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# Efficient synthesis and biological evaluation of two modafinil analogues

Carmela De Risi [a,*], Luca Ferraro [b], Gian P. Pollini [a], Sergio Tanganelli [b], Filippo Valente [a], Augusto C. Veronese [a]

[a] Dipartimento di Scienze Farmaceutiche, Via Fossato di Mortara 19, 44100 Ferrara, Italy
[b] Dipartimento di Medicina Clinica e Sperimentale, Sezione di Farmacologia, Via Fossato di Mortara 19, 44100 Ferrara, Italy

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ABSTRACT

Non classical bioisosters of modafinil featuring interesting biological profile have been easily produced through replacement of the sulfoxide function with a carbonyl group and modification of the carboxylic acid amide functionality.



## 1. Introduction

Modafinil, 2-[(diphenylmethyl)sulfinyl]acetamide [Provigil] (±)-**1**, Adrafinil, 2-[(diphenylmethyl)sulfinyl]-*N*-hydroxyacetamide [Olmifon] (±)-**2**, the hydroxamic acid derivative of modafinil (Fig. 1) and Armodafinil [Nuvigil], the *R*-enantiomer of modafinil, are among the most widely used and most effective pharmaceutical agents for the treatment of excessive sleepiness caused by narcolepsy, shift work sleep disorder and obstructive sleep apnea.[1–3]

Modafinil has a complex and still uncertain mode of action and is theorized to work in a localized manner, utilizing hypocretin, histamine, epinephrine, γ-aminobutyric acid, and glutamate.[2] Moreover, modafinil has a postulated large potential for many uses in psychiatry and general medicine. Recent work suggests that modafinil might also be of utility in the treatment of attention deficit/hyperactivity disorder (ADHD),[4] and in treating opioid-induced sedation.[5]

Although modafinil contains an asymmetric sulfoxide functional group, the racemic sulfoxide has been marketed in the United States by Cephalon as Provigil[6] since its approval in 1998.

In June 2007, Armodafinil, the *R*-enantiomer of modafinil, was approved by US Food and Drug Administration for the same indications.

Modafinil and its chemical predecessor adrafinil have been firstly prepared by the procedure patented by L. Lafon[7] and later reported by Mu et al.[8]

A facile preparation of both racemic modafinil and its achiral oxidized derivative 2-[(diphenylmethyl)sulfonyl]acetamide has been recently described.[9]

Interestingly, owing to the uncomplicated chemistry involved, a microscale synthesis of racemic modafinil has been described as an instructive experiment for undergraduate students, keeping them surely awake![10]

The limited data available in the public domain on armodafinil, with particular regard to chemistry, have been recently enriched by a paper describing the investigations that led to the development of the commercial route providing the chiral sulfoxide.[11]

The importance of studying the biological activity of each enantiomer stimulated efforts to obtain the two enantiomers of modafinil. Among the reported methods,[12–15] the microbial oxidation/amidation of benzhydrylsulfanyl acetic acid was a very interesting approach.[14] The two operations, namely a highly enantioselective oxidation of benzhydrylsulfanyl acetic acid to the corresponding (*S*)-sulfinyl carboxylic acid and the subsequent amidation were achieved in very good yield employing the fungus *Beauveria bassiana* and the bacteria *Bacillus subtilis,* respectively.

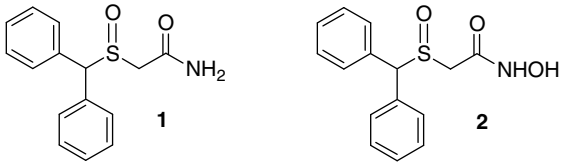


**Figure 1.** Chemical structures of Modafinil (1) and Adrafinil (2).

* Corresponding author. Tel.: +39 0532 455922; fax: +39 0532 455953.
*E-mail address:* drc@unife.it (C. De Risi).

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Studies related to the anticonvulsant properties of modafinil and its sulfone derivative led to discover that the oxidized derivative of modafinil is also non-toxic and almost as effective as an anticonvulsant as the parent compound.[9]

These data seem to indicate that the oxidation state at sulphur atom is not essential, the sulfone moiety being as important as the sulfoxide. Moreover, modafinil analogs have been prepared introducing different substituents (*e.g.* F, Cl, Br, $CF_3$, $NO_2$, $NH_2$, alkyl and alkyloxy with 1 to 4 carbon atom chain length) into both aromatic rings or modifying the primary amide moiety not only as the hydroxamic acid **2** but also as secondary or tertiary amide function bearing different alkyl residues.

The known modafinil analogs **1**–**9** featuring modifications on both the phenyl groups and the carboxamide function act on CNS either as stimulating or sedative agents,[16] as summarized in the following Table 1.

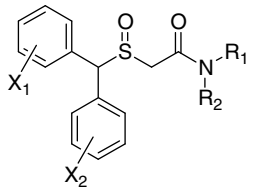
Our continuous interest in the field,[17] prompted us to explore the effect of replacement of the sulfoxide function in **1** with a carbonyl group, which represents a common isosteric replacement.[18] This choice favoured a functional group that could be introduced in a straightforward way with concomitant removal of problems associated with sulphur chirality.

