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Research Article

Monoamino Oxidase Inhibitors Activities of Some Synthesized 2,6-bis (Tetracarboxamide)-pyridine and Macrocyclic Octacarboxamide Derivatives

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Abstract

A series of chiral linear and macrocyclic bridged pyridines (1-8) has been prepared starting from pyridine-2,6-dicarbonyl dichloride and they screened as antimicrobial agents before. Screening of the compounds for their Inhibition of type A and type B monoamine oxidase activities in mitochondria preparation revealed that the tested compounds showed selective inhibition of type A monoamine oxidase activities in the following order 4a, 6, 5a, 3, 4b, 5b, 1, 4c, 7, 8 and 2, this confirmed by the *in vivo* tryptamine seizure potentiation model in rats. The tested compounds showed *in vivo* good pharmacokinetic and pharmacodynamic profiles.

Key words: Chiral linear compounds, macrocyclic pyridines, monoamino oxidase inhibitors

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

In the previous study, some of carboxamide pyridine derivatives have been pharmacological and biological activities such as: Reductase inhibitors (Al-Mohizea *et al*., 2012; Abdalla *et al*., 2012), Monoamine oxidase A and B inhibitors (Abdulla *et al*., 2013), EGFR, VEGFR-2 Kinase inhibitors (Abdulla *et al*., 2014), Orally Bioavailable CHK1 Inhibitors (Said *et al*., 2015) and SARS-CoV 3C like protease inhibitors (Mohamed *et al*., 2015). Monoamine oxidase inhibitors (MAOIs) are a class of medications used to treat depression. The MAOIs work with the chemicals in your brain-neurotransmitters that allows brain cells to communicate with each other. Depression is thought to be caused by low levels of the neurotransmitters dopamine, serotonin and norepinephrine, which collectively are called monoamines. A chemical found naturally in the body, monoamine oxidase, removes these neurotransmitters in the body. By inhibiting the monoamine oxidase, MAOIs allow more of the neurotransmitters to remain in the brain, thus elevating mood through improved brain cell communication (Rudorfer and Potter, 1989; Grady and Stahl, 2012; Gerlach *et al*., 2003; Riederer *et al*., 2004). Monoamine oxidase is a type of enzyme that helps neurons fire throughout the body. It is formed in the liver and cleans up neurotransmitters in the brain once they have done their jobs. Besides clearing out the neurotransmitters, monoamine oxidase cleans out tyramine, a chemical that helps regulate blood pressure (Shih and Thompson, 1999; Chiba *et al*., 1984; Fritz *et al*., 1985). The major side effect with the use of first generation of non-selective monoamine oxidase (MAO) inhibitors as neuropsychiatric drugs was what became known as the "Cheese reaction". Namely, potentiation of sympathomimetic activity of ingested tyramine present in cheese and other food stuff, resulting from its ability to release noradrenaline, when prevented from metabolism by MAO (Knoll and Magyar, 1972; Westlund *et al*., 1985). The identification of two forms of MAO, termed types A and B and their selective irreversible inhibitors resolved some of this problems (Bach *et al*., 1988; Johnston, 1968). However irreversible MAO-A inhibitors continue to induce a cheese reaction, whereas MAO-B inhibitors at their selective dosage did not and led to introduction of L-deprenyl (selegiline) as an anti-Parkinson drug, since dopamine is equally well metabolized by both enzyme forms (Liebowitz *et al*., 1990). In the previous study, some heterocyclic coumarin derivatives have been synthesized and evaluated as monoamine oxidase A inhibitors (Abdelhafez *et al*., 2012; Matos *et al*., 2015). The design, synthesis, pharmacological evaluation and theoretical studies of a new series of halogenated 3-arylcoumarins were carried out with the aim of finding new structural and biological features. Finally, the prediction of passive blood-brain partitioning, based on in silico derived physicochemical descriptors was performed (Matos *et al*., 2014, 2011). In view of these observations, we screened some of synthesized 2,6-bis(tetracarboxamide)-pyridine and macrocyclic octacarboxamide derivatives as monoamino oxidase inhibitors.

MATERIALS AND METHODS

Chemistry: All the tested compounds were confirmed by physical and spectroscopic evidences according to the previously reported procedures (Al-Omar and Amr, 2010; Al-Salahi *et al*., 2010).

