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Brief Article

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Novel Reversible Monoamine Oxidase A Inhibitors: Highly Potent and Selective 3-(1*H*-Pyrrol-3-yl)-2-oxazolidinones

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Supporting Information

ABSTRACT: Monoamine oxidases (MAOs) are involved in various psychiatric and neurodegenerative disorders; hence, MAO inhibitors are useful agents in the therapy of Parkinson's disease, Alzheimer's dementia, and depression syndrome. Herein we report a novel series of 3-(1*H*-pyrrol-3-yl)-2-oxazolidinones **3**−**7** as reversible, highly potent and selective anti-MAO-A agents. In particular, **4b**, **5b**, and **4c** showed a $K_{i\text{-MAO-A}}$ of 0.6, 0.8, and 1 nM, respectively, **4c** being 200000-fold selective for MAO-A with respect to MAO-B.

INTRODUCTION

Mitochondrial monoamine oxidases (MAOs, EC 1.4.3.4) are primarily involved in the metabolism of the biogenic monoamines. They catalyze the oxidative deamination of structurally different amines including the neurotransmitters dopamine, norepinephrine, serotonin (5-HT), tyramine, 2-phenethylamine (PEA), and exogenous arylalkylamines.[1,2] The electron acceptor of the reaction is O_2, which is converted to H_2O_2 by the enzymes. MAOs are flavin adenine dinucleotide (FAD) containing enzymes located in the outer mitochondrial membrane of neuronal, glial, and other cells. Two different isoenzymatic forms have been identified, MAO-A and MAO-B, and are distinguishable by their differences in their amino acids sequences,[3] three-dimensional structures,[4−8] substrate specificity, and sensitivity to inhibitors.[9] MAO-A preferentially catalyzes the oxidation of 5-HT and norepinephrine, and it is selectively inhibited by clorgyline, whereas MAO-B catalyzes the oxidation of PEA and benzylamine, and it is selectively inhibited by selegiline (l-deprenyl) and rasagiline.[10] Tyramine and tryptamine appear to be substrates for both isoforms. Most human tissues express both isoenzyme, nevertheless blood platelets and myocardium are particularly rich in MAO-B, while high levels of MAO-A are detected in the human placenta, lung, and small intestine.[11]

Isoenzyme A occurs in catecholaminergic neurons, whereas isoenzyme B is mainly present in neurons and glial cells of the human brain and also in other different cell types. The different localization suggests that the two subtypes have different physiological functions. In fact, MAO-A and -B are probably related to psychiatric and neurological disorders such as depression and Parkinson's disease (PD), respectively.[12] Several selective and reversible MAO-A inhibitors[13] have been described as antidepressants (i.e., moclobemide, brofaromine, toloxatone, Chart S1 in Supporting Information), and selective and reversible/irreversible MAO-B inhibitors have been shown as useful in the treatment of PD (i.e., rasagiline, lazabemide, safinamide, Chart S1). Recent reversible MAO-A inhibitors include amifuraline,[14] a selective peripheral inhibitor, and CX157,[15] specific for inhibition of MAO-A in human brain. Against MAO-B PF9601N,[16] endowed with antioxidant/neuroprotective properties in an experimental model of PD, and M-30,[17] a brain selective agent with antioxidant and neuroprotective properties for Alzheimer's disease, have been reported. In addition to neurological disorders, MAO-A seems to play a role in cardiac cellular degeneration[18] and high expression of MAO-A in normal basal prostatic epithelium, and high-grade primary prostate cancer (PCa) has been identified. Moreover, clorgyline has been shown to inhibit several oncogenic pathways in PCa cells, suggesting MAO-A inhibitors as prodifferentiation and antioncogenic agents for high-risk PCa.[19] Phenelzine directly and potently inhibits adipocyte lipid storage and differentiation,[20] while selegiline was a potent inducer for bone marrow stromal cell differentiation into neuronal phenotype.[21] Finally, MAO-A and -B are the major enzyme systems involved in vivo in the oxidative metabolism of xenobiotic amines, drugs in particular.[22]

Toloxatone (Humoryl), characterized by the presence of the oxazolidin-2-one as a core structure, was the first reversible and selective MAO-A inhibitor introduced in the clinical practice as antidepressant agent. Between 2002 and 2005, we reported a new series of 3-(1*H*-pyrrol-1-yl)-2-oxazolidinones (**1**) active as reversible, potent, and MAO-A selective inhibitors[23,24] (Figure 1) and the 3-(1*H*-pyrrol-2-yl)-2-oxazolidinone derivatives (**2**),[25] in which the 2-oxazolidinone nucleus was inserted at the C2 position of the pyrrole.

