European Journal of Medicinal Chemistry 54 (2012) 949–951

Contents lists available at SciVerse ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Preliminary communication

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

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ARTICLE INFO

Article history:
Received 17 March 2012
Received in revised form
27 May 2012
Accepted 29 May 2012
Available online 8 June 2012

Keywords:
Wake-promoting agents
Modafinil
Diphenylether

ABSTRACT

In search of a next generation molecule to the novel wake promoting agent modafinil, a series of diphenyl ether derived wakefulness enhancing agents (in rat) was developed. From this work, racemic compound **16** was separated into its chiral enantiomers to profile them individually.

1. Introduction

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) as well as norepinephrine transporter (NET) as either causal or indirect contributors to modafinil's wake promoting pharmacology [2–4].

While modainil 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 CYP2C19 ($IC_{50} = 11$ μM) but shows virtually no interaction with CYP3A4 and CYP2D6. 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 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. In this regard, our laboratories explored a series of diphenyl ether derivatives, exemplified by generic structure **2** (Fig. 1). Herein, a preliminary communication of this effort has been disclosed.

2. Results

2.1. Chemistry

Scheme 1 depicts a representative synthetic scheme that was utilized to generate a series of ortho analogs **11**–**19** (Table 1) [5]. Coupling of commercially available compounds **3** and **4** generated ether derivative **5** that was reduced to corresponding alcohol **6**. Coupling of compound **6** and thiourea in acidic medium generated compound **7**. Compound **7** on basic hydrolysis followed by treatment with chloroacetic acid generated carboxylic acid **8** that in turn, via compound **9**, was converted to amide **10**. Controlled oxidation of compound **10** generated corresponding racemic

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http://dx.doi.org/10.1016/j.ejmech.2012.05.038

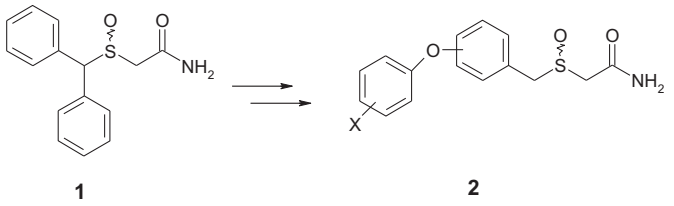


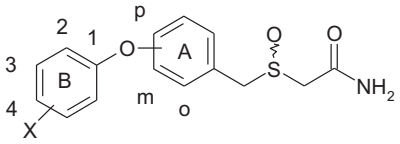
Fig. 1. Chemical structures of compound **1** and new generation of wake-promoting agents **2**.

sulfinyl compounds **11**–**19**. Racemic compound **16** was separated into corresponding enantiomers employing chiral-HPLC with **(−)-16** eluting first followed by **(+)-16**.

2.2. Biological activity

At the outset of our synthetic program, no well-defined molecular target(s) [4] and no historical database of modafinil's wake promotion structure–activity relationships existed in the literature. Thus the members of the new series were initially evaluated for their brain permeability in rat PK studies. Subsequently, following a disclosed experimental protocol [6], 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 displays the biological data for a subset of compounds from the series as well as data for reference compound **1**.

Table 1
Biological data of compounds.

