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Central nervous system stimulant This article is about the stimulant drug. For other uses, see Caffeine (disambiguation). Pharmaceutical compound Caffeine Clinical dataPronunciation/kæˈfiːn, ˈkæfiːn/ Other namesGuaranineMethyltheobromine1,3,7-Trimethylxanthine7-methyltheophylline[1] TheineAHFS/Drugs.comMonographLicense data US DailyMed: Caffeine Pregnancycategory AU: A DependenceliabilityPhysical: Moderate 13% and variable low–high 10–73%[2] Psychological: Low–moderate[2]AddictionliabilityRelatively low: 9%[3] [failed verification]Routes ofadministrationCommon: By mouth Medical: Intravenous Uncommon: Insufflation, rectal, transdermal, topicalDrug classStimulant;Adenosinergic; Eugeroic;Nootropic;Anxiogenic; Analeptic; PDE inhibitor;DiureticATC codeN06BC01 (WHO) D11AX26 (WHO), V04CG30 (WHO)Legal statusLegal status AU: Unscheduled BR: Unscheduled CA: Unscheduled DE: Unscheduled NZ: Unscheduled UK: General sales list (GSL, OTC) US: Unscheduled UN: Unscheduled CN: OTC In general Legal for all usesPharmacokinetic dataBioavailability99%[4]Protein binding10–36%[5]MetabolismPrimary: CYP1A2[5]Minor: CYP2E1,[5] CYP3A4,[5]CYP2C8,[5] CYP2C9[5]Metabolites• Paraxanthine 84% • Theobromine 12% • Theophylline 4%Onset of action45 minutes–1 hour[4][6]Elimination half-lifeAdults: 3–7 hours[5]Infants (full term): 8 hours[5]Infants (premature): 100 hours[5]Duration of action3–4 hours[4]ExcretionUrine (100%)Identifiers IUPAC name 1,3,7-Trimethyl-3,7-dihydro-1H-purine-2,6-dione CAS Number58-08-2PubChem CID2519IUPHAR/BPS407DrugBankDB00201ChemSpider2424UNII3G6A5W338EKEGGD00528ChEBICHEBI:27732ChEMBLChEMBL113NIAID ChemDBnonePDB ligandCFF (PDBe, RCSB PDB)CompTox Dashboard (EPA)DTXSID0020232 ECHA InfoCard100.000.329 Chemical and physical dataFormula$C_8H_{10}N_4O_2$Molar mass194.194 g·mol−13D model (JSmol)Interactive imageDensity1.23 g/cm3Melting point235 to 238 °C (455 to 460 °F) (anhydrous)[7][8] SMILES CN1C=NC2=C1C(=O)N(C(=O)N2C)C InChI InChI=1S/C8H10N4O2/c1-10-4-9-6-5(10)7(13)12(3)8(14)11(6)2/h4H,1-3H3Key:RYYVLZVUVIJVGH-UHFFFAOYSA-N Data pageCaffeine (data page) Caffeine is a central nervous system (CNS) stimulant of the methylxanthine class and is the most commonly consumed psychoactive substance globally.[9][10] It is mainly used for its eugeroic (wakefulness promoting), ergogenic (physical performance-enhancing), or nootropic (cognitive-enhancing) properties.[11][12] Caffeine acts by blocking the binding of adenosine at a number of adenosine receptor types, inhibiting the centrally depressant effects of adenosine and enhancing the release of acetylcholine.[13] Caffeine has a three-dimensional structure similar to that of adenosine, which allows it to bind and block its receptors.[14] Caffeine also increases cyclic AMP levels through nonselective inhibition of phosphodiesterase, increases calcium release from intracellular stores, and antagonizes GABA receptors, although these mechanisms typically occur at concentrations beyond usual human consumption.[10][15] Caffeine is a bitter, white crystalline purine, a methylxanthine alkaloid, and is chemically related to the adenine and guanine bases of deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It is found in the seeds, fruits, nuts, or leaves of a number of plants native to Africa, East Asia and South America[16] and helps to protect them against herbivores and from competition by preventing the germination of nearby seeds,[17] as well as encouraging consumption by select animals such as honey bees.[18] The most common sources of caffeine are the tea leaves of the Camellia sinensis plant, and the coffee bean, the seed of the Coffea plant. People may drink beverages containing caffeine to relieve or prevent drowsiness and to improve cognitive performance. To make these drinks, caffeine is extracted by steeping the plant product in water, a process called infusion. Caffeine-containing drinks, such as tea, coffee, and cola, are consumed globally in high volumes. In 2020, almost 10 million tonnes of coffee beans were consumed globally.[19] Caffeine is the world's most widely consumed psychoactive drug.[20][21] Unlike most other psychoactive substances, caffeine remains largely unregulated and legal in nearly all parts of the world. Caffeine is also an outlier as its use is seen as socially acceptable in most cultures with it even being encouraged. Caffeine has both positive and negative health effects. It can treat and prevent the premature infant breathing disorders bronchopulmonary dysplasia of prematurity and apnea of prematurity. Caffeine citrate is on the WHO Model List of Essential Medicines.[22] It may confer a modest protective effect against some diseases,[23] including Parkinson's disease.[24] Some people experience sleep disruption or anxiety if they consume caffeine,[25] but others show little disturbance. Evidence of a risk during pregnancy is equivocal; some authorities recommend that pregnant women limit caffeine to the equivalent of two cups of coffee per day or less.[26][27] Caffeine can produce a mild form of drug dependence – associated with withdrawal symptoms such as sleepiness, headache, and irritability – when an individual stops using caffeine after repeated daily intake.[28][29][2] Tolerance to the autonomic effects of increased blood pressure and heart rate, and increased urine output, develops with chronic use (i.e., these symptoms become less pronounced or do not occur following consistent use).[30] Caffeine is classified by the U.S. Food and Drug Administration (FDA) as generally recognized as safe. Toxic doses, over 10 grams per day for an adult, are much higher than the typical dose of under 500 milligrams per day.[31] The European Food Safety Authority reported that up to 400 mg of caffeine per day (around 5.7 mg/kg of body mass per day) does not raise safety concerns for non-pregnant adults, while intakes up to 200 mg per day for pregnant and lactating women do not raise safety concerns for the fetus or the breast-fed infants.[32] A cup of coffee contains 80–175 mg of caffeine, depending on what "bean" (seed) is used, how it is roasted, and how it is prepared (e.g., drip, percolation, or espresso).[33] Thus it requires roughly 50–100 ordinary cups of coffee to reach the toxic dose. However, pure powdered caffeine, which is available as a dietary supplement, can be lethal in tablespoon-sized amounts. Main article: Caffeine citrate Caffeine is used for both prevention[34] and treatment[35] of bronchopulmonary dysplasia in premature infants. It may improve weight gain during therapy[36] and reduce the incidence of cerebral palsy as well as reduce language and cognitive delay.[37][38] On the other hand, subtle long-term side effects are possible.[39] Caffeine is used as a primary treatment for apnea of prematurity,[40] but not prevention.[41][42] It is also used for orthostatic hypotension treatment.[43][42][44] Some people use caffeine-containing beverages such as coffee or tea to try to treat their asthma.[45] Evidence to support this practice is poor.[45] It appears that caffeine in low doses improves airway function in people with asthma, increasing forced expiratory volume (FEV1) by 5% to 18% for up to four hours.[46] The addition of caffeine (100–130 mg) to commonly prescribed pain relievers such as paracetamol or ibuprofen modestly improves the proportion of people who achieve pain relief.[47] Consumption of caffeine after abdominal surgery shortens the time to recovery of normal bowel function and shortens length of hospital stay.[48] Caffeine was formerly used as a second-line treatment for ADHD. It is considered less effective than methylphenidate or amphetamine but more so than placebo for children with ADHD.[49][50] Children, adolescents, and adults with ADHD are more likely to consume caffeine, perhaps as a form of self-medication.[50][51] Caffeine is a central nervous system stimulant that may reduce fatigue and drowsiness.[9] At normal doses, caffeine has variable effects on learning and memory, but it generally improves reaction time, wakefulness, concentration, and motor coordination.[52][53] The amount of caffeine needed to produce these effects varies from person to person, depending on body size and degree of tolerance.[52] The desired effects arise approximately one hour after consumption, and the desired effects of a moderate dose usually subside after about three or four hours.[4] Caffeine can delay or prevent sleep and improves task performance during sleep deprivation.[54] Shift workers who use caffeine make fewer mistakes that could result from drowsiness.[55] Caffeine in a dose dependent manner increases alertness in both fatigued and normal individuals.[56] A systematic review and meta-analysis from 2014 found that concurrent caffeine and L-theanine use has synergistic psychoactive effects that promote alertness, attention, and task switching;[57] these effects are most pronounced during the first hour post-dose.[57] Caffeine is a proven ergogenic aid in humans.[58] Caffeine improves athletic performance in aerobic (especially endurance sports) and anaerobic conditions.[58] Moderate doses of caffeine (around 5 mg/kg[58]) can improve sprint performance,[59] cycling and running time trial performance,[58] endurance (i.e., it delays the onset of muscle fatigue and central fatigue),[58][60][61] and cycling power output.[58] Caffeine increases basal metabolic rate in adults.[62][63][64] Caffeine ingestion prior to aerobic exercise increases fat oxidation, particularly in persons with low physical fitness.[65] Caffeine improves muscular strength and power,[66] and may enhance muscular endurance.[67] Caffeine also enhances performance on anaerobic tests.[68] Caffeine consumption before constant load exercise is associated with reduced perceived exertion. While this effect is not present during exercise-to-exhaustion exercise, performance is significantly enhanced. This is congruent with caffeine reducing perceived exertion, because exercise-to-exhaustion should end at the same point of fatigue.[69] Caffeine also improves power output and reduces time to completion in aerobic time trials,[70] an effect positively (but not exclusively) associated with longer duration exercise.[71] For the general population of healthy adults, Health Canada advises a daily intake of no more than 400 mg.[72] This limit was found to be safe by a 2017 systematic review on caffeine toxicology.[73] In healthy children, moderate caffeine intake under 400 mg produces effects that are "modest and typically innocuous".[74][75] As early as six months old, infants can metabolize caffeine at the same rate as that of adults.[76] Higher doses of caffeine (>400 mg) can cause physiological, psychological and behavioral harm, particularly for children with psychiatric or cardiac conditions.[74] There is no evidence that coffee stunts a child's growth.[77] The American Academy of Pediatrics recommends that caffeine consumption, particularly in the case of energy and sports drinks, is not appropriate for children and adolescents and should be avoided.[78] This recommendation is based on a clinical report released by American Academy of Pediatrics in 2011 with a review of 45 publications from 1994 to 2011 and includes inputs from various stakeholders (Pediatricians, Committee on nutrition, Canadian Pediatric Society, Centers for Disease Control & Prevention, Food and Drug Administration, Sports Medicine & Fitness committee, National Federations of High School Associations).[78] For children age 12 and under, Health Canada recommends a maximum daily caffeine intake of no more than 2.5 milligrams per kilogram of body weight. Based on average body weights of children, this translates to the following age-based intake limits:[72] Age range Maximum recommended daily caffeine intake 4–6 45 mg (slightly more than in 355 ml (12 fl. oz) of a typical caffeinated soft drink) 7–9 62.5 mg 10–12 85 mg (about 1⁄2 cup of coffee) Health Canada has not developed advice for adolescents because of insufficient data. However, they suggest that daily caffeine intake for this age group be no more than 2.5 mg/kg body weight. This is because the maximum adult caffeine dose may not be appropriate for light-weight adolescents or for younger adolescents who are still growing. The daily dose of 2.5 mg/kg body weight would not cause adverse health effects in the majority of adolescent caffeine consumers. This is a conservative suggestion since older and heavier-weight adolescents may be able to consume adult doses of caffeine without experiencing adverse effects.[72] The metabolism of caffeine is reduced in pregnancy, especially in the third trimester, and the half-life of caffeine during pregnancy can be increased up to 15 hours (as compared to 2.5 to 4.5 hours in non-pregnant adults).[79] Evidence regarding the effects of caffeine on pregnancy and for breastfeeding are inconclusive.[26] There is limited primary and secondary advice for, or against, caffeine use during pregnancy and its effects on the fetus or newborn.[26] The UK Food Standards Agency has recommended that pregnant women should limit their caffeine intake, out of prudence, to less than 200 mg of caffeine a day – the equivalent of two cups of instant coffee, or one and a half to two cups of fresh coffee.[80] The American Congress of Obstetricians and Gynecologists (ACOG) concluded in 2010 that caffeine consumption is safe up to 200 mg per day in pregnant women.[27] For women who breastfeed, are pregnant, or may become pregnant, Health Canada recommends a maximum daily caffeine intake of no more than 300 mg, or a little over two 8 oz (237 mL) cups of coffee.