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Ease of free radical formation of various drugs involved in oxidative and reductive stress: neurological protection, nootropics, CNS stimulants, antioxidant and anti-inflammatory properties

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Keywords: MDMA; methamphetamine; pyritinol; piracetam; sertraline; memantine; modafinil; pentoxifylline; methylphenidate; Mitochondria; Redox cycles; Reactive oxygen species; Oxidative stress; Hydrated electrons; Reductive stress; Free radicals; Quantum mechanics;

Abbreviations

ROS Reactive Oxygen Species, ETC Electron Transport Chain, G free energy, ΔG free energy change of reaction in water, DET Dissociative Electron Transfer, DEA Dissociative Electron Attachment, mt mitochondrial, HAT hydrogen atom transfer, SET single electron transfer

Abstract

This study examines several well known xenobiotic free radical scavenger drugs: MDMA, methamphetamine, pyritinol, piracetam, sertraline, memantine, modafinil, methylphenidate, pentoxifylline. The free radicals scavenged include the hydroxyl radical, the oxygen superoxide radical anion, the peroxy radical, the nitroxyl radical, as well as reactions with singlet oxygen and hydrated electrons.

The free energies ΔG of the notional $\bullet H$ abstraction (HAT) reactions or single electron transfer (SET) reactions of the hydrated electron and oxygen superoxide radical anion $O_2^{\bullet -}$ for duloxetine, fluoxetine, pentoxifylline, sertraline, MDMA, methamphetamine, memantine, modafinil and pyritinol in water have been examined.

The hydroxyl radical $\bullet OH$ generally is the most favoured HAT reaction, while the second most favoured HAT reaction is with singlet oxygen 1O_2 . Only memantine and modafinil undergo HAT reactions with the nitroxyl radical $\bullet NO$, but modafinil is unusually reactive as it undergoes both HAT reactions with $O_2^{\bullet -}$ and SET reactions with $O_2^{\bullet -}$ and hydrated electrons.

The therapeutic and nootropic abilities of modafinil may be related to oxidative stress related conditions which induce an $O_2^{\bullet -}$ SET reaction rather than reductive stress conditions induced by hydrated electron $e^{\bullet -}$.

Disruption of the S—S bond of pyritinol is more facile (-32.4 kcal/mol) than that of the C—S bond in modafinil (-3.9 kcal/mol) in the Dissociative Electron Attachment (DEA) process

Introduction

In the mitochondrial electron transport chain (ETC), the transfer of electrons derived from substrate oxidation and ATP synthesis are coupled, but the transfer of electrons is not totally efficient. Due to the existence of electron leaks and proton leaks, not all electrons in the ETC are transferred to the final electron acceptor O_2 and the energy released by the transferred electrons is not fully coupled with ATP generation. However, both the reactive oxygen species (ROS) generated by electron leak and the uncoupling proteins involved in proton leak play an important role in the physiology and pathology of cells. The dominant route of ROS production by the ETC is the premature leak of electrons from the mitochondrial inner membrane complexes to mediate the one electron reduction of oxygen to superoxide ($O_2^{\bullet-}$), which can then dismutate to hydrogen peroxide (H_2O_2). In contrast to $O_2^{\bullet-}$, H_2O_2 is stable and uncharged, and thus able to leave the mitochondrion to mediate cytosolic cell signaling and processes such as Systemic Inflammatory Response Syndrome (SIRS) in distant organs. [Zhao, Nolfi-Donagan, Closa, Biswas] Pshenichnyuk has described the dissociative electron attachment (DEA) and transfer (DET) mechanisms that occur in vivo under reductive conditions, in the intermembrane space of mitochondria when xenobiotic molecules react with electrons “leaked” from the ETC.

ROS such as superoxide radicals ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($\bullet OH$), hydroperoxyl radicals ($\bullet OOH$), peroxy radicals ($\bullet OOR$), and possibly singlet oxygen (1O_2), are generated as metabolic by-products in the body. The physiological relevance of 1O_2 is controversial. [Moreira, Tarr] It was found that laser-induced generation of 1O_2 in neurons and astrocytes led to the increase of mitochondrial membrane potential, activation of NADH- and FADH-dependent respiration, and importantly, increased the rate of maximal respiration in isolated mitochondria. [Sokolovski] Singlet oxygen is known to be formed in cellular enzymatic reactions in a range of peroxidase enzymes during lipoxygenase-catalysed reactions. [Davies, Kanofsky] Singlet oxygen also inserts into weakly activated C—H bonds in saturated hydrocarbons with steric conservation. [Sagadevan]

Onyango has extensively summarized the evidence that singlet oxygen may be commonly generated in human tissues through a range of enzymatic and nonenzymatic reactions, including human neutrophils (via myeloperoxidase), the Russell reaction (via the reaction of glutathione with superoxide anion for example), the dismutation of alkoxyl radicals, and the endogenous formation of ozone. The reaction of the superoxide anion with hydrogen peroxide is known to form singlet oxygen, the hydroxyl radical and hydroxyl anion in vitro.

