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BRIEF ARTICLE

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3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles: A New Scaffold for the Selective Inhibition of Monoamine Oxidase B

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Supporting Information

ABSTRACT: 3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles were designed, synthesized, and tested as inhibitors against human monoamine oxidase (MAO) A and B isoforms. Several compounds, obtained as racemates, were identified as selective MAO-B inhibitors. The enantiomers of some derivatives were separated by enantioselective HPLC and tested. The *R*-enantiomers always showed the highest activity. Docking study and molecular dynamic simulations demonstrated the putative binding mode. We conclude that these 1,3,4-oxadiazoles derivatives are promising reversible and selective MAO-B inhibitors.

INTRODUCTION

The pivotal role of both isoforms of monoamine oxidase (MAO, EC 1.4.3.4) (MAO-A and MAO-B) in the metabolism of neurotransmitters has been extensively reported. MAO-B is involved in the pathogenesis of Parkinson's disease (PD), and the therapeutic potential of MAO-B selective inhibitors in this pathology has been pointed out.[1,2] Moreover there is evidence that the activity of the B isoform has increased in several neurodegenerative disorders, like Alzheimer's disease, Huntington chorea, and amyotrophic lateral sclerosis.[3,4] For this reason, selective MAO-B inhibitors have received considerable attention in the treatment of several neurological pathologies. Therefore, drugs like selegiline, [*R*-(−)-deprenyl], rasagiline, *N*-propargyl-1-*R*-aminoindan (Azilect), and safinamide have demonstrated their utility in the treatment of PD.[5,6] Recently variously substituted 1-acetyl-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazole derivatives have been reported.[7] These compounds were found to be selective on MAO-A over MAO-B.

Pursuing this field of research, we designed and synthesized a set of 1-carbothioamide-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazole derivatives[8,9] whose activity and selectivity toward MAO-A and MAO-B are strongly influenced by the nature of the substituents in positions 3 and 5 and by the configuration of the chiral carbon in position 5 of the dihydropyrazole ring. Moreover, the synthesis and the biological activity of a series of 5-[4-(benzyloxy)phenyl]-1,3,4-oxadiazol-2(3*H*)-one derivatives have been described and their high and selective activity toward MAO-B pointed out.[10]

DESIGN OF NEW COMPOUNDS

It is well-known that bioisosterism is a rational and efficient concept for the design of new bioactive leads, and its importance in building new drug congeners has been also highlighted in a recent review.[11] With the aim of improving the activity and the selectivity of the previously reported compounds and with the intention of setting new leads, we designed and synthesized a series of dihydrooxadiazoles that can be considered isosters of the previously reported 1-acetyl-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazoles and 1-carbothioamide-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazoles. In fact, the isosteric substitution of the methylene in position 4 of the 3,5-diaryl-4,5-dihydro-(1*H*)-pyrazole nucleus with an oxygen atom gives rise to the formation of the 2,5-diaryl-2,3-dihydro-1,3,4-oxadiazole molecule. Moreover, the carbothioamide group, a pharmacophoric feature of the previously reported compounds, was replaced by the isosteric acetyl moiety. Moreover, the oxadiazole derivatives are gaining importance in the heterocyclic family because of their broad-spectrum of biological activities.[11−14] Thus, a better pharmaceutical profile could be expected for the 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazole, compared to the 1-acetyl-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazoles and 1-carbothioamide-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazoles.

The design of these derivatives was joined by docking experiments. Their predicted binding conformations and energies confirmed the good fitting into the MAO-B binding pocket and led us to be more confident of the possible inhibition of this enzyme. In addition, computational experiments highlighted a preferential enantioselective binding for the *R* enantiomers.

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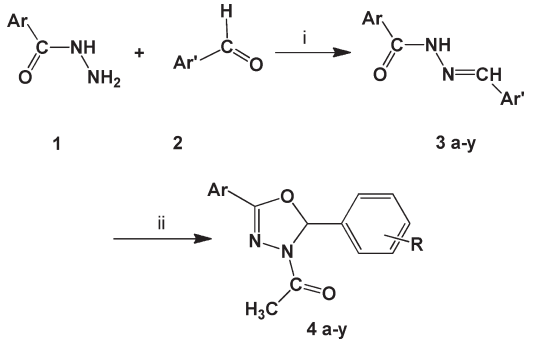
Scheme 1. Synthetic Pathway to Compounds 4a−y[a]



[a] Reagents: (i) EtOH, CH_3COOH; (ii) $(CH_2CO)_2$.

