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SARs at the Monoamine Transporters for a Novel Series of Modafinil Analogues

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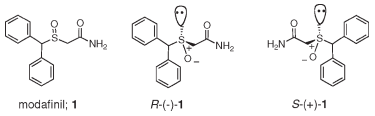
ABSTRACT A series of modafinil (**1**) analogues were synthesized wherein (1) *para*-halo-substitutents were added to the aryl rings, (2) the sulfoxide function was removed, and (3) the primary amide group was replaced with secondary and tertiary amides and amines to investigate the effects of these chemical modifications on dopamine transporter, serotonin transporter, and norepinephrine transporter binding. In addition, the locomotor-stimulant effects in mice of (±)-modafinil (**1**), its *R*- and *S*-enantiomers, and its *para*-chloro sulfinylacetamide analogue (**5c**) were compared to those of cocaine.

KEYWORDS SAR, monoamine transporters, modafinil analogues



Modafinil {(±)**1**, 2-[(diphenylmethyl)sulfinyl]acetamide} is used clinically as a wake-promoting agent for the treatment of narcolepsy and other sleep disorders.[1] Modafinil has been described as a psychostimulant but does not appear to be amphetamine-like in either pharmacological profile or mechanism of action[2] and, as such, has piqued interest for the treatment of cognitive dysfunction in disorders such as attention deficit hyperactivity disorder.[1,2] Recently, modafinil has also attracted attention for the treatment of cocaine[3,4] and methamphetamine dependence.[5] In addition, the emerging emphasis on cognitive impairment in neuropsychiatric disorders, including addiction, has stimulated investigations into the potential pro-cognitive effects of modafinil.[6,7]

The mechanisms of action by which modafinil produces its wake-promoting and psychostimulant effects appear to be complex and have not been clearly delineated. Several studies suggest that modafinil modulates the activity of hypocretin, histamine, α-adrenergic, γ-aminobutyric acid (GABA), and/or glutamate receptors.[1,8] Moreover, modafinil has been shown to bind the dopamine transporter (DAT) and block dopamine reuptake both in vitro and in vivo, although with low affinity as compared to cocaine.[9−11] Recently, studies in human subjects, using positron emission tomography (PET),[12] show modafinil binding to the DAT, leading to speculation that modafinil may have abuse potential. However, results of animal studies have been equivocal[13−16] with at least one study of human stimulant abusers reporting cocaine-like effects of modafinil,[17] whereas most studies indicate a low liability for abuse.[18]

Modafinil is structurally dissimilar to stimulant drugs, such as methamphetamine, and contains an asymmetric sulfoxide group (Figure 1). It was originally prescribed clinically as the racemate (Provigil), as both isomers were presumed to contribute to its pharmacological effects.[19] However, more recent studies suggest that *R*-(−)-modafinil is the more metabolically stable and longer-acting enantiomer [Armodafinil; *R*-(−)-**1**].[20−22] Comparative pharmacological studies with modafinil, its enantiomers, and structural analogues have not appeared in the literature nor have detailed structure−activity relationship (SAR) studies at any of the suggested pharmacological targets. Therefore, in the present study, we synthesized the *R*- and *S*-enantiomers of modafinil and several sets of structural analogues and compared their binding affinities at the monoamine transporters: DAT, serotonin (SERT), and norepinephrine (NET). We first synthesized *para*-halo-substituted analogues, as the F- and Cl-substituted benztropine [3α-(diphenylmethoxy)tropane] analogues, which also have a biphenyl structural motif, show higher affinity at the DAT than the unsubstituted parent compound.[23] In addition, several F and Cl analogues of modafinil have been reported to be "stimulating", although no binding data were reported.[24,25] Furthermore, the optimal S-oxidation state for monoamine transporter binding had not been described, although replacement of this function with a carbonyl group has been reported.[24] Finally, modification of the terminal amide through substitution and/or reduction to the amine is reported herein. In addition to the synthesis and in vitro binding profiles of the resulting novel compounds, we report for the first time comparative behavioral effects of (±)-, *R*-(−)-, and *S*-(+)-modafinil to cocaine.