Pharmacological screening

Experimental animals: All animals were obtained from National Research Center, Cairo, Egypt, Giza, Egypt and were acclimatized for 10 days under standard housing conditions (24±1°C, 45-55% RH with 12:12 h light per dark cycle). The animals had free access to rat food (Lipton Gold Mohr, India) and water. The animals were habituated to laboratory conditions for 48 h prior to the experimental protocol to minimize any nonspecific stress. The experimental protocol was approved by the Institutional Animal Ethics Committee by Government College of Pharmacy, Karad, India and animals were maintained under standard conditions in the animal house approved by Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA).

Inhibition of type A and type B monoamine oxidase activities in Mitochondria preparation

Mitochondria preparation: Mitochondria were prepared according to Basford (1967). Reagents: Medium A contained 0.4 M sucrose, 0.001 EDTA, 0.02% polyethersulfone (PES) or heparin and pH was adjusted to 6.8-7.0 with KOH, Medium F made was made up of the medium A to which ficoll was added to a final concentration of 8%. Calf or beef brains were removed from the animals within 5-10 min after their death. The brains were immediately placed in cold medium A, stored on ice and then transported to the laboratory. In a cold room, at 5°C, the cerebral hemispheres were removed from the brains and the meninges were taken up with forceps. The gray matter was scraped from the cortices using a dull spatula. Two brains yield corresponded to about 100 g of wet tissue, which was homogenized in Medium A (2 mL g^{-1} of wet tissue). The

homogenate was kept at pH 7.0 by adding some drops of tris-buffer 2 M; 1 mg of e-aminocaproic acid/g of tissue was added and then the mixture was stirred at 0-4°C for 15 min. The suspension was diluted with medium A (20 mL g^{-1} of the original tissue), centrifuged first at 184 g for 20 min and then at 1153 g for 20 min, without transferring of the supernatant. The residue R1 was discarded while the supernatant S1 was centrifuged at 12,000 g for 15 min, to yield a crude mitochondria pellet R2 (the supernatant S2 which is discarded). The fraction R2 was dissolved in Medium F (6 mL g^{-1} of original tissue), gently homogenized and centrifuged at 12,000 g for additional 30 min. The resulting mitochondria fraction R3 was washed using 4 mL of Medium A/g of original tissue and again centrifuged at 12,000 g for 15 min. The final mitochondria fraction R4 was homogenized in potassium phosphate buffer pH 7.4, 0.25 M. Yield of mitochondria protein obtained was between 100 and 140 mg/50 g wet weight of original tissue.

Monoamine oxidase activity assay: Monoamine oxidase activity was determined using kinuramine as a substrate, at four different final concentrations ranging from 5 μM to 0.1 mM, by a sensitive fluorometric assay according to Matsumoto *et al.* (1985). In all assays the incubation mixtures contained: Potassium phosphate buffer, pH 7.4, mitochondria (6 mg mL^{-1}), drug solutions in DMSO, added to the reaction mixture at a final concentration ranging from 0 to 10-9. Solutions were preincubated for 30 min before adding the substrate and then incubated for others 30 min. The inhibitory activities against MAO-A and MAO-B were determined at 38°C, after incubation of the mitochondrial fractions for 30 min in the presence of the specific inhibitor (L-deprenyl (1 μM) or clorgyline (1 μM) to estimate the MAO-A and MAOB activity, respectively). The addition of perchloric acid ended the reaction. Then the samples were centrifuged at 10,000g for 5 min and the supernatant was added to 2.7 mL NaOH 1N.

Fluorometric measurements were recorded at λ_{max}. The 317 nm and λ_{max} 393 nm using a Perkin-Elmer LS 50B spectrofluorometer. Dixon plot were used to estimate the inhibition constant (Ki) of the inhibitors. Data are the means of three or more experiments each performed in duplicate (Matsumoto *et al.*, 1985).

Monoamine oxidase inhibition

Inhibition of type A and type B monoamine oxidase activities in rat brain synaptosomes

Tissue preparation: Male Wistar rats weighing 150-250 g are sacrificed and the brains rapidly removed. Whole brain minus cerebellum is homogenized in 9 volumes of ice-cold, phosphate-buffered 0.25 M sucrose, using a Potter-Elvejhem homogenizer. The homogenate is centrifuged at 1 000 g for 10 min and the supernatant decanted and recentrifuged at 18000 g for 20 min. The resulting Pellet (P2) is resuspended in fresh 0.25 M sucrose and re-centrifuged at 18000 g for 20 min. The washed pellet is resuspended in the original volume of 0.25 M sucrose and serves as the tissue source for mitochondrial monoamine oxidase.