The bioisosterism represents a successful strategy in rational drug design,[19] useful in the molecular modification and design of new therapeutically attractive substances of different pharmacological classes. Nonclassical bioisosteres do not obey the strict steric and electronic definition of classical isosteres and they do not have the same number of atoms as the substituent moiety for which they are used as a replacement. These isosteres are capable of maintaining similar biological activity by mimicking the spatial arrangement, electronic properties, or some other physicochemical property of the molecule or functional group that is critical for the retention of biological activity. Moreover, replacement of a group with a bioisostere frequently results in a new compound that retains the activity of the parent one. Thus, this approach is common in the pharmaceutical industry, since it allows to generate marketable analogues of a known drug that has a patentable composition of matter.

The preparation of modafinil analogues as those described in this paper is lead by the increasing interest in study the pharmacological behaviour of modafinil isomers and their implicancies in other diseases.

In particular, we were interested in the evaluation of the effects of modafinil analogues on the spontaneous and the electrically-evoked tritiated serotonin ([$^3$H]5-HT) efflux from rat cortical slices, in order to preliminary compare their biological activity with that displayed by the parent compound. In fact, it has been reported that modafinil (0.3–30 μM) increased electrically-evoked, but not spontaneous, serotonin ([$^3$H]5-HT) efflux from cortical slices in a concentration-dependent manner.[20]

**Table 1**
Activity of known modafinil analogs on CNS




| Entry | $X_1$ | $X_2$ | $NR_1R_2$ | Action on CNS |
|---|---|---|---|---|
| **1** | H | H | $NHCH_3$ | Stimulating |
| **2** | H | H | $NHCH(CH_3)_2$ | Stimulating |
| **3** | H | H | $NHC(CH_3)_3$ | Stimulating |
| **4** | H | H | $NHCH_2CH_3$ | Sedative |
| **5** | H | H | Piperidine | Sedative |
| **6** | H | H | Morfoline | Sedative |
| **7** | 4-Cl | H | $NH_2$ | Stimulating |
| **8** | 4-F | 4-F | $NH_2$ | Stimulating |
| **9** | 4-F | H | $NH_2$ | Stimulating |

## 2. Results and discussion

### 2.1. Chemistry

Among the existing methodologies for preparing 3-oxobutanoate derivatives we investigated the Blaise reaction[21] and the Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) acylation[22] starting from commercially available materials such as diphenylacetonitrile **3** or diphenylacetic acid **7** as summarized in Scheme 1.

In both cases, the starting materials required a two-carbon elongation to install the desired carbon chain length.

The protocol based on Blaise reaction involved the reaction of cyanide **3** with a twofold molar excess of ethyl bromoacetate in the presence of activated zinc dust in refluxing tetrahydrofuran to yield the corresponding β-enamino ester **4** in 90% isolated yield. Subsequent acid hydrolysis afforded the β-ketoester **5** in essentially quantitative yield as a rather unstable oil. This could be also obtained through a modified protocol for performing the Blaise reaction,[23] involving *in situ* zinc activation in the presence of catalytic methanesulfonic acid followed by acid hydrolysis of the intermediate β-enamino ester **4**.

The alternative approach entailed on the use of the acyl-Meldrum derivative **10**, which was obtained through triethylamine-mediated reaction between Meldrum's acid **9** and diphenylacetic acid chloride **8**.

Alternatively, preparation of the intermediate **10** could be achieved through a one-step procedure by reaction of **9** with diphenylacetic acid **7** activated with *N,N'*-dicyclohexylcarbodiimide (DCC),[24,25] providing an enhanced yield and purity of the desired compound.

Treatment of β-ketoester **5** with methanolic ammonia at 0 °C resulted in a clean formation of compound **6** in 54% yield, while reaction of the acyl-Meldrum derivative **10** with the same ammonia source in different experimental conditions (from 0 to 100 °C in sealed glass tube) proved unsuccessful, mainly decomposition of the starting material being observed.