[72] A 2017 systematic review on caffeine toxicology found evidence supporting that caffeine consumption up to 300 mg/day for pregnant women is generally not associated with adverse reproductive or developmental effect.[73] There are conflicting reports in the scientific literature about caffeine use during pregnancy.[81] A 2011 review found that caffeine during pregnancy does not appear to increase the risk of congenital malformations, miscarriage or growth retardation even when consumed in moderate to high amounts.[82] Other reviews, however, concluded that there is some evidence that higher caffeine intake by pregnant women may be associated with a higher risk of giving birth to a low birth weight baby,[83] and may be associated with a higher risk of pregnancy loss.[84] A systematic review, analyzing the results of observational studies, suggests that women who consume large amounts of caffeine (greater than 300 mg/day) prior to becoming pregnant may have a higher risk of experiencing pregnancy loss.[85] Main effects of moderate consumption of Caffeine Main side effects of Caffeine Caffeine in coffee and other caffeinated drinks can affect gastrointestinal motility and gastric acid secretion.[86][87][88] In postmenopausal women, high caffeine consumption can accelerate bone loss.[89][90] Caffeine, alongside other factors such as stress and fatigue, can also increase the pressure in various muscles, including the eyelids.[91] Acute ingestion of caffeine in large doses (at least 250–300 mg, equivalent to the amount found in 2–3 cups of coffee or 5–8 cups of tea) results in a short-term stimulation of urine output in individuals who have been deprived of caffeine for a period of days or weeks.[92] This increase is due to both a diuresis (increase in water excretion) and a natriuresis (increase in saline excretion); it is mediated via proximal tubular adenosine receptor blockade.[93] The acute increase in urinary output may increase the risk of dehydration. However, chronic users of caffeine develop a tolerance to this effect and experience no increase in urinary output.[94][95][96] Minor undesired symptoms from caffeine ingestion not sufficiently severe to warrant a psychiatric diagnosis are common and include mild anxiety, jitteriness, insomnia, increased sleep latency, and reduced coordination.[52][97] Caffeine can have negative effects on anxiety disorders.[98] According to a 2011 literature review, caffeine use may induce anxiety and panic disorders in people with Parkinson's disease.[99] At high doses, typically greater than 300 mg, caffeine can both cause and worsen anxiety.[100] For some people, discontinuing caffeine use can significantly reduce anxiety.[101] In moderate doses, caffeine has been associated with reduced symptoms of depression and lower suicide risk.[102] Two reviews indicate that increased consumption of coffee and caffeine may reduce the risk of depression.[103][104] Some textbooks state that caffeine is a mild euphoriant,[105][106][107] while others state that it is not a euphoriant.[108][109] Caffeine-induced anxiety disorder is a subclass of the DSM-5 diagnosis of substance/medication-induced anxiety disorder.[110] Whether caffeine can result in an addictive disorder depends on how addiction is defined. Compulsive caffeine consumption under any circumstances has not been observed, and caffeine is therefore not generally considered addictive.[111] Some diagnostic sources, such as the ICDM-9 and ICD-10, include a classification of caffeine addiction under a broader diagnostic model.[112] Some state that certain users can become addicted and therefore unable to decrease use even though they know there are negative health effects.[3][113] Caffeine does not appear to be a reinforcing stimulus, and some degree of aversion may actually occur, with people preferring placebo over caffeine in a study on drug abuse liability published in an NIDA research monograph.[114] Some state that research does not provide support for an underlying biochemical mechanism for caffeine addiction.[28][115][116][117] Other research states it can affect the reward system.[118] "Caffeine addiction" was added to the ICDM-9 and ICD-10. However, its addition was contested with claims that this diagnostic model of caffeine addiction is not supported by evidence.[28][119][120] The American Psychiatric Association's DSM-5 does not include the diagnosis of a caffeine addiction but proposes criteria for the disorder for more study.[110][121] Main articles: Caffeine dependence and Caffeine withdrawal See also: Caffeine-induced anxiety disorder, caffeine-induced sleep disorder, and caffeinism Caffeine withdrawal can cause mild to clinically significant distress or impairment in daily functioning. The frequency at which this occurs is self-reported at 11%, but in lab tests only half of the people who report withdrawal actually experience it, casting doubt on many claims of dependence.[122] and most cases of caffeine withdrawal were 13% in the moderate sense. Moderately physical dependence and withdrawal symptoms may occur upon abstinence, with greater than 100 mg caffeine per day, although these symptoms last no longer than a day.[28] Some symptoms associated with psychological dependence may also occur during withdrawal.[2] The diagnostic criteria for caffeine withdrawal require a previous prolonged daily use of caffeine.[123] Following 24 hours of a marked reduction in consumption, a minimum of 3 of these signs or symptoms is required to meet withdrawal criteria: difficulty concentrating, depressed mood/irritability, flu-like symptoms, headache, and fatigue.[123] Additionally, the signs and symptoms must disrupt important areas of functioning and are not associated with effects of another condition.[123] The ICD-11 includes caffeine dependence as a distinct diagnostic category, which closely mirrors the DSM-5's proposed set of criteria for "caffeine-use disorder".[121][124] Caffeine use disorder refers to dependence on caffeine characterized by failure to control caffeine consumption despite negative physiological consequences.[121][124] The APA, which published the DSM-5, acknowledged that there was sufficient evidence in order to create a diagnostic model of caffeine dependence for the DSM-5, but they noted that the clinical significance of the disorder is unclear.[125] Due to this inconclusive evidence on clinical significance, the DSM-5 classifies caffeine-use disorder as a "condition for further study".[121] Tolerance to the effects of caffeine occurs for caffeine-induced elevations in blood pressure and the subjective feelings of nervousness though the effects are not drastic. Sensitization, the process whereby effects become more prominent with use, may occur for positive effects such as feelings of alertness and wellbeing.[122] Tolerance varies for daily, regular caffeine users and high caffeine users. High doses of caffeine (750 to 1200 mg/day spread throughout the day) have been shown to produce complete tolerance to some, but not all of the effects of caffeine. Doses as low as 100 mg/day, such as a 6 oz (170 g) cup of coffee or two to three 12 oz (340 g) servings of caffeinated soft-drink, may continue to cause sleep disruption, among other intolerances. Non-regular caffeine users have the least caffeine tolerance for sleep disruption.[126] Some coffee drinkers develop tolerance to its undesired sleep-disrupting effects, but others apparently do not.[127] See also: Health effects of coffee A neuroprotective effect of caffeine against Alzheimer's disease and dementia is possible but the evidence is inconclusive.[128][129] Caffeine may lessen the severity of acute mountain sickness if taken a few hours prior to attaining a high altitude.[130] One meta analysis has found that caffeine consumption is associated with a reduced risk of type 2 diabetes.[131] Regular caffeine consumption may reduce the risk of developing Parkinson's disease and may slow the progression of Parkinson's disease.[132][133][24] Caffeine increases intraocular pressure in those with glaucoma but does not appear to affect normal individuals.[134] The DSM-5 also includes other caffeine-induced disorders consisting of caffeine-induced anxiety disorder, caffeine-induced sleep disorder and unspecified caffeine-related disorders. The first two disorders are classified under "Anxiety Disorder" and "Sleep-Wake Disorder" because they share similar characteristics. Other disorders that present with significant distress and impairment of daily functioning that warrant clinical attention but do not meet the criteria to be diagnosed under any specific disorders are listed under "Unspecified Caffeine-Related Disorders".[135] Caffeine is reputed to cause a fall in energy several hours after drinking, but this is not well researched.[136][137][138][139] This section needs expansion with: practical management of overdose, see PMID 30893206. You can help by adding to it. (November 2019) Main article: caffeinism Primary symptoms of caffeine intoxication[140] Consumption of 1–1.5 grams (1,000–1,500 mg) per day is associated with a condition known as caffeinism.[141] Caffeinism usually combines caffeine dependency with a wide range of unpleasant symptoms including nervousness, irritability, restlessness, insomnia, headaches, and palpitations after caffeine use.[142] Caffeine overdose can result in a state of central nervous system overstimulation known as caffeine intoxication, a clinically significant temporary condition that develops during, or shortly after, the consumption of caffeine.[143] This syndrome typically occurs only after ingestion of large amounts of caffeine, well over the amounts found in typical caffeinated beverages and caffeine tablets (e.g., more than 400–500 mg at a time). According to the DSM-5, caffeine intoxication may be diagnosed if five (or more) of the following symptoms develop after recent consumption of caffeine: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of inexhaustibility, and psychomotor agitation.[144] According to the International Classification of Diseases (ICD-11), cases of very high caffeine intake (e.g. > 5 g) may result in caffeine intoxication with symptoms including mania, depression, lapses in judgment, disorientation, disinhibition, delusions, hallucinations or psychosis, and rhabdomyolysis.[143] High caffeine consumption in energy drinks (at least one liter or 320 mg of caffeine) was associated with short-term cardiovascular side effects including hypertension, prolonged QT interval, and heart palpitations. These cardiovascular side effects were not seen with smaller amounts of caffeine consumption in energy drinks (less than 200 mg).[79] As of 2007[update] there is no known antidote or reversal agent for caffeine intoxication. Treatment of mild caffeine intoxication is directed toward symptom relief; severe intoxication may require peritoneal dialysis, hemodialysis, or hemofiltration.[140][145][146] Intralipid infusion therapy is indicated in cases of imminent risk of cardiac arrest in order to scavenge the free serum caffeine.[146] Death from caffeine ingestion appears to be rare, and most commonly caused by an intentional overdose of medications.[147] In 2016, 3702 caffeine-related exposures were reported to Poison Control Centers in the United States, of which 846 required treatment at a medical facility, and 16 had a major outcome; and several caffeine-related deaths are reported in case studies.[147] The LD50 of caffeine in rats is 192 milligrams per kilogram of body mass. The fatal dose in humans is estimated to be 150–200 milligrams per kilogram, which is 10.5–14 grams for a typical 70 kg (150 lb) adult, equivalent to about 75–100 cups of coffee.[148][149] There are cases where doses as low as 57 milligrams per kilogram have been fatal.[150] A number of fatalities have been caused by overdoses of readily available powdered caffeine supplements, for which the estimated lethal amount is less than a tablespoon.[151] The lethal dose is lower in individuals whose ability to metabolize caffeine is impaired due to genetics or chronic liver disease.[152] A death was reported in 2013 of a man with liver cirrhosis who overdosed on caffeinated mints.[153][154] Caffeine is a substrate for CYP1A2, and interacts with many substances through this and other mechanisms.[155] See also: Caffeinated alcoholic drink According to DSST, alcohol causes a decrease in performance on their standardized tests, and caffeine causes a significant improvement.[156] When alcohol and caffeine are consumed jointly, the effects of the caffeine are changed, but the alcohol effects remain the same.[157] For example, consuming additional caffeine does not reduce the effect of alcohol.[157] However, the jitteriness and alertness given by caffeine is decreased when additional alcohol is consumed.[157] Alcohol consumption alone reduces both inhibitory and activational aspects of behavioral control. Caffeine antagonizes the effect of alcohol on the activational aspect of behavioral control, but has no effect on the inhibitory behavioral control.[158] The Dietary Guidelines for Americans recommend avoidance of concomitant consumption of alcohol and caffeine, as taking them together may lead to increased alcohol consumption, with a higher risk of alcohol-associated injury. Smoking tobacco has been shown to increase caffeine clearance by 56% as a result of polycyclic aromatic hydrocarbons inducing the CYP1A2 enzyme.[159][10] The CYP1A2 enzyme that is induced by smoking is responsible for the metabolism of caffeine; increased enzyme activity leads to increased caffeine clearance, and is associated with greater coffee consumption for regular smokers.