The lifetime of 1O_2 in water solutions is longer than most of the other ROS, with exception of hydrogen peroxide [Hirakawa] In viable, metabolically-functioning, and H_2O -containing cell, the lifetime of singlet oxygen is approximately 3 micros. The singlet oxygen lifetime in a cell is much longer than hitherto believed, showing that singlet oxygen is best characterized as a selective rather than reactive intermediate. [Hatz, Skovsen] Because of its long-life in a cell, 1O_2 can diffuse over appreciable distances including across the cell membrane into the extra-cellular environment. This is important when considering roles played by singlet oxygen as a signaling agent and as a component in events that result in cell death.

Reactive nitrogen species (RNS) include nitric oxide, nitrogen dioxide, and peroxynitrite can be formed particularly under hypoxic conditions in the mitochondria. RNS can cause nitrosative stress, complementary to ROS causing oxidative stress. [Poynton, Turrens, Sumbayev] It is known that increased mitochondrial ROS production occurs during hypoxia involving HIF-1 (hypoxia-inducible factor-1), which plays a central role in the response of cells to hypoxia. [Murphy] Hypoxia is a critical factor in the pathogenesis of major causes of mortality including cancer, myocardial ischemia, metabolic diseases, and chronic heart and kidney diseases, and in reproductive diseases such as preeclampsia and endometriosis. [Chen] Other non-radicals such as hydrogen peroxide and peroxynitrite, can lead to the generation of free radicals through various chemical reactions. Hydrogen peroxide can form hydroxyl radicals, and peroxynitrite, formed by the reaction of nitric oxide with superoxide, is a highly reactive molecule that also breaks down to form hydroxyl radicals. The $\bullet\text{OH}$ is the most reactive oxygen species and is generally thought to be a major player in oxidative damage. The hydroxyl radical is produced in the Fenton reaction by the interactions between H_2O_2 and metal ions. [Galano]

While the oxidizing power of superoxide is moderate compared with the hydroxyl radical, [Halliwell] superoxide is the primary radical that either provides an electron to or abstracts one from other compounds, which results in the production of other radical species via a chain reaction until the radical electron is eventually eliminated. While electron leakage in the mitochondrial ETC is the major sources of superoxide, superoxide and other ROS are formed not only inside cells but also extracellularly, via membrane oxidases that utilize electrons from NADPH. Superoxide can also be produced non-enzymatically, via glycation under conditions of hyperglycemia, which may involve diabetic complications, neurodegenerative diseases and cancer. [Fujii]

Protein phosphorylation, activation of several transcriptional factors, apoptosis, immunity, and differentiation, are processes dependent on a proper ROS production and presence inside cells but must be maintained at low levels. At high ROS levels, harmful effects on important cellular structures like proteins, lipids, and nucleic acids can occur. It is well established that oxidative stress is involved in several diseases (such as ADHD, Parkinson's disease, Alzheimer's disease, cancer, diabetes, depression, metabolic disorders, SIRS, atherosclerosis, and cardiovascular diseases). There is a progressive loss of neurons in neurodegenerative diseases. Neurons are particularly sensitive to oxidation because of their high polyunsaturated fatty acid content, weak antioxidant defense and high oxygen consumption. Peroxidation products of fatty acids are among the biomarkers of oxidative stress in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD). Peroxyl radicals are involved in the oxidation of lipoproteins which play a key role in the initial development of atherosclerosis. [Collin] ROS can be beneficial, as they are used by the immune system as a way to attack and kill pathogens. Cells have an inbuilt antioxidant defensive system based mainly on enzymatic components, such as superoxide dismutase, catalase, and glutathione peroxidase, to protect themselves from ROS-induced cellular damage. Oxidative stress results from an imbalance between the body's production of ROS and the body's ability to detoxify the excess ROS or to repair the damage caused by the excess ROS. [Sharifi-Rad, Pizzino, Malekmohammad, Chaudhary]

Hydrated electrons (e^-_{aq}) are considered to be involved in many human physiological processes. [Getoff] For example human serum albumin scavenges hydrated electrons at neutral pH at diffusion controlled rates, mainly by electron attachment to the protein disulfide bond (Cys-SCy•-). [Konarska] Halliwell quotes the standard reduction potential of the hydrated electron as -2.84V compared to $O_2/O_2^{\cdot-}$ as -0.35V, and $O_2, H^+/HO_2^{\cdot}$ couple as -0.46V, and $O_2^{\cdot-}, 2H^+/H_2O_2$ as +0.94V oxidising, and $^{\cdot}OH, H^+/H_2O$ as +2.31V highly oxidizing, the highest reduction potential, with $^{\cdot}OH$ being the most reactive oxygen free radical known. $O_2^{\cdot-}$ can act as a reducing agent $O_2/O_2^{\cdot-}$ as -0.35V, and as an oxidizing agent, $O_2^{\cdot-}, 2H^+/H_2O_2$ as +0.94V oxidizing agent. [Halliwell] The reversible potential of the four-electron transferred triplet oxygen generation is 1.23 V, while the reversible potential of singlet oxygen evolution has been calculated to be $1.23 + 0.98/4 = 1.475$ V based on the Gibbs free energy $\Delta G = -nEF$. [Chen]

