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Wake-promoting agents: Search for next generation modafinil: Part I

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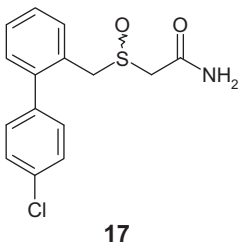
ABSTRACT

In search of a next generation molecule to the novel wake promoting agent modafinil, a series of bi-phenyl derived wakefulness enhancing agents (in rat) was developed. From this work, compound **17** has been selected for additional studies.

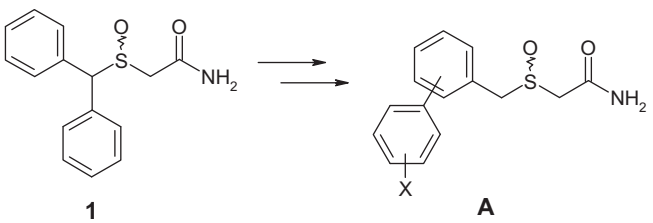


17

Disorders of 'wakefulness', including states of impaired alertness, vigilance and attention affect millions of individuals. Relatively few pharmacotherapies are available to treat such symptoms. Stimulants (caffeine, amphetamine and methylphenidate) are among the main pharmacological interventions that can improve or enhance waking but suffer from various limiting side effects. Modafinil (compound **1**, Fig. 1), a novel agent, pharmacologically distinct from classical stimulants, improves wakefulness in a variety of species and is efficacious in humans with few peripheral or central side effects.[1] While the precise mode of action of modafinil has yet to be well-defined, mechanistic studies frequently have centered on the involvement of dopamine transporter (DAT) and norepinephrine transporter (NET) as either causal or indirect contributors to modafinil's wake promoting pharmacology.[2–4]

While modafinil continues to be evaluated in a variety of expanded clinical applications, a few aspects of its overall profile have served as the cornerstone for efforts to identify a follow-on molecule. Modafinil demonstrates modest inhibition of CYP 2C19 (IC_{50} = 11 μM) but shows virtually no interaction with CYP 3A4 and CYP 2D6. Since clinical studies demonstrated that human plasma concentrations can reach levels greater than 30 μM at efficacious dose, the potential for drug–drug interactions is possible which will become important as modafinil is used as an adjunctive therapy in many patients with psychiatric and/or neurological disorders. In addition, it was anticipated that a follow-on molecule from a different chemical class with modafinil-like (or better) profile, distinct from classical psychostimulants, might shed more light in elucidating the mechanism of action of modafinil and wake promoting mechanisms in general, especially contributory roles played by various transporters.

Scheme 1 depicts the general synthetic scheme that was utilized to generate the target compounds. Coupling of compounds **2** and **3** in acidic media generated compound **4** that on basic hydro-



1 **A**

Figure 1. Chemical structures of modafinil and new generation of wake-promoting agents.

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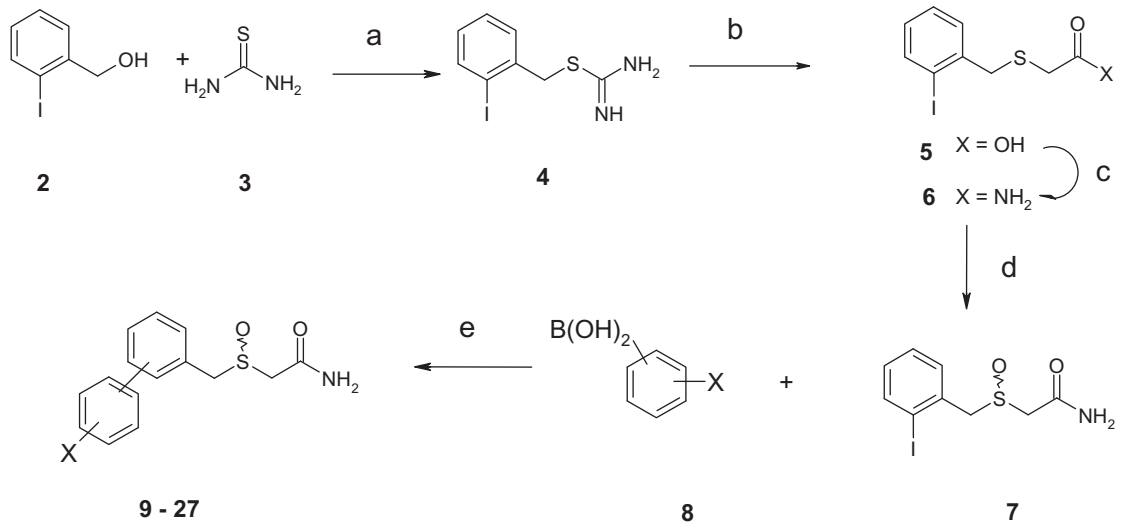