[160] Birth control pills can extend the half-life of caffeine by as much as 40%, requiring greater attention to caffeine consumption.[161][162] Caffeine sometimes increases the effectiveness of some medications, such as those for headaches.[163] Caffeine was determined to increase the potency of some over-the-counter analgesic medications by 40%.[164] The pharmacological effects of adenosine may be blunted in individuals taking large quantities of methylxanthines like caffeine.[165] Some other examples of methylxanthines include the medications theophylline and aminophylline, which are prescribed to relieve symptoms of asthma or COPD.[166] Postsynaptic density Voltage-gated Ca^{++} channel Synaptic vesicle Neurotransmitter transporter Receptor Neurotransmitter Axon terminal Synaptic cleft DendriteStructure of a typical chemical synapse Caffeine's primary mechanism of action is as an adenosine receptor antagonist in the brain. In the absence of caffeine and when a person is awake and alert, little adenosine is present in CNS neurons. With a continued wakeful state, over time adenosine accumulates in the neuronal synapse, in turn binding to and activating adenosine receptors found on certain CNS neurons; when activated, these receptors produce a cellular response that ultimately increases drowsiness. When caffeine is consumed, it antagonizes adenosine receptors; in other words, caffeine prevents adenosine from activating the receptor by blocking the location on the receptor where adenosine binds to it. As a result, caffeine temporarily prevents or relieves drowsiness, and thus maintains or restores alertness.[5] Caffeine is an antagonist of adenosine A2A receptors, and knockout mouse studies have specifically implicated antagonism of the A2A receptor as responsible for the wakefulness-promoting effects of caffeine.[167] Antagonism of A2A receptors in the ventrolateral preoptic area (VLPO) reduces inhibitory GABA neurotransmission to the tuberomammillary nucleus, a histaminergic projection nucleus that activation-dependently promotes arousal.[168] This disinhibition of the tuberomammillary nucleus is the downstream mechanism by which caffeine produces wakefulness-promoting effects.[168] Caffeine is an antagonist of all four adenosine receptor subtypes (A1, A2A, A2B, and A3), although with varying potencies.[5][167] The affinity (KD) values of caffeine for the human adenosine receptors are 12 μM at A1, 2.4 μM at A2A, 13 μM at A2B, and 80 μM at A3.[167] Antagonism of adenosine receptors by caffeine also stimulates the medullary vagal, vasomotor, and respiratory centers, which increases respiratory rate, reduces heart rate, and constricts blood vessels.[5] Adenosine receptor antagonism also promotes neurotransmitter release (e.g., monoamines and acetylcholine), which endows caffeine with its stimulant effects;[5][169] adenosine acts as an inhibitory neurotransmitter that suppresses activity in the central nervous system. Heart palpitations are caused by blockade of the A1 receptor.[5] Because caffeine is both water- and lipid-soluble, it readily crosses the blood–brain barrier that separates the bloodstream from the interior of the brain. Once in the brain, the principal mode of action is as a nonselective antagonist of adenosine receptors (in other words, an agent that reduces the effects of adenosine). The caffeine molecule is structurally similar to adenosine, and is capable of binding to adenosine receptors on the surface of cells without activating them, thereby acting as a competitive antagonist.[170] In addition to its activity at adenosine receptors, caffeine is an inositol trisphosphate receptor 1 antagonist and a voltage-independent activator of the ryanodine receptors (RYR1, RYR2, and RYR3).[171] It is also a competitive antagonist of the ionotropic glycine receptor.[172] While caffeine does not directly bind to any dopamine receptors, it influences the binding activity of dopamine at its receptors in the striatum by binding to adenosine receptors that have formed GPCR heteromers with dopamine receptors, specifically the A1–D1 receptor heterodimer (this is a receptor complex with one adenosine A1 receptor and one dopamine D1 receptor) and the A2A–D2 receptor heterotetramer (this is a receptor complex with two adenosine A2A receptors and two dopamine D2 receptors).[173][174][175][176] The A2A–D2 receptor heterotetramer has been identified as a primary pharmacological target of caffeine, primarily because it mediates some of its psychostimulant effects and its pharmacodynamic interactions with dopaminergic psychostimulants.[174][175][176] Caffeine also causes the release of dopamine in the dorsal striatum and nucleus accumbens core (a substructure within the ventral striatum), but not the nucleus accumbens shell, by antagonizing A1 receptors in the axon terminal of dopamine neurons and A1–A2A heterodimers (a receptor complex composed of one adenosine A1 receptor and one adenosine A2A receptor) in the axon terminal of glutamate neurons.[173][168] During chronic caffeine use, caffeine-induced dopamine release within the nucleus accumbens core is markedly reduced due to drug tolerance.[173][168] Caffeine, like other xanthines, also acts as a phosphodiesterase inhibitor.[177] As a competitive nonselective phosphodiesterase inhibitor,[178] caffeine raises intracellular cyclic AMP, activates protein kinase A, inhibits TNF-alpha[179][180] and leukotriene[181] synthesis, and reduces inflammation and innate immunity.[181] Caffeine also affects the cholinergic system where it is a moderate inhibitor of the enzyme acetylcholinesterase.[182][183] Caffeine is metabolized in the liver via a single demethylation, resulting in three primary metabolites, paraxanthine (84%), theobromine (12%), and theophylline (4%), depending on which methyl group is removed. Urinary metabolites of caffeine in humans at 48 hours post-dose[184] Caffeine from coffee or other beverages is absorbed by the small intestine within 45 minutes of ingestion and distributed throughout all bodily tissues.[185] Peak blood concentration is reached within 1–2 hours.[186] It is eliminated by first-order kinetics.[187] Caffeine can also be absorbed rectally, evidenced by suppositories of ergotamine tartrate and caffeine (for the relief of migraine)[188] and of chlorobutanol and caffeine (for the treatment of hyperemesis).[189] However, rectal absorption is less efficient than oral: the maximum concentration (Cmax) and total amount absorbed (AUC) are both about 30% (i.e., 1/3.5) of the oral amounts.[190] Caffeine's biological half-life – the time required for the body to eliminate one-half of a dose – varies widely among individuals according to factors such as pregnancy, other drugs, liver enzyme function level (needed for caffeine metabolism) and age. In healthy adults, caffeine's half-life is between 3 and 7 hours.[5] The half-life is decreased by 30-50% in adult male smokers, approximately doubled in women taking oral contraceptives, and prolonged in the last trimester of pregnancy.[127] In newborns the half-life can be 80 hours or more, dropping rapidly with age, possibly to less than the adult value by age 6 months.[127] The antidepressant fluvoxamine (Luvox) reduces the clearance of caffeine by more than 90%, and increases its elimination half-life more than tenfold, from 4.9 hours to 56 hours.[191] Caffeine is metabolized in the liver by the cytochrome P450 oxidase enzyme system (particularly by the CYP1A2 isozyme) into three dimethylxanthines,[192] each of which has its own effects on the body: Paraxanthine (84%): Increases lipolysis, leading to elevated glycerol and free fatty acid levels in blood plasma. Theobromine (12%): Dilates blood vessels and increases urine volume. Theobromine is also the principal alkaloid in the cocoa bean (chocolate). Theophylline (4%): Relaxes smooth muscles of the bronchi, and is used to treat asthma. The therapeutic dose of theophylline, however, is many times greater than the levels attained from caffeine metabolism.[46] 1,3,7-Trimethyluric acid is a minor caffeine metabolite.[5] 7-Methylxanthine is also a metabolite of caffeine.[193][194] Each of the above metabolites is further metabolized and then excreted in the urine. Caffeine can accumulate in individuals with severe liver disease, increasing its half-life.[195] A 2011 review found that increased caffeine intake was associated with a variation in two genes that increase the rate of caffeine catabolism. Subjects who had this mutation on both chromosomes consumed 40 mg more caffeine per day than others.[196] This is presumably due to the need for a higher intake to achieve a comparable desired effect, not that the gene led to a disposition for greater incentive of habituation. Pure anhydrous caffeine is a bitter-tasting, white, odorless powder with a melting point of 235–238 °C.[7][8] Caffeine is moderately soluble in water at room temperature (2 g/100 mL), but quickly soluble in boiling water (66 g/100 mL).[197] It is also moderately soluble in ethanol (1.5 g/100 mL).[197] It is weakly basic (pKa of conjugate acid = ~0.6) requiring strong acid to protonate it.[198] Caffeine does not contain any stereogenic centers[199] and hence is classified as an achiral molecule.[200] The xanthine core of caffeine contains two fused rings, a pyrimidinedione and imidazole. The pyrimidinedione in turn contains two amide functional groups that exist predominantly in a zwitterionic resonance the location from which the nitrogen atoms are double bonded to their adjacent amide carbons atoms. Hence all six of the atoms within the pyrimidinedione ring system are sp2 hybridized and planar. The imidazole ring also has a resonance. Therefore, the fused 5,6 ring core of caffeine contains a total of ten pi electrons and hence according to Hückel's rule is aromatic.[201] One biosynthetic route of caffeine, as performed by Camellia and Coffea species[202][203] One laboratory synthesis of caffeine[204][205] The biosynthesis of caffeine is an example of convergent evolution among different species.[206][207][208] Caffeine may be synthesized in the lab starting with 1,3-dimethylurea and malonic acid.[clarification needed][204][205][209] Production of synthesized caffeine largely takes place in pharmaceutical plants in China. Synthetic and natural caffeine are chemically identical and nearly indistinguishable. The primary distinction is that synthetic caffeine is manufactured from urea and chloroacetic acid, while natural caffeine is extracted from plant sources, a process known as decaffeination.[210] Despite the different production methods, the final product and its effects on the body are identical. Research on synthetic caffeine supports that it has the same stimulating effects on the body as natural caffeine.[211] And although many claim that natural caffeine is absorbed slower and therefore leads to a gentler caffeine crash, there is little scientific evidence supporting the notion.[210] Main article: Decaffeination Fibrous crystals of purified caffeine. Dark-field microscopy image, about 7 mm × 11 mm. Germany, the birthplace of decaffeinated coffee, is home to several decaffeination plants, including the world's largest, Coffein Compagnie.[212] Over half of the decaf coffee sold in the U.S. first travels from the tropics to Germany for caffeine removal before making its way to American consumers.[citation needed] Extraction of caffeine from coffee, to produce caffeine and decaffeinated coffee, can be performed using various solvents. Following are main methods: Water extraction: Coffee beans are soaked in water. The water, which contains many other compounds in addition to caffeine and contributes to the flavor of coffee, is then passed through activated charcoal, which removes the caffeine. The water can then be put back with the beans and evaporated dry, leaving decaffeinated coffee with its original flavor. Coffee manufacturers recover the caffeine and resell it for use in soft drinks and over-the-counter caffeine tablets.[213] Supercritical carbon dioxide extraction: Supercritical carbon dioxide is an excellent nonpolar solvent for caffeine, and is safer than the organic solvents that are otherwise used. The extraction process is simple: CO_2 is forced through the green coffee beans at temperatures above 31.1 °C and pressures above 73 atm. Under these conditions, CO_2 is in a "supercritical" state: It has gaslike properties that allow it to penetrate deep into the beans but also liquid-like properties that dissolve 97–99% of the caffeine. The caffeine-laden CO_2 is then sprayed with high-pressure water to remove the caffeine. The caffeine can then be isolated by charcoal adsorption (as above) or by distillation, recrystallization, or reverse osmosis.[213] Extraction by organic solvents: Certain organic solvents such as ethyl acetate present much less health and environmental hazard than chlorinated and aromatic organic solvents used formerly. Another method is to use triglyceride oils obtained from spent coffee grounds.[213] "Decaffeinated" coffees do in fact contain caffeine in many cases – some commercially available decaffeinated coffee products contain considerable levels. One study found that decaffeinated coffee contained 10 mg of caffeine per cup, compared to approximately 85 mg of caffeine per cup for regular coffee.[214] Caffeine can be quantified in blood, plasma, or serum to monitor therapy in neonates, confirm a diagnosis of poisoning, or facilitate a medicolegal death investigation. Plasma caffeine levels are usually in the range of 2–10 mg/L in coffee drinkers, 12–36 mg/L in neonates receiving treatment for apnea, and 40–400 mg/L in victims of acute overdosage. Urinary caffeine concentration is frequently measured in competitive sports programs, for which a level in excess of 15 mg/L is usually considered to represent abuse.