Assay (Fankhauser *et al.*, 1994):

- 50 μL 0.5 M PO_4 buffer, pH 7.4
- 450 μL H_2O
- 100 μL H_2O or appropriate drug concentration
- 200 μL tissue suspension

The tubes are preincubated for 15 min at 37°C and the assay is started by adding 100 μL of substrate (^{14}C-5-HT or ^{14}C β-phenylethylamine) at 10 sec intervals. The tubes are incubated for 30 min at 37°C and the reaction is stopped by the addition of 0.3 mL of 2 N HCl. Tissue blank values are determined by adding the acid before the substrate. Seven milliliter of diethylether are added, the tubes are capped and shaken vigorously for 10 min to extract the deaminated metabolites into the organic phase, which is separated from the aqueous phase by centrifugation at 1000 g for 5 min. A 4 mL aliquot of the ether layer is counted in 10 mL of liquid scintillation counting cocktail. The percent inhibition at each drug concentration is the mean of triplicate determinations. IC_{50} values are determined by log-probit analyses. For example, deprenyl shows IC_{50} values of 3.9×10^{-6} against MAO A and 3.0×10-8 against MAO B.

***In vivo* tryptamine seizure potentiation in rats:** Groups of 5 male Wistar rats weighing 150-200 g are used. Test compounds, standard or vehicle controls are administered intraperitoneally 0.5, 1, 2 and 4 h prior testing. At the time of testing 5 mg kg^{-1} tryptamine HCl freshly dissolved in saline are injected intravenously. Immediately after tryptamine HCl administration, the animals are observed individually for 3 min for the appearance of clonic "Pedalling" movements of the forepaws which is considered a positive response. Frequently, these clonic seizures are preceded by a kyphotic curvature of the spine but this sign does not constitute a positive response. In addition to the vehicle control group, a series of five positive control animals receiving tranylcypromine at 5 mg kg^{-1} i.p. with a 0.5 h pretreatment time are subjected to the test in order to check

the effectiveness of the tryptamine HCl solution which is relatively unstable. A 100% response is expected. Fresh tryptamine HCl solution should be prepared hourly as needed. An ED_{50} is calculated using probit analysis (Grahame-Smith, 1971).

Measurement of drug levels in plasma and in different organ samples: Drug levels in plasma and in different organ samples were measured by liquid chromatography as previously described (Weggen *et al*., 2003). Briefly, samples were prepared by adding 300 µL acetonitrile and 40% phosphoric acid 40-100 µL plasma or organ homogenate and placing the mixture in a vortex for 5 sec plasma and brain samples were then centrifuged at 14,000 rpm for 5 min and the supernatants (15 and 50 µL, respectively) were injected into the HPLC system coupled with MS. Equipment system with mass spectrometry (API 2000, applied biosystems, Foster City, CA, USA with MassLynx Showroom) detector were used. The chromatographic conditions were adapted to each compound to obtain good peak separation and detection sensitivity. Temperature was maintained at 25°C by a thermo stated cell holder. Measurements with The flow rate 0.22 mL min^{-1} a mixture of ammonium formate (20 µM) bufferacetonitrile-methanol was used as mobile phase. For drugs s in Mass the assay was liner between 400 and 20,000 ng g^{-1} in the organ and 100-8500 ng mL^{-1} in plasma.

RESULTS AND DISCUSSION

Chemistry: In continuation of our previous study, a series of peptide derivatives 1-8 (Fig. 1) were synthesized in advance and screened as antimicrobial agents (Al-Omar and Amr, 2010; Al-Salahi *et al*., 2010). Herein, these compounds for used evaluation of monoamino oxidase inhibitors.

