HIGH POTENCY EUGEROICS— WAKE-PROMOTING AGENTS BEYOND MODAFINIL

A Senior Project

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by

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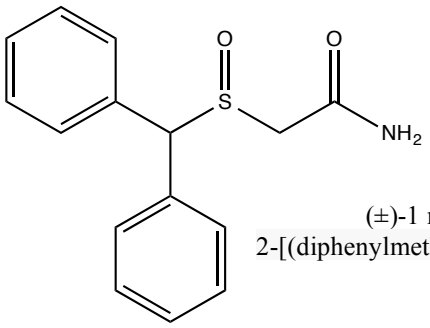
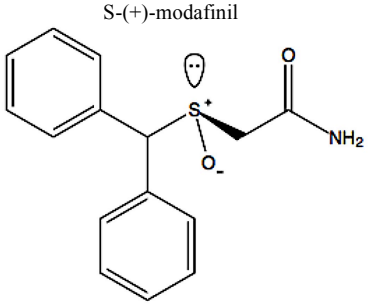
Modafinil (Provigil) belongs to a new pharmaceutical class known as eugeroics- translating to 'good arousal' agents. A distinct structure from classical psychostimulants, modafinil's unique pharmacological property demonstrates wake-promoting and neuroprotective effects. This literature review presents a hypothesized mechanism of action, consolidates research of modafinil analogues and hybridizes a novel compound in search of a next generation molecule.

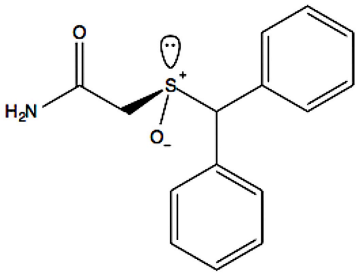


(±)-1 modafinil
2-[(diphenylmethyl)sulfinyl]acetamide

S-(+)-modafinil



R-(-)-modafinil



Modafinil (±)-1 contains an asymmetric sulfoxide moiety, where modest enantioselectivity is observed between R-(-)- and S-(+)-modafinil. Investigations into the pharmacokinetic profile of armodafinil confirmed enantioselectivity at DAT for the R- and S-enantiomers was three-fold (Cao et al. 2011) and increased metabolic stability, eliminated three-times more slowly than the S-enantiomer (Robertson et al. 2003). Cephalon Inc. has marketed the racemic sulfoxide, Provigil, since approval in 1998 for

narcolepsy. Expansion of its labeling from the initial indications, in 2004 modafinil was approved for treatment of excessive daytime sleepiness (EDS), obstructive sleep apnea/hypopnea syndrome (OSAHS) and shift-work sleep disorder (SWSD). With significance of these prescribing indications rapidly being eroded, the enantiopure R-(-)-isomer, armodafinil (Nuvigil), was approved in 2007 for the same indications. There is now consistent evidence that modafinil can improve prefrontal-dependent cognitive functions of healthy individuals in processes requiring cognitive control. Related neural circuitry and the remediation of cognitive dysfunction may form a basis of future clinical efficacy of this agent across many neuropsychiatric disorders (Minzenberg et al 2008).

With discovery of this novel pharmaceutical class, research into analogues of the chemical structure is current and widespread- in aims for clinical development of a more efficacious compound than the original FDA approved drug. Comparative pharmacological studies with modafinil, its enantiomers, and structural analogues have appeared in literature. Screenings of receptors and transporters in an attempt to elucidate its pharmacology frequently has centered on the indirect involvement of monoamine transporters: dopamine transporter (DAT), norepinephrine transporter (NET), serotonin transporter (SERT). With these suggested pharmacological targets, research into novel ligands pertaining to their potency and selectivity profiles has been quantified through structure activity relationship (SAR) studies.

Cephalon's numerous publications "Wake-promoting agents: Search for the Next Generation Modafinil" (Chatterjee et al. 2012) demonstrate they look to be streamlining the molecule as a lead compound. Selecting candidate compounds based on waking time in physiological assays and highest DAT selectivity indicates Chatterjee et al. are screening analogues for a more stimulating compound. Cephalon Inc. has since disclosed numerous publications of their work on lead modifications, creating biphenylic, tricyclic and aryl-heteroaryl modafinil derivatives. For the purpose of this paper, we will focus on a biphenyl derived wake-promoting agent. Maintaining the sulfinylacetamide moiety intact, Chatterjee et al., a Cephalon research group, rearranged the two phenyl rings of the parent molecule, generating a series of ortho-, meta- and para-oriented biphenyls. Ortho-substitution of aromatic rings in the parent compound displayed equal potency in wake-promoting activity of rats, whereas explored meta- and ortho-orientations yielded no additional benefit. P-halogen substitution increased activity in the order H < F < Br < Cl.

