR and noted an attenuation when compared to the compound alone[152]. In addition, serotonin and norepinephrine receptor antagonists proved ineffective. These results allude to the possibility that increased locomotor activity in rats could be attributed to high extracellular dopamine levels and that it is dose-dependent. It has been unveiled for (±)-*cis*-4,4'-DMAR that the substance also increases locomotor activity[215].

Drug users have described the effects of aminorex derivatives as feeling euphoric, stimulated, energized and social and the experience of taking the drugs has been described as being similar to both methamphetamine and MDMA[144,210,221,222] although further studies are warranted to assess similarity to MDMA's psychopharmacology in humans. With the animal model results in mind, one can conclude that aminorex and its derivatives are liable to abuse and that they might display dependence potential similar to amphetamine and cocaine.

Adverse Effects and Toxicity

A trial of aminorex as an anorectic drug revealed that it can cause insomnia, restlessness, gastrointestinal, dermatological and cardiovascular side-effects, as well as proteinuria[14,189]. Acute overdoses (between 1-2 mg/kg for humans) can cause symptoms such as seizures, hyperreflexia, respiratory depression, mydriasis, tachycardia, hypertension and hyperpnea, occurring occur between 15 and 120 mins after consumption[189]. The fact that aminorex also acts as a substrate and releaser at SERT has been linked to pulmonary arterial hypertension[43,185]. Drug users have mentioned hand, muscle twitches, numbness, hallucinations, panic attacks, nausea, tachycardia and hyperthermia as unwanted side-effects of the consumption of 4-MAR and 4,4'-DMAR[144,221]. The clinical and autopsy reports of 4,4'-DMAR patients have described short-term complications such as hyperthermia, seizures, hallucinations, agitation, internal bleeding, edema and heart and lung failure[133]. These

symptoms might be explained as the immediate effects of considerable monoamine release, caused by this particular drug.[135]

Hallucinations caused by high doses of aminorex or derivatives are difficult to measure in rodents but have been reported for primates subjected to high-dose self-administration regimes[206].

Bunker and colleagues have reported that rats receiving 20 mg/kg 4-MAR suffered from clonic seizures in the first hour following the treatment and died in the next two to 17 hours[204]. Frequent amphetamine-induced seizures can (in rare cases) lead to the development of epilepsy and the formation of epileptogenic brain lesions[223]. It has been shown that seizures caused by 4-MAR ingestion can be antagonized by the administration of flunarizine, a calcium channel blocker[205].

Zheng et al. have examined the neurotoxic properties of several aminorex analogs in comparison to MDMA quantified via long-term depletions in monoamine content [155]. They concluded that only the *trans*-(4S,5S)-isomer of 3,4-dimethylaminorex depletes dopaminergic and serotonergic neurons with a potency similar to MDMA. It has recently been shown that 4,4'-DMAR inhibits the vesicular monoamine transporter 2 (VMAT2; SLC18A2) with a potency similar to that of MDMA[135]. Perturbed function of VMAT2 has been associated with neurotoxicity[224,225]. Still, MDMA has been shown to only be neurotoxic when consumed in high doses over a long periods of time[226–230]. As mentioned before, in contrast to other amphetamine-type stimulants, 4,4'-DMAR does not interact with TAAR1 and therefore lacks the auto-inhibitory pathway that attenuates monoamine release and mediates the neuroprotective effects[231,232]. It has however been shown that many psychoactive compounds stimulate human TAAR1 less potently than the receptor's rodent counterparts[184]. It is currently not confirmed whether aminorex and its derivatives are neurotoxic. The absence of the auto-inhibitory pathway and the inhibition of VMAT2 might be relevant factors in the determination of the potential neurotoxicity of the compound. Current knowledge would suggest that toxic effects might only appear after high dosage consumption over prolonged time periods.

The 5-HT_2 receptors (5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}) are expressed in the endocardium, myocardium and the heart valves[233,234]. It has been shown for MDMA (but also other psychostimulants) that binding to the 5-HT_{2B} receptor in particular might possibly be associated with valvular heart disease[234]. On the other hand, these findings could not be replicated in other studies[235,236]. While it has been shown that 4,4'-DMAR binds to the 5-HT_{2A} and 5-HT_{2C} receptors[135], receptor binding assays for 5-HT_{2B} have not been conducted yet. In addition, the interaction of aminorex and other derivatives with the 5-HT_{2B} receptor has not yet been subject of investigation. Hence, concerning the long-term cardiotoxicity of aminorex and derivatives, at this point in time one can only speculate that, because of their similarity to MDMA, a potential interaction with the 5-HT_{2B} receptor might be possibly implicated in cardiotoxic effects.