[215] Some analog substances have been created which mimic caffeine's properties with either function or structure or both. Of the latter group are the xanthines DMPX[216] and 8-chlorotheophylline, which is an ingredient in dramamine. Members of a class of nitrogen substituted xanthines are often proposed as potential alternatives to caffeine.[217][unreliable source?] Many other xanthine analogues constituting the adenosine receptor antagonist class have also been elucidated.[218] Some other caffeine analogs: Dipropylcyclopentylxanthine 8-Cyclopentyl-1,3-dimethylxanthine 8-Phenyltheophylline Caffeine, as do other alkaloids such as cinchonine, quinine or strychnine, precipitates polyphenols and tannins. This property can be used in a quantitation method.[clarification needed][219] Roasted coffee beans Around thirty plant species are known to contain caffeine.[220] Common sources are the "beans" (seeds) of the two cultivated coffee plants, Coffea arabica and Coffea canephora (the quantity varies, but 1.3% is a typical value); and of the cocoa plant, Theobroma cacao; the leaves of the tea plant; and kola nuts. Other sources include the leaves of yaupon holly, South American holly yerba mate, and Amazonian holly guayusa; and seeds from Amazonian maple guarana berries. Temperate climates around the world have produced unrelated caffeine-containing plants. Caffeine in plants acts as a natural pesticide: it can paralyze and kill predator insects feeding on the plant.[221] High caffeine levels are found in coffee seedlings when they are developing foliage and lack mechanical protection.[222] In addition, high caffeine levels are found in the surrounding soil of coffee seedlings, which inhibits seed germination of nearby coffee seedlings, thus giving seedlings with the highest caffeine levels fewer competitors for existing resources for survival.[223] Caffeine is stored in tea leaves in two places. Firstly, in the cell vacuoles where it is complexed with polyphenols. This caffeine probably is released into the mouth parts of insects, to discourage herbivory. Secondly, around the vascular bundles, where it probably inhibits pathogenic fungi from entering and colonizing the vascular bundles.[224] Caffeine in nectar may improve the reproductive success of the pollen producing plants by enhancing the reward memory of pollinators such as honey bees.[18] The differing perceptions in the effects of ingesting beverages made from various plants containing caffeine could be explained by the fact that these beverages also contain varying mixtures of other methylxanthine alkaloids, including the cardiac stimulants theophylline and theobromine, and polyphenols that can form insoluble complexes with caffeine.[225] Caffeine content in select food and drugs[226][227][228][229][230] Product Serving size Caffeine per serving (mg) Caffeine (mg/L) Caffeine tablet (regular-strength) 1 tablet 100 — Caffeine tablet (extra-strength) 1 tablet 200 — Excedrin tablet 1 tablet 65 — Percolated coffee 207 mL (7.0 US fl oz) 80–135 386–652 Drip coffee 207 mL (7.0 US fl oz) 115–175 555–845 Coffee, decaffeinated 207 mL (7.0 US fl oz) 5–15 24–72 Coffee, espresso 44–60 mL (1.5–2.0 US fl oz) 100 1,691–2,254 Tea – black, green, and other types, – steeped for 3 min. 177 mL (6.0 US fl oz) 22–74[229][230] 124–418 Guayakí yerba mate (loose leaf) 6 g (0.21 oz) 85[231] approx. 358 Coca-Cola 355 mL (12.0 US fl oz) 34 96 Mountain Dew 355 mL (12.0 US fl oz) 54 154 Pepsi Zero Sugar 355 mL (12.0 US fl oz) 69 194 Guaraná Antarctica 350 mL (12 US fl oz) 30 100 Jolt Cola 695 mL (23.5 US fl oz) 280 403 Red Bull 250 mL (8.5 US fl oz) 80 320 Coffee-flavored milk drink 300–600 mL (10–20 US fl oz) 33–197[232] 66–354[232] Cocoa, dry powder, unsweetened [unspecified strain] 100 g 230[233] — Cocoa solids, defatted, Criollo strain 100 g 1130[234] — Cocoa solids, defatted, Forastero strain 100 g 130[234] — Cocoa solids, defatted, Nacional strain 100 g 240[234] — Cocoa solids, defatted, Trinitario strain 100 g 630[234] — Chocolate, dark, 70-85% cacao solids 100 g 80[235] — Chocolate, dark, 60-69% cacao solids 100 g 86[236] — Chocolate, dark, 45- 59% cacao solids 100 g 43[237] — Candies, milk chocolate 100 g 20[238] — Hershey's Special Dark (45% cacao content) 1 bar (43 g or 1.5 oz) 31 — Hershey's Milk Chocolate (11% cacao content) 1 bar (43 g or 1.5 oz) 10 — Products containing caffeine include coffee, tea, soft drinks ("colas"), energy drinks, other beverages, chocolate,[239] caffeine tablets, other oral products, and inhalation products. According to a 2020 study in the United States, coffee is the major source of caffeine intake in middle-aged adults, while soft drinks and tea are the major sources in adolescents.[79] Energy drinks are more commonly consumed as a source of caffeine in adolescents as compared to adults.[79] Main article: Caffeinated drink The world's primary source of caffeine is the coffee "bean" (the seed of the coffee plant), from which coffee is brewed. Caffeine content in coffee varies widely depending on the type of coffee bean and the method of preparation used;[240] even beans within a given bush can show variations in concentration. In general, one serving of coffee ranges from 80 to 100 milligrams, for a single shot (30 milliliters) of arabica-variety espresso, to approximately 100–125 milligrams for a cup (120 milliliters) of drip coffee.[241][242] Arabica coffee typically contains half the caffeine of the robusta variety.[240] In general, dark-roast coffee has slightly less caffeine than lighter roasts because the roasting process reduces caffeine content of the bean by a small amount.[241][242] Tea contains more caffeine than coffee by dry weight. A typical serving, however, contains much less, since less of the product is used as compared to an equivalent serving of coffee. Also contributing to caffeine content are growing conditions, processing techniques, and other variables. Thus, teas contain varying amounts of caffeine.[243] Tea contains small amounts of theobromine and slightly higher levels of theophylline than coffee. Preparation and many other factors have a significant impact on tea, and color is a poor indicator of caffeine content. Teas like the pale Japanese green tea, gyokuro, for example, contain far more caffeine than much darker teas like lapsang souchong, which has minimal caffeine content.[243] Caffeine is also a common ingredient of soft drinks, such as cola, originally prepared from kola nuts. Soft drinks typically contain 0 to 55 milligrams of caffeine per 12 ounce (350 mL) serving.[244] By contrast, energy drinks, such as Red Bull, can start at 80 milligrams of caffeine per serving. The caffeine in these drinks either originates from the ingredients used or is an additive derived from the product of decaffeination or from chemical synthesis. Guarana, a primary ingredient of energy drinks, contains large amounts of caffeine with small amounts of theobromine and theophylline in a naturally occurring slow-release excipient.[245] Maté is a drink popular in many parts of South America. Its preparation consists of filling a gourd with the leaves of the South American holly yerba mate, pouring hot but not boiling water over the leaves, and drinking with a straw, the bombilla, which acts as a filter so as to draw only the liquid and not the yerba leaves.[246] Guaraná is a soft drink originating in Brazil made from the seeds of the Guaraná fruit. The leaves of Ilex guayusa, the Ecuadorian holly tree, are placed in boiling water to make a guayusa tea.[247] The leaves of Ilex vomitoria, the yaupon holly tree, are placed in boiling water to make a yaupon tea. Commercially prepared coffee-flavoured milk beverages are popular in Australia.[248] Examples include Oak's Ice Coffee and Farmers Union Iced Coffee. The amount of caffeine in these beverages can vary widely. Caffeine concentrations can differ significantly from the manufacturer's claims.[232] Cocoa solids (derived from cocoa bean) contain 230 mg caffeine per 100 g.[233] The caffeine content varies between cocoa bean strains. Caffeine content mg/g (sorted by lowest caffeine content):[234] Forastero (defatted): 1.3 mg/g Nacional (defatted): 2.4 mg/g Trinitario (defatted): 6.3/g Criollo (defatted): 11.3 mg/g Caffeine per 100 g: Dark chocolate, 70-85% cacao solids: 80 mg[235] Dark chocolate, 60-69% cacao solids: 86 mg[236] Dark chocolate, 45- 59% cacao solids: 43 mg[237] Milk chocolate: 20 mg[238] The stimulant effect of chocolate may be due to a combination of theobromine and theophylline, as well as caffeine.[249] No-Doz 100 mg caffeine tablets Tablets offer several advantages over coffee, tea, and other caffeinated beverages, including convenience, known dosage, and avoidance of concomitant intake of sugar, acids, and fluids. The use of caffeine in this form is said to improve mental alertness.[250] These tablets are commonly used by students studying for their exams and by people who work or drive for long hours.[251] One U.S. company is marketing oral dissolvable caffeine strips.[252] Another intake route is SpazzStick, a caffeinated lip balm.[253] Alert Energy Caffeine Gum was introduced in the United States in 2013, but was voluntarily withdrawn after an announcement of an investigation by the FDA of the health effects of added caffeine in foods.[254] Similar to an e-cigarette, a caffeine inhaler may be used to deliver caffeine or a stimulant like guarana by vaping.[255] In 2012, the FDA sent a warning letter to one of the companies marketing an inhaler, expressing concerns for the lack of safety information available about inhaled caffeine.[256][257] Some beverages combine alcohol with caffeine to create a caffeinated alcoholic drink. The stimulant effects of caffeine may mask the depressant effects of alcohol, potentially reducing the user's awareness of their level of intoxication. Such beverages have been the subject of bans due to safety concerns. In particular, the United States Food and Drug Administration has classified caffeine added to malt liquor beverages as an "unsafe food additive".[258] Ya ba contains a combination of methamphetamine and caffeine. Painkillers such as propyphenazone/paracetamol/caffeine combine caffeine with an analgesic. Coffeehouse in Palestine, c. 1900 Main articles: History of chocolate, History of coffee, History of tea, and History of yerba mate According to Chinese legend, the Chinese emperor Shennong, reputed to have reigned in about 3000 BCE, inadvertently discovered tea when he noted that when certain leaves fell into boiling water, a fragrant and restorative drink resulted.[259] Shennong is also mentioned in Lu Yu's Cha Jing, a famous early work on the subject of tea.[260] The earliest credible evidence of either coffee drinking or knowledge of the coffee plant appears in the middle of the fifteenth century, in the Sufi monasteries of the Yemen in southern Arabia.[261] From Mokha, coffee spread to Egypt and North Africa, and by the 16th century, it had reached the rest of the Middle East, Persia and Turkey. From the Middle East, coffee drinking spread to Italy, then to the rest of Europe, and coffee plants were transported by the Dutch to the East Indies and to the Americas.[262] Kola nut use appears to have ancient origins. It is chewed in many West African cultures, in both private and social settings, to restore vitality and ease hunger pangs.[263] The earliest evidence of cocoa bean use comes from residue found in an ancient Mayan pot dated to 600 BCE. Also, chocolate was consumed in a bitter and spicy drink called xocolatl, often seasoned with vanilla, chile pepper, and achiote. Xocolatl was believed to fight fatigue, a belief probably attributable to the theobromine and caffeine content. Chocolate was an important luxury good throughout pre-Columbian Mesoamerica, and cocoa beans were often used as currency.[264] Xocolatl was introduced to Europe by the Spaniards, and became a popular beverage by 1700. The Spaniards also introduced the cacao tree into the West Indies[265] and the Philippines.[266] The leaves and stems of the yaupon holly (Ilex vomitoria) were used by Native Americans to brew a tea called asi or the "black drink".[267] Archaeologists have found evidence of this use far into antiquity,[268] possibly dating to Late Archaic times.[267] Friedlieb Ferdinand Runge, discoverer of caffeine In 1819, the German chemist Friedlieb Ferdinand Runge isolated relatively pure[vague] caffeine for the first time; he called it "Kaffebase" (i.e., a base that exists in coffee).[269][270] In 1821, caffeine was isolated both by the French chemist Pierre Jean Robiquet and by another pair of French chemists, Pierre-Joseph Pelletier and Joseph Bienaimé Caventou, according to Swedish chemist Jöns Jacob Berzelius in his yearly journal. Furthermore, Berzelius stated that the French chemists had made their discoveries independently of any knowledge of Runge's or each other's work.[271] However, Berzelius later acknowledged Runge's priority in the extraction of caffeine, stating:[272] "However, at this point, it should not remain unmentioned that Runge (in his Phytochemical Discoveries, 1820, pages 146–147) specified the same method and described caffeine under the name Caffeebase a year earlier than Robiquet, to whom the discovery of this substance is usually attributed, having made the first oral announcement about it at a meeting of the Pharmacy Society in Paris." Pelletier's article on caffeine was the first to use the term in print (in the French form Caféine from the French word for coffee: café).