Chatterjee's publication "Search for the Next Generation Modafinil" part I selected a fairly promising successor to modafinil for further investigation in part II.
Referred to as 'Compound 2,' 2-{[2-(4-chlorophenyl)phenyl]methylsulfinyl}acetamide (figure 1) was assayed for transporter binding/uptake inhibition in rats (table 1). Racemic 'Compound 2' or (±)-2 displayed selectivity for DAT and NET, whereas SERT binding was unaltered- remaining negligible. Micromolar binding affinities of (±)-2 improved six-fold at both DAT and NET relative to (±)-modafinil. Results describe 'Compound 2' as a pure eugeroic with a long half life- in the modafinil range.

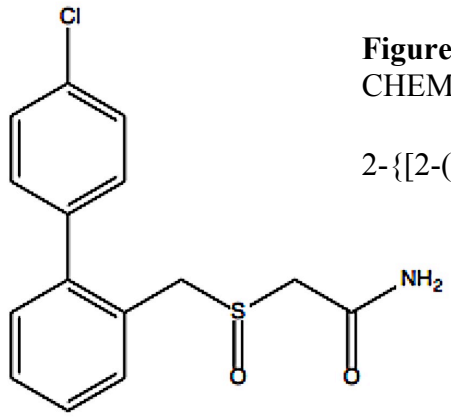


Figure 1- Compound 2
CHEMBL1956397

2-{[2-(4-chlorophenyl)phenyl]methylsulfinyl}acetamide

Table 1-

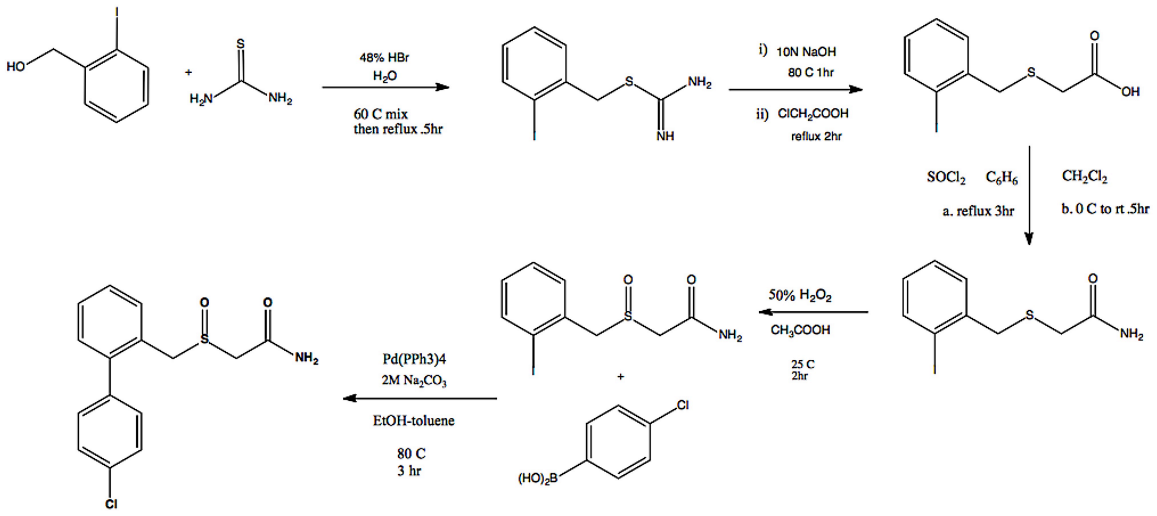
Transporter binding/uptake inhibition data for compounds (±)-1, (±)-2, (-)-2, and (+)-2

Assay (rat) 100mg/kg	Modafinil	(±)-2	(-)-2	(+)-2
DAT binding (IC_{50} µM)	3.70	0.6	0.40	4.20
NET binding (IC_{50} µM or % inhibition)	N/A	N/A	16%@10µM	12%@10µM
SERT binding (IC_{50} µM or % inhibition)	N/A	N/A	3%@10µM	4%@10µM
CYP2C19 (IC_{50} µM or % inhibition)	11	19	174	112
CYP3A4 (IC_{50} µM or % inhibition)	<10%@10 µM	<10%@10 µM	139	159
CYP2D6 (IC_{50} µM or % inhibition)	<10%@10 µM	<10%@10 µM	177	151
Rat waking time (min) over 4hr	*117± 13	*176± 4	238.5± 0.8	227.1± 7.8

* Data represents waking time over 3hr

Scheme 1-

Synthesis Route "Compound 2" as executed by Chatterjee et al.