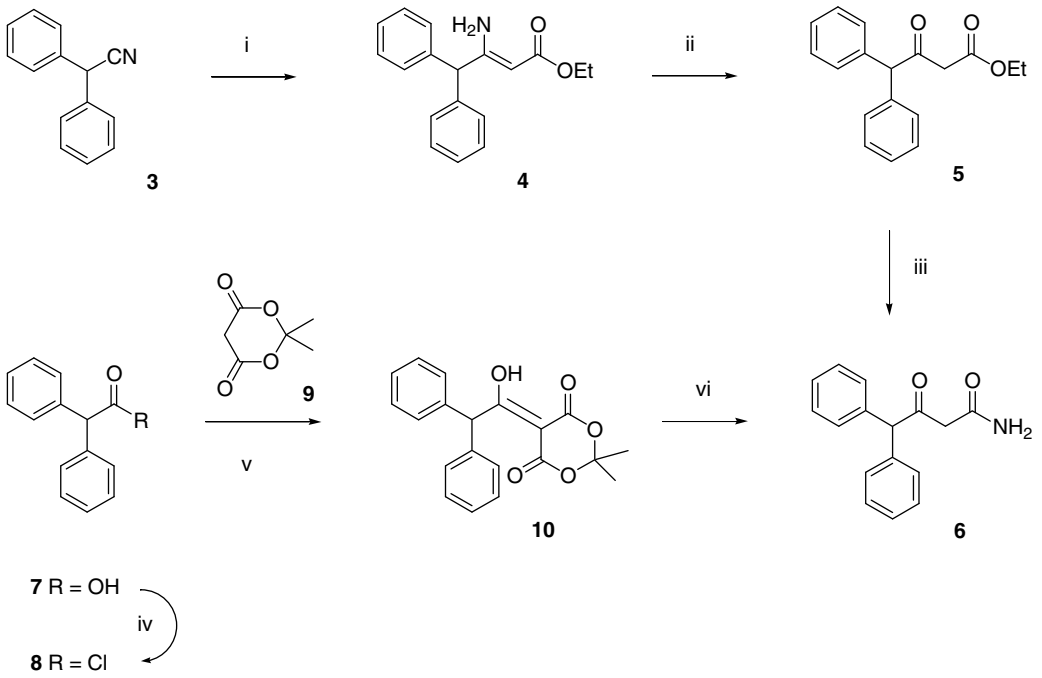
The formation of a salt between ammonia and the completely enolized **10** may likely account for the difficulties encountered in this operation, as previously observed in the literature.[26]

However, amide formation was eventually achieved in 49% yield by treatment of a $CH_3CN$ solution of **10** with an ammonia gas-saturated THF solution at 70 °C, according to a reported protocol.[26]

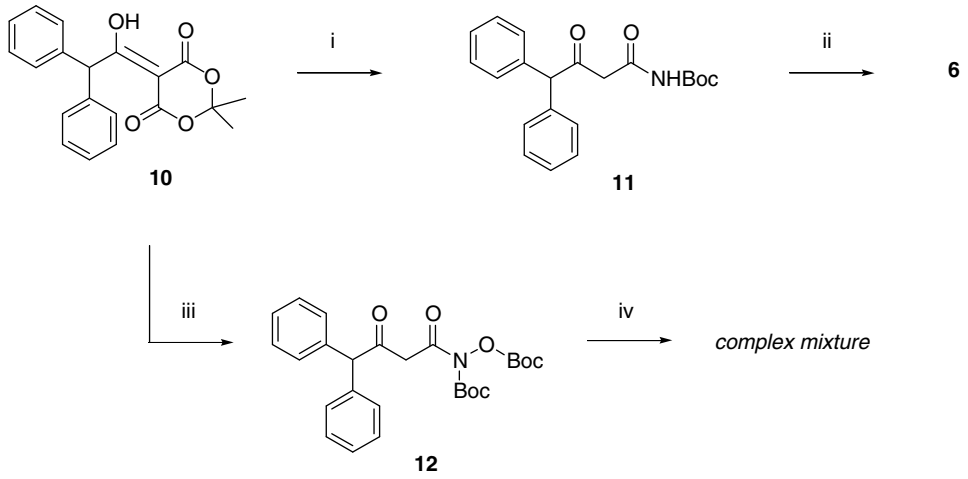
In order to overcome this hurdle we envisaged the use of *tert*-butyl carbamate as a different ammonia precursor, since the urethane group is less basic than ammonia. Thus, amidation of the acyl-Meldrum derivative **10** with *tert*-butyl carbamate following known directions,[25] produced in excellent yield the corresponding amide **11**, that was easily taken to the modafinil analogue **6** in essentially quantitative yield by action of HCl in EtOAc (Scheme 2).

We also attempted the preparation of an analogue of **2** using *N,O*-di-*tert*-butoxycarbonyl hydroxylamine[27] as the nitrogen nucleophilic counterpart of the acyl-Meldrum derivative **10** (Scheme 2). We found this reaction gave the β-ketohydroxamic acid **12** in good yield, but every attempt to cleanly remove the nitrogen protecting groups failed. As a matter of fact, we obtained unseparable complex mixtures in which only traces of the desired *N*-hydroxy amide were present.