As a logical succession, we have now investigated the C3 position of the pyrrole, and we planned the synthesis of the 3-(1*H*-pyrrol-3-yl)-2-oxazolidinone derivatives **3**−**7**, shifting the 2-oxazolidinone nucleus at the pyrrole C3 position and introducing at the pyrrole N1 position three different alkyl

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groups (Figure 1), obtaining compounds active up to subnanomolar concentration.

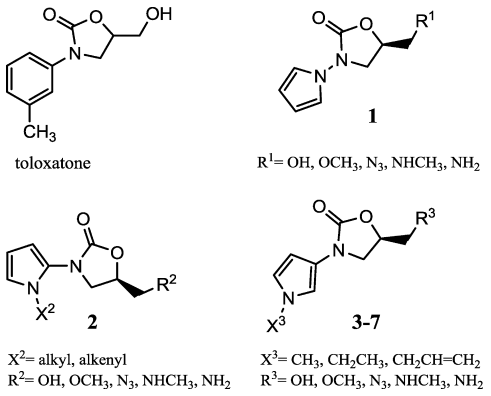


Figure 1. 1*H*-Pyrrolyl-2-oxazolidinones series.

CHEMISTRY

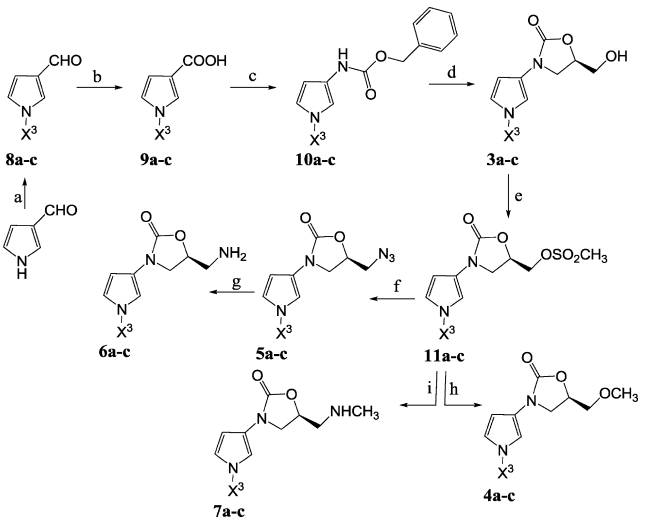
1-Alkyl-1*H*-pyrrole-3-carboxaldehydes **8a−c**, key intermediates for the synthesis of title compounds, were obtained by alkylation of 1*H*-pyrrole-3-carboxaldehyde[26] with the proper alkyl halide using potassium hydroxide as a base in dimethylsulfoxide. Afterward, 1-alkyl-1*H*-pyrrole-3-carboxylic acids **9a−c** were prepared by oxidation of the aldehydes **8a−c** with silver nitrate and 6 N sodium hydroxide in methanol or with potassium permanganate in water/2-propanone. After treatment with diphenylphosphorylazide, triethylamine, and benzyl alcohol in benzene at 80 °C, the carboxylic acids **9a−c** afforded the 1-alkyl-3-benzyloxycarbonylamino-1*H*-pyrroles **10a−c** through Curtius rearrangement of the intermediate acylazides. Further reaction of **10a−c** with *n*-butyllithium in hexane at −78 °C followed by addition of (*R*)-glycidyl butyrate to the lithiated species furnished directly, after spontaneous hydrolysis of the butyrate function, the (*R*)-5-hydroxymethyl-3-(1-alkyl-1*H*-pyrrol-3-yl)-2-oxazolidinones **3a−c**.