The application of halogen substituents exist in many pharmaceuticals, however only recently has stabilizing interactions of halogen bonding been explored. (Xu et al. 2012). In a database survey, Xu et al. validate the contributions of halogen bonds to enhance drug-target binding affinity and selectivity. Halogenation has potential to improve ligand bioactivity in pharmacokinetics and pharmacodynamics (Xu et al. 2014). Wilcken et al. further revealed that, granted favorable orientation, a ligand's ability to form a halogen bond interaction at receptor target may result in an increase of affinity. Accordingly, fluoro- bromo- and chloro- substituted modafinil analogues have been reported as stimulating (De Risi et al. 2008). Previous studies lacking any binding assay have been substantiated by Cao et al. Synthesis of several aryl halide analogues elucidated para-halogen substitution at the diphenylmethyl moiety of racemic modafinil improves affinities selective for DAT over SERT and NET.

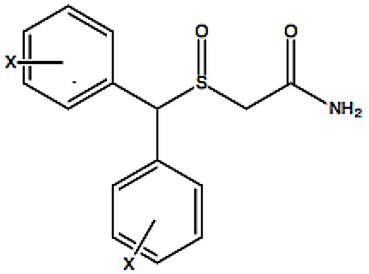


Table 2-

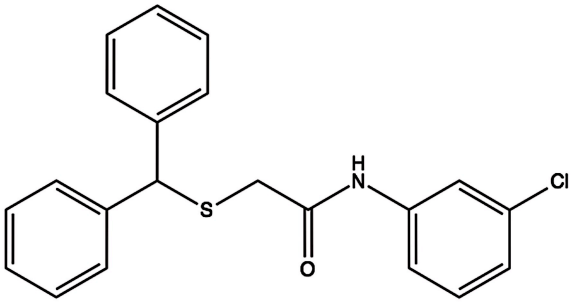
MAT Binding Data for Sulfinylacetamide Analogues (Cao et al. 2014)

	Substitution X, Y	K_i [SE interval or ± SEM] nM		
		DAT	SERT	NET
(±)-1 modafinil	H	2520 ± 204	ND/IA	ND/IA
S-(+)-1	H	7640 ± 395	ND/IA	ND/IA
R-(-)-1	H	3260 ± 195	ND/IA	ND/IA
5b	4,4'-di-F	2190 ± 139	ND	ND
5c	4,4'-di-Cl	919 ± 52.8	39000 ± 2410	ND
5d	4,4'-di-Br	600 ± 47.3	10600 ± 1110	ND
3b	3,3'-di-F	5930 [4990-7060]	IA	IA
3c	3,3'-di-Cl	881 [763-1020]	IA	IA
3d	H, 3-Br	550 [542-557]	IA	IA

IA = inactive, defined as <50% inhibition at 100 μM. ND = no displacement up to concentration 10 μM

China Pharmaceutical University research group, Zhu et al., synthesized a series of 2-[(diphenylmethyl)thio]acetamide and 2-[(diphenylmethyl)sulfinyl]acetamide (Modafinil) analogues with moiety alterations of the primary amide to various secondary amides. In a biological-activity assay, Zhu et al. measured "Inhibition rate of independent activity (after administration)", and after 3hr the control mice scored -50.4 and the modafinil mice scored 69.1 (Table 3). One of the analogues, “Compound 6h,” with a 3-chloroaniline attached at terminal amide beat modafinil at the 3-hour mark, scoring 81.5. Zhu's ‘Compound 6h’ looks to be fairly long half-lived, at least longer than modafinil, given marginal improvement was testing stimulant activity versus eugerocity.

Figure 3- Zhu 6h



2-[(diphenylmethyl)sulfinyl]-N-(3-chlorophenyl)acetamide

The 3-chloroaniline moiety, as a substituted amide, was only synthesized onto a 2-[(diphenylmethyl)thio]N-(3-chlorophenyl)acetamide. Zhu et al. did not substitute modafinil’s original sulfinylacetamide appendage with this 3-chloroaniline group. Work by Zhu et al. support a stimulatory influence of the sulfoxide through biological assay of novel modafinil derivatives. Identical moieties of Pyrrolidine and Piperdine were studied on both sulfinyl- and thio-acetamides, substituted as R-group to the terminal amide. Secondary amide substitution of Pyrrolidine and Piperdine are ‘6c’ and ‘6d’ respectively on a sulfinylacetamide, whereas Pyrrolidine and Piperdine are ‘6j’ and ‘6i’ coupled to a thioacetamide appendage (see table 3).