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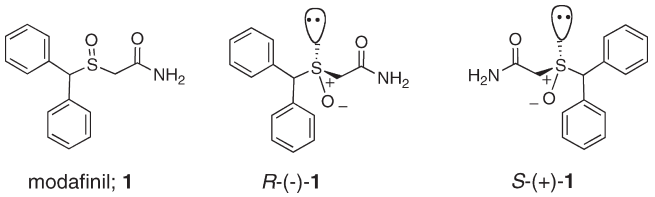
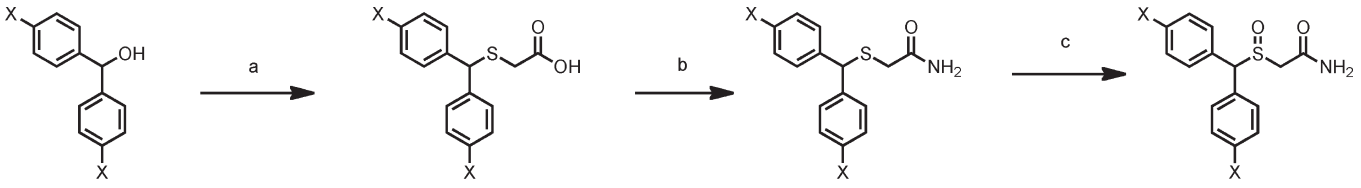


Figure 1. Racemic modafinil and its enantiomers.

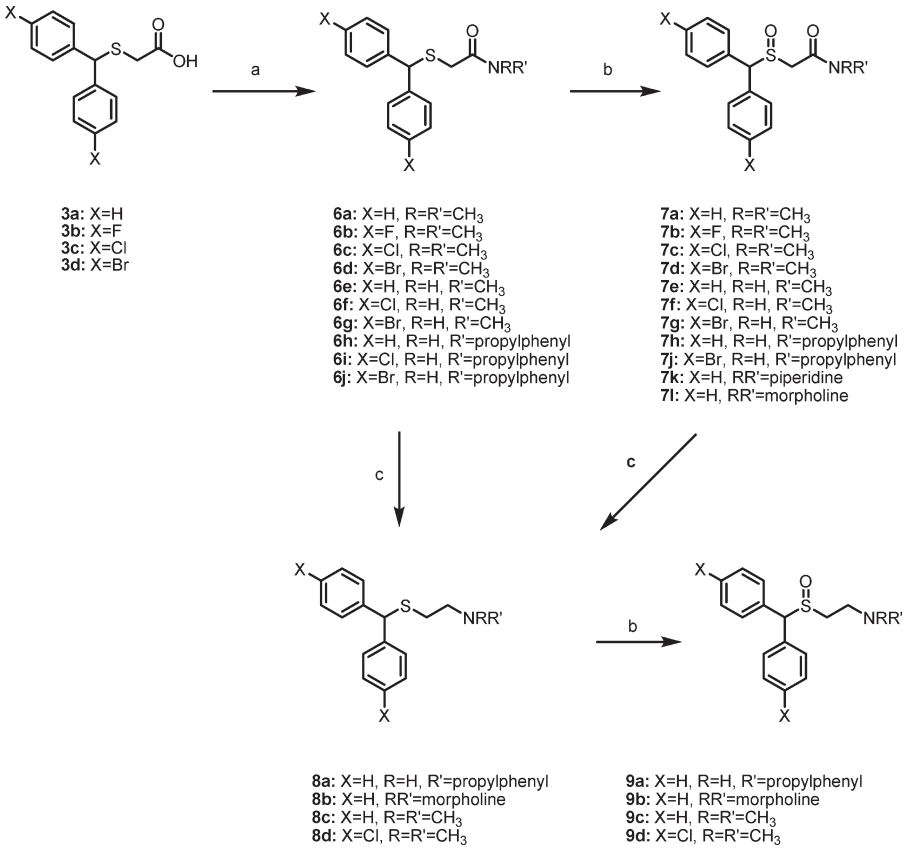
R-(−)- and *S*-(+)-modafinil enantiomers were synthesized according to the literature procedure,[26] with minor modifications described in the Experimental Section in the Supporting Information. Synthesis of novel *para*-halo-substituted sulfinylacetamide **5b**−**d** was achieved as depicted in Scheme 1. Dihalophenylmethanols **2b**−**d** were coupled with thioglycolic acid in trifluoroacetic acid followed by esterification of the resulting carboxylic acids **3b**−**d**. The esters

Scheme 1. Synthesis of Modafinil Analogues[a]



[a] Reagents and conditions: (a) Thioglycolic acid (1 equiv), TFA, room temperature, overnight. (b) i) CH_3I, K_2CO_3, acetone, reflux, 4 h; (ii) NH_4OH, NH_4Cl, MeOH, 50 °C, 72 h. (c) H_2O_2 (30%), AcOH:MeOH (1:3), 40 °C, 24 h.

Scheme 2. Synthesis of Modafinil Analogues[a]



[a] Reagents and conditions: (a) (i) CDI, THF, room temperature, 2 h; (ii) HNRR′, THF, room temperature, overnight. (b) H_2O_2 (30%), AcOH:MeOH (1:3), 40 °C, 24 h. (c) $LiAlH_4$, H_2SO_4, THF.

