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

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ABSTRACT

In search of a next generation molecule to modafinil, a novel wake promoting agent, we previously disclosed bi-phenyl derived racemate compound (±)-**2** as a new generation of wake-promoting agent. Here we describe the profiles of the individual enantiomers (−)-**2** and (+)-**2**, respectively.

Disorders of 'wakefulness' or vigilance affect millions of individuals. 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 defined, mechanistic studies frequently have centered on the involvement of the dopamine transporter (DAT) as well as the norepinephrine (NET) and serotonin (SERT) transporters as either causal or indirect contributors to modafinil's wake promoting pharmacology.[2–4] Recently, we disclosed bi-phenyl derived racemate compound **2** as a new generation of wake-promoting agent (Fig. 1).[5] Subsequently, the research team separated the enantiomers of compound **2** to profile them individually. Herein we disclose some preliminary results from our ongoing investigation.

Scheme 1 depicts the synthetic scheme that was utilized to generate compound **2**. Coupling of commercially available compounds **3** and **4** in acidic media generated compound **5** that, on basic hydrolysis followed by treatment with chloroacetic acid, generated carboxylic acid **6** that in turn was converted to amide **7**. Controlled oxidation of compound **7** generated corresponding racemic sulfinyl compound **8**. Suzuki coupling between compound **8** and commercially available boronic acid **9** yielded target racemic compound **2** that was separated by chiral HPLC to generate individual enantiomers (−)-**2** (eluting as the first peak) and (+)-**2** (eluting as the second peak).[6,7]

Due to the implication of involvement of various transporters in the mechanism of action of modafinil in recent literature, each enantiomer was profiled in both transporter binding and uptake inhibition assays. Results are shown in Table 1.

In parallel, both compounds were profiled in various CYP450 isoform inhibition assays to get a sense of their potential liability issues in a clinical setting. Results are shown in Table 2.

In order to investigate their wake promotion activity in a rodent species, both enantiomers were evaluated for their brain permeability in rat PK studies (data not shown). Subsequently cumulative wake-promoting activity in rat [i.e., total time (minutes) awake over a period of 4 h after dosing (4 h AUC) at 100 mg/kg ip] was determined (Table 3) following previously disclosed procedure.[5]

As shown in Table 1, the enantiomers behave differently both in the DAT binding and uptake inhibition assays (rat) indicating the role chirality plays in this class of molecules for binding to this transporter. While both enantiomers displayed some level of activity in NET uptake inhibition assay, they lacked activity in SERT uptake inhibition assay. Currently, the relative contribution of DAT and NET in the biological activity of these molecules is not known (vide infra).

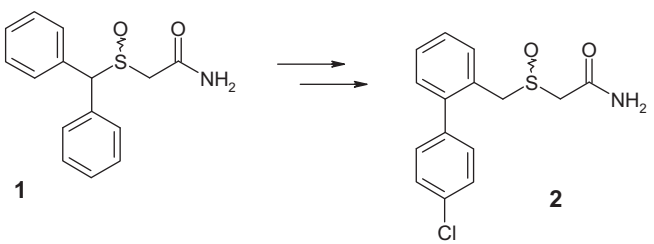

Figure 1. Evolution of compound **2**.

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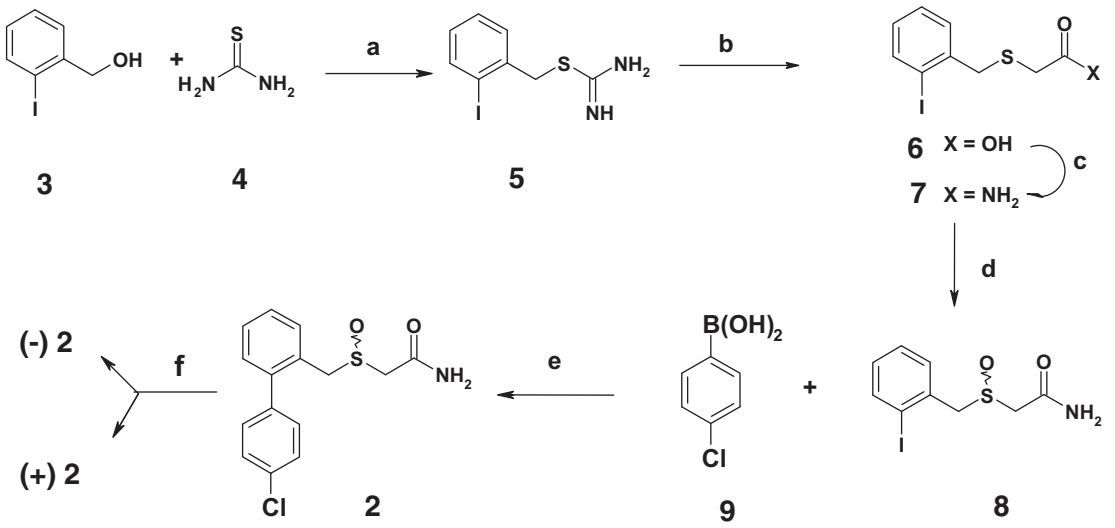