The alcohols **3a−c** were then converted into the corresponding (*R*)-5-methanesulfonyloxymethyl derivatives **11a−c** with methanesulfonyl chloride and triethylamine, and the mesylates **11a−c** were subjected to nucleophilic displacement with sodium methoxide in methanol (room temperature) or with sodium azide in *N*,*N*-dimethylformamide (65 °C) or methylamine in tetrahydrofuran (65 °C) to afford the (*R*)-5-methoxymethyl-, the (*R*)-5-azidomethyl-, or the (*S*)-5-methylaminomethyl-3-(1-alkyl-1*H*-pyrrol-3-yl)-2-oxazolidinones **4a−c**, **5a−c**, or **7a−c**, respectively. From the (*R*)-5-azidomethyl derivatives **5a−c**, the corresponding aminomethyl compounds **6a−c** have been obtained by catalytic reduction (Scheme 1). Chemical and physical data for **3−7** and **8−11** are listed in Tables S1 and S2 of Supporting Information. Synthetic procedures for the synthesis of **3**, **4**, and **6** are reported below. Synthetic procedures for the synthesis of **5** and **7−11** are reported in Supporting Information.

RESULTS AND DISCUSSION

3-(1*H*-Pyrrol-3-yl)-2-oxazolidinones **3−7** have been tested against MAO-A and MAO-B enzymes, in comparison with toloxatone as a reference drug. Inhibitory data of befloxatone,[27] a more recent oxazolidinone anti-MAO, have been also added for comparison. Bovine brain mitochondria have been used as

Scheme 1[a]



[a](a) (1) KOH, DMSO, room temp, 30 min; (2) X^3-I or X^3-Br, room temp, 1 h; (b) $AgNO_3$, NaOH, methanol, 70 °C or $KMnO_4$, 2-propanone/H_2O, room temp, overnight; (c) (1) $(PhO)_2PON_3$, Et_3N, benzene, 80 °C; (2) $PhCH_2OH$, benzene, 80 °C, overnight; (d) (1) *n*-BuLi, THF, N_2, −78 °C, 30 min; (2) (*R*)-glycidyl butyrate, N_2, 1 h, −78 °C, overnight at room temp; (e) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 15 min; (f) NaN_3, DMF, N_2, 65 °C, overnight; (g) H_2, Pd/C, 1 h, room temp; (h) CH_3ONa, MeOH, N_2, room temp, overnight; (i) CH_3NH_2, THF, 80 °C, sealed tube, overnight.

the enzyme source and were isolated according to Basford.[28] Activities of MAO-A and MAO-B have been determined by a fluorimetric method with kynuramine as a substrate at several different concentrations.[29] The K_i values against the two MAO isozymes and the A-selectivity (expressed as $K_{i\text{-MAO-B}}/K_{i\text{-MAO-A}}$) are reported in Table 1. All tested compounds showed higher

Table 1. Monoamine Oxidase Inhibitory Activity of Compounds 3−7[a]

			K_i, μM		
compd	X^3	R^3	MAO-A	MAO-B	SI[c]
3a	methyl	OH	1	>10	>10
3b	ethyl	OH	0.003	0.3	100
3c	allyl	OH	0.35	625	1786
4a	methyl	OCH_3	0.3	170	567
4b	ethyl	OCH_3	0.0006	1.3	2167
4c	allyl	OCH_3	0.001	200	200000
5a	methyl	N_3	0.2	360	1800
5b	ethyl	N_3	0.0008	20	25000
5c	allyl	N_3	0.004	100	25000
6a	methyl	NH_2	0.01	180	18000
6b	ethyl	NH_2	0.13	25	192
6c	allyl	NH_2	0.7	8	11
7a	methyl	$NHCH_3$	0.007	>100	>14286
7b	ethyl	$NHCH_3$	0.08	18	225
7c	allyl	$NHCH_3$	0.1	2	20
toloxatone			0.38	15	40
befloxatone[b]			0.0025	0.22	88

[a]Data represent mean values of at least three separate experiments. [b]Reference 27. [c]Selectivity index SI = K_i(MAO-B)/K_i(MAO-A).

anti-MAO-A than -MAO-B activity. Moreover, all derivatives displayed a reversible mode of action, since dialysis for 24 h in a

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cold room against 0.1 M potassium phosphate buffer (pH 7.2) was able to restore 90−100% of the enzyme activity.