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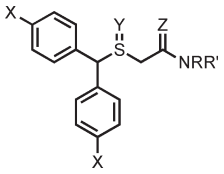
Table 1. Binding Data for Modafinil Analogues[a]



		K_i (nM) ± SEM		
compound	substitution X, Y, Z, R, R′	DAT	SERT	NET
(±)-**1**	H, O, O, H, H	2520 ± 204	ND	ND
(+)-**1**	H, O, O, H, H	7640 ± 395	ND	ND
(−)-**1**	H, O, O, H, H	3260 ± 195	ND	ND
4b	F, −, O, H, H	1570 ± 68.2	ND	ND
4c	Cl, −, O, H, H	2230 ± 166	12700 ± 520	52100 ± 5510
4d	Br, −, O, H, H	1930 ± 95.2	2200 ± 278	77700 ± 6610
5b	F, O, O, H, H	2190 ± 139	ND	ND
5c	Cl, O, O, H, H	919 ± 52.8	39000 ± 2410	ND
5d	Br, O, O, H, H	600 ± 47.3	10600 ± 1110	ND
6a	H, −, O, Me, Me	16500 ± 2360	ND	ND
6b	F, −, O, Me, Me	9510 ± 960	25900 ± 1040	ND
6c	Cl, −, O, Me, Me	4510 ± 332	5980 ± 197	42500 ± 7950
6d	Br, −, O, Me, Me	2450 ± 374	3210 ± 442	19200 ± 2760
7a	H, O, O, Me, Me	ND	ND	ND
7b	F, O, O, Me, Me	ND	16200 ± 760	ND
7c	Cl, O, O, Me, Me	34600 ± 3600	22300 ± 1890	ND
7d	Br, O, O, Me, Me	21300 ± 2930	14200 ± 1740	ND
7f	Cl, O, O, Me, H	2440 ± 323	ND	ND
7g	Br, O, O, Me, H	1650 ± 124	33200 ± 4380	ND
7h	H, O, O, H, prPh	2660 ± 122	ND	ND
7k	H, O, O, $-(CH_2)_4-$	ND	ND	ND
9a	H, O, H, H, prPh	194 ± 16.8	1000 ± 120	2350 ± 267
9b	H, O, H, morph	ND	ND	ND
9c	H, O, H, Me, Me	ND	45800 ± 6740	ND
9d	Cl, O, H, Me, Me	2890 ± 344	406 ± 18.7	36200 ± 3590
cocaine		71.8 ± 4.6[b]	286 ± 38[c]	3300 ± 170[c]

[a] Each K_i value represents data from at least three independent experiments, each performed in triplicate. K_i values were analyzed by PRISM. [b] Binding methods were conducted as previously reported.[27] [c] Previously reported.[28] ND, no displacement up to a concentration of 10 μM.

were then subjected to aminolysis to obtain the thioacetamides **4b**−**d** in 62−92% yield. Oxidation of the thioether was achieved using hydrogen peroxide (30%) in an acetic acid−methanol solution to give sulfinylacetamides **5b**−**d** in 66−76% yield.

The N-substituted sulfinylacetamides **7a**−**l** were obtained by (1) amidation of carboxylic acids **3a**−**d** using the respective amines and CDI to obtain amides **6a**−**j** followed by (2) oxidation of the thioether moiety to give the desired **7a**−**l** as shown in Scheme 2. N-Substituted sulfinylethanamines **9a**−**d** were obtained by the reduction of **6h**, **7l**, **7a**, and **6c**, respectively, using alane in 64−89% yield to give **8a**−**d**, followed by oxidation of the thioether moiety as described in Scheme 1 in 60−76% yield.

In this study, we synthesized a series of (±)-modafinil analogues wherein (1) *para*-halo-substitutents were added to the aryl rings, (2) the sulfoxide function was removed, and (3) the primary amide group was replaced with secondary and tertiary amides and amines according to synthetic strategies outlined in Schemes 1 and 2. The amino analogues were also designed to improve water solubility, through the formation of salts, as the parent compound is poorly water-soluble. All final compounds were evaluated for binding at the DAT, NET, and SERT in rat brain membranes, using methods previously described.[27] These results can be found in Table 1.