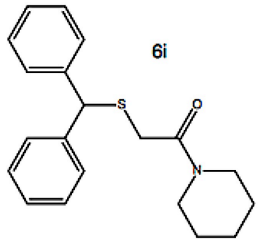
Behavioral responses indicate a marked increase in activity with each moiety attached to a sulfinylacetamide. Therefore, 2-[(diphenylmethyl)sulfinyl]-N-(3-chlorophenyl)-acetamide analogue would likely elicit an even stronger biological response than 'compound 6h.'

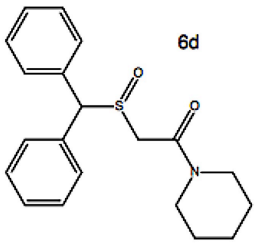
Table 3- Effect of target compounds on independent activities of mice

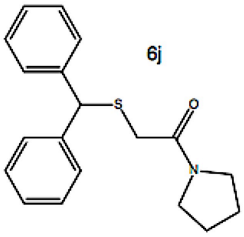
$$\text{Inhibition Rate of Independent Activity} = \frac{(\#\text{ of activities after administration} - \#\text{ of activities before administration})}{\text{Number of activities before administered}} \times 100\%$$

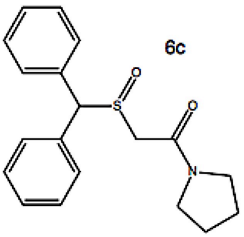
(n = 8 mice)

Compound	Inhibition Rate of Independent Activity (%)			
	30min	1 hr	2 hr	3 hr
Control	-16.5	-33.2	-45.8	-50.4
Modafinil	29.9	48.2	58.1	69.1
6h	30.6	68.9	69.4	81.5
6c	5.2	7.8	21.4	24.3
6d	-27.7	-31.6	-21.1	-27.8
6i	-18.8	-11.4	-39.3	-50.4
6j	-22.2	-36.4	-38.7	-54.2

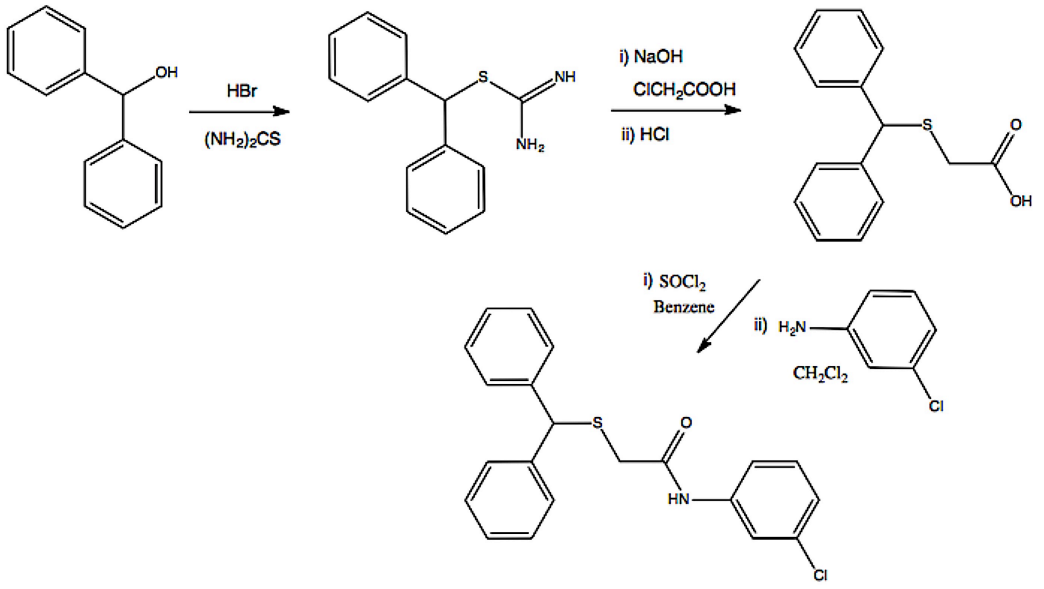




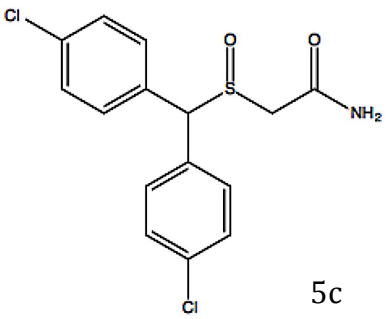




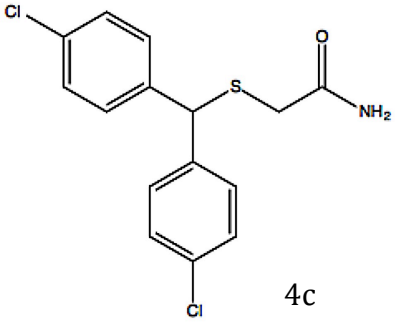
Scheme 3- Synthesis Route "Zhu 6h"