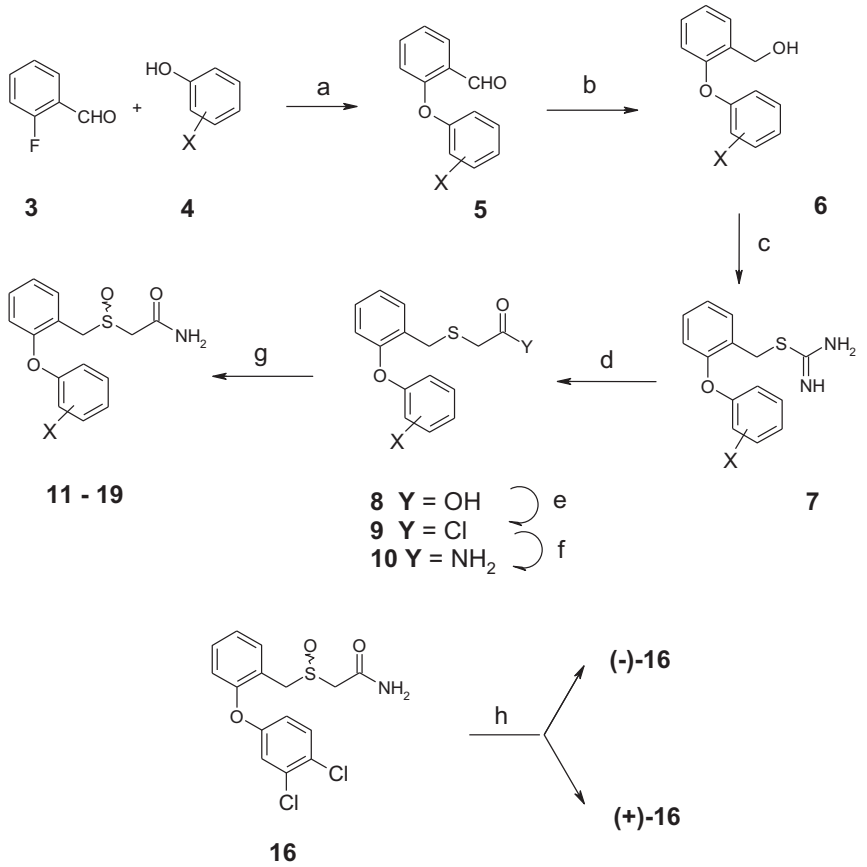


Compound	Confign. of rings	X	Rat wake 3 h AUC (minutes[a])
1	–	–	117 ± 13*
11	ortho	4-F	123 ± 8**
12	ortho	4-Cl	165 ± 5***
13	ortho	2,3-Cl_2	120 ± 9**
14	ortho	2,4-Cl_2	74 ± 16
15	ortho	3,5-Cl_2	117 ± 8*
16	ortho	3,4-Cl_2	180 ± 0.3***
17	ortho	3-Cl,4-F	160 ± 11***
18	ortho	3-F,4-Cl	176 ± 4***
19	ortho	2-Naphthyl	131 ± 11 *
20	para	3,4-Cl_2	88 ± 3
Vehicle[b]	–	–	65 ± 9

[a] Mean ± SEM; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, vs. within-experiment vehicle.
[b] Average of vehicle group: Mean and SEM values ($N = 11$) for compounds shown.

3. Discussion

As mentioned previously, at the outset of our synthetic program, a specific molecular target entirely responsible for modafinil-SAR was unknown. Thus exploration began with the rearrangement of two



Scheme 1. Synthesis of compounds **11**–**19** and chiral separation of racemate compound **16**. *Reagents and conditions*: a. Cs_2CO_3, DMF, heat to reflux, 3–5 h, 60–70%; b. $NaBH_4$, isopropanol, room temp., overnight, 70–80%; c. 48% HBr, H_2O, mixing at 60 °C, thiourea, followed by reflux, 0.5 h, 75–80%; d. (i) 10 N NaOH, 80 °C, 1h; (ii) $ClCH_2COOH$, reflux, 2h, 70–80% over two steps; e. $SOCl_2$, 2–3 h; f. 28% NH4OH, MeOH, room temp, overnight, 60–70 % over two steps; g. 30% H_2O_2, gl. acetic acid, room temp., 1–2 h, 80–85%; h. HPLC-separation utilizing chiral AS column eluting with EtOH–MeOH (1:1).

Table 2
Transporter binding/uptake inhibition data for compounds **1**, **(−)-16** and **(+)-16**.

Assay	**1**	**(−)-16**	**(+)-16**
DAT binding, (rat IC_{50} μM)	3.70[a]	0.20	0.90
DAT uptake inhibition (rat IC_{50} μM)	4.30[a]	1.10	1.10
NET binding, (rat % inhibition @10 μM)	NA[b]	48	39
NET uptake inhibition (rat IC_{50} μM)	63.90[a]	1.30	3.10
SERT binding, (rat % inhibition @10 μM)	NA[b]	30	24
SERT uptake inhibition (rat IC_{50} μM)	>300[a]	31	33

[a] Ref. 1.
[b] Not available.