CHEMISTRY AND HPLC ENANTIOSEPARATIONS

3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles **4a−y** were synthesized by slightly modifying previously reported procedures.[15,16] Briefly, after the appropriate *N*′-arylidenearylhydrazides were obtained, this was reacted with equimolar amounts of acetic anhydride as depicted in Scheme 1. All products were characterized by analytical and spectroscopic methods. Their analytical and chemical−physical properties are reported in Table S1 (Supporting Information). The substituents' positions were further confirmed by comparison with the crystal structure of 2-(3,4-dichlorophenyl)-3-acetyl-5-phenyl-2,3-dihydro-1,3,4-oxadiazole (**5**) previously synthesized by analogous procedure. Direct separation of the enantiomers of **4p**, **4s**, and **4y** was achieved by HPLC using pure dichloromethane as the eluent. The resolving power of the immobilized-type was sufficiently high to achieve a baseline enantioseparation of all compounds in a short-time analysis (Figure S1, Supporting Information). The optimized analytical conditions were easily scaled up to semipreparative level employing a 1 cm i.d. IA column. An amount of ∼20 mg of racemic samples was resolved for each chromatographic run, and both enantiomers were collected with high enantiomeric purity (≥99% ee, Table S2, Supporting Information). The stereochemical characterization was performed by CD correlation comparing the maximum and minimum of ellitipticity of the CD spectra of the isolated enantiomers with those of the enantiomers of the analogue **5** of known stereochemistry.[17] A comparison between CD spectra of the enantiomers of **4p**, **4s**, and **4y** and those of the enantiomers of **5** is shown in Figure S2, Supporting Information. In the 330−210 nm spectral region, the CD spectra of the less-retained enantiomers obtained by enantioselective preparative HPLC showed the same sequence as the signs of CD bands of the (*R*)-(+)- 2-(3,4-dichlorophenyl)-3-acetyl-5-phenyl-2,3-dihydro-1,3,4-oxadiazole (**5**). Thus, the following absolute configuration assignment and consequently enantiomeric elution order could be established: the (*R*)-(+) enantiomers of **4p**, **4s**, and **4y** were eluted before the (*S*)-(−) enantiomers.

BIOCHEMISTRY

The inhibitory effects of test drugs on hMAO activity were evaluated by measuring the production of H_2O_2 from *p*-tyramine, using the Amplex Red MAO assay kit and microsomal MAO isoforms prepared from insect cells (BTI-TN-5B1-4) infected with recombinant baculovirus containing cDNA inserts for hMAO-A or hMAO-B. The MAO activity was evaluated using the general procedure previously described by us.[18] The test compounds (new compounds and reference inhibitors) themselves were unable to react directly with the Amplex Red reagent, indicating no interference of these molecules with the measurements.

Table 1. Inhibitory Activities of 3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles: Derivatives 4a−y[a]

compd	Ar	R	MAO-A (IC_{50})	MAO-B (IC_{50})	ratio
4a	Py	4-OCH_3	**	**	
4b	Py	3,4-diOCH_3	**	**	
4c	Py	4-Cl	**	**	
4d	Py	2,4-diCl	**	**	
4e	Py	4-$N(CH_3)_2$	**	46.82 ± 2.64 μM	>2.14
4f	Py	4-CH_3	**	**	
4g	Py		**	**	
4h	4-CH_3Ph	4-OCH_3	**	74.70 ± 4.98 μM	>1.34
4i	4-CH_3Ph	3,4-diOCH_3	**	***	
4j	4-CH_3Ph	4-Cl	**	***	
4k	4-CH_3Ph	2,4-di-Cl	**	***	
4l	4-CH_3Ph	4-$N(CH_3)_2$	**	**	
4m	4-CH_3Ph	4-CH_3	**	66.64 ± 3.63 μM	>1.50
4n	4-CH_3Ph		**	***	
4o	4-NO_2Ph	4-Cl	**	121.62 ± 9.63 nM	>822#
4p	4-ClPh	4-Cl	**	115.31 ± 8.39 nM	>867#
4q	4-OCH_3Ph	4-Cl	**	***	
4r	Ph	4-Cl	**	**	
4s	4-BrPh	4-Cl	**	220.61 ± 12.61 nM	>453#
4t	Ph	4-NO_2	**	***	
4u	Ph	4-OCH_3	**	5.16 ± 0.21 μM	>19#
4v	Ph		**	**	
4w	Ph	4-F	**	9.53 ± 0.41 μM	>10#
4x	Ph	4-$N(CH_3)_2$	**	**	
4y	Ph	4-CH_3	**	19.36 ± 0.82 μM	>5.2#