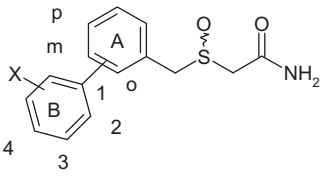
Scheme 1. Reagents and conditions: (a) 48% HBr, H_2O, mixing at 60 °C followed by reflux, 0.5 h, 90%; (b) (i) 10 N NaOH, 80 °C, 1 h; (ii) $ClCH_2COOH$, reflux, 2 h, 80% over two steps; (c) (i) $SOCl_2$, C_6H_6, reflux, 3 h; (ii) 28% NH_4OH, CH_2Cl_2, 0 °C to rt 0.5 h 70% over two steps; (d) 50% H_2O_2, gl. acetic acid, rt, 2 h, 90%; (e) Tetrakis (triphenylphosphine)Pd, 2 M Na_2CO_3, EtOH–toluene, 80 °C, 1–3 h, 60–80%.

lysis followed by treatment with chloroacetic acid generated carboxylic acid **5** that in turn was converted to amide **6**. Controlled oxidation of compound **6** generated corresponding racemic sulfinyl compound **7**. Suzuki coupling between compound **7** and various commercially available boronic acids **8** yielded target compounds **9**–**27**.

At the outset of our synthetic program, no well-defined molecular target(s)[4b,c] and no historical database of modafinil's wake promotion structure–activity relationships existed in the literature.[5] Thus the members of the new series were initially evaluated for their brain permeability in rat PK studies (data not shown). Subsequently, their cumulative wake-promoting activity in rat (i.e., total time (minutes) awake over a period of 3 h after dosing (3 h AUC) at 100 mg/kg ip) compared to modafinil was utilized as the principal parameter in generating an in vivo SAR correlation (Table 1).[6]

As mentioned previously, at the outset of our synthetic program, no known molecular target describing modafinil-SAR existed in literature. Thus exploration began with the rearrangement of two phenyl rings of the parent molecule maintaining the sufinylacetamide moiety, thought to be unique for a CNS drug, intact. Thus, a series of bi-phenyls (*ortho*-, *meta*- and *para*-orientations) were generated (structure **A**, Fig. 1). As shown in Table 1, in *ortho*-series the parent compound **9** displayed equal activity to compound **1** while substitution at the 2-position of ring B diminished wake-promoting activity (cf. compound **1** vs compounds **10**, **11** and **12**). On the other hand, while a cyano group and a carboxamide group at position-3 of ring B (compounds **13** and **14**) were detrimental, chlorine at the same position was beneficial (cf. compound **15** vs compound **12**). Substitution at 4-position of ring B with halogens (compounds **16**, **17** and **18**), methyl (compound **19**) and trifluoromethoxy (compound **20**) were tolerated but an acetyl group (compound **21**) and a cyano group (compound **22**) were not tolerated. Effect of *meta*- and *para*-orientations of two phenyl groups were explored in compounds **23**–**27**, but without any additional advantage. Two SAR trends in Table 1 are worth noting. In *ortho*-bi-phenyl series, a chlorine dance in ring B, going from position 2 (compound **12**) to position 3 (compound **15**) to position 4 (compound **17**) made a significant improvement in activity. On the other hand, maintaining the 4-chloro substitution fixed in ring B, the orientation of two phenyl rings going from *ortho*- (compound **17**) to *meta*- (compound **25**) to *para*-(compound **27**) had a detrimental effect on activity.

Table 1
Structure–activity relationship of new analogs



9 - 27

Compound	Orientation of phenyl rings	X	Rat wake 3 h AUC minutes[a]
1 (modafinil)	—	—	117 ± 13*
9	*o*-	H	119 ± 14*
10	*o*-	2-F	64
11	*o*-	2-OMe	86 ± 13
12	*o*-	2-Cl	49 ± 10.6
13	*o*-	3-CN	99 ± 20
14	*o*-	3-CONH2	62 ± 8
15	*o*-	3-Cl	106 ± 14*
16	*o*-	4-F	147 ± 11*
17	*o*-	4-Cl	176 ± 4*
18	*o*-	4-Br	174 ± 4*
19	*o*-	4-Me	146 ± 2*
20	*o*-	4-OCF_3	108 ± 22
21	*o*-	4-COMe	77 ± 5
22	*o*-	4-CN	65 ± 8
23	*m*-	H	NT[b]
24	*m*-	2-Me	117 ± 11*
25	*m*-	4-Cl	96 ± 11*
26	*p*-	H	100 ± 6
27	*p*-	4-Cl	92 ± 17
Vehicle[c]	—	—	65 ± 9

[a] Mean ± SEM.
[b] Not tested.
[c] Average of vehicle group: mean and SEM values ($N = 11$) for compounds shown.
* $P < 0.05$ versus within-experiment vehicle.