Scheme 1. Reagents and conditions: (a) 48% HBr, H_2O, mixing at 60 °C followed by reflux, 0.5 h, 90%; (b) (i) 10 N NaOH, 80 °C, 1 h; (ii) $ClCH_2COOH$, reflux, 2 h, 80% over two steps; (c) (i) $SOCl_2$, C_6H_6, reflux, 3 h; (ii) 28% NH_4OH, CH_2Cl_2, 0 °C to rt 0.5 h 70% over two steps; (d) 50% H_2O_2, gl. acetic acid, room temp, 2 h, 90%; (e) tetrakis (triphenylphosphine)Pd, 2 M Na_2CO_3, EtOH–toluene, 80 °C, 3 h, 80%; (f) HPLC-separation utilizing chiral AS column eluting with CH_3CN.

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

Assay	1	(±)-2	(−)-2	(+)-2
DAT binding, (rat IC_{50} μM)	3.7[a]	0.6[a]	0.4	4.2
DAT uptake inhibition (rat IC_{50} μM)	4.3[a]	0.83[a]	0.6	3.8
NET binding, (rat% inhibition)	NA[b]	NA[b]	16% at 10 μM	12% at 10 μM
NET uptake inhibition (rat IC_{50} μM)	63.9[a]	10[a]	11	32
SERT binding, (rat% inhibition)	NA[b]	NA[b]	3% at 10 μM	4% at 10 μM
SERT uptake inhibition (rat IC_{50} μM)	>300[a]	>300[a]	>300	>300

[a] From Ref. 5.
[b] Not available.

Table 2
CYP450 Inhibition data (human microsome) for compounds 1, (±) 2, (−) 2 and (+) 2.

Assay	1 (IC_{50} μM)	(±)-2 (IC_{50} μM)	(−)-2 (IC_{50} μM)	(+)-2 (IC_{50} μM)
2C19	11[a]	19[a]	174	112
3A4/5	<10% @10 μM[a]	<10% @10 μM[a]	139	159
2D6	<10% @10 μM[a]	<10% @10 μM[a]	177	151
2C9	NA[b]	NA[b]	233	129
1A1/2	NA[b]	NA[b]	14% at 100 μM	20% at 100 μM

[a] From Ref. 5.
[b] Not available.

Table 3
Wake promoting activity of compounds 1, (±)-2, (−)-2 and (+)-2.

Compound	Rat wake 4 h AUC Minutes[a]
1[b]	117 ± 13*
(±)-**2**[b]	176 ± 4*
(−)-**2**	238.5 ± 0.8*
(+)-**2**	227.1 ± 7.8*
Vehicle[c]	79.2 ± 7.2

[a] Mean ± SEM; *$P < 0.05$ versus vehicle.
[b] Data represents 3 h AUC (minutes).[5]
[c] Average of vehicle group: $N = 3$–4 per group.

Table 2 displays activity of the enantiomers against various CYP450 isoforms, indicating drug–drug interaction in a clinical setting might not be a potential issue for the pair.

In the rat wake promotion assay (Table 3), both compounds displayed activity. Detailed mechanistic studies will be needed to answer to the question of relative contributions of the transporters in explaining their individual activity.[8] Each enantiomer is currently being evaluated in various behavioral assays.

In conclusion, in this Letter we disclosed various characteristics of the enantiomers of racemate compound **2** from our ongoing studies in order to identify a next generation molecule to the novel wake promoting agent modafinil. Both compounds are currently being evaluated in various behavioral assays, results of which will be the subject of future publications.

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6. Physical properties: (−) **2**: mp 175–176 °C; optical rotation: $[\alpha]_D^{20}$ −69° (*c* = 0.3% MeOH). (+) **2**: mp 175–176 °C; optical rotation: $[\alpha]_D^{20}$ +69° (*c* = 0.3% MeOH).
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