[a] IC_{50} and MAO-B selectivity ratios [IC_{50}(MAO-A)]/[IC_{50}(MAO-B)] for the inhibitory effects of test drugs (new compounds and reference inhibitors) on the enzymatic activity of human recombinant MAO isoforms expressed in baculovirus infected BTI insect cells. Each IC_{50} is the mean ± SEM from five experiments. (**) Inactive at 100 μM (highest concentration tested). At higher concentration the compounds precipitate. (***) 100 μM inhibits the corresponding MAO activity by approximately 40−50%. At higher a concentration the compounds precipitate. (#) Value obtained under the assumption that the corresponding IC_{50} against MAO-A is the highest concentration tested (100 μM).

RESULTS AND DISCUSSION

Compounds **4a−y** were evaluated for their ability to inhibit the two isoforms of MAO. In Table 1 the structures, the MAO-A and MAO-B IC_{50}, and ratios [IC_{50}(MAO-A)]/[IC_{50}(MAO-B)] of all the synthesized compounds are listed. Some of the tested compounds exhibit interesting biological properties with IC_{50} toward the B isoform of the enzyme ranging from micromolar to nanomolar values. None of the tested compounds show a significant inhibitory ability toward the MAO-A, indicating the 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazole scaffold as a promising candidate for the design of MAO-B selective inhibitors. In particular, **4o**, **4p**, and **4s** are active at inhibiting MAO-B at nanomolar concentration. The introduction of a 4-chlorophenyl

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Table 2. Inhibitory Activities of 3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles 4p, 4s, and 4y as Racemates and Single Enantiomers[a]

Compound	MAO-A (IC_{50})	MAO-B (IC_{50})	Ratio
(±) **4p**	**	115.31 ± 8.39 nM	> 867[#]
(*R*)-(+) **4p-1**	**	100.64 ± 7.12 nM	> 994[#]
(*S*)-(-) **4p-2**	**	**	
(±) **4s**	**	220.61 ± 12.61 nM	> 453[#]
(*R*)-(+) **4s-1**	**	82.54 ± 7.29 nM	> 1211[#]
(*S*)-(-) **4s-2**	**	**	
(±) **4y**	**	19.36 ± 0.82 μM	> 5.2[#]
(*R*)-(+) **4y-1**	**	8.46 ± 0.30 μM	> 12[#]
(*S*)-(-) **4y-2**	**	**	

[a] IC_{50} and MAO-B selectivity ratios [IC_{50}(MAO-A)]/[IC_{50}(MAO-B)] for the inhibitory effects of test drugs on the enzymatic activity of human recombinant MAO isoforms expressed in baculovirus infected BTI insect cells. Each IC_{50} is the mean ± SEM from five experiments. (**) Inactive at 100 μM (highest concentration tested). (#) Values obtained under the assumption that the corresponding IC_{50} against MAO-A is the highest concentration tested (100 μM).

moiety in position 2 of the dihydro-1,3,4-oxadiazole ring appears as the most efficient for the inhibition of MAO-B, if associated with the presence of a 4-nitrophenyl, 4-chlorophenyl, or 4-bromophenyl moiety in position 5.

A similar behavior was observed in previously studied compounds,[8] where the introduction of a 4-chlorophenyl group in an analogous position led to the most active and selective derivatives regarding the B isoform of monoamine oxidase. In contrast, the introduction of a 4-pyridinyl substituent ring in position 5 (**4a-g**) does not favor biological activity. It is noteworthy that all compounds have a stereogenic center at position 2 of the dihydro-1,3,4-oxadiazole ring leading to the formation of two different enantiomers. Docking experiments previously performed by means of Glide software[19] helped to rationalize the structure−activity and selectivity relationships concerning the MAO-B enzyme. Furthermore the results of this study also account for the high enantioselectivity of *R*-configuration.