Transferrin does not react with superoxide $O_2^{\cdot-}$ but does react with hydrated electrons. [Buettner] Bimolecular rate constants for e^-_{aq} and $^{\cdot}OH$ reactions of some nitrosonitramines and nitramines showed the reaction of the hydrated electron to form a transient radical anion was faster than the hydroxyl radical reaction which resulted in hydrogen atom abstraction from an alkyl group. [Mezyk] The hydrated electron and hydroxyl radical rate constants with vinylic acid esters are close to the diffusion-controlled limit. It is shown that $k(e^-_{aq})$ and $k(^{\cdot}OH)$ change in opposite direction: if $k(e^-_{aq})$ is high then $k(^{\cdot}OH)$ is small. This tendency is related with the nucleophilic character of e^-_{aq} and the electrophilic character of $^{\cdot}OH$, although the site of attack of e^-_{aq} and $^{\cdot}OH$ can be different: carbonyl versus vinyl group for example. [Biro] In bulk water, the hydrated electron's lifetime is relatively long, reaching up to microseconds, but its strong reducing potential renders it highly reactive, and thus short-lived, in the presence of electron acceptors. [Abel] Hydrated electrons can damage DNA, create radicals, and induce many reductive reactions, including dissociative electron attachment. [Simons,Wang, Gu]

DEA (or DET) is known to be the mechanism of secondary low energy electrons (typically below 12 eV) formed during high energy radiolysis, which react with many biologically important species, eg DNA. DET can generate negatively charged fragment ions and neutral radicals at electron energies significantly below the corresponding bond dissociation energy. [Baccarelli, Boudaiffa, Westphal, Fong 2016]

Redox homeostasis in the body preserves physiological processes by balancing oxidative stress and reductive stress. *Redox equilibrium is essential for cellular homeostasis. Feedback regulation can occur when chronic reductive stress induces oxidative stress, which in turn, can again stimulate reductive stress.* Oxidative stress has been widely studied in aerobic conditions in the body, but less attention has been given to reductive stress, where for example, reductive stress can occur in hypoxic cancerous conditions. [Rajasekaran] Generally reductive stress is associated with redox couples of $NADH/NAD^+$, $NADPH/NADP^+$ and $GSH/GSSG$. [Chatgililoglu] Hydrated electrons generated without radiation are thought to control the reactivity of vitamins E, C, and carotenoids. [Getoff]

Inflammatory diseases associated with reductive stress include aggregation protein cardiomyopathy, hypertrophic cardiomyopathy, muscular dystrophy, pulmonary hypertension, rheumatoid arthritis, Alzheimer's disease, and metabolic syndrome. Also chronic over-consumption of antioxidant supplements, such as vitamins and or flavonoids, can have pro-oxidant effects that alter the redox cellular equilibrium and contribute to reductive stress. [Perez-Torres]

Redox balance is important in the regulation of cellular processes in cancer cells: oxidative stress, if extremely high, is cytotoxic; whereas moderate concentrations of ROS induces the proliferation and metastasis of cancer cells; but reductive stress caused by low levels of ROS generation can lead to cancer cell survival, resistance to cancer therapy. [Chun]

The superoxide anion radical can abstract a H atom from hydrocarbons to initiate autooxidation chain processes. [Lee-Ruff, Frimer] Because of its charge $O_2^{\cdot-}$ superoxide tends to remain in the aqueous phase and is largely excluded even from the headgroup region when interacting with cell membranes. Although passage through the lipid region of membranes is unfavorable, superoxide can use anion channels in the membrane such as anion exchange 1 (band 3) in erythrocytes and thus also traverses plasma membranes. $O_2^{\cdot-}$ can cause lipid peroxidation of membranes presumably from leakage from anion channels. $O_2^{\cdot-}$ has a pKa of 4.7. The peroxy HOO^{\cdot} radical which is neutrally charged can also cause lipid peroxidation through diffusion into membranes. HOO^{\cdot} reacts favorably with the headgroup region, via hydrogen bonding with the acyl chain carbonyls, and has a lower energy barrier to traverse the membrane than hydrogen peroxide. [Moller]