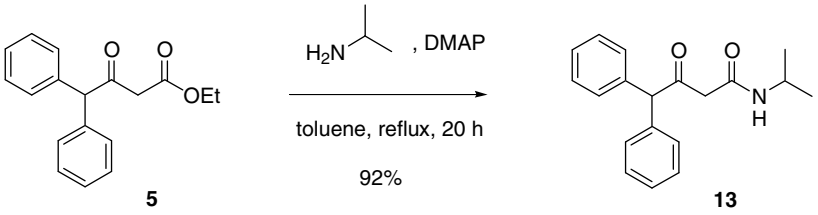
Furthermore, we were intrigued to apply this chemistry to the synthesis of modafinil analogues incorporating not only a carbonyl




**Scheme 1.** Reagents and conditions: (i) Method A: Zn, $BrCH_2CO_2Et$, THF, reflux, 30 min; Method B: Zn, $MeSO_3H$ cat., $BrCH_2CO_2Et$, THF, reflux, 30 min; (ii) 1N HCl, THF, rt, 6 h, 88% (Method A) or 90% (Method B) from **3**; (iii) $NH_3$, MeOH, rt, 24 h, 54%; (iv) $SOCl_2$, benzene, reflux, 2 h, 96%; (v) From **7**: DCC, $Et_3N$, $CH_2Cl_2$, 12 h, 78%; From **8**: $Et_3N$, $CH_2Cl_2$, rt, 5 h, 65%; (vi) $NH_3$, THF, $CH_3CN$, 70 °C, 48 h, 49%.




**Scheme 2.** Reagents and conditions: (i) $H_2N$-Boc, $CH_3CN$, reflux, 2 h, 83%; (ii) 3 N HCl in EtOAc, rt, 3 h, 98%; (iii) (Boc)NHO(Boc), benzene, 65 °C, 4 h, 71%; (iv) HCl, EtOAc, rt, 12 h.




**Scheme 3.** Synthesis of compound **13**.

group instead of the sulfoxide moiety but also a modified amide functionality. Preliminary studies in this field allowed us to obtain compound **13**, through reaction of the β-ketoester **5** with two equivalents of *N*-isopropylamine in refluxing toluene in the presence of 4-(dimethylamino)pyridine (DMAP) (Scheme 3), basing on a literature procedure.[28]

### 2.2. Biological activity: effects of modafinil and its analogues on spontaneous and electrically-evoked [$^3$H]5-HT efflux from cortical slices

#### 2.2.1. Spontaneous tritium efflux

In control slices, spontaneous [$^3$H]5-HT efflux at the 45th min was 0.029 ± 0.003 pmol/min, corresponding to a fractional rate of 3.25 ± 0.06%/5 min, and slowly declined during the collection period (from the 30th to the 110th min from the onset of the superfusion). Neither modafinil (1–30 μM)[20] nor compound **6** (0.1–100 μM) and compound **13** (0.1–30 μM), added to the superfusion medium after three basal collection periods (45th min of superfusion) affected spontaneous [$^3$H]5-HT efflux from rat cortical slices (*data not shown*).

#### 2.2.2. Electrically-evoked tritium efflux

The net [$^3$H]5-HT overflow induced by the electrical stimulation in $St_1$ was (0.036 ± 0.006 pmol/min. Under the present experimental conditions the $St_2/St_1$ ratio remained close to unity (0.92 ± 0.05). As previously reported,[20] the addition to the superfusion medium of modafinil (0.1–30 μM), 15 min before $St_2$, increased the [$^3$H]5-HT evoked-release in a concentration-dependent manner, the threshold concentration being 0.3 μM. The maximal effect (30 μM) was in the order of 217% of control values (Fig. 2A). A similar profile of action was displayed by compound **13** (Fig. 2C), while compound **6** increased the [$^3$H]5-HT evoked-release only at the higher concentration tested (Fig. 2B).

These results suggest that either compound **6** or compound **13** retained the bioactivity of the parent compound in increasing the electrically-evoked, but not spontaneous, [$^3$H]5-HT efflux. However, while compound **13** and modafinil display a similar profile of action, compound **6** possesses a lower potency in affecting cortical serotonergic transmission, at least under the present experimental conditions. Further experiments will be necessary in order to evaluate the pharmacokinetic profile and the possible therapeutic prospective of the two compounds.

## 3. Conclusion

In summary, two novel analogues of modafinil **1** have been synthesized through a synthetically simple isosteric replacement of the sulfoxide function with a carbonyl group. Evaluation of their effects on the spontaneous and the electrically-evoked tritiated serotonin ([$^3$H]5-HT) efflux from rat cortical slices showed a loss of biological activity for compound **6**, which could be restored modifying the primary amide function into the corresponding *N*-isopropyl derivative **13**. We are currently in the process of synthesizing several new derivatives in this series.

## 4. Experimental

Melting points were determined on a Büchi-Tottoli apparatus and were uncorrected.

IR spectra were recorded using a Perkin Elmer Paragon 500 FTIR spectrophotometer.

Nuclear magnetic resonance (NMR) spectra were taken on a Varian VXR-200 and a Varian Mercury Plus-400 spectrometers.

Solvents were distilled prior to use and reactions were performed under nitrogen or argon atmosphere.

Silica gel plates were used to monitor synthetic transformations, visualization being done under UV light and using 2% aqueous $KMnO_4$ solution or 2% ethanolic $FeCl_3$ solution. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator.