[273] It corroborates Berzelius's account: Caffeine, noun (feminine). Crystallizable substance discovered in coffee in 1821 by Mr. Robiquet. During the same period – while they were searching for quinine in coffee because coffee is considered by several doctors to be a medicine that reduces fevers and because coffee belongs to the same family as the cinchona [quinine] tree – on their part, Messrs. Pelletier and Caventou obtained caffeine; but because their research had a different goal and because their research had not been finished, they left priority on this subject to Mr. Robiquet. We do not know why Mr. Robiquet has not published the analysis of coffee which he read to the Pharmacy Society. Its publication would have allowed us to make caffeine better known and give us accurate ideas of coffee's composition ... Robiquet was one of the first to isolate and describe the properties of pure caffeine,[274] whereas Pelletier was the first to perform an elemental analysis.[275] In 1827, M. Oudry isolated "théine" from tea,[276] but in 1838 it was proved by Mulder[277] and by Carl Jobst[278] that theine was actually the same as caffeine. In 1895, German chemist Hermann Emil Fischer (1852–1919) first synthesized caffeine from its chemical components (i.e. a "total synthesis"), and two years later, he also derived the structural formula of the compound.[279] This was part of the work for which Fischer was awarded the Nobel Prize in 1902.[280] Because it was recognized that coffee contained some compound that acted as a stimulant, first coffee and later also caffeine has sometimes been subject to regulation. For example, in the 16th century Islamists in Mecca and in the Ottoman Empire made coffee illegal for some classes.[281][282][283] Charles II of England tried to ban it in 1676,[284][285] Frederick II of Prussia banned it in 1777,[286][287] and coffee was banned in Sweden at various times between 1756 and 1823. In 1911, caffeine became the focus of one of the earliest documented health scares, when the US government seized 40 barrels and 20 kegs of Coca-Cola syrup in Chattanooga, Tennessee, alleging the caffeine in its drink was "injurious to health".[288] Although the Supreme Court later ruled in favor of Coca-Cola in United States v. Forty Barrels and Twenty Kegs of Coca-Cola, two bills were introduced to the U.S. House of Representatives in 1912 to amend the Pure Food and Drug Act, adding caffeine to the list of "habit-forming" and "deleterious" substances, which must be listed on a product's label.[289] See also: Energy drink § Regulations The examples and perspective in this section deal primarily with the United States and do not represent a worldwide view of the subject. You may improve this section, discuss the issue on the talk page, or create a new section, as appropriate. (October 2020) (Learn how and when to remove this message) The US Food and Drug Administration (FDA) considers safe beverages containing less than 0.02% caffeine;[290] but caffeine powder, which is sold as a dietary supplement, is unregulated.[291] It is a regulatory requirement that the label of most prepackaged foods must declare a list of ingredients, including food additives such as caffeine, in descending order of proportion. However, there is no regulatory provision for mandatory quantitative labeling of caffeine, (e.g., milligrams caffeine per stated serving size). There are a number of food ingredients that naturally contain caffeine. These ingredients must appear in food ingredient lists. However, as is the case for "food additive caffeine", there is no requirement to identify the quantitative amount of caffeine in composite foods containing ingredients that are natural sources of caffeine. While coffee or chocolate are broadly recognized as caffeine sources, some ingredients (e.g., guarana, yerba maté) are likely less recognized as caffeine sources. For these natural sources of caffeine, there is no regulatory provision requiring that a food label identify the presence of caffeine nor state the amount of caffeine present in the food.[292] The FDA guidance was updated in 2018.[293] Global consumption of caffeine has been estimated at 120,000 tonnes per year, making it the world's most popular psychoactive substance.[20] The consumption of caffeine has remained stable between 1997 and 2015.[294] Coffee, tea and soft drinks are the most common caffeine sources, with energy drinks contributing little to the total caffeine intake across all age groups.[294] The Seventh-day Adventist Church asked for its members to "abstain from caffeinated drinks", but has removed this from baptismal vows (while still recommending abstention as policy).[295] Some from these religions believe that one is not supposed to consume a non-medical, psychoactive substance, or believe that one is not supposed to consume a substance that is addictive. The Church of Jesus Christ of Latter-day Saints has said the following with regard to caffeinated beverages: "... the Church revelation spelling out health practices (Doctrine and Covenants 89) does not mention the use of caffeine. The Church's health guidelines prohibit alcoholic drinks, smoking or chewing of tobacco, and 'hot drinks' – taught by Church leaders to refer specifically to tea and coffee."[296] Gaudiya Vaishnavas generally also abstain from caffeine, because they believe it clouds the mind and overstimulates the senses.[297] To be initiated under a guru, one must have had no caffeine, alcohol, nicotine or other drugs, for at least a year.[298] Caffeinated beverages are widely consumed by Muslims. In the 16th century, some Muslim authorities made unsuccessful attempts to ban them as forbidden "intoxicating beverages" under Islamic dietary laws.[299][300] Caffeine effects on spider webs See also: Effect of psychoactive drugs on animals The bacteria Pseudomonas putida CBB5 can live on pure caffeine and can cleave caffeine into carbon dioxide and ammonia.[301] Caffeine is toxic to birds[302] and to dogs and cats,[303] and has a pronounced adverse effect on mollusks, various insects, and spiders.[304] This is at least partly due to a poor ability to metabolize the compound, causing higher levels for a given dose per unit weight.[184] Caffeine has also been found to enhance the reward memory of honey bees.[18] Caffeine has been used to double chromosomes in haploid wheat.[305] Adderall Amphetamine Cocaine Health effects of coffee Health effects of tea List of chemical compounds in coffee Low caffeine coffee Methylliberine Nootropic Theobromine Theophylline Wakefulness-promoting agent

^ "Caffeine". ChemSpider. Archived from the original on 14 May 2019. Retrieved 16 November 2021. ^ a b c d Juliano LM, Griffiths RR (October 2004). "A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features". Psychopharmacology. 176 (1): 1–29. doi:10.1007/s00213-004-2000-x. PMID 15448977. S2CID 5572188. Results: Of 49 symptom categories identified, the following 10 fulfilled validity criteria: headache, fatigue, decreased energy/ activeness, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, and foggy/not clearheaded. In addition, flu-like symptoms, nausea/vomiting, and muscle pain/stiffness were judged likely to represent valid symptom categories. In experimental studies, the incidence of headache was 50% and the incidence of clinically significant distress or functional impairment was 13%. 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(eds.). Psychiatry and Pedopsychiatry. Prague: Karolinum Press. pp. 153–154. ISBN 9788024633787. At a high dose, caffeine shows a euphoric effect. ^ Schulteis G (2010). "Brain stimulation and addiction". In Koob GF, Le Moal M, Thompson RF (eds.). Encyclopedia of Behavioral Neuroscience. Elsevier. p. 214. ISBN 978-0-08-091455-8. Therefore, caffeine and other adenosine antagonists, while weakly euphoria-like on their own, may potentiate the positive hedonic efficacy of acute drug intoxication and reduce the negative hedonic consequences of drug withdrawal. ^ Salerno BB, Knights EK (2010). Pharmacology for health professionals (3rd ed.). Chatswood, N.S.W.: Elsevier Australia. p. 433. ISBN 978-0-7295-3929-6. In contrast to the amphetamines, caffeine does not cause euphoria, stereotyped behaviors or psychoses. ^ Ebenezer I (2015). Neuropsychopharmacology and Therapeutics. John Wiley & Sons. p. 18. ISBN 978-1-118-38578-4. 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GMD MS Spectrum Caffeine: ChemSub Online Caffeine at The Periodic Table of Videos (University of Nottingham) Portals: Chemistry Coffee Medicine Retrieved from " 2Pharmaceutical compound 2C-OClinical dataOther names2,4,5-TMPEA; TMPEA-2; TMPEA; 4-Methoxy-2,5-dimethoxyphenethylamine; 2,5-Dimethoxy-4-methoxyphenethylamine; 2C-O; 2C-OMe; 2C-MeO; 2C-TMA-2; 25ORoutes ofadministrationOralDrug classSerotonin receptor agonist; Serotonin 5-HT2 receptor agonistATC codeNoneLegal statusLegal status CA: Schedule III UK: Class A US: Schedule I Identifiers IUPAC name 2-(2,4,5-trimethoxyphenyl)ethan-1-amine CAS Number15394-83-9 YPubChem CID151954ChemSpider133931 YUNIIS27QYQ708UChEMBLChEMBL354924 YCompTox Dashboard (EPA)DTXSID30165499 Chemical and physical dataFormulaC11H17NO3Molar mass211.261 g·mol−13D model (JSmol)Interactive imageMelting point187 to 188 °C (369 to 370 °F) SMILES O(c1cc(c(OC)cc1OC)CCN)C InChI InChI=1S/C11H17NO3/c1-13-9-7-11(15-3)10(14-2)6-8(9)4-5-12/h6-7H,4-5,12H2,1-3H3 YKey:GKATTZLSNLYADI-UHFFFAOYSA-N Y (verify) 2C-O, also known as 2,4,5-trimethoxyphenethylamine (2,4,5-TMPEA) or TMPEA-2, is a chemical compound of the phenethylamine and 2C families.[1][2][3] It is a positional isomer of mescaline (3,4,5-trimethoxyphenethylamine)[1][2][4] and is the α-desmethyl analogue of 2,4,5-trimethoxyamphetamine (TMA-2).[1][2][4] The drug is the parent compound of the 2C-O series of drugs.[5] 2C-O appears to be inactive in terms of psychoactive effects in humans.[1][6][5][7] It was first described by Jansen in 1931.[1][3] 2C-O is a member of a class of chemical compounds commonly known as phenethylamines. Its full chemical name is 2-(2,4,5-trimethoxyphenyl)ethanamine; it is also known as 2,4,5-trimethoxyphenethylamine and 2,4,5-TMPEA. A variety of derivatives of 2C-O, named 2C-O-2 (4-ethoxy-2,5-dimethoxyphenethylamine) through 2C-O-27, have been developed and studied.[5] One particularly notable derivative is 2C-O-4 (4-isopropoxy-2,5-dimethoxyphenethylamine).[5] 2C-O at a dose of under 300 mg was reported to produce similar psychedelic effects as mescaline by Jansen in 1931, albeit with more nausea and no euphoria.[1][3] Conversely, in a subsequent report, it was said to be indistinguishable from placebo at a dose of up to 300 mg.[1][6][5] The present-day consensus appears to be that 2C-O is inactive.[1][6][5][7] In PiHKAL, its dosage is listed as greater than 300 mg and its duration as unknown.[1] Although 2C-O does not seem to produce effects by itself, 2C-O at a dose of 200 mg was reported to strongly potentiate the action of 100 mg mescaline when employed as pretreatment 45 minutes prior to the administration of mescaline.[1] The apparent inactivity of 2C-O (2,4,5-trimethoxyphenethylamine) has been described as enigmatic, since other 2C drugs are active, since 2C-O's substituted amphetamine (α-methyl) counterpart 2,4,5-trimethoxyamphetamine (TMA-2) is active, and since its positional isomer mescaline (3,4,5-trimethoxyphenethylamine) is active.[4] The toxicity of 2C-O is not known. 2C-O has been found to act as full agonist of the serotonin 5-HT2A, 5-HT2B, and 5-HT2C receptors.[8] However, it showed more than two orders of magnitude lower potency in activating the serotonin 5-HT2A receptor than 2C-B and 2C-I.[8] It has been said in the past that it is unclear whether the apparent inactivity of 2C-O is due to strong metabolism or low affinity and/or efficacy at the serotonin 5-HT2A receptor.[6][5] However, an in-vitro study using rabbit liver tissue found that 2C-O was deaminated 25% alone and 25% with the monoamine oxidase inhibitor (MAOI) semicarbazide after 1 hour whereas mescaline was deaminated 60% alone and 0% with semicarbazide after 1 hour.[9] These findings suggest that 2C-O may be less susceptible to metabolism by monoamine oxidase (MAO) than mescaline.[9] Moreover, it is now known that 2C-O shows far lower potency as a serotonin 5-HT2A receptor agonist than other 2C drugs.[8] Although 2C-O and certain derivatives such as 2C-O-4 appear to be inactive or of very low potency in humans, 2C-O derivatives show potent serotonin 5-HT2A receptor agonism in vitro and the amphetamine (α-methyl) analogue TMA-2 as well as derivatives like MEM are potent psychedelics in humans.[5][1][7] 2C-O was first described by Jansen in 1931 and was reported by him to produce psychedelic effects similar to those of mescaline.[10][3] However, subsequent tests in the 1960s and 1970s suggested that 2C-O is actually inactive as a psychedelic in animals and humans.[10][1] As of October 31, 2016, 2C-O is a controlled substance (Schedule III) in Canada.[11] 2C-O is a Schedule I substance, as a positional isomer of mescaline. 2C-O and all other compounds featured in PiHKAL are Class A drugs in the United Kingdom. 2,3,4,5-Tetramethoxyphenethylamine (TeMPEA) Substituted methoxyphenethylamine ^ a b c d e f g h i j k l Shulgin, Alexander; Shulgin, Ann (September 1991). PiHKAL: A Chemical Love Story. Berkeley, California: Transform Press. ISBN 0-9630096-0-5. OCLC 25627628. ^ a b c Shulgin A, Manning T, Daley PF (2011). "#124. TMPEA-2". The Shulgin Index, Volume One: Psychedelic Phenethylamines and Related Compounds. Vol. 1. Berkeley, CA: Transform Press. pp. 307–309. ISBN 978-0-9630096-3-0. OCLC 709667010. ^ a b c d Jansen, MPJM (1931). "β-2: 4: 5-Trimethoxyphenylethylamine, an isomer of mescaline". Recueil des Travaux Chimiques des Pays-Bas. 50 (4): 291–312. doi:10.1002/recl.19310500403. Retrieved 22 November 2022. ^ a b c Shulgin AT (2003). "Basic Pharmacology and Effects". In Laing RR (ed.). Hallucinogens: A Forensic Drug Handbook. Forensic Drug Handbook Series. Elsevier Science. pp. 67–137. ISBN 978-0-12-433951-4. Retrieved 1 February 2025. An exceptionally rich family of compounds has come from the substitution of groups at the 4-position of 2C-D which are not simple alkyl homologues. [...] An enigma is 2,4,5-trimethoxyphenethylamine, a positional isomer of mescaline (the 3,4,5-counterpart). It is devoid of activity even at doses that with mescaline would be fully effective. (See Table 3.8.) And yet, the addition of an alpha-methyl group to mescaline (a move that presumably protects it from oxidative deamination) only doubles the potency, whereas the same protective modification of this "inactive" isomer (to give the compound TMA-2), there is an