The increased stimulatory effect elicited by addition of S=O moiety is made intelligible through enhanced affinity for the DAT relative its thioether isostere. Cao et al. evaluated binding affinities of several novel analogues at the monoamine transporters (MATs) in rat brain membranes. Utilizing bioisosteric replacement of the sulfoxide with thioether, Cao et al. compared SARs of the sulfinylacetamide appendage to that of thioacetamide derivatives. Reducing the S=O to sulfur decreased DAT affinity five-fold, while binding at SERT was improved (Cao et al. 2014).



5c

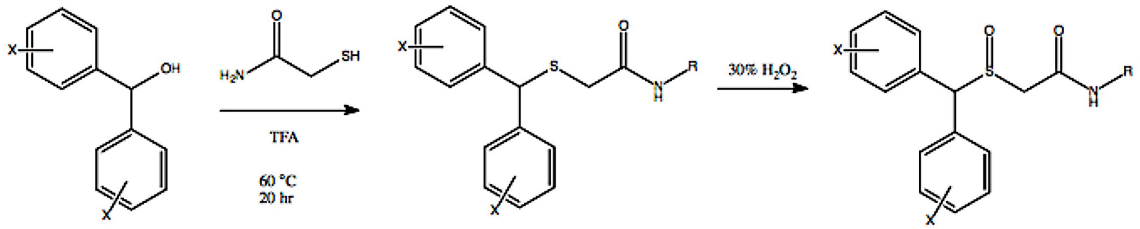


4c

MAT Binding Data for Sulfinylacetamide Analogues

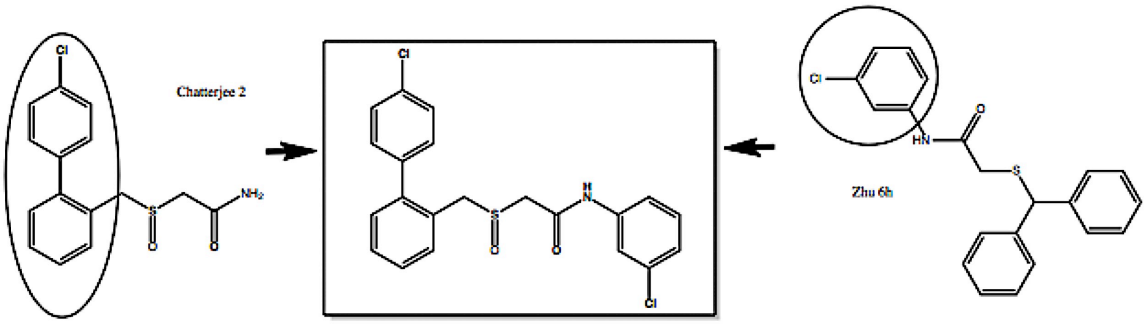
	K_i nM ± SEM		
	DAT	SERT	NET
4c	2230 ± 166	12700 ± 520	52100 ± 5510
5c	919 ± 52.8	39000 ± 2410	ND

Synthetic route (Cao et al. 2014)