Concluding Remarks

The historical events linked to aminorex and its derivatives are representative of what has occasionally been termed the NPS/"designer drug" phenomenon[8,237]. The parental drug aminorex was originally used as approved medication, yet failed to persist on the market

when evidence on adverse side effects accumulated. With the help of existing literature describing the properties of a range of closely related drugs, however, new analogs appeared on the streets (e.g. 4-MAR). Because of its sympathomimetic effects, a patent claim has been filed for the usage of 4-MAR as a nasal decongestant[238]. Other examples exist where an emerging drug that has no history in the scientific (including patent) literature appears for sale on the Internet (e.g. 4,4'-DMAR). Today, (*4S,5S*)-*trans*-4,4'-DMAR is mentioned in a patent as a phospholipase A2 inhibitor and therefore claimed as an anti-inflammatory agent[133,239]. In addition, several isomers of 4,4'-DMAR and related compounds have been patented to be utilized in the treatment of CNS disorders[133].

The 4,4'-DMAR case has also illustrated that this drug has escaped the Internet realm predominantly relevant to users who had a specific interest in this substance as it surreptitiously appeared on the traditional illicit street market where it has been supplied to unsuspecting users with tragic consequences. Some Internet suppliers removed the substance from their product catalog once information of the adverse effects emerged. Given the information available on a range of yet unexplored compounds and the interest of the NPS community in the substance group, one might predict further commercial exploitations by NPS entrepreneurs and organized crime groups. The gloomy aspect of the NPS phenomenon is that information on long-term effects, acute toxicity or pharmacology remains limited, combined with the fact that increasingly toxic substances have appeared in recent years[5]. An appreciable body of scientific studies has aimed to elucidate the pharmacodynamic and pharmacokinetic properties of NPS. However, considering the rate by which NPS are introduced into the markets, the scientific community is constantly trailing and chasing after new developments. Furthermore, scientific literature may serve as a rich source for creative drug dealers to identify preferable adulterants (such as levamisole) for their products. However, the immense amount of data collected on stimulant-type NPS and their structure-activity relationships may help to identify crucial structural determinants to pave the way for the development of improved pharmacotherapies to neuropsychiatric disorders arising from imbalances in monoaminergic neurotransmission.

Author Contributions

J.M. outlined, wrote and edited the manuscript. F.P.M., S.D.B. and H.H.S. provided guidance and further ideas, contributed written parts and edited the manuscript.

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Conflict of Interest

The authors declare no competing financial interest.

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Figures

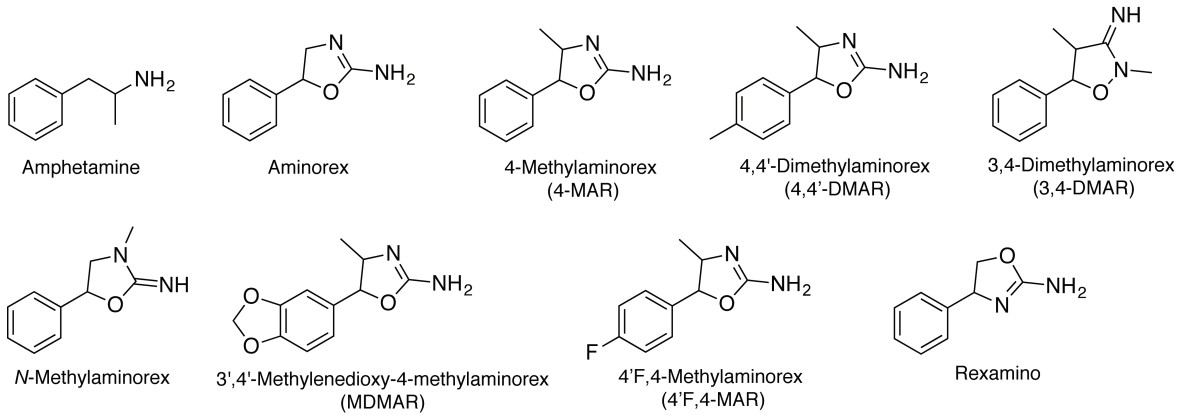
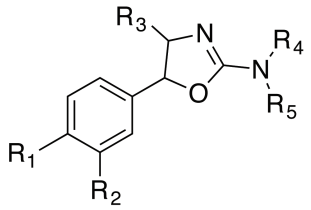


Figure 1. Chemical structures of amphetamine and known aminorex analogs.



R_1	R_2	R_3	R_4	R_5		ED_{50} (mg/kg)
F	H	H	H	H		1.2
Cl	H	H	H	H		2.5
H	CF_3	H	H	H		4.0
Br	H	H	H	H		4.6
H	H	H	H	H	(Aminorex)	5.8
CF_3	H	H	H	H		7.0
H	H	CH_3	CH_3	CH_3		7.0
H	H	CH_3	H	H	(4-MAR)	8.8 (*cis*)

Figure 2. List of aminorex analogs in decreasing order of potency concerning their anorectic activity in rats (reduction in consumption of beef broth after oral administration)[9,162]. In comparison, the ED_{50} value for dextroamphetamine sulfate was 6.8 mg/kg[9].