increase of more than an order of magnitude. ^ a b c d e f g h Kolaczynska KE, Luethi D, Trachsel D, Hoener MC, Liechti ME (2019). "Receptor Interaction Profiles of 4-Alkoxy-Substituted 2,5-Dimethoxyphenethylamines and Related Amphetamines". Front Pharmacol. 10: 1423. doi:10.3389/fphar.2019.01423. PMC 6893898. PMID 31849671. Although the 2C-O derivatives initially examined by Shulgin were shown to be fairly inactive in humans (2C-O-1; 21 and 2C-O-4; 22, Figure 3) some derivatives such as 19 [(TMA-2)] and 2,5-dimethoxy-4-ethoxyamphetamie (MEM) (24) displayed psychedelic activity (Figure 3) (Shulgin and Shulgin, 1991). However, upon further increasing chain length to a 4-propyloxy (MPM; 26) or 4-butyloxy (MBM; structure not shown) substituent, again no psychoactive effects could be observed on comparable doses as used for 19 and 24. The rather mixed results of low human potency and inactivity was one of the reasons Shulgin did not further evaluate the structure-activity relationship (SAR) of the 2C-O and 3C-O derivatives. Up-to-date, it remains unclear whether the early observations are due to pharmacokinetic properties such as a difference in metabolism or pharmacodynamic properties like differences in 5-HT receptor target interaction potency. [...] Compounds 2C-O-1 (21) and 2C-O-4 (22), two members of the 2C-O family, were not psychoactive in humans, at least at the doses tested so far (Shulgin and Shulgin, 1991). It has been suggested that this may be due to a rapid metabolism or low binding affinity to the 5-HT2A receptor (Clark et al., 1965; Nelson et al., 1999; Trachsel, 2012). The 5-HT2A activation mediates psychedelic effects (Glennon et al., 1992; Chambers et al., 2002; Kraehenmann et al., 2017) and receptor binding affinity has been shown to be a good predictor of the dose needed (clinical potency) to induce a psychedelic effect (Luethi and Liechti, 2018). ^ a b c d Trachsel D (2012). "Fluorine in psychedelic phenethylamines". Drug Test Anal. 4 (7–8): 577–590. doi:10.1002/dta.413. PMID 22374819. Within the group of the 2,4,5-trisubstituted phenethylamines, a few 4-alkoxy analogs have been described before (Figure 3, B).[3] Both 2C-O (43; >300 mg) and 2C-O-4 (44; >60 mg) proved to be inactive in humans, at least at the levels tested.[3] Whether they underlie a strong metabolism[70] or show low affinities towards the serotonin 5-HT2A receptor[36] remains to be established. In humans, the α-methylated 3C analogs TMA-2 (45; 20–40 mg, 8–12 h) and MEM (46; 20– 50 mg, 10–14 h) are fairly active compounds,[3] probably resulting from increased metabolic resistance, higher lipophilicity and pronounced receptor activation. [...] Similar to 2C-O (43: >300 mg[3]), Ψ-2C-O (2,4,6-TMPEA, 61: >300 mg) did not show any human activity (P. Rausch, personal communication in 2009) and interestingly, the 3,4,5-trimethoxy isomer mescaline (22: 180–360 mg) does.[3] ^ a b c Nichols DE, Glennon RA (1984). "Medicinal Chemistry and Structure-Activity Relationships of Hallucinogens". In Jacobs BL (ed.). Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives. New York: Raven Press. pp. 95–142. ISBN 978-0-89004-990-7. OCLC 10324237. The simplest modification is to remove the α-methyl group completely, since mescaline lacks an α-methyl group and is active. On the other hand, 2,4,5-trimethoxyphenethylamine is completely inactive whereas its α-methylated analog 2,4,5 trimethoxyamphetamine (TMA-2; Table I) is quite potent (Shulgin, 1978). Many of the non-α-methylated analogs of hallucinogenic amphetamines retain potency within about one order of magnitude of their amphetamine congeners (e.g., Shulgin and Caner, 1975). Although a decrease of this magnitude may seem dramatic from the perspective of structure-activity relationships, these compounds still remain active in humans with relatively small acute oral dosages. For example, 2,5-dimethoxy-4-bromophenethylamine (2C-B) and 2,5-dimethoxy-4-iodophenethylamine (2C-I) possess only about one-tenth the potency of their amphetamine counterparts DOB and DOI, respectively. DOI are two of the most potent hallucinogenic amphetamines known. Therefore, oral human dosages of 2C-B and 2C-I are in the 5-20 mg range. ^ a b c Wallach J, Cao AB, Calkins MM, Heim AJ, Lanham JK, Bonniwell EM, Hennessey JJ, Bock HA, Anderson EI, Sherwood AM, Morris H, de Klein R, Klein AK, Cuccurazzu B, Gamrat J, Fannana T, Zauhar R, Halberstadt AL, McCorvy JD (December 2023). "Identification of 5-HT2A receptor signaling pathways associated with psychedelic potential". Nat Commun. 14 (1): 8221. doi:10.1038/s41467-023-44016-1. PMC 10724237. PMID 38102107. ^ a b Clark LC, Benington F, Morin RD (May 1965). "The Effects of Ring-Methoxyl Groups on Biological Deamination of Phenethylamines". J Med Chem. 8 (3): 353–355. doi:10.1021/jm00327a016. PMID 14323146. ^ a b Shulgin AT (1978). "Psychotomimetic Drugs: Structure-Activity Relationships". In Iversen LL, Iversen SD, Snyder SH (eds.). Stimulants. Boston, MA: Springer US. pp. 243–333. doi:10.1007/978-1-4757-0510-2_6. ISBN 978-1-4757-0512-6. ^ Government of Canada, Public Works and Government Services Canada (May 4, 2016). "Canada Gazette – Regulations Amending the Food and Drug Regulations (Part J — 2C-phenethylamines)". gazette.gc.ca. TMPEA (2C-O) - Isomer Design TMPEA - PiHKAL - Erowid TMPEA - PiHKAL - Isomer Design Retrieved from " 3 2C-O-4 Names Preferred IUPAC name 2-{2,5-Dimethoxy-4-[(propan-2-yl)oxy]phenyl}ethan-1-amine Identifiers CAS Number 952006-65-4 N 3D model (JSmol) Interactive image ChemSpider 21106225 Y PubChem CID 44719510 UNII 1GFL65O0VB CompTox Dashboard (EPA) DTXSID70894771 InChI InChI=1S/C13H21NO3/c1-9(2)17-13-8-11(15-3)10(5-6-14)7-12(13)16-4/h7-9H,5-6,14H2,1-4H3 YKey: KAKXJLWAEMHHTL-UHFFFAOYSA-N Y SMILES CC(C)Oc1cc(OC)c(cc1OC)CCN Properties Chemical formula C13H21NO3 Molar mass 239.31 g/mol Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa). N verify (what is YN ?) Infobox references Chemical compound 2C-O-4, also known as 4-isopropoxy-2,5-dimethoxyphenethylamine, is a phenethylamine of the 2C family. It is also a positional isomer of isoproscaline and was probably first synthesized by Alexander Shulgin. It produces hallucinogenic, psychedelic, and entheogenic effects.[1] Because of the low potency of 2C-O-4, and the inactivity of 2C-O, Shulgin felt that the 2C-O series would not be an exciting area for research, and did not pursue any further analogues.[1] 2C-O-4 is in a class of compounds commonly known as phenethylamines, and the systematic chemical name is 2-(4-isopropoxy-2,5-dimethoxyphenyl)ethanamine. Little is known about the psychopharmacological effects of 2C-O-4. Based on the one report available in his book PiHKAL, Shulgin lists the dosage of 2C-O-4 as being >60 mg.[1] The pharmacology of 2C-O-4 has been studied.[2] The toxicity of 2C-O-4 is not known. As of October 31, 2016, 2C-O-4 is a controlled substance (Schedule III) in Canada.[3] 2C-O-4 is unscheduled and unregulated in the United States; however, because of its close similarity in structure and effects to mescaline and 2C-T-7, possession and sale of 2C-O-4 may be subject to prosecution under the Federal Analog Act. 2C-O 2C-T-4 ^ a b c Shulgin, Alexander; Shulgin, Ann (September 1991). PiHKAL: A Chemical Love Story. Berkeley, California: Transform Press. ISBN 0-9630096-0-5. OCLC 25627628. 2C-O-4 Entry in PiHKAL ^ Kolaczynska KE, Luethi D, Trachsel D, Hoener MC, Liechti ME (2019). "Receptor Interaction Profiles of 4-Alkoxy-Substituted 2,5-Dimethoxyphenethylamines and Related Amphetamines". Front Pharmacol. 10: 1423. doi:10.3389/fphar.2019.01423. PMC 6893898. PMID 31849671. ^ "Canada Gazette – Regulations Amending the Food and Drug Regulations (Part J — 2C-phenethylamines)". 4 May 2016. Retrieved from " 4 Pharmaceutical compound 2C-T-4Clinical dataOther names4-Isopropylthio-2,5-dimethoxyphenethylamine; 2,5-Dimethoxy-4-isopropylthiophenethylamineRoutes ofadministrationOral[1]Drug classSerotonin; 5-HT2 receptor agonist; Serotonergic psychedelic; HallucinogenATC codeNonePharmacokinetic dataDuration of action12–18 hours[1]Identifiers IUPAC name 2-{2,5-Dimethoxy-4-[(propan-2-yl)sulfanyl]phenyl}ethan-1-amine CAS Number207740-25-8 Y[chemspider]PubChem CID44350070ChemSpider21106232 YUNII558WSD71D4KEGGC22735 YChEMBLChEMBL338259 YCompTox Dashboard (EPA)DTXSID60893915 Chemical and physical dataFormulaC13H21NO2SMolar mass255.38 g·mol−13D model (JSmol)Interactive image SMILES CC(C)Sc1cc(OC)c(cc1OC)CCN InChI InChI=1S/C13H21NO2S/c1-9(2)17-13-8-11(15-3)10(5-6-14)7-12(13)16-4/h7-9H,5-6,14H2,1-4H3 YKey:HDYZSVKZKDPLDT-UHFFFAOYSA-N Y NY (what is this?) (verify) 2C-T-4, also known as 4-isopropylthio-2,5-dimethoxyphenethylamine, is a psychedelic phenethylamine of the 2C family.[1][2] It was first synthesized by Alexander Shulgin and is used as entheogenic recreational drug.[1] 2C-T-4 produces psychedelic and entheogenic effects that develop slowly and can last 12 to 18 hours.[1] While users may experience virtually no effects for the first hour after ingestion, results vary drastically between individuals and range from hallucination and euphoria to intense sickness and anxiety.[1] Shulgin devoted a chapter in the first part of his book PiHKAL to this compound, describing an intense "plus-four" psychedelic experience mediated by a twelve milligram dose. See also: Psychedelic drug § Interactions, and Trip killer § Serotonergic psychedelic antidotes 2C drugs are metabolized by the monoamine oxidase (MAO) enzymes MAO-A and MAO-B.[3][4] Monoamine oxidase inhibitors (MAOIs) such as phenelzine, tranylcypromine, moclobemide, and selegiline may potentiate the effects of 2C drugs.[3][4][5] This may result in overdose and serious toxicity.[5][3] 2C-T-4 activities Target Affinity (Ki, nM) 5-HT1A 470–916 5-HT1B ND 5-HT1D ND 5-HT1E ND 5-HT1F ND 5-HT2A 27.9–54 (Ki)5.5–220 (EC50Tooltip half-maximal effective concentration)56–87% (EmaxTooltip maximal efficacy) 5-HT2B ND (Ki)63–160 (EC50)68–75% (Emax) 5-HT2C 180–295 (Ki)ND (EC50)ND (Emax) 5-HT3 ND 5-HT4 ND 5-HT5A ND 5-HT6 ND 5-HT7 ND α1A 11,000 α1B, α1D ND α2A 130–217 α2B, α2C ND β1–β3 ND D1 20,000 D2 16,000 D3 19,000 D4, D5 ND H1 >25,000 H2–H4 ND M1–M5 ND I1 ND σ1, σ2 ND TAAR1Tooltip Trace amine-associated receptor 1 2,337–4,500 (Ki) (mouse)19–53 (Ki) (rat)3,700 (EC50) (mouse)83 (EC50) (rat)>30,000 (EC50) (human)51% (Emax) (mouse)67% (Emax) (rat) SERTTooltip Serotonin transporter >30,000 (Ki)113,000 (IC50Tooltip half-maximal inhibitory concentration)ND (EC50) NETTooltip Norepinephrine transporter 17,000 (Ki)134,000 (IC50)ND (EC50) DATTooltip Dopamine transporter >30,000 (Ki)294,000 (IC50)ND (EC50) Notes: The smaller the value, the more avidly the drug binds to the site. All proteins are human unless otherwise specified. Refs: [6][7][8][9] 2C-T-4 acts as a serotonin 5-HT2 receptor agonist, including of the serotonin 5-HT2A receptor.[8][7] The mechanism that produces 2C-T-4's hallucinogenic and entheogenic effects has not been specifically established, however it is most likely to result from 5-HT2A receptor activation in the brain, a mechanism of action shared by all of the hallucinogenic tryptamines and phenethylamines for which the mechanism of action is known. 2C-T-4 is the 2-carbon homolog of Aleph-4. The full chemical name is 2-[4-(isopropylthio)-2,5-dimethoxyphenyl]-ethanamine. The drug has structural and pharmacodynamic properties similar to 2C-T-7 and 2C-T-19.[citation needed] Ψ-2C-T-4, the homologue of 2C-T-4. 2C-T-4 has a homologue, the structural isomer Ψ-2C-T-4 (2,6-dimethoxy-4-(i)-propylthiophenethylamine). This compound was tested by Alexander Shulgin at a dose of 12 mg. At this dosage its duration was very short and it produced few effects, however based on the research into the better characterized compound Ψ-DOM, the potency of Ψ-2C-T-4 is likely to be around 1/3 that of 2C-T-4 itself, so a more effective dosage of Ψ-2C-T-4 might be in the region of 20–60 mg;[1] however high doses such as this might well be associated with toxic side effects, and so extreme caution would be advised. 2C-T-4 is relatively unknown on the black market, but has been sold to a limited extent on the research chemical market.[citation needed] As of October 31, 2016, 2C-T-4 is a controlled substance (Schedule III) in Canada.[10] As of October 2015 2C-T-4 is a controlled substance in China.[11] 2C-T-4 is added to the list of Schedule B controlled substances.