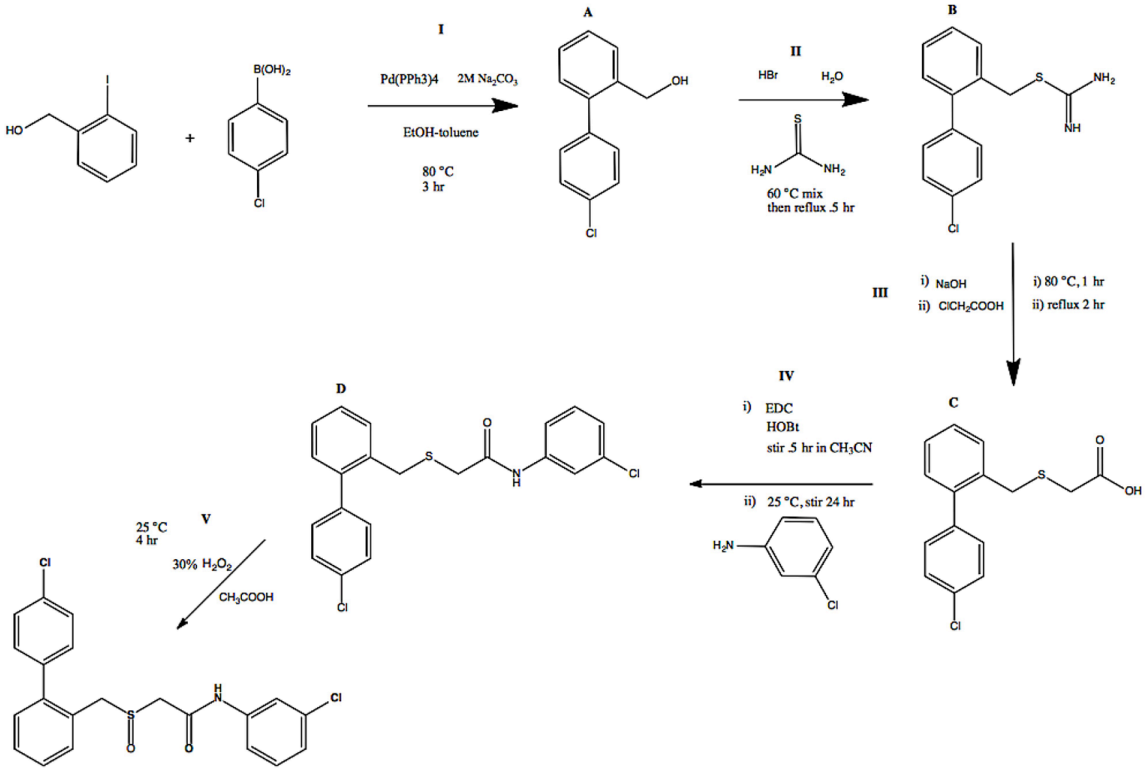
The S=O moiety was found to be optimal for DAT binding; further, this sulfoxide group significantly decreases binding at SERT relative its isostere, sulfur. Knowing the sulfoxide plays a key role in stimulating effects of modafinil and its analogues, its presence remains in this work's choice compound.

Compound 2 and Zhu 6h outlined in this paper, independently exhibit more selectively stimulatory pharmacological profiles than (±)-1 modafinil. Although potency does not always translate to efficacy, a successful modafinil analogue needs to be more selective, with less ancillary side effects. Seeing that the surface has barely been scratched on 2-substituted biphenyl modafinil derivatives, we hybridized Chatterjee et al. 'Compound 2' with Zhu et al. 'Compound 6h' and further expand the library of modafinil successors.



2-{[2-(4-chlorophenyl)phenyl]methylsulfinyl}-N-(3-chlorophenyl)acetamide

Theoretical synthesis scheme based on literature procedure:



Theoretical synthetic procedure:

I—

2-iodobenzyl alcohol (0.64mol, 150g) is coupled with 4-chlorophenyl boronic acid (0.64mol, 100g) in a vessel containing 2 equivalents of 2M sodium carbonate, solvent EtOH-toluene and the driving palladium catalyst Pd(PPh3)4. Raise temperature to 80 °C for 3hr to yield 2-[2-(4-chlorophenyl)phenyl]methanol **A**.

We assume 80% yield (111g, 51mol) **A** [Chatterjee et al. report 80% yield]

II—

To form the isothiouronium salt 2-[2-(4 chlorophenyl)phenyl]isothiouronium **B**, combine **A** (111g, 0.71mol) and thiourea (0.85mol, 65g) in 0.5L vessel with 325mL water. Heat mixture to 60 °C to obtain emulsion, then add 2.3 equivalents 48% HBr (130g, 1.6mol) gradually over 0.5 hr. Achieve reflux for .5 hr, then slowly cool to 25 °C. Filter product (crystals) and wash with water.

We assume 90% yield **(**176g, .64mol) **B** [achieved by similar reactions outlined in US Patent 6,649,796 and Chatterjee et al.]

III—

Hydrolysis of thiouronium salt to 2-[2-(4–Chlorophenyl)phenyl]methylthioacetamide **C**: To a vessel containing **B** (176g), water (600ml), add 2 equivalents 30% NaOH 100ml, 1.7 mol), heat reaction mixture to 80 °C and stir for 1 hr until a homogenous solution is achieved. Cool mildly and add chloroacetic acid (81g, 0.84 mol) in portions. Then reflux the suspension for 2 hr. Filter and wash with hot water.

We assume a 90% yeild (169g, 0.57mol) **C** [US Patent 6,649,796].