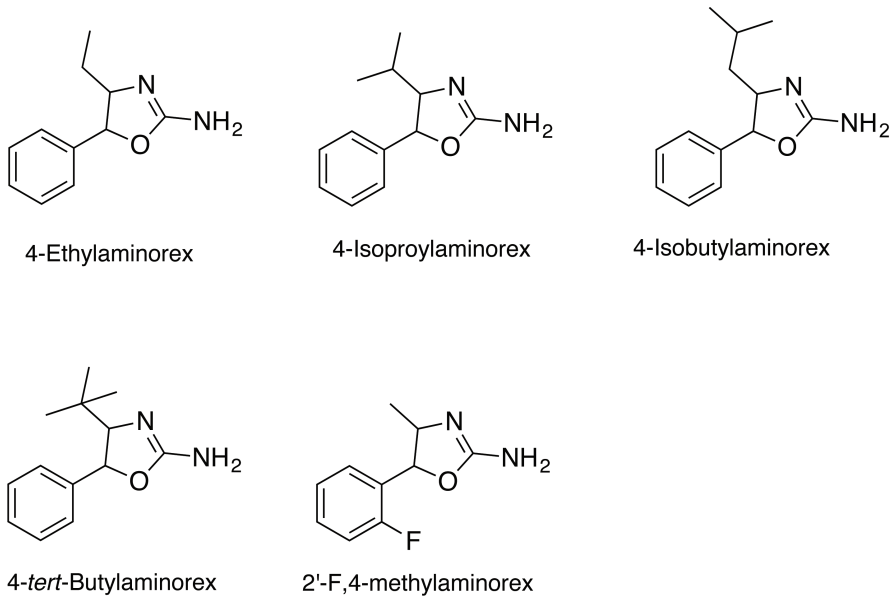


Figure 3. Aminorex analogs claimed to have CNS stimulant activity[10]. The synthesis and exploration of effects of 2'-F,4-Methylaminorex has been described by a contributor to an online user forum.

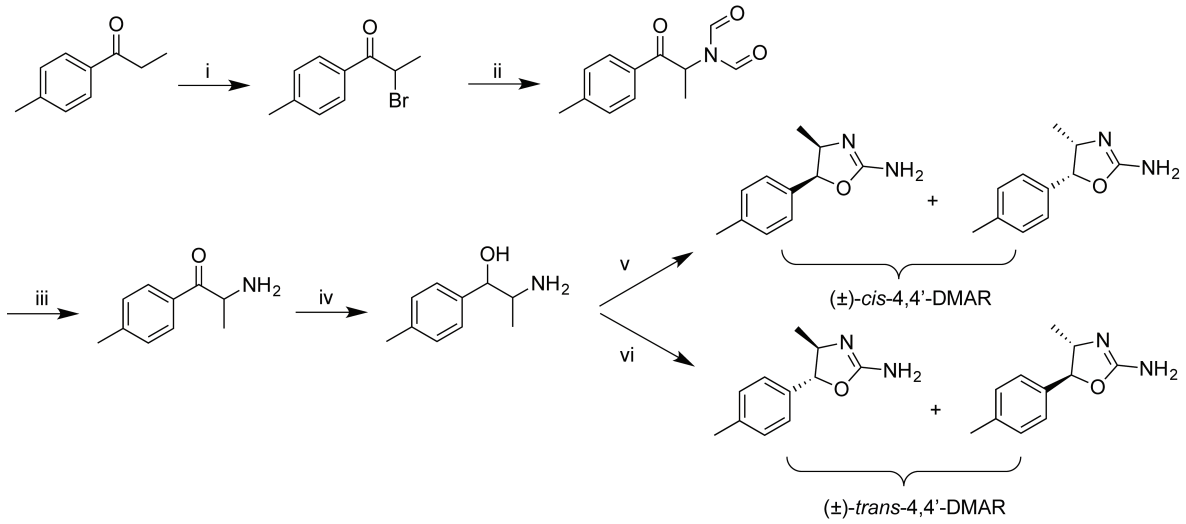


Figure 4. Synthesis of racemic 4,4'-DMAR[134]. i) Br2/dichloromethane, 1h at room temperature; ii) sodium diformylamide/acetonitrile, 4 h at reflux; iii) HCl/ethanol, overnight at room temperature; iv) sodium borohydride/methanol, addition over 1.5 h period; v) cyanogen bromide/anhydrous sodium acetate/methanol, 3.5 h on ice, saturated sodium carbonate; vi) potassium cyanate/water, 3 h at reflux, 2 M HCl, 2 h at reflux, saturated aqueous sodium carbonate.