In the alcoholic series (**3a−c**), the MAO-A inhibitory activity depends on the substituent at the pyrrole N1 position. In fact, when we changed the methyl or allyl group with the ethyl one, the inhibiting activity shifted from micromolar (**3a**, $K_{i\text{-}MAO\text{-}A}$ = 1 μM; **3c**, $K_{i\text{-}MAO\text{-}A}$ = 0.35 μM) to nanomolar level (**3b**, $K_{i\text{-}MAO\text{-}A}$ = 3 nM).

The 5-methoxymethyl derivatives **4a−c** showed an anti-MAO-A activity increasing from low micromolar to sub-nanomolar range (**4a**, $K_{i\text{-}MAO\text{-}A}$ = 0.3 μM; **4c**, $K_{i\text{-}MAO\text{-}A}$ = 1 nM; **4b**, 0.6 nM). Even in this series the ethyl group at the pyrrole N1 position was the most efficient substituent, despite the fact that the pyrrole N1-allyl derivative **4c** showed the highest MAO-A selectivity ratio (200000).

Among the azides **5a−c**, the 5-azidomethyl-3-(1-ethyl-1*H*-pyrrol-3-yl)-2-oxazolidinone (**5b**, $K_{i\text{-}MAO\text{-}A}$ = 0.8 nM) was almost as active as **4b** against MAO-A, while its MAO-B inhibitory concentration is 25000-fold higher than MAO-B. This series showed an activity trend similar to that of the 5-hydroxymethyl and 5-methoxymethyl series (N1-substituents potency degree: ethyl > allyl > methyl). In the 5-aminomethyl series **6a−c**, the compounds were endowed with a moderate inhibitory activity and MAO-A selectivity, they being active in the low micromolar range, with the exception of the pyrrole N1-methyl derivative **6a** that showed $K_{i\text{-}MAO\text{-}A}$ = 10 nM and SI = 18000.

Finally, the 5-methylaminomethyl compounds **7a−c** showed an inversion of the reported structure−activity relationship: an increase in the size of the pyrrole N1-substituent produced less active and selective derivatives (**7a**, $K_{i\text{-}MAOA}$ = 7 nM, $K_{i\text{-}MAOB}$ > 100 μM, SI ≥ 14286; **7c**, $K_{i\text{-}MAOA}$ = 0.1 μM, $K_{i\text{-}MAOB}$ = 2 μM, SI = 20).

In conclusion, we have reported a novel series of 5-substituted 3-(1-alkyl-1*H*-pyrrol-3-yl)-2-oxazolidinones **3−7** as reversible, highly potent, and selective anti-MAO-A agents. Compared to the related 3-(1*H*-pyrrol-1-yl)- and 3-(1*H*-pyrrol-2-yl)-2-oxazolidinones **1** and **2**,[23,25] **3−7** were in general more efficient in inhibiting MAO-A: the most potent derivatives **4b** and **5b** are about 5-fold more effective than the best-scoring compounds of the **1** and **2** series, and the unique SI shown by **4c** (200000) is about 20-fold higher than those displayed by the best compounds of **1** and **2**. With respect to toloxatone, **4b**, **4c**, and **5b** show 633-, 380-, and 475-fold higher MAO-A inhibitory activity, respectively. In comparison with befloxatone, **4b**, **4c**, and **5b** present similar anti-MAO-A activity but increased A-selectivity ratio. Such results suggest that these compounds could be useful as novel promising antidepressant agents.