This study examines several well known xenobiotic free radical scavenger drugs: MDMA, methamphetamine, pyritinol, piracetam, sertraline, memantine, modafinil, methylphenidate, pentoxifylline. The common therapeutic uses of these drugs are given in the Appendix. The psychostimulants MDMA and methamphetamine are known to cause oxidative stress in disruption of brain functions. Neurotoxic effects of MDMA and amphetamines and cocaine are related to the formation of ROS, which may be involved in damage to cortical DNA. [Basmadjian, Górska, Cunha-Oliveira] The neurotoxicity of MDMA is a controversial and highly topical current issue. [Costa] Pyritinol acts as an antioxidant and anti-inflammatory agent, and reduces plasma viscosity. It is indicated in pediatric cognitive disorders and dysphasia, postnatal hypoxia. It is known for improving cognition and memory in adults, Alzheimer's disease and multi-infarct dementia, as well as treating rheumatoid arthritis. [Singh] The protective effect of pyritinol against hydroxyl free-radical induced derangement of cell proteins is an important part of its nootropic effect. The efficient scavenging of hydroxyl radicals by pyritinol was confirmed by electron spin resonance spectroscopy. [Pavlik] Electrochemical S—S bond scission of pyritinol (at pH 7) occurs after the protonation of both nitrogen atoms by the exchange of two electrons and two protons in two-process stages. [Apetrei]

Piracetam is a clinically indicated and widely used nootropic drug, but its neuroprotective mechanism is not fully known. The effect of piracetam on rotenone induced oxidative stress in vivo has shown that piracetam enhances the antioxidant capacity in brain cells in a region specific manner. [Verma] Piracetam can improve mitochondrial dysfunction associated with oxidative stress and/or aging. Mitochondrial stabilization and protection might be an important mechanism to explain many of piracetam's beneficial effects in elderly patients. There is evidence that piracetam may not possess radical scavenging properties, but acts directly at the mitochondrial level, by improving mitochondrial membrane fluidity properties. [Keil] But other studies suggest piracetam possesses antioxidative, anti-inflammatory and anti-apoptotic activity. [Verma] Piracetam may be involved in enhanced mitochondrial membrane potential, enhanced ATP production, and reduced sensitivity for apoptosis in aging and Alzheimer disease, and there is evidence for elevated neuronal plasticity caused by piracetam. [Keil, Leuner]

Methylphenidate, or Ritalin is a central nervous system stimulant used to treat attention deficit hyperactivity disorder and, to a lesser extent, narcolepsy. It is a primary medication for ADHD in the UK and USA. It is believed to work by blocking the reuptake of dopamine and norepinephrine by neurons. [Berridge]

The effects of sertraline antidepressant therapy on total antioxidant capacity and $O_2^{\bullet-}$ and $\bullet OH$ free radical levels in patients with major depressive disorder (MDD) resulted in significantly lower levels of superoxide and hydroxyl radicals. MDD patients showed by lowered antioxidant capacity than healthy individuals. Antidepressant treatment resulted in increased antioxidant capacity and a decrease in circulating free radicals. [Chang]

It has been shown [Tanaka] that memantine, an anti-Alzheimers drug, exerts partially neuroprotective effects against cerebral ischemic injury in mice. Also memantine significantly reduced hydroxyl radical metabolites during ischemia and reperfusion and reduced oxidative stress in hippocampal CA1 neurons after reperfusion. The formation of peroxynitrite ($ONOO^-$) from $O_2^{\bullet-}$ and NO was shown to induce neuronal injury via several mechanisms. The combination therapy with memantine and metformin for elderly patients with prediabetic state and mild cognitive impairment has been shown to decrease oxidant indexes and increase the antioxidant indice. [Alimoradzadeh, Xiaoxin] Memantine suppressed inflammation, rescued the reduction in mitochondrial membrane potential but also decreased oxidative stress. Memantine confers protective effects against acute myocardial infarction while promoting recovery through increased angiogenesis.

Animal studies on nootropic drugs piracetam, pyritinol, co-dergocrine, meclophenoxat, pentoxifylline, and nimodipine have shown improvements in cerebral blood flow and improvements in neurotransmission and receptors essential for cognitive functioning and antioxidant activity. [Wojszel]

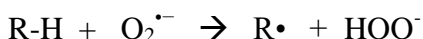
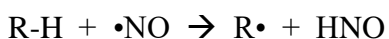
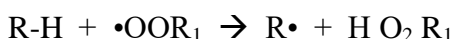
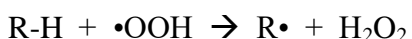
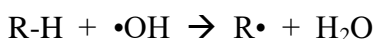
This study investigates how some xenobiotic free radical scavenger drugs which are widely prescribed for neurological protection, nootropics, CNS stimulants can be assessed as likely antioxidants to reduce oxidative stress by forming free radicals. Also the potential of these drugs

to reduce reductive stress by scavenging hydrated electrons is also examined. That is, the ease or otherwise, that the drugs can form free radicals by reacting with various ROS, RNS and hydrated electrons formed during oxidative stress and reductive stress.