IV—

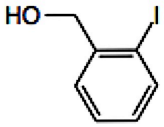
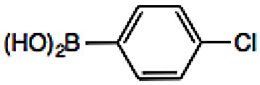
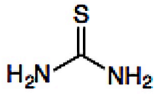
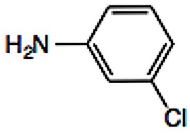
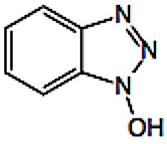
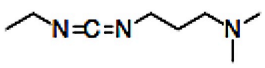
Stir mixture of **C** (169g, 0.57mol), EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) (89g, 0.57mol) and HOBt (hydroxybenzotriazole) (77g, 0.57mol) at 25 °C for .5 hr in acetonitrile solvent to activate acid. Next, add 3-chloroanaline (72.7g, 0.57mol) and stir for 24hours. Recrystallize with ethyl acetate to yield 158g, 0.39mol **D** 2-{[2-(4–Chlorophenyl)phenyl]methylthio}-N-(3-chlorophenyl)acetamide

[Lari et al. accomplish a 68% yield via this procedure].

V—

Oxidation of sulfur to sulfoxide. Dissolve **D** (150g, 0.38mol) in glacial acetic acid (610ml), then stir in 30% H2O2 (57mL) dropwise. Keep reaction stirring below 25 °C for 4 hrs; promptly wash with cold water. Note: oxidation reaction via H_2O_2 must remain cool and workup done soon thereafter, otherwise risk forming sulfone. Recrystallization via ethanol:water (3:1) [80% yield by both Mu et al. and Lari et al.] 129g, 0.3mol product 2-{[2-(4-chlorophenyl)phenyl]methylsulfinyl}-N-(3-chlorophenyl)acetamide.

List of reagents utilized in synthetic route:

Structure	Name	MW (g/mol)	Properties	Cost (USD) Sigma Aldrich
	2-iodobenzyl alcohol	234.03	m.p. = 89 - 92 °C	50g- 274.50
	4-chlorophenyl boronic acid	156.3	m.p. = 284-289 °C	25g- 197.50
	Thiourea	76.12	m.p. = 170-176 °C	100g- 35.10
	3-chloroaniline	127.57	m.p. = -10 °C b.p. = 95 - 96 °C ρ = 1.206g/ml	100g- 35.70
$Pd(PPh3)4$	Tetrakis (triphenylphosphine)Pd	1155.56		5g- 105.50
	HOBt	135.12	m.p. = 155-158 °C	25g- 53.00
$ClCH_2COOH$	chloroacetic acid	94.50	m.p. = 60 - 63 °C	1kg- 48.00
CH_3CN	acetonitrile	41.05	m.p. = -48 °C b.p. = 81 - 82 °C	1L- 108.50
CH_3COOH	acetic acid, glacial	60.05	d = 1.049 g/mL	1L- 112.00
Na_2CO_3	sodium carbonate	105.99	m.p. = 851 °C	500g- 72.20
H_2O_2	hydrogen peroxide	34.01		100mL- 42.60
	EDC	155.24	ρ = .877 g/mL	25g- 205.00
NaOH	sodium hydroxide	105.99	m.p. = 851 °C	500g- 91.60
HBr	hydrobromic acid	80.91	ρ = 1.49 g/mL	250mL- 32.80

Hypothesized Mechanism of Action:

Despite copious research publications, modafinil's mechanism of action (MoA) as-yet remains to be elucidated. Neurochemical substrates of modafinil currently uncovered include agonism at dopamine (D2) and alpha-1-adrenergic receptors. Directly enhancing conductance across neuronal membranes, modafinil, amplifies presynaptic Na/Ca influx; resultant widespread depolarization of cortical interneurons could theoretically allow transient, voltage-dependent inhibition of monoamine reuptake- resembling action of conventional stimulants, minus the stereotypy, euphoria, and locomotor effects.

Modafinil's direct dopaminergic inhibition is related to D2-receptor-activation, an action that remains independent of the adrenergic system. Investigating midbrain dopaminergic neurons in rat brain slices, Lin et al 2007, describe a novel agonistic action of modafinil on D2-like-receptors. Sulpride (D2 pre-synaptic antagonist), but not prazosin (α_1-AR antagonist) abolished modafinil-induced inhibition of dopaminergic neurons (Lin et al 2007). Furthermore, pre-treatment with the voltage-gated sodium channel blocker tetrodotoxin did not prevent reduction in firing rate in DA neurons, providing good evidence that this result was a consequence of a direct postsynaptic effect. Activation of D2-like receptors can be further attributed to the influence by which modafinil ameliorates serotonin (5-HT) exocytosis and attenuates gamma-aminobutyric acid (GABA) release. The excitatory function of D2 receptors increases serotonin release of dorsal raphe 5-HT neurons (Haj-Dahmane, 2007) and inhibits GABAergic tone in the striatum (Ferraro et al., 1998).