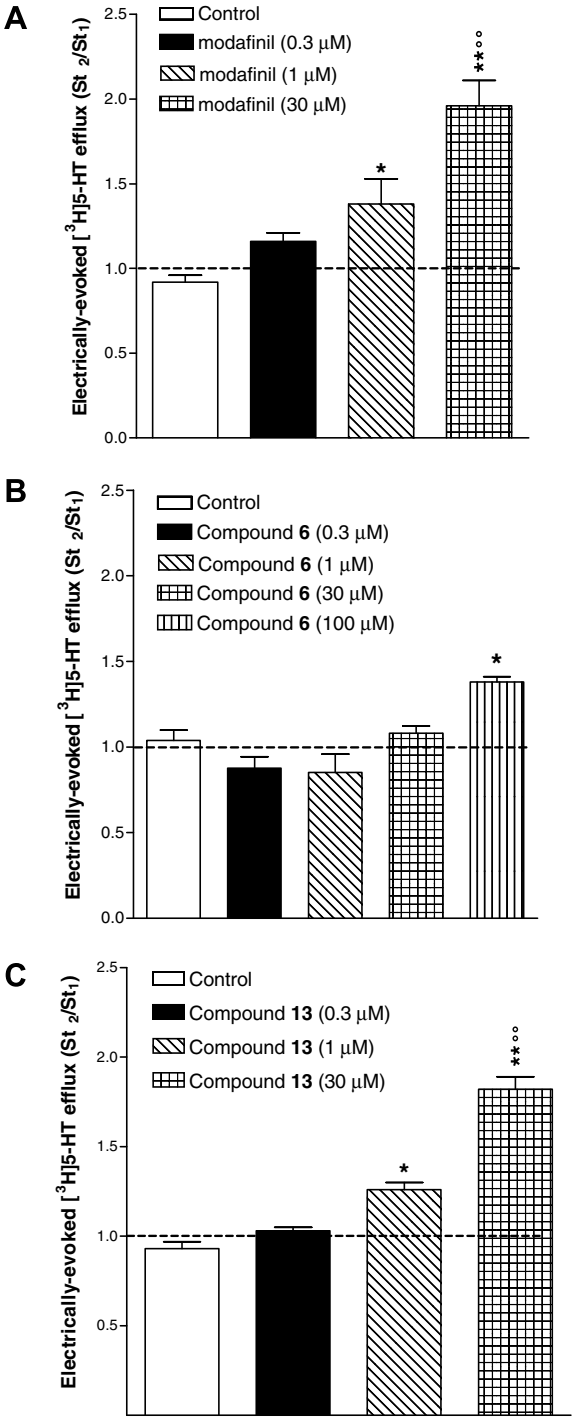



**Figure 2.** Effects of different concentrations of modafinil (0.1–30 μM; *Panel A*), compound **6** (0.1–100 μM; *Panel B*) and compound **13** (0.1–30 μM; *Panel C*), on the electrically-evoked [$^3$H]5-HT efflux from rat brain cortex slices superfused with Krebs solution containing paroxetine (3 μM) from the onset of the experiment. The slices were electrically stimulated twice at the 45th ($St_1$) and 85th ($St_2$) min from the onset of superfusion by applying two trains of rectangular pulses of alternate polarity (40 mA, 2 ms, 3 Hz×2 min). The drugs were added to the superfusion medium 15 min before ($St_2$) and maintained till the end of the collection period. Each histogram represents the mean ± SEM. of 8–11 experiments. *Panel A*: $^{*}P < 0.05$, $^{**}P < 0.01$ significantly different versus control as well as modafinil (0.3 μM); $^{\circ\circ}P < 0.01$ significantly different versus modafinil (1 μM); *Panel B*: $^{*}P < 0.005$ significantly different versus the other groups; *Panel C*: $^{*}P < 0.05$, $^{**}P<0.01$ significantly different vs control as well as compound **13** (0.3 μM); $^{\circ\circ}P < 0.01$ significantly different vs compound **13** (1 μM). The statistical analysis was carried out according to one-way ANOVA followed by the Newman–Keuls test for multiple comparisons.

Chromatographic purifications were carried out using 70–230 mesh silica gel.

### 4.1. Ethyl 3-Oxo-4,4-diphenylbutanoate (5)

#### 4.1.1. Method A

Ethyl bromoacetate (0.25 mL, 2.25 mmol) was added dropwise to a refluxing suspension of activated zinc dust (0.70 g, 10.71 mmol) in THF (5 mL) until it turned green. Compound **3** (1.00 g, 5.17 mmol) was added and successively ethyl bromoacetate (1 mL, 9.02 mmol) was dropped over a period of 30 min. Heating was continued for 30 min, then the reaction mixture was cooled to room temperature, saturated aqueous $NaHCO_3$ solution (10 mL) was added and the solution stirred for about 15 min. After being filtered through a bed of Celite, the solution was extracted with $Et_2O$ (3 × 15 mL), the combined extracts were washed with brine (3 × 15 mL), dried and concentrated in vacuo. The crude product was purified by flash chromatography ($Et_2O$/petroleum ether 4:6) to give enamino ester **4** (1.30 g, 90%) as a white solid, mp 58 °C. IR (KBr): 3460, 3310, 1663, 1608, 1554, 1165 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ (ppm) 1.24 (t, $J$ = 7.0 Hz, 3H), 4.10 (q, $J$ = 7.0 Hz, 2H), 4.56 (s, 1H), 4.92 (s, 1H), 7.23–7.36 (m, 10H), 7.00–9.00 (br, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ (ppm) 14.5, 57.1, 58.8, 86.6, 127.2, 128.7, 129.2, 139.8, 163.7, 170.4. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.70; H, 6.82; N, 4.97.