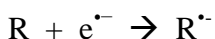
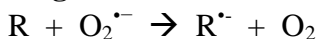
Figure 1 shows the structures of the examined drugs, while Figures 2-5 show the structures of the most stable radical species, formed either by •H abstraction reactions or single electron transfer reactions of the examined drugs.

Schematically a xenobiotic drug R can react with various ROS (eg $O_2^{\bullet-}$, •OH, •OOH, •OOR, and 1O_2), RNS (eg •NO, peroxynitrite) or hydrated electrons ($e^{\bullet-}$) to form R^{\bullet} or $R^{\bullet-}$ plus byproducts either by •H abstraction or by single electron transfer processes. Whether such reactions can occur for the various drugs depends on the free energy ΔG of the following *notional* reactions.

•H abstraction reactions:



Single electron transfer reactions:



Results and Discussion

Table 1 shows the free energies ΔG of the notional •H abstraction (HAT) reactions or single electron transfer (SET) reactions for various drugs in water. Figures 1 – 6 shows the structures of the examined drugs and the radical species derived from these drugs. $O_2^{\bullet-}$ and $e^{\bullet-}$ the hydrated electron are SET reactions, with $O_2^{\bullet-}$ examined as either HAT or SET reactions.

Examination of the highlighted **green ΔG values** in Table 1 shows HAT or SET reactions which are thermodynamically *significantly* favoured. For the HAT reactions, as expected, the •OH generally is the most favoured reaction, while the second most favoured HAT reaction is with 1O_2 . Only memantine and modafinil undergo HAT reactions with •NO, but modafinil is unusually reactive as it undergoes both HAT and SET reactions.

Table 1 shows that only modafinil and pyritinol undergo HAT reactions with $O_2^{\bullet-}$. Duloxetine, pentoxifyline, modafinil and pyritinol undergo SET reactions with the hydrated electron.

Modafinil is unusual in that it undergoes both SET reactions with $\text{O}_2^{\bullet-}$ and hydrated electrons, and HAT reactions with $\text{O}_2^{\bullet-}$.

It is known that certain carotenoids (Car) can oxidize $\text{O}_2^{\bullet-}$ resulting in $\text{Car}^{\bullet-}$ and O_2 . [Galano, Fong 2023] It is also known that $\text{O}_2^{\bullet-}$ can SET an electron to certain acceptor molecules such as quinones and nitro-aromatic hydrocarbons, with the reduced semi-quinone radical anions being detected by ESR spectroscopy at -196°C . [Poupko]

We have previously [Fong 2022] shown that modafinil can easily form free radical species either by: (a) abstraction of a hydrogen radical (HAT) from the methine position by ROS (such as $\bullet\text{OH}$, $\bullet\text{OOH}$, $\bullet\text{NO}$ or $^1\text{O}_2$) typically found in the brain under oxidative stress, or (b) by dissociative electron attachment (reductive stress) which results in bond elongation of the benzylic methine C---S bond to form a $\text{C}^{\bullet}\text{---}\text{S}$ bond following hydrated electron attachment, or from $\text{O}_2^{\bullet-}$ the addition of an electron by single electron SET reactions. Table 1 shows that modafinil can undergo HAT and SET reactions with ease, which can explain its well known therapeutic properties.

Comparison of the SET reactions with $\text{O}_2^{\bullet-}$ and hydrated electron $e^{\bullet-}$ shows duloxetine and pentoxifylline can undergo reductive hydrated electron transfer, but not with $\text{O}_2^{\bullet-}$ consistent with their standard reduction potentials [Halliwell]. Pyritinol undergoes more highly favoured hydrated electron transfer SET reactions than those with $\text{O}_2^{\bullet-}$ but modafinil does not, showing that SET with $\text{O}_2^{\bullet-}$ (-55 kcal/mol) is much more favoured than a SET reaction with a hydrated electron $e^{\bullet-}$ (-3.9 kcal/mol). This suggests that the therapeutic and nootropic abilities of modafinil may be related to oxidative stress related conditions which induce an $\text{O}_2^{\bullet-}$ SET reaction rather than reductive stress conditions induced by the hydrated electron $e^{\bullet-}$.