[12] Sveriges riksdags health ministry Statens folkhälsoinstitut classified 2C-T-4 as "health hazard" under the act Lagen om förbud mot vissa hälsofarliga varor (translated Act on the Prohibition of Certain Goods Dangerous to Health) as of Jul 15, 2007, in their regulation SFS 2007:600 listed as 2,5-dimetoxi-4-isopropyltiofenetylamin (2C-T-4), making it illegal to sell or possess.[13] As of July 9, 2012, 2C-T-4 is a Schedule I substance in the United States, under the Synthetic Drug Abuse Prevention Act of 2012.[14] ^ a b c d e f g Shulgin A, Shulgin A (September 1991). PiHKAL: A Chemical Love Story. Berkeley, California: Transform Press. ISBN 0-9630096-0-5. OCLC 25627628. ^ Shulgin A, Manning T, Daley P (2011). The Shulgin Index, Volume One: Psychedelic Phenethylamines and Related Compounds. Vol. 1. Berkeley: Transform Press. ISBN 978-0-9630096-3-0. ^ a b c Dean BV, Stellpflug SJ, Burnett AM, Engebretsen KM (June 2013). "2C or not 2C: phenethylamine designer drug review". J Med Toxicol. 9 (2): 172–178. doi:10.1007/s13181-013-0295-x. PMC 3657019. PMID 23494844. ^ a b Theobald DS, Maurer HH (January 2007). "Identification of monoamine oxidase and cytochrome P450 isoenzymes involved in the deamination of phenethylamine-derived designer drugs (2C-series)". Biochem Pharmacol. 73 (2): 287–297. doi:10.1016/j.bcp.2006.09.022. PMID 17067556. ^ a b Halman A, Kong G, Sarris J, Perkins D (January 2024). "Drug-drug interactions involving classic psychedelics: A systematic review". J Psychopharmacol. 38 (1): 3–18. doi:10.1177/02698811231211219. PMC 10851641. PMID 37982394. ^ "K_i Database". PDSP. 9 May 2025. Retrieved 9 May 2025. ^ a b Rickli A, Luethi D, Reinisch J, Buchy D, Hoener MC, Liechti ME (December 2015). "Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs)" (PDF). Neuropharmacology. 99: 546–553. doi:10.1016/j.neuropharm.2015.08.034. PMID 26318099. ^ a b Luethi D, Trachsel D, Hoener MC, Liechti ME (May 2018). "Monoamine receptor interaction profiles of 4-thio-substituted phenethylamines (2C-T drugs)". Neuropharmacology. 134 (Pt A): 141–148. doi:10.1016/j.neuropharm.2017.07.012. PMID 28720478. ^ Simmler LD, Buchy D, Chaboz S, Hoener MC, Liechti ME (April 2016). "In Vitro Characterization of Psychoactive Substances at Rat, Mouse, and Human Trace Amine-Associated Receptor 1" (PDF). J Pharmacol Exp Ther. 357 (1): 134–144. doi:10.1124/jpet.115.229765. PMID 26791601. ^ "Regulations Amending the Food and Drug Regulations (Part J — 2C-phenethylamines)". Canada Gazette. 4 May 2016. ^ "关于印发《非药用类麻醉药品和精神药品列管办法》的通知" [Notice on the issuance of the "Regulations on the Listing of Non-Medicinal Narcotic Drugs and Psychotropic Drugs"] (in Chinese). China Food and Drug Administration. 27 September 2015. Archived from the original on 1 October 2015. Retrieved 1 October 2015. ^ "Bekendtgørelse om euforiserende stoffer" [Executive Order on Euphoriant Drugs]. Retsinformation (legal information) (in Danish). ^ Larsson M (14 June 2007). "Förordning om ändring i förordningen (1999:58) om förbud mot vissa hälsofarliga varor" [Ordinance amending the Ordinance (1999:58) on the prohibition of certain goods hazardous to health] (PDF). Svensk författningssamling (Swedish Constitution) (in Swedish). Archived from the original (PDF) on September 29, 2013. Retrieved January 24, 2022. ^ Portman RJ. "Synthetic Drug Abuse Prevention Act of 2012". Govtrack. Retrieved 22 July 2012. 2C-T-4 - Isomer Design 2C-T-4 - Erowid The Big & Dandy 2C-T-4 Thread - Bluelight 2C-T-4 - PiHKAL - Erowid 2C-T-4 - PiHKAL - Isomer Design Retrieved from " 5Psychedelic phenthylamine drug Pharmaceutical compound 2C-T-7Clinical dataOther names2,5-Dimethoxy-4-propylthiophenethylamine; 2,5-Dimethoxy-4-propylsulfanylphenethylamine; 4-Propylthio-2,5-dimethoxyphenethylamine; 4-Propylsulfanyl-2,5-dimethoxyphenethylamine; Blue Mystic; Tweety-Bird MescalineRoutes ofadministrationOralDrug classSerotonin 5-HT2 receptor agonist; Serotonergic psychedelic; HallucinogenATC codeNoneLegal statusLegal status BR: Class F2 (Prohibited psychotropics) CA: Schedule III US: Schedule I Pharmacokinetic dataDuration of action8–15 hours[1]Identifiers IUPAC name 2-[2,5-dimethoxy-4-(propylsulfanyl)phenyl]ethan-1-amine CAS Number207740-26-9 YPubChem CID24728635ChemSpider21106233 YUNIITJG366J9BAKEGGC22737ChEMBLChEMBL126432 YCompTox Dashboard (EPA)DTXSID90861566 Chemical and physical dataFormulaC13H21NO2SMolar mass255.38 g·mol−13D model (JSmol)Interactive imageMelting point206 to 207 °C (403 to 405 °F) SMILES COc1cc(SCCC)c(cc1CCN)OC InChI InChI=1S/C13H21NO2S/c1-4-7-17-13-9-11(15-2)10(5-6-14)8-12(13)16-3/h8-9H,4-7,14H2,1-3H3 YKey:OLEVEPDJOFPJTF-UHFFFAOYSA-N Y (verify) 2C-T-7, also known as 4-propylthio-2,5-dimethoxyphenethylamine, is a psychedelic phenethylamine of the 2C family.[1] In his book PiHKAL: A Chemical Love Story, Alexander Shulgin lists the dosage range as 10–30 mg.[1] 2C-T-7 is generally taken orally, and produces psychedelic and entactogenic effects that last 8 to 15 hours.[1] Up until Operation Web Tryp and three deaths, two of which involved the use of other drugs in addition to 2C-T-7, and one which involved an excessive insufflated dose, 2C-T-7 was sold commercially in Dutch and Japanese smartshops and online. It has been known on the streets as Blue Mystic or 7th Heaven.[2][3] There has been little real research done on this chemical other than Shulgin's comments in PiHKAL and a few small animal studies mostly aimed at detecting metabolites. 2C-T-7 is psychedelic.[4][5] In PiHKAL, Shulgin records that the hallucinations are unique, and that the chemical may cause muscle tension and an altered vocal quality.[6] Shulgin rated it as one of the "magical half-dozen" most important psychedelic phenethylamine compounds, together with mescaline, 2C-B, and 2C-T-2.[7] See also: Psychedelic drug § Interactions, and Trip killer § Serotonergic psychedelic antidotes 2C-T-7 is metabolized by the monoamine oxidase (MAO) enzymes MAO-A and MAO-B.[8][9] Monoamine oxidase inhibitors (MAOIs) such as phenelzine, tranylcypromine, moclobemide, and selegiline may potentiate the effects of 2C-T-7.[8][9][10] This may result in overdose and serious toxicity.[10][8] There have been at least three reported deaths related to 2C-T-7 use as of August 2007, mainly at insufflated (snorted) doses of 30 mg or more.[11][12] In the fall of 2000, a young healthy male died following insufflation of an excessive amount of 2C-T-7. Two additional deaths reported in April 2001 have been linked to 2C-T-7. These two deaths were reported by the DEA as being the result of the co-abuse of 2C-T-7 with MDMA.[13] In January 2002, Rolling Stone published an article about 2C-T-7 entitled "The New (legal) Killer Drug".[14] Although the article suggested that the drug was legal, the legal status of 2C-T-7 was ambiguous at the time due to the United States' Federal Analogue Act. [15] A detailed response on the website disinfo.com challenged the accuracy of much of the reporting in the aforementioned Rolling Stone article.[16] 2C-T-7 has since been officially made illegal and declared a schedule 1 substance in the United States.[17] The Partnership for a Drug-Free America reported in 2006 that 2C-T-7 can be lethal even in small doses;[18] however, they provide no source for their claim and of the three known deaths (as of August 2007) of 2C-T-7 intoxicated individuals, all involved either uncommonly large insufflated doses or the concomitant ingestion of other stimulants such as ephedrine and/or MDMA. All of the three aforementioned known deaths of individuals under the influence of 2C-T-7 occurred in those known to be either intoxicated with other stimulants such as ephedrine or MDMA (which are known to be potentially lethal in certain situations or at excessive doses)[19] or after the individual insufflated an amount of 2C-T-7 much greater than necessary to induce the full range of effects typically sought after by users of the drug; for example, the reported 35 mg insufflated dose taken by the individual who died in the fall of 2000. This reported dose was characterized as "excessive" by the US DEA. 2C-T-7 activities Target Affinity (Ki, nM) 5-HT1A 520–878 5-HT1B ND 5-HT1D ND 5-HT1E ND 5-HT1F ND 5-HT2A 5.3–6.5 (Ki)1.2–130 (EC50Tooltip half-maximal effective concentration)49–101% (EmaxTooltip maximal efficacy) 5-HT2B ND (Ki)52–350 (EC50)45–46% (Emax) 5-HT2C 39–54 (Ki)ND (EC50)ND (Emax) 5-HT3 ND 5-HT4 ND 5-HT5A ND 5-HT6 ND 5-HT7 ND α1A 13,000 α1B, α1D ND α2A 180–335 α2B, α2C ND β1–β3 ND D1 15,000 D2 5,000 D3 7,500 D4, D5 ND H1 >25,000 H2–H4 ND M1–M5 ND I1 ND σ1, σ2 ND TAAR1Tooltip Trace amine-associated receptor 1 311–560 (Ki) (mouse)10–33 (Ki) (rat)910 (EC50) (mouse)79 (EC50) (rat)>30,000 (EC50) (human)67% (Emax) (mouse)83% (Emax) (rat) SERTTooltip Serotonin transporter 12,000 (Ki)44,000 (IC50Tooltip half-maximal inhibitory concentration)ND (EC50) NETTooltip Norepinephrine transporter 27,000 (Ki)135,000 (IC50)ND (EC50) DATTooltip Dopamine transporter 34,000 (Ki)261,000 (IC50)ND (EC50) MAO-ATooltip Monoamine oxidase A 46,000 (IC50) MAO-BTooltip Monoamine oxidase B 180,000 (IC50) Notes: The smaller the value, the more avidly the drug binds to the site. All proteins are human unless otherwise specified. Refs: [20][21][22][23][24][25][26][27] The mechanism that produces the psychedelic and entactogenic effects of 2C-T-7 is most likely to result from action as a 5-HT2A serotonin receptor agonist in the brain, a mechanism of action shared by most currently-known hallucinogenic tryptamines and phenethylamines.[27] 2C-T-7 has structural and pharmacodynamic properties similar to those of 2C-T-2. Around the year 2000, 2C-T-7 began to change from an obscure chemical to a drug used at parties and clubs in North America and Europe as it became available through a number of grey-market commercial vendors. This aroused the attention of the authorities, and many countries have since scheduled the chemical. In Australia, 2C-T-2 and 2C-T-7 are covered by the country's analogue drug laws. As of October 31, 2016, 2C-T-7 is a controlled substance (Schedule III) in Canada.[28] As of October 2015 2C-T-7 is a controlled substance in China.[29] 2C-T-7 is scheduled in Germany. (BTMG) The Netherlands was the first country in the world to ban 2C-T-7, after being sold in smartshops for a short period. After 2C-T-2 was first banned, 2C-T-7 quickly appeared on the market, but was soon banned as well. 2C-T-7 is a list I drug of the Opium Law. Schedule I in Sweden.[30] 2C-T-7 was first classified as "health hazard" under the act Lagen om förbud mot vissa hälsofarliga varor (translated Act on the Prohibition of Certain Goods Dangerous to Health) as of April 1, 1999, under SFS 1999:58[31] that made it illegal to sell or possess. In 1999, Alexander Shulgin was sent a copy of a letter from the British Home Office to several of its administrative associates that in effect placed all compounds listed in PiHKAL into Class A.[citation needed] On September 20, 2002, 2C-T-7 was classified as a Schedule I substance in the United States by an emergency ruling by the DEA. On March 18, 2004, the DEA published a Final Rule in the Federal Register permanently placing 2C-T-7 in Schedule I. (69 FR 12794)[17][32][33] As of April 2024, law enforcement have encountered 2C-T-7 in 16 states, with the highest number of encounters being in Florida. Purchases made over the internet are believed by the DEA to be the most common source by which users of the drug acquire it in the United States, and one laboratory manufacturing the drug was discovered by police in Las Vegas, Nevada.[17] ^ a b c d Shulgin A. "PIHKAL #43". ^ Platoni K (May 1, 2002). "2C-T-7's Bad Trip". East Bay Express. In 1999 it made its first commercial appearance in the Netherlands' drug-dealing smart shops in both tablet and powder form. It was given the street name "Blue Mystic," perhaps in order to differentiate it from its chemical cousin, another Shulgin creation named 2C-T-2 ^ O'Connell C (August 19, 2002). "A psychedelic summer". Newsweek. ^ Hardison C (2000). "An Amateur Qualitative Study of 48 2C-T-7 Subjective Bioassays". maps.org. Bulletin of the Multidisciplinary Association for Psychedelic Studies MAPS. Retrieved October 30, 2023. ^ "Erowid 2C-T-7 Vault: Sulfurous Samadhi: Stolaroff's & Well's Study". erowid.org. February 6, 2001. Retrieved October 30, 2023. ^ Shulgin A (June 28, 2001). "2C-T-7". Ask Dr Shulgin. Centre for Cognitive Liberty and Ethics (COLE). Retrieved August 28, 2009. ^ Shulgin A (1990). ""PIHKAL" - The Chemical Story". www.erowid.org. Retrieved October 30, 2023. ^ a b c Dean BV, Stellpflug SJ, Burnett AM, Engebretsen KM (June 2013). "2C or not 2C: phenethylamine designer drug review". J Med Toxicol. 9 (2): 172–178. doi:10.1007/s13181-013-0295-x. PMC 3657019. PMID 23494844. ^ a b Theobald DS, Maurer HH (January 2007). "Identification of monoamine oxidase and cytochrome P450 isoenzymes involved in the deamination of phenethylamine-derived designer drugs (2C-series)". Biochem Pharmacol. 73 (2): 287–297. doi:10.1016/j.bcp.2006.09.022. PMID 17067556. ^ a b Halman A, Kong G, Sarris J, Perkins D (January 2024). "Drug-drug interactions involving classic psychedelics: A systematic review". J Psychopharmacol. 38 (1): 3–18. doi:10.1177/02698811231211219. PMC 10851641. PMID 37982394. ^ Curtis B, Kemp P, Harty L, Choi C, Christensen D (October 2003). "Postmortem identification and quantitation of 2,5-dimethoxy-4-n-propylthiophenethylamine using GC-MSD and GC-NPD". Journal of Analytical Toxicology. 