A solution of **4** (0.45 g, 1.60 mmol) in THF (6 mL) was treated with 1 N HCl (3 mL) and the solution stirred at room temperature for 3 h. Saturated aqueous $NaHCO_3$ solution (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The organic phases were combined and washed with brine (2 × 100 mL). The organic layer was dried and evaporated to dryness. The oily residue was purified by flash chromatography (EtOAc/petroleum ether 4:6) to furnish **5** (0.44 g, 98%) as a yellow oil. IR (neat): 1741, 1714, 1497, 1028 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ (ppm) 1.25 (t, $J$ = 7.0 Hz, 3H), 3.54 (s, 2H), 4.16 (q, $J$ = 7.0 Hz, 2H), 5.36 (s, 1H), 7.23-7.36 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ (ppm) 14.0, 48.6, 61.3, 64.0, 127.4, 127.6, 128.7, 137.3, 167.1, 200.7. Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.65; H, 6.41.

#### 4.1.2. Method B

A stirred suspension of zinc dust (0.68 g, 10.40 mmol) in THF (5 mL) was treated with $MeSO_3H$ (25 μL, 0.38 mmol) and heated at reflux for 10 min. Ethyl bromoacetate (0.25 mL, 2.25 mmol) was added dropwise until it turned green, then **3** (1.00 g, 5.18 mmol) was added. Ethyl bromoacetate (1 mL, 9.02 mmol) was successively added over a period of 30 min, then the reaction mixture was heated for 30 min, cooled to 0 °C and treated with 3 N HCl (5 mL). The solution was stirred for 3 h at room temperature, then the solvent was concentrated in vacuo. The residue was extracted with EtOAc (3 × 15 mL), the combined organic phases were washed with brine (2 × 100 mL) and dried. The solvent was evaporated, and the residue was purified by flash chromatography (EtOAc/petroleum ether 4:6) to afford **5** (1.32 g, 90%), showing the same analytical and spectroscopic data as the compound obtained by Method A.

#### 4.1.3. Diphenylacetyl chloride (8)

A solution of **7** (5.00 g, 23.60 mmol) in benzene (50 mL) was treated with $SOCl_2$ (6 mL, 82.25 mmol) and heated at reflux for 2 h. Evaporation of the solvent gave **8** (5.20 g, 96%) as a colorless oil, which solidified on standing, mp 56–59 °C. IR (KBr): 3029, 1774, 1495, 1453 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ (ppm) 5.48 (s, 1H), 7.33–7.38 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ (ppm) 68.7, 128.5, 128.7, 129.0, 136.2, 173.5. Anal. Calcd for $C_{14}H_{11}ClO$: C, 72.89; H, 4.81. Found: C, 72.70; H, 4.82.

### 4.2. 5-(1-Hydroxy-2,2-diphenylethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (10)

#### 4.2.1. Method A

To a cooled (0 °C) solution of **9** (3.40 g, 23.60 mmol) in $CH_2Cl_2$ (15 mL), $Et_3N$ (8.51 mL, 59.00 mmol) was added over a period of 20 min and the solution stirred at the same temperature for 15 min. A solution of **8** (5.44 g, 23.60 mmol) in $CH_2Cl_2$ (20 mL) was successively added dropwise over a period of 2 h and stirring was continued for 5 h with gradual warming to ambient temperature. The reaction mixture was diluted with $CH_2Cl_2$ (20 mL), cooled at 0 °C and treated with 2 N HCl (20 mL). After being stirred at 0 °C for 15 min, the aqueous phase was separated from the organic layer and extracted with $CH_2Cl_2$ (2 × 10 mL), the combined organic phases were dried and concentrated to dryness. The yellow solid thus obtained was recrystallized from EtOAc/petroleum ether 1:10 and filtered to give **10** (5.20 g, 65%) as a white solid, mp 49-51 °C. IR (KBr): 1729, 1668, 1569, 1415 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ (ppm) 1.71 (s, 6H), 5.06 (s, 1H), 7.25-7.37 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ (ppm) 27.8, 57.0, 92.0, 105.1, 127.5, 128.7, 129.3, 137.9, 171.1, 178.3, 195.8. Anal. Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 71.00; H, 5.34.