To obtain a reliable relationship between stereochemistry and biological activity, milligram amounts of single enantiomers of three active compounds **4p**, **4s**, and **4y**, were separated by HPLC on the Chiralpak IA CSP in polar organic conditions. The pure enantiomers were then evaluated for their ability to inhibit the two isoforms of the MAO. The results are reported in Table 2. Only

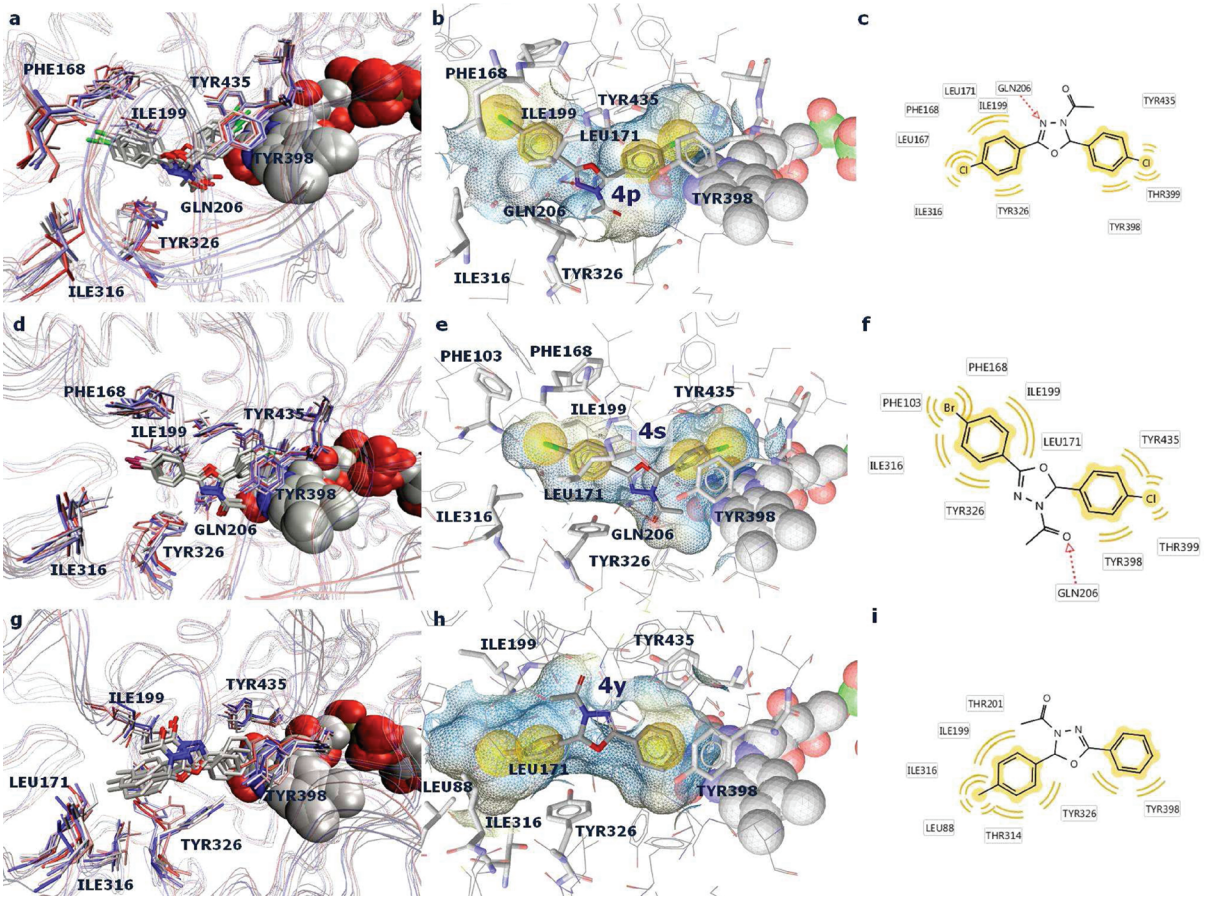

Figure 1. (a, d, g) Superimposed frames structures of 3 ns MD simulations of MAO-B complexes with (*R*)-**4p**, (*R*)-**4s**, (*R*)-**4y** colored by time step. (b, e, h) Close-up of the binding cavity colored according to lipophilicity: light blue for hydrophilic and pale yellow for hydrophobic residues. Pharmacophoric features are visualized as red arrows (HB acceptor) and yellow spheres (hydrophobic interactions). (c, f, i) 2D visualization of interactions of putative binding mode of each compound examined. The analyzed molecules are represented in sticks. FAD is in space fill models, and water molecules are shown as spheres.