Table 3
CYP450 inhibition data (human microsome) for compounds **1**, **(−)-16** and **(+)-16**.

Assay	**1** IC_{50} μM	**(−)-16** IC_{50} μM	**(+)-16** IC_{50} μM
2C19	11[a]	30	20
3A4/5	<10% @10 μM[a]	40	32
2D6	<10% @10 μM[a]	106	89
2C9	NA[b]	216	2443
1A1/2	NA[b]	10% @100 μM	18% @100 μM

[a] Ref. 1.
[b] Not available.

phenyl rings of the parent molecule maintaining the sufinylacetamide moiety, thought to be unique for a CNS drug. In the current series, they were attached by an ether linkage. A major effort was expended in generating several ortho analogs (vide infra). As shown in Table 1, compound **11** containing a 4-F substitution in ring B, maintained the activity of reference compound **1**. Replacement of fluorine atom in compound **11** with chlorine atom produced compound **12** that displayed superior activity compared to compound **1**. In a series of dichloro substituted ring B derivatives, while 2,3- (compound **13**), 2,4- (compound **14**) and 3,5- (compound **15**) substitution were not beneficial, 3,4- substitution (compound **16**) produced superior activity. Returning to the theme of 3,4-disubstition in ring B, replacement of a chlorine atom with a fluorine atom generated a pair of regioisomers, compounds **17** and **18** that maintained the superior activity. In a similar way, replacement of 3,4-dichlorophenoxy moiety (ring B) with an isosteric 2-naphthyl group generated compound **19** maintaining the superior activity compared to compound **1**. However, going from ortho-orientation to para-orientation of two rings resulted in loss of activity (cf. compound **16** vs. compound **20**). This observation prevented us to generate corresponding meta-isomer.

Based on its superior activity vs. modafinil in the rat wake promotion assay, representative compound **16** was selected for chiral separation into enantiomers **(−)-16** and **(+)-16**. Absolute configuration of either enantiomer is currently unknown; efforts are underway to determine.

As shown in Table 2, the enantiomers differentiated in the DAT binding assay (rat), **(−)-16** being ca. five-fold more potent than **(+)-16** indicating the role of chirality on binding. However, in DAT uptake inhibition assay (rat), they displayed equal activity. It is difficult to predict how this will manifest in a clinical setting. While both enantiomers displayed a low level of activity in NET binding assay (rat), in NET uptake inhibition assay, both displayed some level of activity. However, both displayed low level of activity in SERT binding as well as uptake inhibition assay (rat).

Table 4
Wake promoting activity of compounds **1**, **(−)-16** and **(+)-16**.

Compound	Rat wake 3 h AUC Minutes[a]
1	117 ± 13*
(−)-16	168 ± 7.8
(+)-16	167 ± 0.9*
Vehicle[b]	79.2 ± 7.2

[a] Mean ± SEM; $^{*}P < 0.05$, $^{**}P < 0.001$ vs. vehicle, unpaired *t*-test.
[b] Average of vehicle group: $N = 3–4$ per group.

Table 3 indicates that both **(−)-16** and **(+)-16** exhibit better 2C19 profile than compound **1** as well as low levels of activity against several other CYP450 isoforms, indicating drug–drug interactions in a clinical setting might not be a potential issue for the pair.

In the rat wake promotion assay (Table 4), both **(−)-16** and **(+)-16** displayed similar activity. Detailed mechanistic studies will be needed to answer to the question of relative contributions of the transporters in explaining their individual activity. Each enantiomer is currently being evaluated in several behavioral assays.

4. Conclusion

In this Communication, we disclosed a series of diphenyl ether derived wakefulness promoting agents (in rat). From this research, racemic compound **16** emerged as a lead molecule and was separated into enantiomers **(−)-16** and **(+)-16**. Each enantiomer is currently being evaluated in several behavioral assays.

Acknowledgment

Authors wish to acknowledge the scientific support and encouragement of Drs. Donna Bozyczko-Coyne, John P. Mallamo and Jeffry L. Vaught during the course of this research. Authors sincerely thank all the reviewers for their constructive criticism and valuable suggestions to improve the quality of the manuscript.

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