#### 4.2.2. Method B

$Et_3N$ (0.30 mL, 2.10 mmol) was added to a 0 °C cold solution of **7** (0.42 g, 2.00 mmol) in $CH_2Cl_2$ (15 mL). After being stirred at the same temperature for 10 min, a solution of **9** (0.28 g, 2.00 mmol) in $CH_2Cl_2$ (10 mL) and *N,N'*-dicyclohexylcarbodiimide (0.45 g, 2.20 mmol) were successively added. The mixture was stirred at room temperature for 20 h, then it was diluted with $CH_2Cl_2$ (20 mL) and filtered. Brine (20 mL) was added to the filtrate and the phases were separated. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL) and the organic fractions were collected, dried, and evaporated. The crude solid residue was purified by flash cromatography (EtOAc/petroleum ether/AcOH 1:9:0.1) to give **10** (0.52 g, 78%), showing the same analytical and spectroscopic data as the compound obtained by Method A.

#### 4.2.3. *tert*-Butyl (3-Oxo-4,4-diphenylbutanoyl)carbamate (11)

A solution of **10** (0.34 g, 1.00 mmol) and *tert*-butyl carbamate (0.12 g, 1.00 mmol) in $CH_3CN$ (20 mL) was heated at reflux for 2 h. Evaporation of the solvent, followed by flash cromatography of the residue (EtOAc/petroleum ether 1:2) gave **11** (0.29 g, 83%) as a white solid, mp 147 °C. IR (KBr): 3236, 1753, 1722, 1690 $cm^{-1}$. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ (ppm) 1.46 (s, 9H), 3.89 (s, 2H), 5.31 (s, 1H), 7.20–7.38 (m, 10H), 7.60 (br, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ (ppm) 28.0, 50.4, 64.6, 83.1, 127.5, 128.8, 129.1, 137.3, 150.5, 172.2, 208.3. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.45; H, 6.55; N, 3.97.

### 4.3. 3-Oxo-4,4-diphenylbutanamide (6)

#### 4.3.1. Method A

A solution of **5** (0.25 g, 0.88 mmol) in saturated methanolic ammonia (5 mL) was stirred at room temperature for 24 h, then the solvent was evaporated. Flash chromatography of the residue (EtOAc/petroleum ether 1:2 increasing to 2:1) gave a colorless oil, which was triturated with EtOAc/petroleum ether 1:10. After some time, a solid started separating out. The obtained suspension was stirred for about 30 min, then it was filtered to afford **6** (0.12 g, 54%) as a white solid, mp 85 °C. IR (KBr): 3418, 3180, 1715, 1668, 1379 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ (ppm) 3.52 (s, 2H), 5.23 (s, 1H), 5.49 (br, 1H), 6.84 (br, 1H), 7.18-7.40 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ (ppm) 48.4, 65.1, 127.8, 129.0, 129.1, 136.9, 167.6, 204.5. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.05; H, 5.95; N, 5.54.

#### 4.3.2. Method B

An ammonia gas-saturated THF solution (2 mL) was added to a solution of **10** (0.20 g, 0.59 mmol) in $CH_3CN$ (10 mL). The reaction mixture was vigorously stirred at 70 °C for 48 h, then the solvent was evaporated. The residue was dissolved in EtOAc (30 mL) and 2 N HCl (20 mL) was added. The biphasic mixture was stirred at room temperature for 15 min, the organic phase separated, washed with brine (2 × 10 mL) and evaporated. Flash chromatography of the residue (EtOAc/petroleum ether 1:2 increasing to 2:1) gave a colorless oil, which was processed as described in Method A to afford **6** (73 mg, 49%), showing the same analytical and spectroscopic data as the compound obtained by Method A.

#### 4.3.3. Method C

A solution of **11** (0.29 g, 0.82 mmol) in 3 N HCl solution in AcOEt (10 mL) was stirred at room temperature for 3 h. The mixture was kept to pH 9–10 by careful addition of saturated aqueous $NaHCO_3$ solution and then extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried and evaporated. The resulting oil was treated as described in Method A to give **6** (0.20 g, 98%), showing the same analytical and spectroscopic data as the compound obtained by Method A.

#### 4.3.4. *N,O*-Bis-(*tert*-butoxycarbonyl)-*N*-hydroxy-3-oxo-4,4-diphenylbutanamide (12)

*N,O*-Bis-(*tert*-butoxycarbonyl)hydroxylamine (0.35 g, 1.50 mmol) was added to a solution of **10** (0.51 g, 1.50 mmol) in benzene (10 mL) and the mixture was heated at 65 °C for 4 h. Evaporation of the solvent and flash chromatography of the residue (EtOAc/hexanes 1:19) gave **12** (0.50 g, 71%) as a yellow oil. IR (KBr): 1785, 1711, 1629 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ (ppm) 1.49 (s, 9H), 1.52 (s, 9H), 3.95 (part of a AB system, $J$ = 16.0 Hz, 1H), 4.13 (part of a AB system, $J$ = 16.0 Hz, 1H), 5.33 (s, 1H), 7.23–7.34 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$): δ (ppm) 27.5, 27.8, 27.9, 51.3, 64.1, 86.0, 86.4, 127.4, 128.6, 129.05, 137.3, 149.7, 150.8, 163.4, 200.2. Anal. Calcd for $C_{26}H_{31}NO_7$: C, 66.51; H, 6.65; N, 2.98. Found: C, 66.60; H, 6.64; N, 2.97.