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the (*R*) configuration enantiomer is active and characterized by increased activity and selectivity with respect to the racemates.

Computational experiments were able to explain inhibitory activity results and selectivity. In fact most of the compounds could not enter the MAO-A binding pocket except for **4nR**, **4wS**, and **4v**, which show low predicted binding affinity. The reason for their ability to enter the MAO-A pocket may be attributed to the steric hindrance of the aromatic substituents on the oxadiazole core being lower than that of other compounds of the series. Conversely the MAO-B binding pocket is larger because of the presence of an additional open "entrance cavity" with respect to the A isoform. Therefore, bulkier derivatives are generally favored to enter the MAO-B catalytic pocket compared to MAO-A.[20] Interestingly the substitution at position 2 with a 4-chlorophenyl group led to increased inhibitory activity of our compounds. Docking experiments highlighted that the complexes with these derivatives (**4o**−**s**) are stabilized by the interaction between the 4-chlorophenyl portion and the "aromatic cage"[21] close to the flavin adenine dinucleotide (FAD) cofactor (Figure 1b,e). Such a contact is favored by the presence of electron-withdrawing (EWD) groups reducing the electron density around the aromatic ring and, consequently, the repulsive interactions with the Tyr residues.[22] The presence of a halogen was also important for the stabilization of the other interaction at position 5, due to the hydrophobic contacts within the pocket formed by Phe103, Tyr326, Ile316, Leu171, Phe168, Ile199. The EWD effect seemed to be crucial at this position; in fact halophenyl and nitrophenyl groups show favorable effects (**4o**, **4p**, **4s**) compared to phenyl (**4r**) and 4-methoxyphenyl (**4q**) substituents. The presence of pyridinyl (**4a**−**g**), 4-methylphenyl (**4h**−**n**), phenyl (**4t**−**y**) moieties at position 5 induces a different orientation of the molecules in the binding pocket and leads to less stable complexes with the enzyme (e.g., binding mode **4y** in Figure 1h). The putative binding modes suggested by the docking experiments were also supported by GRID[23] maps analysis (Figure S3, Supporting Information). The CL probe confirmed as energetically favorable area the position of the chlorine atom obtained by the docking program. In the case of **4y** the DRY probe indicated favorable hydrophobic areas where the 5-aryl substitution of the oxadiazoline ring was docked.

After biological testing, and with the objective of highlighting the important requirements and the essential interactions of active molecules, we focused our attention on **4p**, **4s**, **4y**. These compounds were tested after enantiomeric separation; therefore, their activity data were not biased by the other enantiomer. For all three mixtures the eutomer turned out to be in the *R* configuration. After docking experiments the best poses were refined by 3 ns of molecular dynamics (MD) simulation. Such an approach allowed us to study the complex stability in explicit water solvent and the induced fit effect upon ligand binding. The trajectories were qualitatively and energetically analyzed. The nonbonded van der Waals and electrostatic terms proved to be the most important factors for the binding affinity as shown in Table 3 and Figures S4 and S5 (Supporting Information), which depict details of energy variation during the simulation. Figure 1 shows the putative binding mode of **4p**, **4s**, **4y** and the important host−guest interactions. In particular **4p** and **4s** are able to form a hydrogen bond (HB) with Gln206. The other productive interactions are hydrophobic contacts as expected from the van der Waals energy. During the MD simulation, as indicated in Figure S4d (Supporting Information), a reduction of the distance between the amido group of Gln206 and the carbonyl group of **4s** was noticed. Such a geometrical observation is consistent with a significant stabilization of the complex (Figure S4a and S4b, Supporting Information) due to an increased occurrence of HB.