Based on its superior activity versus modafinil in the rat wake promotion assay, compound **17** was selected for further profiling. Table 2 displays a selected set of data for both compounds. While

Table 2
Selected comparative profile of compound **17** versus compound **1**

Assay	**1**	**17**
Solubility: μg/mL at pH 7.4	>100	>100
Human S9 metabolism (% parent remaining at 2 h)	77	94
DAT binding/DAT uptake inhibition (rat IC_{50} μM)	3.7/4.3	0.6/0.83
NET/SERT uptake inhibition (rat IC_{50} μM)	63.9/>300	10/>300
CYP 3A4/2D6 inhibition at 10 μM	<10%	<10%
CYP 2C19 inhibition (IC_{50} μM)	11	19
Mini-Ames	Clean	Clean
hERG (% inhibition at 10 μM)	Not tested	Clean
Wake promotion in rat (100 mg/kg, ip)	Active	Active

both displays acceptable level of water solubility, compound **17** was metabolically more stable than compound **1** in a human liver S9 metabolism assay. Compound **17** appeared to be more potent than compound **1** both in DAT binding and DAT reuptake inhibition assays (rat). However, it is not known how this will translate in human. While both compounds displayed low activity in SERT uptake inhibition assay, compound **17** was slightly more potent in the NET uptake inhibition assay. While both compounds did not display liability in CYP 3A4 and 2D6 assays, compound **17** was ca. twofold less potent in 2C19 assay. Compound **17** did not display any liability either in mini-Ames or hERG inhibition assay. In rat wake promotion assay, compound **17** also displayed potency via oral route (data not shown). Accordingly, compound **17** was selected for additional in vivo behavioral profiling and was also selected for separation into its corresponding enantiomers and profiling of each isomer individually.

In this Letter, we disclosed a series of bi-phenyl derived wakefulness promoting agents (in rat) in search of a next generation molecule to modafinil. From this work racemate compound **17** emerged as a lead molecule. This compound was selected for chiral separation into corresponding enantiomers to profile each isomer individually. Outcome of that research will be the subject of a future publication.

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References and notes

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6. *Experimental protocol for wake promotion study.* Adult, male Sprague Dawley rats were used. Room lights were on from 7 AM to 7 PM. Test compounds were administered in 0.5% methylcellulose/0.2% tween-80 in distilled water, pH 6.2 at 5 ml/kg IP. Sleep/wake data was recorded and scored according to methods described by Edgar and Seidel,[7] Opp and Krueger,[8] and Scammell et al.[9] Cortical EEG and neck EMG activity were recorded differentially using screw electrodes over the frontal cortex (+3.0 mm AP from bregma, ±2.0 mm mediolateral) and hippocampus (−4.0 mm AP from bregma, ±2.5 mm mediolateral). Electrodes were chronically implanted in rats under Nembutal anesthesia. The day before recording, rats were placed in individual containers (31 × 31 × 31 cm) in sound-attenuating cabinets and connected by cables to the recording equipment. Food and water were available ad libitum. Each cabinet contained a fan, a light (12 h light/12 h dark cycle), and a speaker to provide background noise. EEG and EMG signals were amplified (10 and 1 K, respectively) and band pass filtered between 0.3 and 500 Hz for EEG and between 10 and 500 Hz for EMG. These signals were digitized at 128 samples per second using ICELUS sleep scoring software (M. Opp). Animals were dosed at 1 PM (5 h after lights on, CT-5) by IP injection, which produces a brief awakening.
Data Analysis. Approximately 30–60 min of EEG/EMG data prior to dosing was scored manually into wake, slow-wave sleep (SWS), and REM sleep (REMS) stages using 6 s epochs based on published criteria. The remainder of the data was scored with an autoscoring algorithm utilizing parameters optimized to match manually scored data. The primary outcome measures were cumulative time awake for 3 h after dosing (3 h AUC).
Statistical analysis. Values are listed as mean of data from at least three animals. Treatment effects were evaluated using ANOVA. Treatment group comparisons were made using unpaired, two-tailed *t*-tests or Dunnett's *t*-test for multiple comparisons as appropriate. Statistical comparisons were made against vehicle-treated animals in the same experiment.
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