EXPERIMENTAL SECTION

Chemistry. Melting points were determined on a Buchi 530 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz on a Bruker AC 400 spectrometer. Chemical shifts are reported in δ (ppm) units relative to the internal reference tetramethylsilane (Me_4Si). EIMS spectra were recorded with a Fisons Trio 1000 spectrometer; only molecular ions (M^+) and base peaks are given. All compounds were routinely checked by TLC and ^{1}H NMR. TLC was performed on aluminum-backed silica gel plates (Merck DC, Alufolien Kieselgel 60 F254) with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standard methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at reduced pressure of ~20 Torr. Organic solutions were dried over anhydrous sodium sulfate. Elemental analysis has been used to determine purity of the described compounds, that is >95%. Analytical results are within ±0.40% of the theoretical values (see Table S3 in Supporting Information). All chemicals were purchased from Aldrich Chimica, Milan (Italy), or from Alfa Aesar, Milan (Italy), and were of the highest purity.

General Procedure for the Synthesis of (*R*)-5-Hydroxymethyl-3-(1-alkyl-1*H*-pyrrol-3-yl)-2-oxazolidinones (3a−c). Example: Synthesis of (*R*)-5-Hydroxymethyl-3-(1-ethyl-1*H*-pyrrol-3-yl)-2-oxazolidinone (3b). *n*-Butyllithium (2.5 M in hexane, 3.3 mmol, 1.32 mL) was added dropwise, over a period of 5 min, under nitrogen atmosphere at −78 °C to a solution of 1-ethyl-1*H*-2-benzyloxycarbonylaminopyrrole **10b** (3.24 mmol, 0.79 g) in dry THF (10 mL). The mixture was stirred at −78 °C for 1 h. Then it was followed by addition of (*R*)-glycidyl butyrate (3.3 mmol, 0.47 mL). The resulting mixture was stirred initially at −78 °C for 1 h, and then it was kept at room temperature overnight. Afterward, the reaction was quenched by addition of saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL) and dried. The residue obtained upon evaporation of solvent was chromatographed over silica gel by eluting with ethyl acetate to give the alcohol **3b**. ^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3H, CH_2CH_3), 2.73 (bs, 1H, O*H* exchangeable with D_2O), 3.73−3.82 (m, 2H, NCH_2), 3.87−3.96 (m, 4H, CH_2OH and CH_2CH_3), 4.74 (m, 1H, OC*H*), 6.07 (m, 1H, pyrrole α proton), 6.56 (m, 1H, pyrrole β proton), 6.92 (m, 1H, pyrrole α proton) ppm. ^{13}C NMR ($CDCl_3$) δ 15.60, 47.0, 47.80, 62.30, 84.80, 103.60, 117.10, 121.80, 122.80, 153.0 ppm. MS (EI), m/z $[M]^+$: 210.1004.

General Procedure for the Synthesis of (*R*)-5-Methoxymethyl-3-(1-alkyl-1*H*-pyrrol-3-yl)-2-oxazolidinones (4a−c). Example: Synthesis of (*R*)-5-Methoxymethyl-3-(1-ethyl-1*H* -pyrrol-3-yl)-2-oxazolidinone (4b). A solution of sodium metal (3.43 mmol, 0.079 g atom) in methanol (5 mL) was added to (*R*)-5-methanesulfonyloxymethyl-3-(1-ethyl-1*H*-pyrrol-3-yl)-2-oxazolidinone **11b** (0.86 mmol, 0.25 g) in methanol (5 mL), and the resulting mixture was stirred under nitrogen atmosphere at room temperature overnight. The reaction was quenched with water and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL) and dried. The residue obtained upon evaporation of solvent was purified by column chromatography (silica gel, ethyl acetate/chloroform 1:1) to give the methoxymethyl derivative **4b** as a pure oil. ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3H, CH_2CH_3), 3.42 (s, 1H, OCH_3), 3.59−3.61 (m, 2H, NCH_2 and CH_2O), 3.72−3.76 (m, 1H, NCH_2), 3.85−3.94 (m, 3H, CH_2CH_3 and CH_2O), 4.69−4.76 (m, 1H, OC*H*), 6.05 (m, 1H, pyrrole β proton), 6.54 (m, 1H, pyrrole α proton), 6.91 (m, 1H, pyrrole α proton). ^{13}C NMR ($CDCl_3$) δ 15.60, 47.0, 52.20, 55.10, 103.60, 113.10, 117.10, 121.80, 122.80, 153.0 ppm. MS (EI), m/z $[M]^+$: 210.1004.