Modafinil but not pyritinol undergoes HAT reactions with $\text{O}_2^{\bullet-}$. Pyritinol undergoes far more favoured hydrated electron transfer than does modafinil, indicating DEA resulting in disruption of the S—S bond of pyritinol is more facile (-32.4 kcal/mol) than that of the C—S bond in modafinil (-3.9 kcal/mol) in the DEA process. The reactivity of pyritinol as the di-protonated ion at the NH^+ di-pyridyl position is also shown to be more favoured than pyritinol itself for the di-HAT $\text{O}_2^{\bullet-}$ (-15.3 kcal/mol), but is particularly favoured for the reductive di-hydrated electron attachment DEA for the pyritinol di-ion which shows a TS (-133 kcal/mol) compared to a TS (-46.0 kcal/mol) for the pyritinol DEA.

Disulfide bonds have a typical bond dissociation energy of ca 60 kcal/mol about 40% weaker than C—C and C—H bonds. The S—S bond is susceptible to scission by polar reagents, both electrophiles and especially nucleophiles. The disulfide bond is normally about 2.05\AA in length (2.08\AA in water in this study), about 0.5\AA longer than a C—C bond. Rotation about the S—S bond has a low barrier. [Cremlyn, Fong 2024]

Conclusion

The free energies ΔG of the notional $\bullet\text{H}$ abstraction (HAT) reactions or single electron transfer (SET) reactions of the hydrated electron and oxygen superoxide radical anion $\text{O}_2^{\bullet-}$ for duloxetine, fluoxetine, pentoxifyline, sertraline, MDMA, methamphetamine, memantine, modafinil and pyritinol in water have been examined.

The hydroxyl radical $\bullet\text{OH}$ generally is the most favoured HAT reaction, while the second most favoured HAT reaction is with singlet oxygen $^1\text{O}_2$. Only memantine and modafinil undergo HAT reactions with the nitroxyl radical $\bullet\text{NO}$, but modafinil is unusually reactive as it undergoes both HAT reactions with $\text{O}_2^{\bullet-}$ and SET reactions with $\text{O}_2^{\bullet-}$ and hydrated electrons.

The therapeutic and nootropic abilities of modafinil may be related to oxidative stress related conditions which induce an $\text{O}_2^{\bullet-}$ SET reaction rather than reductive stress conditions induced by hydrated electron $e^{\bullet-}$.

Disruption of the S—S bond of pyritinol is more facile (-32.4 kcal/mol) than that of the C—S bond in modafinil (-3.9 kcal/mol) in the Dissociative Electron Attachment (DEA) process.

Table 1 Free energies ΔG of notional $\bullet\text{H}$ abstraction reactions or single electron transfer reactions for various drugs

	$\bullet\text{OH}$	$\bullet\text{OOH}$	$\bullet\text{NO}$	$^1\text{O}_2$	$\text{O}_2^{\bullet-}$	hydrated $e^{\bullet-}$
Duloxetine					48.5 ^{SET}	-10.4
Duloxetine NH^+ Ion					51.0 ^{SET}	-7.9
Duloxetine radical[%]	-36.0	-2.5	29.0	-13.3	13.4	
Duloxetine radical^{%%}	-12.0	-12.0	53.0	10.7	3.7	
Fluoxetine					57.6 ^{SET}	-1.2
Fluoxetine $\text{NH}^+(\text{Me})$ Ion					61.1 ^{SET}	2.2
Fluox radical[#]	-33.2	0.4	31.8	-10.5	16.2	
Fluox radical^{##}	-31.8	1.8	32.7	-9.1	17.6	
FluoxNH^+ Ion radical^{###}	-30.9	2.7	34.1	-8.2	18.6	
Pentoxifyline					50.7 ^{SET}	-8.2
Pentoxifyline radical^{@*}	4.6	38.2	69.6	27.3	54.0	
Pentoxifyline radical^{@**}	-17.8	15.8	47.3	4.9	31.6	
Sertraline					57.3 ^{SET}	-1.6
Sertraline$\text{N}^+\text{H}(\text{Me})$ Ion					58.7 ^{SET}	-0.2
SertralineNH_2^+ Ion radical^{@#}	-39.1	-5.6	25.9	-16.5	10.3	
Sertraline radical[@]	-36.4	-2.8	28.7	-13.6	13.1	
MDMA					68.6 ^{SET}	9.8
MDMA Ion-$\text{NH}_2^+(\text{Me})$					64.5 ^{SET}	5.6
MDMA radical[^]	-31.8	1.8	33.3	-9.1	17.6	