Table 3. Average of Total, van der Waals (vdW), and Electrostatic (Coulomb) Interaction Energies Terms Expressed in kcal/mol per Complex

complex	total	vdW	Coulomb
MAO-B, (*R*)-**4p**	−51.3	−45.7	−2.2
MAO-B, (*R*)-**4s**	−57.4	−46.9	−7.3
MAO-B, (*R*)-**4y**	−44.6	−41.4	−4.2

CONCLUSIONS

We designed, synthesized, and characterized variously substituted dihydro-1,3,4-oxadiazoles. Their in vitro activity was determined regarding the two isoforms of the monoamine oxidase. None of the tested compounds exhibit activity up to 100 μM toward the A isoform of this enzyme. Stereochemistry demonstrated to be essential for activity and selectivity. The *R* enantiomer is significantly more active and selective in comparison to the racemic mixture, while no activity was observed for the *S* enantiomer of **4p**, **4s**, and **4y**. The molecular modeling approaches applied in this study not only drove us to the design of active and selective compounds but also put in evidence, as important requirements for selectivity and activity of this series of compounds, the ability to occupy both "entrance" and catalytic cavity and the substitution with EWD groups of aryl moieties. The information derived can be employed as a starting point to optimize this new series of MAO-B inhibitors. On the basis of the above observations, the 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazole scaffold can be considered as a new lead structure for the selective inhibition of the B isoform of MAO. Moreover this scaffold appears more selective and active compared to the previously reported 1-carbothioamide-3,5-diaryl-4,5-dihydro-(1*H*)-pyrazole derivatives. Furthermore, the workflow followed could be used to prioritize the new compounds to be synthesized.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of *N*-Arylidenearylhydrazides (3a−y). Equal amounts of aromatic aldehyde (0.018 mol) and the appropriate arylhydrazide (0.018 mol) are refluxed in 2-propanol (60 mL) under vigorous stirring from 1 to 3 h. With respect to the different aromatic substituents in positions 2 and 5 of the oxadiazole ring, a differently colored solution is obtained. The reaction solution is monitored by TLC (eluent chloroform−methanol 20:1). After the mixture is cooled at room temperature, the product precipitated is filtered off and then washed with isopropyl ether. By use of this method *N*-arylidenearylhydrazides (**3a**−**y**) where synthesized with yields ranging from 70% to 90%.

General Procedure for the Synthesis of 3-Acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles (4a−y). *N*′-Arylidenearylhydrazides (0.003 mol) are refluxed in 6 mL of acetic anhydride under vigorous stirring from 15 min to 2 h. The suspension is monitored by TLC (eluent chloroform−methanol 20:1). Generally the complete solubilization of the suspension and the formation of an intense orange color indicates the end of the reaction. The solution is then poured onto ice−water (100 g) and vigorously stirred. A precipitate is formed which is washed with $NaHCO_3$ (10% water solution) to remove the acetic acid. The obtained solid is further purified by crystallization with an appropriate solvent or by chromatography.

By use of the same procedure, **4a**−**y** were synthesized.

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All reactions were monitored by TLC performed on silica gel plates 0.2 mm thick (60 F254 Merck); spots were visualized by UV light. Melting points were uncorrected and were determined on a Stuart SMP11 melting point apparatus (Table S1, Supporting Information). ^{1}H NMR spectra were recorded on a Bruker AMX (300 MHz) or a Varian Unity 600 (600 MHz); deuterated chloroform ($CDCl_3$) was used as solvent. Chemical shifts are expressed as δ units (parts per million) using TMS as an internal standard. Coupling constants J are in hertz (Hz) (Supporting Information). Electron ionization (EI) mass spectra were obtained using a Fisons QMD 1000 mass spectrometer (70 eV, 200 μA, ion source temperature of 200 °C). The samples were introduced directly into the ion source. Elemental analysis results for C, H, and N were recorded on a Perkin-Elmer 240 B microanalyzer and were within ±0.4% of the theoretical values for all compounds.

■ ASSOCIATED CONTENT

Supporting Information. Chemical−physical properties of 1,3,4-oxadiazoles, ^{1}H NMR spectra, enantioselective HPLC chromatograms, enantiomeric purity and specific rotations of the first and second eluted enantiomers, absolute configuration assignment by CD correlation, biological assay and molecular modeling details, GRID maps, MD analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

MAO, monoamine oxidase; PD, Parkinson's disease; CD, circular dichroism; HPLC, high-performance liquid chromatography; TLC, thin layer chromatography; FAD, flavin adenine dinucleotide; vdW, van der Waals; EWD, electron-withdrawing; HB, hydrogen bond; MD, molecular dynamics

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