Next, we present a hypothesized MoA linking alpha-1-adrenergic receptor agonism to a theory of enhanced electrotonic coupling. In contrast to chemical synapses, groups of cortical neurons are electrically coupled, such that changes in membrane potential are rapidly communicated to adjacent cells. Gap junctions permit diffusion of current across linked cells, allowing more rapid membrane polarization. This enhanced conductance across membranes lowers electrical resistance of the neuronal network. Decreased electrical resistance of the network relative to an individual cell requires a larger current to reach a voltage sufficient to trigger action potentials (Siegel 2008). Knowing that tonic response of a nerve ending is typified by slow, continuous action over duration of stimulus, once an action potential does arise in cells connected by gap junctions, the entire populations tend to fire in a synchronized manner. Thus, enhanced electrotonic coupling results in lower tonic activity of the coupled cells while increasing rhythmicity of neuronal communication.

Beck et al. present data suggesting that modafinil acts by 'opening' gap junctions between neurons. This means increased permeability of membranes allows direct connection of the cytoplasm of two cells, hence ameliorating bidirectional diffusion of ion currents. Further, through measurements of the arousal-specific P13 evoked potential, Beck et al. suggest a direct link between electrotonic coupling and wakefulness as one mechanism by which modafinil increases arousal. Upon administration of modafinil to freely moving rats, amplitudes of P13 markedly increased; however, with pretreatment of the gap junction blocker, mefloquine, this effect was abolished (Beck et al. 2008). Interestingly, Urbano et al. independently demonstrated modafinil's mechanistic

mediation of gap junctions to be non-compete with mefloquine. After implementing mefloquine, irreversibly blocking gap junction protein (connexin) permeability, modafinil restored electrotonic coupling within 30 minutes of administration.

Urbano et al. determined that modafinil increases electrical coupling between cortical interneurons implemented through a Ca^{2+}/calmodulin protein kinase II-dependent step. In vitro treatment of KN-93, a calcium/calmodulin dependent protein kinase II (CaMKII) inhibitor, abolished modafinil's enhancement of electrotonic coupling (Urbano 2007). Acting from intracellular side, CaMKII is shown to potentiate channel activity (Dietrich 2007). This enhanced ionic current through pours that link adjacent cells amplifies Na/Ca influx, leading to widespread depolarization. Therefore, modafinil could modulate exocytosis of gap junctions via a Ca^{2+}/calmodulin dependent enzyme.

Interestingly, this theoretical reuptake-inhibition/release mechanism- that does not involve specific binding sites at the transporter molecules- would be similar to that of hyperforin, a major constituent chemical in St John's Wort. Broad-spectrum reuptake inhibition of monoamines via presynaptic TRPC6 activation induces influx of Na^{+}, Ca^{2+} and effectively elevates intracellular concentrations (Leuner et al 2007; Zanoli 2004). Widespread depolarization of cortical interneurons, consistent with hypothesized mechanisms of modafinil and hyperforin, throws into stark relief a transient, voltage-dependent inhibition of monoamine re-uptake.

Transient receptor potential channel, TRPC6, is a non-selective cation channel, which as

demonstrated by Dietrich et al, exhibits nearly coequal electrophysiological properties to adrenergic non-specific cation channels, α1-AR-NSCC. Expressed in the brain and smooth muscle tissue, Ca^{2+} permeable TRPC6 currents are activated by α_1-AR stimulation (Dietrich et al 2007). In the manner that Urbano et al. displayed CaMKII inhibition to abolish modafinil's enhancement of electrotonic coupling, inhibition of Ca^{2+}/Calmodulin-dependent protein kinase II was further extended to an inhibitory effect on TRPC6. Boulay et al. showed the calmodulin inhibitor, calmidazolium, abolished calcium influx into TRPC6 cells. Action of calmidazolium inhibits calmodulin-dependent phosphodiesterase, which alludes to a hypothesis by Shi et al.- TRPC6 activation involves phosphorylation by CaMKII.

Modafinil's capacity to modulate gap junction through a Ca^{2+}/calmodulin dependent enzyme can be further extrapolated as a downstream effect of TRPC6 channel activation. Subsequent research by Dietrich et al. pertaining to potentiating action of Ca^{2+} on TRPC6 and α_1-AR–NSCC strongly suggests TRPC6 protein may be an essential molecular component of α_1-adrenoceptors. Stone et al. observed marked attenuation of behavioral activation caused by modafinil from either pharmacological blockade or genetic ablation of alpha1-adrenoceptors (α_1-AR). Therefore, central a_1-adrenergic tone being indispensable of the manifestation of the stimulant or waking effects of modafinil relates theory of enhanced conductance to noradrenergic transmission.

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