MDMA NH ₂ ⁺ (Me) Ion radical ^{^^}	-32.8	0.8	32.3	-10.1	16.6	
Methamphetamine Meth Ion-NH ₂ ⁺ (Me)					68.9 ^{SET} 66.3 ^{SET}	10.0 7.5
Meth Ion-NH ₂ ⁺ (Me) radical ***	-30.0	3.6	35.1	-7.3	19.5	
Meth radical*	-30.2	3.4	34.9	-7.5	19.3	
Meth radical**	-31.5	2.1	33.6	-8.8	18.0	
Memantine MemantineNH ₃ ⁺ Ion					86.1 ^{SET} 72.3 ^{SET}	27.2 13.4
Memantine radical ^{###}	-22.5	11.1	-42.6	0.0	26.9 ^{HAT}	
Modafinil					-55.0 ^{SET}	-3.9
Modafinil radical****	-82.5	-48.9	-17.5	-98.4	-33.1 ^{HAT}	
Modafinil-TS• *****						-84.2
Pyritinol					26.5(x1) ^{SET}	-32.4(x1)
Pyritinol Dione(NH ⁺) ₂ + TS ^{@@} Pyritinol + TS ^{@@@}					-15.3 ^{HAT} (x2)	-133.0(x2) @@ -46.0(x2) @@@
Piracetam	-28.8	4.7	1.2	-6.2	61.7 ^{SET}	2.9
Methylphenidate	-31.6	2.0	35.3	-8.9	58.1 ^{SET}	-0.7

Footnotes:

ΔG kcal/mol

* C₆H₅-CH₂-CH(Me)-N•(Me) ** C₆H₅-C•(H)-CH(Me)-NH(Me) *** C₆H₅-C•(H)-CH(Me)-N⁺H₂(Me)

Methamphetamine radicals

% C₄H₃S-C•-(O-C₁₀H₇)-(CH₂)₂-NH-Me %% C₄H₃S-CH-(O-C₁₀H₇)-(CH₂)₂-N•-Me Duloxetine radicals

C₆H₅-C•-(OC₆H₄CF₃)-(CH₂)₂-NH(Me) ## C₆H₅-CH-(OC₆H₄CF₃)-(CH₂)₂-N•(Me) Fluoxetine radicals

C₆H₅-C•-(OC₆H₄CF₃)-(CH₂)₂-N⁺H₂(Me) Fluoxetine radical ion

@* Pentoxifylline radical C8 xanthine ring @** Pentoxifylline radical side chain

^ Methylendioxyphenyl-C•H-CH-(Me)-NH-Me ^^ Methylendioxyphenyl-C•H-CH-(Me)-N⁺H₂-Me MDMA radicals

**** (C₆H₅)₂C•-S(O)-CH₂-C(=O)-NH₂ Modafinil radical •H abstraction C•-S 1.80 Å

***** Modafinil-TS• [(C₆H₅)₂CH----S(O)-CH₂-C(=O)-NH₂]• C----S 3.39 Å Modafinil radical DEA

Modafinil^{SET} + O₂⁻ → Modafinil• + O₂ (SET)

C₁₂H₁₉N•H Memantine radical

@ Sertraline benzylic radical (4-3,4 dichlorophenyl-tetrahydro-) position

@# Sertraline N⁺HMe benzylic radical (4-3,4 dichlorophenyl-tetrahydro-) position

@@ Pyridyl(H⁺)-CH₂-S•-----S-CH₂-Pyridyl(H⁺) 4.31 Å TS Pyritinol radical DEA

@@@ Pyridyl-CH₂-S•-----S-CH₂-Pyridyl 3.54 Å TS Pyritinol radical DEA

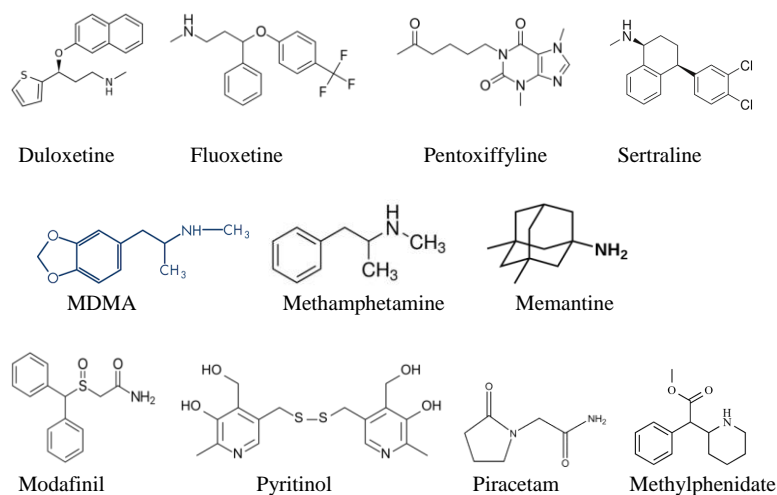


Figure 1. Structures of examined drugs

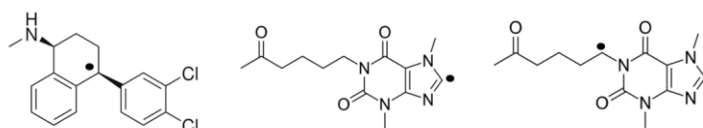


Figure 2. Sertraline Radical (L), Less stable Pentoxifyline radical (C), More stable Pentoxifyline radical (R)