#### 4.3.5. 3-Oxo-4,4-diphenyl-*N*-(propan-2-yl)-butanamide (13)

A solution of **5** (0.50 g, 1.77 mmol) in toluene (20 mL) containing isopropylamine (0.30 mL, 3.55 mmol) and 4-(dimethylamino)pyridine (65 mg, 0.53 mmol) was heated at reflux for 20 h, then the solvent was evaporated. The crude residue was purified by flash chromatography (EtOAc/petroleum ether 1:2 increasing to 2:1) to give a colorless oil, which was triturated with EtOAc/petroleum ether 1:10. After some time, a solid started separating out. The suspension was stirred for about 30 min, then it was filtered to afford **13** (0.48 g, 92%) as white needles, mp 101 °C. IR (KBr): 3285, 1734, 1640, 1570, 1406 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ (ppm) 1.11 (d, $J$ = 6.6 Hz, 6H), 3.44 (s, 2H), 4.03 (m, 1H), 5.25 (s, 1H), 6.64 (br, 1H), 7.19–7.33 (m, 10H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ (ppm) 22.6, 40.0, 41.6, 64.9, 127.7, 129.0, 129.1, 137.1, 164.3, 205.1. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.35; H, 7.18; N, 4.76.

## 5. Biological experiments

### 5.1. Animals

Male adult Sprague–Dawley rats with a body weight of 300–350 g were housed in cages in groups of five animals at a constant room temperature (20 °C) and exposed to a 12 h:12 h light–dark cycle (lights on at 06.00 a.m.). Food and water were provided ad libitum. Following delivery, the animals were allowed to adapt to the environment for at least 1 week before the experiment started.

### 5.2. Preparation and superfusion of cortical slices

Experiments were performed as previously described.[20] Briefly, the animals were killed, their brains promptly isolated and 400-μm-thick slices (25–30 mg each) were obtained from both the left and right frontal cortices by using a fresh tissue vibratome-like apparatus. The tissue was then allowed to equilibrate for 15 min at room temperature in a Krebs solution (mM composition: NaCl 118.5, KCl 4.7, $CaCl_2$ 1.8, $KH_2PO_4$ 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, glucose 10) continuously bubbled with a mixture of 95% $O_2$ plus 5% $CO_2$. Thereafter, the slices were incubated at 37 °C for 30 min in Krebs solution with the addition of ascorbic acid 0.05 mM and disodium EDTA 0.03 mM and containing 50 nM [$^3$H]5-HT (specific activity 27.8 Ci/mmol, DuPont NEN, Boston, MA). The slices were then rinsed, transferred into oxygenated superfusion chambers (0.45 ml volume each; two slices/chamber) and superfused at a flow rate of 0.25 ml/min with Krebs solution containing the 5-HT uptake inhibitor paroxetine (3 μM). After 30 min of superfusion, the release experiment started by collecting superfused samples every 5 min from each chamber.

### 5.3. Experimental protocols: spontaneous and electrically-evoked [$^3$H]5-HT efflux

Spontaneous [$^3$H]5-HT efflux was determined in successive 5-min fractions from the 30th to the 110th min of superfusion. After the collection of three basal samples, modafinil was added to the superfusion medium and maintained until the end of the experiment.

For the experiment on electrically-stimulated slices, [$^3$H]5-HT overflow was evoked by electrical field stimulations (3 Hz, 40 mA, 2 msec, for 2 min) at the 45th ($St_1$) and 85th ($St_2$) min from the onset of superfusion. The effects of modafinil, compound **6** and compound **13** were evaluated by adding the drugs to the superfusion medium 15 min before $St_2$. At the end of the experiment, the slices were solubilized in 1 ml of Soluene 350 (Packard Instruments, Downers Grove, IL). The radioactivity of the 5-min samples and slices was determined by liquid scintillation spectrometry.

### 5.4. Data presentation and statistical analysis

The amount of tritium released per 5-min sample was calculated either as pmol/min or as fraction of the total tissue tritium content at the beginning of the respective collection period (fractional rate). For calculation of the net tritium overflow evoked by the electrical stimulation, the estimated spontaneous [$^3$H]-efflux (the latter was assumed to decline linearly from the 5-min period before to that 15–20 min after the onset of stimulation) was subtracted from the total [$^3$H]-efflux during stimulation and the subsequent 13 min; this difference was calculated as a percentage of the total tissue tritium content at the onset of stimulation.[20] The [$^3$H]-overflow resulting from the first stimulation ($St_1$) has been used as an internal control for the [$^3$H]-overflow produced by the second stimulation ($St_2$). The effects of the drug tested were quantified by evaluating the changes induced in the $St_2/St_1$ ratio in comparison with control slices assayed in parallel. The data were presented as mean ± SEM. The term [$^3$H]5-HT efflux was used as an index of 5-HT (and its metabolites) release.

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