Pharmacological evaluation: Chalcones and aurones that considered as macromolecules were synthesized and evaluated *in vitro* as monoamine oxidase inhibitors (MAOi). The previous results show that aurones, which had not been previously reported as MAOi, are MAO-B inhibitors. Thus, both families inhibited selectively the B isoform of MAO in the micromolar range, offering novel scaffolds for the design of new and potent MAO inhibitors. The main structural requirements for their activity were characterized with the aid of 3D-QSAR and docking studies (Morales-Camilo *et al*., 2015). A series of (coumarin-3-yl)carbamates was synthesized and evaluated in vitro as monoamine oxidase (MAO-A and MAO-B) inhibitors. Most of these compounds selectively inhibited MAO-B isoenzyme with IC_{50} values in the micro or nanomolar ranges (Matos *et al*., 2013). Additionally, some of 2-phenoxyacetamide analogues were synthesized and their inhibitory potency towards monoamine oxidases A (MAO-A) and B (MAO-B) were evaluated using enzyme and cancer cell lysate. 2-(4-Methoxyphenoxy)acetamide (SI = 245) and (2-(4-((prop-2-ynylimino)methyl)phenoxy) acetamide (IC_{50} MAO-A = 0.018 µM, IC_{50} MAO-B = 0.07 µM) were successfully identified as the most specific MAO-A inhibitor and the most potent MAO-A/-B inhibitor, respectively (Shen *et al*., 2014). Some new pharmacological new aspects in the filed of MAOIs have been discovered (Abdulla *et al*., 2013) and several coumarines derivatives having MAOIs activities (Abdelhafez *et al*., 2012; Orallo *et al*., 2002; Matos *et al*., 2009; Binda *et al*., 2007). So far, among several MAO inhibitors, some synthesized derivatives have been described as good inhibitory MAO activity (Matos *et al*., 2010; Chimenti *et al*., 2004, 2009; Gnerre *et al*., 2000; Santana *et al*., 2006).

Monoamine oxidase activity assay: Bovine brain mitochondria were isolated according to Basford (1967) and they used as source of the two MAO isoforms. Clorgyline (A-selective, irreversible), moclobemide (A-selective, irreversible), selegiline (L-deprenyl) (B-selective, irreversible), lazabemide (B-selective, reversible) and ladostigil (non-selective, irreversible) were used as reference drugs. MAO-A and MAO-B activities were determined by a fluorometric assay, using kynuramine as a substrate, in the presence of their specific inhibitors (L-deprenyl 1 µM for MAO-A and clorgyline 1 µM for MAO-B) (Westlund *et al*., 1985).

The inhibitory activities (Ki) and A-selectivity (SI) of the tested compounds are depicted in Table 1. All compounds

Table 1: MAO-A and B inhibitory activities (Ki) and Selectivity (SI) of the tested compounds (1-8)[a]

Compound No	Ki (nM) MAO-A	Ki (nM) MAO-B	Si[a]
1	0.022	56.78	2580.91
2	0.027	77.23	2860.37
3	0.017	43.65	2567.65
4a	0.010	23.45	2345.00
4b	0.018	45.78	2543.33
4c	0.023	59.86	2602.61
5a	0.015	41.56	2770.67
5b	0.021	49.67	2365.24
6	0.013	39.56	3043.08
7	0.025	61.67	2466.80
8	0.026	70.56	2713.84
Clorgyline[b]	0.054	58.00	1074.10
Moclobemide[b]	11.500	>100.00	>87
Selegiline[b]	3.800	0.97	0.25

[a]Data represent mean values (three significant digits) for at least three separate experiments each performed in duplicate. Standard errors were within 1%, [b]Selectivity index (SI): Ki (MAO-B)/Ki (MAO-A) ratio