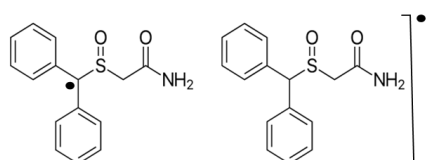


Figure 3. Modafinil radical (L), radical anion formed by Dissociative Electron Attachment (DEA) to Modafinil (R)

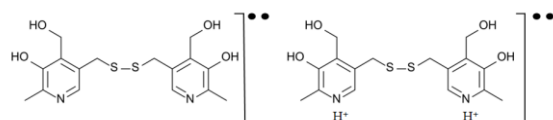


Figure 4. 2 electron DEA Pyritinol (L), 2 electron DEA PyritinolH₂⁺⁺ (R)

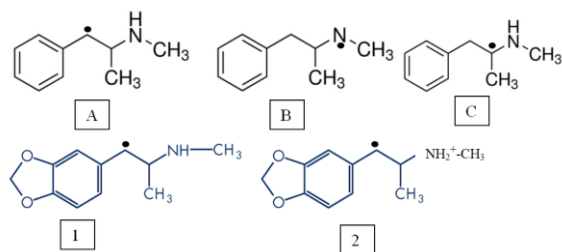


Figure 5. Methamphetamine: (A) most stable radical, (B) less stable radical, (C) more unstable radical; (1) MDMA radical, (2) protonated MDMA radical

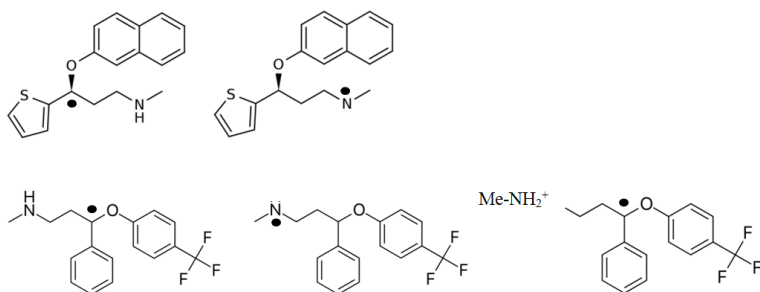


Figure 6. Duloxetine radical most stable (Upper L), Duloxetine radical less stable (Upper R). Fluoxetine radical most stable (Lower L), Fluoxetine radical less stable (Lower C), Fluoxetine protonated N^+H_2 radical (Lower R)

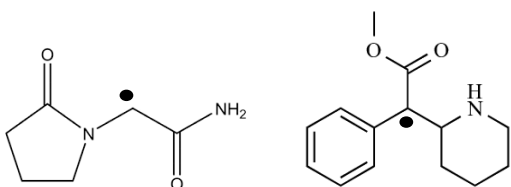


Figure 7. Radical species from piracetam (L) and methylphenidate (R) formed by HAT reaction

Appendix: Common uses of examined drugs

Duloxetine: depressive/anxiety disorders, fibromyalgia, neuropathic pain and central sensitization (Cymbalta)

Fluoxetine: antidepressant used for the treatment of major depressive disorder, obsessive-compulsive disorder, bulimia nervosa, panic disorder (Prozac)

Pentoxifylline: treatment of muscle pain from peripheral artery disease, nootropic

Sertraline: antidepressant (Zoloft)

MDMA: 3,4-methylenedioxy-methamphetamine is an illicit synthetic drug that alters mood and perception

Methamphetamine: central nervous system stimulant mainly used as a recreational drug and less commonly as a second-line treatment for attention deficit hyperactivity disorder

Memantine: treatment of the symptoms of moderate to severe Alzheimer's disease (Axura, Ebixa, Namenda)

Modafinil: stimulant and 'wakefulness promoting agent' and is one of the stimulants used in the treatment of narcolepsy, nootropic or smart cognitive enhancer drug (Provigil)

Pyritinol: cognitive brain disorders, rheumatoid arthritis, and learning disorders in children, nootropic dietary supplement, vitamin B6 analogue (Encephabol)

Piracetam: Breath holding attacks, epilepsy, vertigo, nootropic

Methylphenidate: FDA and UK (Ritalin) approved for treating attention deficit hyperactivity disorder (ADHD) in children and adults and as a second-line treatment for narcolepsy in adults.

Experimental Methods

All calculations were carried out using the Gaussian 09 package. Optimization, energy and thermodynamic calculations were conducted at the DFT/B3LYP/6-31⁺G(d) (6d, 7f) level of theory for all atoms in water. All calculations used the empirical dispersion GD3BJ level of theory and the SMD solvation model. The change in free energy ΔG of the 8 equations has been previously applied to various anti-cancer drugs. [Fong, 2023] The ΔG of the hydrated electron in water is -34.6 kcal/mol. [Zhan]

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