Only modest enantioselectivity was observed for the *R*-(−)- and *S*-(+)-modafinil, at the DAT, with the *R*-(−)-enantiomer having slightly higher affinity than the *S*. All analogues were racemic mixtures, and none showed comparable binding affinities to cocaine (K_i = 71.8 nM) for the DAT, although several showed higher affinity than the parent

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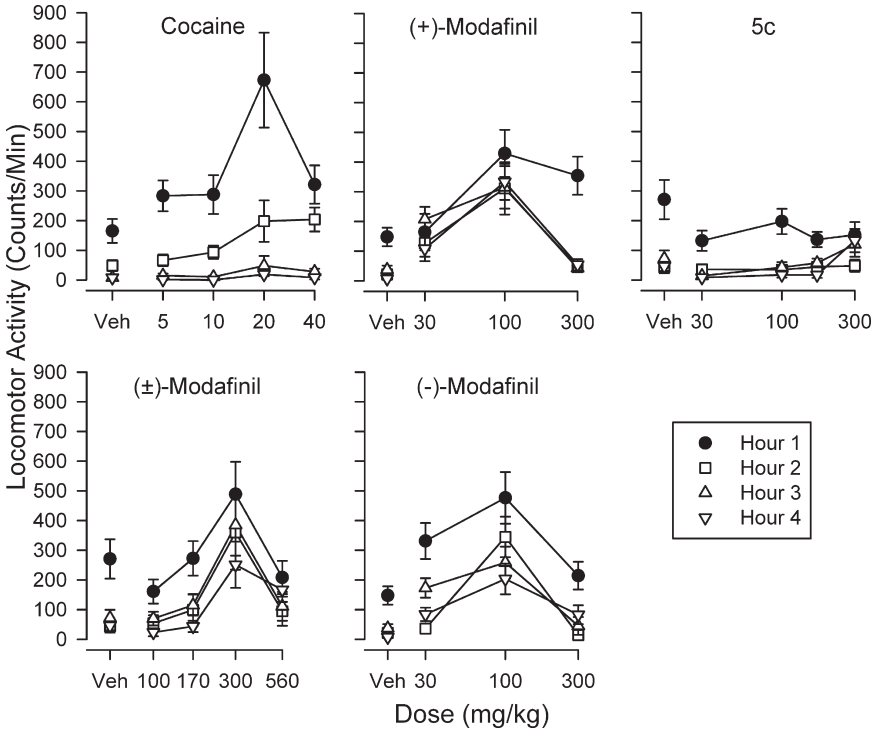

Figure 2. Dose-dependent effects of (±)-**1**, its enantiomers *R*-**1** and *S*-**1**, and **5c** on locomotor activity in mice. Ordinates: horizontal locomotor activity counts after drug administration in counts per min. Abscissae: dose of drug in mg/kg, log scale. Each point represents the average effect determined in six mice. The data are from the 30 min period at the start of each of 4 h after drug administration. Note that neither (±)-modafinil, its enantiomers, or the analogue produced a maximal stimulation of activity that was equivalent to that of cocaine and that compound **5c** only had effects in the third and fourth hour after its administration at the highest dose tested.

compound. The S═O motif appears to be optimal for DAT binding, except when the terminal amide is substituted, for example, $N(CH_3)_2$, although reducing the sulfoxide did not decrease binding affinities appreciably. Interestingly, with the exception of **4b**−**d**, DAT binding affinity typically increased in each series with halogen substitution at the *para*-position of both rings in the order: H ≤ F < Cl < Br, in contrast to the comparably substituted analogues in the benztropine series, which also bind to the DAT. In that series, the order of affinities is Br < H < Cl < F.[29]

Tertiary amides among modafinil analogues were typically less well-tolerated at the DAT, while the amines showed higher binding affinities than the amide analogues, especially the *N*-propylphenyl analogue (**9a**), which was the most potent DAT analogue in the series. Most of compounds were less or inactive at SERT and NET, except the single SERT-selective compound, **9d**.

Several of the compounds were evaluated for locomotor stimulant activity, using methods previously described.[30] Each of the drugs studied increased locomotor activity in mice at some time after their injection (Figure 2). The maximal effects of cocaine were greatest among the drugs and were substantially diminished 1 h after injection and absent thereafter. (±)-Modafinil and the *R*-(−)- and *S*-(+)-enantiomers also increased locomotor activity, although less so than cocaine. In addition, the decreases with time after injection were less pronounced and evident up to 4 h after injection. In contrast, the *para*-chlorosulfinylacetamide analogue **5c** had no effects immediately after injection or in the second hour after injection. However, in the third and fourth hours, a modest stimulant effect was evident at the highest dose studied.

In summary, a series of modafinil analogues have been synthesized and evaluated for binding at DAT, NET, and SERT. SARs suggest binding interactions at the DAT that appear to contrast to the benztropine analogues, which also have a biphenyl structural motif. Studies of locomotor activity in mice suggest behavioral stimulant effects, although the effectiveness of the drugs studied was less than that of cocaine but greater than that of many benztropine analogues (see ref 30 for comparison). The results of the present studies warrant further investigation of these and other modafinil analogues in additional animal models of psychostimulant abuse.

SUPPORTING INFORMATION AVAILABLE

Experimental section. This material is available free of charge via the Internet at http://pubs.acs.org.

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