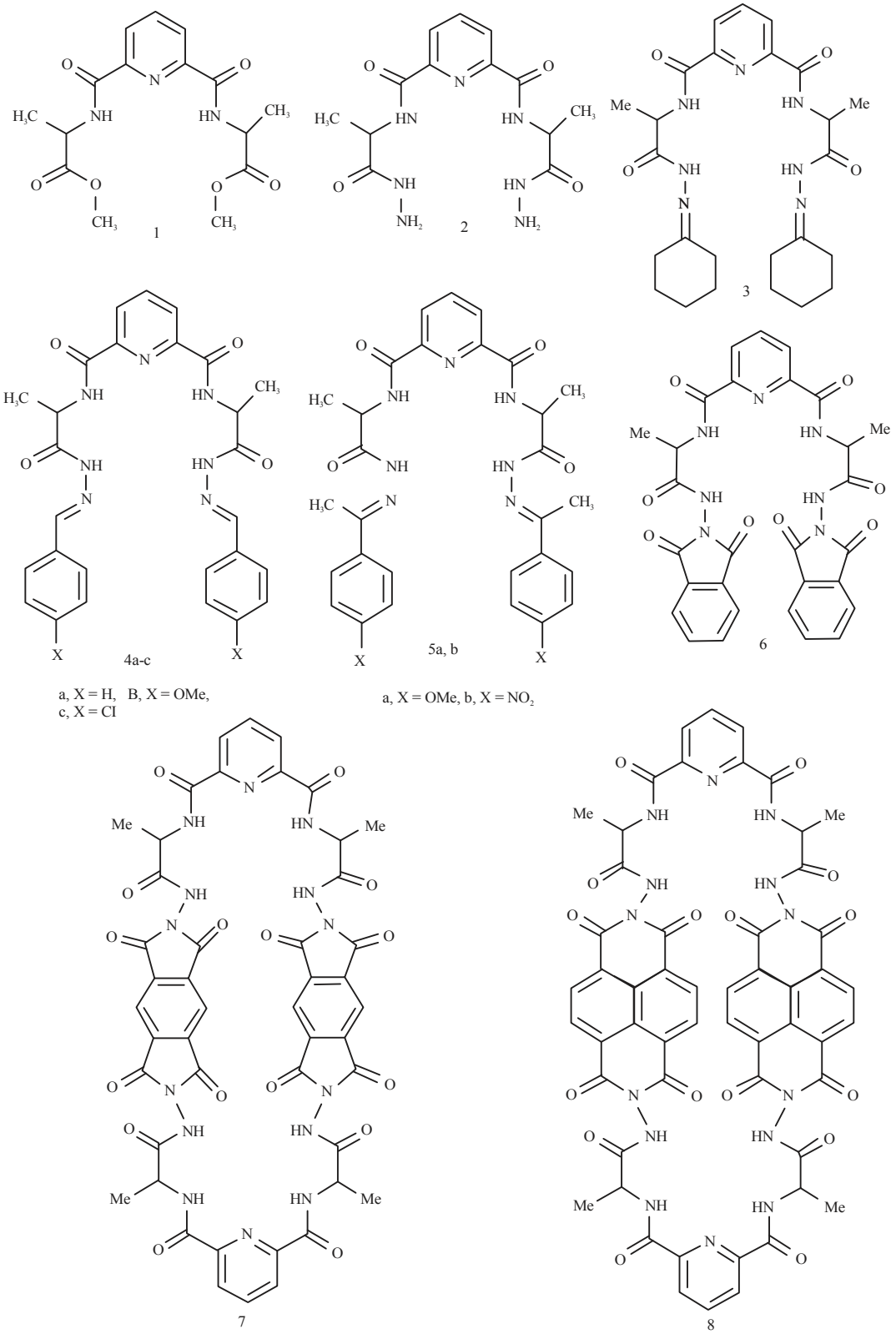

Fig. 1: Chemical structure for the tested compounds

were non competitive reversible inhibitors; the enzyme activity (approx. 95-100%) was restored after 24 h dialysis at 5°C (dialysis was performed in the presence of 0.1 M potassium phosphate buffer at pH 7.2. In these experimental

conditions the substrate did not compete with the inhibitor. Accordingly, a decrease of V_{max} was observed while the Km value was unchanged. All the tested compounds inhibited MAO-A at submicromolar concentration, all compounds had Ki values in the nanomolar range. All compounds inhibited MAO-B at nanomolar concentration and compounds had Kis in the low nanomolar range. Selectivity Indexes (SIs) ranged from 2345.00-3141.82. Generally, all compounds had potent MAO-A inhibitors and MAO-B inhibitors activity (Table 1) but MAO-A inhibitors activity were more potent than the MAO-B inhibitors activity. The compounds are arranged in the following order 4a, 6, 5a, 3, 4b, 5b, 1, 4c, 7, 8 and 2. It is worth mentioned that all compounds are more potent than clorgyline, moclobemide and selegiline.