General Procedure for the Synthesis of (*S*)-5-Aminomethyl-3-(1-alkyl-1*H*-pyrrol-3-yl)-2-oxazolidinones (6a−c). Example: Synthesis of (*S*)-5-Aminomethyl-3-(1-ethyl-1*H*-pyrrol-3-yl)-2-oxazolidinone (6b). A suspension of (*R*)-5-azidomethyl-3-(1-ethyl-1*H*-pyrrol-3-yl)-2-oxazolidinone **5b** (2.38 mmol, 0.56 g), methanol (60 mL), and palladium on 10% carbon placed in a Parr apparatus was hydrogenated at 50 psi and 25 °C for 1 h. At last, palladium was filtered and methanol was evaporated to afford an oily residue that was chromatographed over silica gel by eluting with 9:1 chloroform/methanol to provide the amine derivative **6b** as a pure oil. ^{1}H NMR ($CDCl_3$) δ 1.90 (bs, 2H, NH_2 exchangeable with D_2O), 2.83−2.96 (m, 2H, CH_2NH_2), 3.61−3.69 (m, 1H, NCH_2), 3.85−3.94 (m, 3H, NCH_2 and CH_2CH_3), 4.52−4.67 (m, 1H, OCH), 6.36 (m, 1H, pyrrole β proton), 6.86 (m, 1H, pyrrole α proton), 7.08−7.30 (m, 1H, pyrrole α proton) ppm. ^{13}C NMR ($CDCl_3$) δ 15.60, 43.80, 47.0, 48.90, 87.0, 103.60, 117.1, 121.80, 122.80, 153.0 ppm. MS (EI), m/z $[M]^+$: 209.1164.

Mitochondria Preparation. See Supporting Information.

Biochemical Assay. All chemicals were commercial reagents of analytical grade and were used without further purification. In all experiments, MAO activity of the beef brain mitochondria was determined by a sensitive fluorimetric method according to Matsumoto et al.,[29] using kynuramine as a substrate at four different

final concentrations ranging from 5 μM to 0.1 mM. In all assays, the incubation mixtures contained 0.1 mL of 0.25 M potassium phosphate buffer at pH 7.4, 30 μL of mitochondria (from a homogenate solution, 6 mg/mL), and drug solutions. Drug derivatives were dissolved in dimethylsulfoxide (DMSO), and then added to the reaction mixture, at final concentrations ranging from 0 to 10^{-3} μM. The solutions were preincubated for 30 min at 38 °C before adding the substrate and then incubated for other 30 min at the same temperature. The inhibitory activities on MAO-A and -B were separately determined after incubation of the mitochondrial fractions for 30 min at 38 °C in the presence of their specific inhibitors (1 μM L-deprenyl to estimate MAO A activity and 1 μM clorgyline to assay the B isoform). Addition of perchloric acid ended the reaction. The samples were then centrifuged at 10000*g* for 5 min, and the supernatant was added to 2.7 mL of 0.1 N NaOH. Fluorometric measurements were recorded with a Perkin-Elmer LS 50B spectrofluorimeter, at λ_{exc} = 317 nm and λ_{em} = 393 nm. The protein concentration was determined according to Goa. Dixon plots were used to estimate the inhibition constant (K_i) of the inhibitors. Data represent the mean of three or more experiments each performed in duplicate.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Chemical and physical data for **3**−**11** and general procedures for the synthesis of **5** and **7**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

MAO, monoamine oxidase; 5-HT, 5-hydroxytryptamine; PEA, 2-phenethylamine; FAD, flavin adenine dinucleotide; ROS, reactive oxygen species; DNA, deoxyribonucleic acid; PCa, prostate cancer; MAOI, monoamine oxidase inhibitor; PD, Parkinson's disease; EDTA, ethylenediaminetetraacetic acid; PES, polyethersulfone

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