27 (7): 493–8. doi:10.1093/jat/27.7.493. PMID 14607005. This compound was initially identified from a routine screening procedure in postmortem urine from a 20-year-old male that died in a local emergency room after reportedly insufflating 35 mg. ^ Platoni C (May 1, 2002). A psychedelic summer. East Bay Express (Report). In the same month, Joshua Robbins, a seventeen-year-old from Cordova, Tennessee, died after snorting between thirty and thirty-five milligrams of 2C-T-7, not long after taking several other stimulant drugs. According to Rolling Stone, which ran an article on Robbins' death, in the twelve hours before he died Robbins also had consumed Ecstasy, nitrous oxide, and a 'mini-thin' containing ephedrine and guaifenisen or combined with stimulants such as MDMA ^ "2,5-dimethoxy-4-(n)-propylthiophenethylamine". Drugs and Chemicals of Concern. Office of Diversion Control, Drug Enforcement Administration, U.S. Department of Justice. Archived from the original on October 20, 2008. ^ "The New (Legal) Killer Drug". 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N verify (what is YN ?) Infobox references Chemical compound 2C-T-17, also known as 4-sec-butylthio-2,5-dimethoxyphenethylamine, is a psychedelic phenethylamine of the 2C family. It was presumably first synthesized by Alexander Shulgin and reported in his book PiHKAL (Phenethylamines i Have Known And Loved). 2C-T-17 is the 2 carbon homologue of Aleph-17, which has never been synthesized. The full chemical name is 2-[4-(2-butyl thio)-2,5-dimethoxy phenyl]ethanamine. The drug has structural properties similar to drugs in the 2C-T series, with the most closely related compounds being 2C-T-7 and 2C-T-8. The dosage range of 2C-T-17 is typically 60-100 mg and its duration is approximately 10–15 hours according to Shulgin. 2C-T-17 has highly psychedelic effects on thinking, but produces few to no visuals.[1] The mechanism that produces 2C-T-17's hallucinogenic and entheogenic effects has not been specifically established, however it is most likely to result from action as a 5-HT2A serotonin receptor agonist in the brain, a mechanism of action shared by all of the hallucinogenic tryptamines and phenethylamines for which the mechanism of action is known. The toxicity of 2C-T-17 is not well documented. 2C-T-17 is much less potent than 2C-T-7, but it may be expected that at very high doses it would display similar toxicity to that of other phenethylamines of the 2C-T family. 2C-T-17 is not illegal, but possession and sales of 2C-T-17 could be prosecuted under the Federal Analog Act because of its structural similarities to 2C-T-7. As of October 31, 2016, 2C-T-17 is a controlled substance (Schedule III) in Canada.[2] This substance is a Class A drug in the Drugs controlled by the UK Misuse of Drugs Act.[3] ASR-3001 (5-MeO-iPALT) ^ Shulgin, Alexander; Shulgin, Ann (September 1991). PiHKAL: A Chemical Love Story. Berkeley, California: Transform Press. ISBN 0-9630096-0-5. OCLC 25627628. ^ "Canada Gazette – Regulations Amending the Food and Drug Regulations (Part J — 2C-phenethylamines)". 4 May 2016. ^ "UK Misuse of Drugs act 2001 Amendment summary". Isomer Design. Retrieved 12 March 2014. PiHKAL #48 2C-T-17 2C-T-17 Entry in PiHKAL Retrieved from " 7 2C-T-13 Names Preferred IUPAC name 2-{2,5-Dimethoxy-4-[(2-methoxyethyl)sulfanyl]phenyl}ethan-1-amine Identifiers CAS Number 207740-30-5 N 3D model (JSmol) Interactive image ChEMBL ChEMBL123868 Y ChemSpider 21106228 Y PubChem CID 44350108 UNII SK8JCS3S9B N CompTox Dashboard (EPA) DTXSID10658379 InChI InChI=1S/C13H21NO3S/c1-15-6-7-18-13-9-11(16-2)10(4-5-14)8-12(13)17-3/h8-9H,4-7,14H2,1-3H3Key: PYJLRNOGMKMRTK-UHFFFAOYSA-N YInChI=1/C13H21NO3S/c1-15-6-7-18-13-9-11(16-2)10(4-5-14)8-12(13)17-3/h8-9H,4-7,14H2,1-3H3Key: PYJLRNOGMKMRTK-UHFFFAOYAS SMILES COc1cc(SCCOC)c(cc1CCN)OC Properties Chemical formula C13H21NO3S Molar mass 271.38 g·mol−1 Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa). N verify (what is YN ?) Infobox references Chemical compound 2C-T-13, also known as 4-(2-methoxyethylthio)-2,5-dimethoxyphenethylamine, is a psychedelic phenethylamine of the 2C family. It was presumably first synthesized by Alexander Shulgin and reported in his book PiHKAL.[1] The drug has structural properties similar to mescaline and other drugs in the 2C-T series, with the most closely related compounds being 2C-T-7 and 2C-T-21. The dosage range of 2C-T-13 is typically 25 - 40 mg and its duration is approximately 6–8 hours according to Shulgin.[1] 2C-T-13 produces many closed-eye visuals and geometric patterns. It also produces slight visual distortion.[1] This section needs more reliable medical references for verification or relies too heavily on primary sources. Please review the contents of the section and add the appropriate references if you can. Unsourced or poorly sourced material may be challenged and removed. Find sources: "2C-T-13" – news · newspapers · books · scholar · JSTOR (July 2019) The mechanism that produces 2C-T-13's hallucinogenic and entheogenic effects has not been specifically established; however, it is most likely to result from action as a 5-HT2A serotonin receptor agonist in the brain, a mechanism of action shared by all of the hallucinogenic tryptamines and phenethylamines for which the mechanism of action is known. The toxicity of 2C-T-13 is not well documented. 2C-T-13 is slightly less potent than 2C-T-7, but it may be expected that at higher doses it would display similar toxicity to that of other phenethylamines of the 2C-T family. 2C-T-13 is not scheduled in the United States, but possession and sales of 2C-T-13 could be prosecuted under the Federal Analog Act because of its structural similarities to 2C-T-7. As of October 31, 2016, 2C-T-13 is a controlled substance (Schedule III) in Canada.[2] ^ a b c PiHKAL #46 2C-T-13 ^ "Regulations Amending the Food and Drug Regulations (Part J — 2C-phenethylamines)". 4 May 2016. Retrieved from " 8 2C-T-3 Names Preferred IUPAC name 2-{2,5-Dimethoxy-4-[(2-methylprop-2-en-1-yl)sulfanyl]phenyl}ethan-1-amine Identifiers CAS Number 648957-40-8 3D model (JSmol) Interactive image ChemSpider 129332310 PubChem CID 12063255 CompTox Dashboard (EPA) DTXSID001336717 InChI InChI=1S/C14H21NO2S/c1-10(2)9-18-14-8-12(16-3)11(5-6-15)7-13(14)17-4/h7-8H,1,5-6,9,15H2,2-4H3Key: JCDUUDQZKIXJJP-UHFFFAOYSA-N SMILES CC(=C)CSC1=C(C=C(C(=C1)OC)CCN)OC Properties Chemical formula C14H21NO2S Molar mass 267.39 g·mol−1 Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa). Infobox references Chemical compound 2C-T-3, also initially numbered as 2C-T-20 and also known as 4-methallylthio-2,5-dimethoxyphenethylamine, is a lesser-known psychedelic drug related to compounds such as 2C-T-7 and 2C-T-16. It was named by Alexander Shulgin but was never made or tested by him, and was instead first synthesised by Daniel Trachsel some years later. It has a binding affinity of 11nM at 5-HT2A and 40nM at 5-HT2C. It is reportedly a potent psychedelic drug with an active dose in the 15–40 mg range, and a duration of action of 8–14 hours, with visual effects comparable to related drugs such as methallylescaline.[1][2][3] 2C-T-2 2C-T-4 3C-MAL ^ Trachsel D (2003). "Synthesis of novel (phenylalkyl)amines for the investigation of structure-activity relationships. Part 2. 4-Thio-substituted [2-(2,5-dimethoxyphenyl)ethyl]amines (=2,5-dimethoxybenzeneethanamines)". 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You can help Wikipedia by expanding it.vte Retrieved from " 9 Pharmaceutical compound 2C-T-33Clinical dataOther names4-(3-Methoxybenzylthio)-2,5-dimethoxyphenethylamine; 2,5-Dimethoxy-4-(3-methoxybenzylthio)phenethylamine; 4-(3-Methoxy)benzylthio-2CDrug classSerotonin receptor agonist; Serotonin 5-HT2A receptor partial agonistIdentifiers IUPAC name 2-[2,5-dimethoxy-4-[(3-methoxyphenyl)methylsulfanyl]phenyl]ethanamine PubChem CID12063266Chemical and physical dataFormulaC18H23NO3SMolar mass333.45 g·mol−13D model (JSmol)Interactive image SMILES COC1=CC=CC(=C1)CSC2=C(C=C(C(=C2)OC)CCN)OC InChI InChI=1S/C18H23NO3S/c1-20-15-6-4-5-13(9-15)12-23-18-11-16(21-2)14(7-8-19)10-17(18)22-3/h4-6,9-11H,7-8,12,19H2,1-3H3Key:ADENDGINQJWQOK-UHFFFAOYSA-N 2C-T-33, also known as 4-(3-methoxybenzylthio)-2,5-dimethoxyphenethylamine, is a serotonin receptor agonist of the phenethylamine and 2C families.[1][2][3] It was first synthesized and described by Daniel Trachsel in 2003.[2][3] The drug is not known to have ever been tested in humans and its active human doses have not been reported.[3][4] 2C-T-33 shows high affinity for the serotonin 5-HT2A receptor (Ki = 1.7 nM) and to a much lesser extent for the serotonin 5-HT2C receptor (Ki = 75 nM; 44-fold lower than for 5-HT2A).[5] In terms of serotonin 5-HT2A receptor activation, its EC50Tooltip half-maximal effective concentration is 26 nM and its EmaxTooltip maximal efficacy is 40%.[5] Hence, 2C-T-33 acts as a low-efficacy partial agonist of the serotonin 5-HT2A receptor.[6][5][7] The drug shows higher affinity for the serotonin 5-HT2A receptor but much lower potency and efficacy in activating the receptor compared to 2C-T or 2C-B (which had values of Ki = 6.9–49 nM, EC50 = 2.0–2.1 nM, and Emax = 75–92%).[5] In contrast to most other 2C drugs and serotonergic psychedelics, 2C-T-33 appears to be completely inactive as an agonist of the serotonin 5-HT2B receptor (EC50 > 10,000 nM).[5] The drug has also been assessed at a number of other targets.[5] The drug did not significantly produce the head-twitch response (HTR), a behavioral proxy of psychedelic effects, in rodents, and hence may not have hallucinogenic effects in humans.[6] Its analogue 2C-T-27 (which lacks the methoxy group on the added benzyl ring) significantly and potently induces the HTR in rodents.[6] However, the HTR induced by 2C-T-27 is far weaker in magnitude than that induced by other 2C-T-X drugs and other serotonergic psychedelics.[6] For example, 2C-T (or 2C-T-1) induced about 7-fold more HTR events than 2C-T-33.[6] In contrast to the lack of assessment of 2C-T-33 in humans, 2C-T-27 has been evaluated and found to be active as a psychedelic in humans with a dose range of 80 to 130 mg.[6][1] The lack of HTR with 2C-T-33 may be due to its low-efficacy partial agonism of the serotonin 5-HT2A receptor and the receptor not being activated strongly enoughly.[6] The potencies of psychedelics in inducing the HTR are positively correlated with their efficacies in activating the serotonin 5-HT2A receptor.[6] The bulky 4 substitution of 2C-T-33 may be too large to accommodate the binding pocket of the serotonin 5-HT2A receptor in terms of maintaining robust receptor activation.[6] Similar findings have been observed for other phenethylamines with bulky 4-position substitutions, such as DOHx, DOBz, and 4-PhPr-3,5-DMA.[6] In addition to its potential psychoactive effects, 2C-T-33 has shown anti-inflammatory effects in animal studies similarly to other serotonin 5-HT2A receptor agonists and serotonergic psychedelics.[7] However, 2C-T-33 was the least effective assessed phenethylamine and was far less effective than other phenethylamines such as 2C-I, DOIB, 2C-B, (R)-DOI, and 2,5-DMA, among others.[7] 2C-T-8 Aleph-6 3C-BZ 2C-Ph 2C-BI-8 ^ a b Trachsel D, Lehmann D, Enzensperger C (2013). Phenethylamine: von der Struktur zur Funktion [Phenethylamines: From Structure to Function]. Nachtschatten-Science (in German). Solothurn: Nachtschatten-Verlag. pp. 789–795. ISBN 978-3-03788-700-4. OCLC 858805226. Retrieved 29 January 2025. ^ a b Trachsel D (2003). "Synthese von neuen (Phenylalkyl)aminen zur Untersuchung von Struktur–Aktivitätsbeziehungen. Mitteilung 2: 4-Thio-substituierte [2-(2,5-Dimethoxyphenyl)ethyl]amine (=2,5-Dimethoxybenzolethanamine)" [Synthesis of Novel (Phenylalkyl)amines for the Investigation of Structure–Activity Relationships. Part 2). 4-Thio-Substituted [2-(2,5-Dimethoxyphenyl)ethyl]amines (=2,5-Dimethoxybenzeneethanamines)]. Helvetica Chimica Acta. 86 (7): 2610–2619. doi:10.1002/hlca.200390210. ISSN 0018-019X. ^ a b c Meyers-Riggs B (3 April 2011). "Shulgin's Sulfur Symphony". countyourculture. Retrieved 17 February 2025. 2C-T-33 (2,5-dimethoxy-4-(3-methoxybenzylthio)phenethylamine) A 3-methoxy substituted 2C-T-27. Synthesized by Daniel Trachsel but has not been bioassayed to public knowledge. [...] Trachsel, D. Synthesis of novel (phenylalkyl)amines for the investigation of structure-activity relationships. Part 2. 4-Thio-substituted [2-(2,5-dimethoxyphenyl)ethyl]amines (=2,5-dimethoxybenzeneethanamines). Helv. Chim. Acta, 5 Aug 2003, 86 (7), 2610–2619. ^ Luethi D, Liechti ME (October 2018). "Monoamine Transporter and Receptor Interaction Profiles in Vitro Predict Reported Human Doses of Novel Psychoactive Stimulants and Psychedelics". The International Journal of Neuropsychopharmacology. 21 (10): 926–931. doi:10.1093/ijnp/pyy047. PMC 6165951. PMID 29850881. ^ a b c d e f Luethi D, Trachsel D, Hoener MC, Liechti ME (May 2018). "Monoamine receptor interaction profiles of 4-thio-substituted phenethylamines (2C-T drugs)" (PDF). Neuropharmacology. 134 (Pt A): 141–148. doi:10.1016/j.neuropharm.2017.07.012. PMID 28720478. ^ a b c d e f g h i j Halberstadt AL, Luethi D, Hoener MC, Trachsel D, Brandt SD, Liechti ME (January 2023). "Use of the head-twitch response to investigate the structure-activity relationships of 4-thio-substituted 2,5-dimethoxyphenylalkylamines". Psychopharmacology. 240 (1): 115–126. doi:10.1007/s00213-022-06279-2. PMC 9816194. PMID 36477925. ^ a b c Flanagan TW, Billac GB, Landry AN, Sebastian MN, Cormier SA, Nichols CD (April 2021). "Structure-Activity Relationship Analysis of Psychedelics in a Rat Model of Asthma Reveals the Anti-Inflammatory Pharmacophore". ACS Pharmacology & Translational Science. 4 (2): 488–502. doi:10.1021/acsptsci.0c00063. PMC 8033619. PMID 33860179. 2C-T-33 - isomer design Retrieved from " 10 The following pages link to 2C-T-33 External tools (link count transclusion count sorted list) · See help page for transcluding these entries Showing 50 items. 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