Inhibition of type A and type B monoamine oxidase activities in rat brain synaptosomes: The mood-elevating effects of the antituberculosis drug iproniazid have been observed clinically. The mode of action was elucidated to be the inhibition of the enzyme monoamine oxidase. This was followed by wide use of monoamine oxidase inhibitors for the treatment of depression. However, side effects due to interaction with dietary amines have been observed. The biological role of monoamine oxidase is to regulate the levels of endogenous amines (norepinephrine, dopamine and serotonin) and exogenously administered amines. Based on different substrate and inhibitor specificities two forms of monoamine oxidase (A and B) were described. Dopamine and tyramine are substrates for types, serotonin and epinephrine are substrates for type A and β-phenylethyl amine and benzylamine are substrates for type B. Iproniazid and tranylcypromine are nonselective inhibitors, clorgyline is a selective inhibitor of type A, deprenyl and pargyline are selective inhibitors of type B. It has been suggested that treatment with selective blockers of type B results in less detrimental food interactions. The IC_{50}-values of compounds against were determined and given in Table 2. Generally, all compounds had potent MAO-A inhibitors and MAO-B inhibitors activity (Table 2) but MAOA inhibitors activity were more potent than the MAO-B inhibitors activity. The compounds are arranged in the following order 4a, 6, 5a, 3, 4b, 5b, 1, 4c, 7, 8 and 2. It is worth mentioned that all compounds are more potent than depranyl.

***In vivo* tryptamine seizure potentiation in rats:** Monoamino-oxydase (MAO) inhibitors like iproniazid enhance seizures in rats caused by an intravenous infusion of tryptamine HCl. This procedure can be used to elucidate the *in vivo* MAO inhibiting properties of compounds. Generally, all compounds had potent MAO-inhibitors and arranged in the following order 4a, 6, 5a, 3, 4b, 5b, 1, 4c, 7, 8 and 2 as in Table 3.

The *in vivo* pharmacokinetic and pharmacodynamic profiles of the tested compounds were verestile as shown in Table 4.

Table 2: IC_{50}-values of compounds (1-8) against type A and type B monoamine oxidase activities in rat brain synaptosome

Compound No.	IC_{50} values (nM) of against MAO-A	IC_{50} values (nM) of against MAO-B
1	2.91×10^{-9}	50.67×10^{-6}
2	3.49×10^{-9}	88.12×10^{-6}
3	1.67×10^{-9}	47.54×10^{-6}
4a	1.22×10^{-9}	30.21×10^{-6}
4b	2.76×10^{-9}	48.98×10^{-6}
4c	3.09×10^{-9}	54.78×10^{-6}
5a	1.55×10^{-9}	40.11×10^{-6}
5b	2.89×10^{-9}	49.39×10^{-6}
6	1.31×10^{-9}	37.89×10^{-6}
7	3.22×10^{-9}	67.89×10^{-6}
8	3.27×10^{-9}	74.56×10^{-6}
Deprenyl	3.90×10^{-6}	3.00×10^{-8}

All data represent mean values (three significant digits) for at least three separate experiments each performed in duplicate. Standard errors were within 1%

Table 3: ED_{50} (μM) of the tested compounds (1-8) as *in vivo* tryptamine seizure potentiation in rats

Compound No.	ED_{50} (μM)
1	0.27
2	0.39
3	0.22
4a	0.12
4b	0.23
4c	0.35
5a	0.15
5b	0.24
6	0.13
7	0.37
8	0.38
Deprenyl	0.30

All data represent mean values (three significant digits) for at least three separate experiments each performed in duplicate. Standard errors were within 1%

Table 4: *In vivo* pharmacokinetic and pharmacodynamic profiles of the some tested compounds (1-8) were evaluated in at the end of experiment in (nM)

Compound No.	Plasma drug conc in male wistar rats experiment (nM)	brain drug conc in male Wistar rats experiment (nM)
1	25.53	8.76
2	34.66	5.76
3	12.80	1.43
4a	19.98	2.48
4b	23.35	6.50
4c	32.89	7.75
5a	16.95	2.35
5b	34.64	9.64
6	17.32	4.56
7	23.21	9.84
8	28.76	3.37

CONCLUSION

All compounds showed potent inhibitors activity against MAO A and B but they are more potent against Type A than Type B. Also in the *in vivo* evaluation of MAO inhibitors activity in the tryptamine seizure potentiation in model rats, all the compounds showed potent activity and arranged in the following order 4a, 8, 6, 5a, 3, 4b, 5b, 1, 4c, 7 and 2.

Structural activity relationship: Careful studying of the relation between the chemical scaffold and the pattern of activity leads to the following SAR points:

- Open chain small molecules give more potent activity than cyclic macromolecular ones
- As the size of the macromolecule increases the activity decreases
- Increasing polarity and hydrophillicity decreases the activity (cf., compound 2 less active than compound 3)

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