Monoamine Oxidase A and B Inhibitors of Some Synthesized Heterocyclic Derivatives and Their Structure Activity Relationships

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Abstract: We herein report the monoamine oxidases A and B inhibitors of some synthesized substituted pyrimidines, thiazolopyrimidines and pyrazoles derivatives. Seventeen pyrimidine, thiazolo-pyrimidine, pyrazole, and pyridine derivatives **1-17** containing a carboxamide, ester, amide and ketone groups attached to a heterocyclic moiety synthesized and screened for their monoamine oxidases A and B inhibitors activities. The newly synthesized derivatives containing pyrimidine, thiazolopyrimidine, pyrazole, and pyridine moieties linked with different function groups considered as a lead for potent monoamine oxidases A and B inhibitors agents. The detailed synthetic pathways of obtained compounds and monoamine oxidases A and B inhibitors were reported.
[Mohamed M. Abdulla, Mohamed A. Al-Omar and Abd El-Galil E. Amr. **Monoamine Oxidase A and B Inhibitors of Some Synthesized Heterocyclic Derivatives and Their Structure Activity Relationships.** *Life Sci J* 2013; 10(4):327-335] (ISSN: 1097-8135). http://www.lifesciencesite.com. 43

Keywords: 5-Chloroanisic acid; Pyrimidines; Thiazolopyrimidine; monoamine oxidases A and B inhibitors; SAR.

1. Introduction

In our previous work, we reported that certain substituted pyridines and their chiral macrocyclic derivatives have anticancer, antimicrobial, analgesic, anti-inflammatory and anticonvulsant activities (Al-Mohizea et al., 2012; Al-Harbi et al., 2013; Amr et al., 2006, 2005; Bahashwan et al., 2012; Abo-Ghalia and Amr, 2004 and Hammam et al., 2003). Some substituted heterocyclic derivatives showed anti-inflammatory (Al-Omar et al., 2010; Xu et al., 2001) and anticancer agents (Bailly et al., 1999; van Hattum et al., 2002; He et al., 2003) and also showed analgesic activities (Abdel Salam et al., 2013; Yang et al., 2002; Min et al., 2003). Recently, some new substituted pyridine, and pyrazolopyrimidine derivatives has been synthesized and showed potent analgesic, anticonvulsant, anti-parkinsonism, hypoglycemic and anti-microbial activities (Al-Harbi et al., 2013; Bahashwan et al., 2012; Abdel Salam et al., 2013; Alanazi et al., 2013). On the other hand, substituted heterocyclic derivatives showed different promising biological activities (Attia et al., 1995, 1997, 2000).

Monoamine oxidases (MAOs) are FAD depending enzymes responsible for the regulation and metabolism of major monoamine neurotransmitters [5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA)], modulating their concentrations in the brain and peripheral tissues (Shih, et al., 1999). They are also involved in the biodegradation of exogenous amines such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into 1-methyl-4-phenyl pyridinium (MPP+), a Parkinson producing neurotoxin (Chiba, et al., 1984; Fritz, et al., 1985; Grimsby, et al., 1997). The MAO enzyme exists in two forms, namely MAO-A and MAO-B, distinguishable by their molecular cloning, substrate and inhibitor selectivity, and tissue distribution (Bach et al., 1988; Johnston et al., 1968; Kalgutka et al., 1995; Westlund et al., 1985). MAO-A preferentially oxidizes serotonin and is irreversibly inhibited by low concentrations of clorgyline, while that of the B isoform preferentially oxidizes β-phenylethylamine (PEA) and benzylamine and it is irreversibly inactivated by low concentrations of L-deprenyl (Knoll et al., 1972). Dopamine, tyramine, and tryptamine are common substrates for both MAOs. In fact, human MAO-A inhibitors are antidepressants and antianxiety agents (Rudorfer, et al., 1989), while human MAO-B inhibitors are used alone or in combination with other drugs in the therapy of Alzheimer's and Parkinson's diseases (Gerlach et al., 2003; Riederer et al., 2004). In view of these reports and as a continuation of our previous works in fused poly-heterocyclic ring systems, herein we screened some of newly synthesized substituted thioxopyrimidine, and thiazolopyrimidine for the their monoamine oxidases A and B inhibiting activities.

2. Experimental

Chemistry

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data (in accord with the

calculated values) were obtained from the microanalytical unit, Cairo University, Cairo, Egypt. The IR spectra (KBr) were recorded on a Shimadzu CVT-04 spectrophotometer. The ^{1}H NMR spectra were measured with Jeol 270 MHz in *DMSO-d_6* or $CDCl_3$. The chemical shifts were recorded in (δ, ppm) relative to *TMS*. The mass spectra were obtained using a Varian MAT CH-5 spectrometer (70 eV). All reactions were followed by TLC (silica gel, aluminum sheets 60 F_{254}, Merck). All the tested compounds were synthesized and confirmed by using analytical and spectral data according to the previously reported literature (Mohamed, 2008).

Biological assay

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 ºC, 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 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 ºC for 15 min. The suspension was diluted with Medium A (20 mL/g of the original tissue), centrifuged first at 184g for 20 min and then at 1153g for 20 min, without transferring of the supernatant. The residue R1 was discarded while the supernatant S1 was centrifuged at 12,000g 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 of original tissue), gently homogenized and centrifuged at 12,000g 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 12,000g 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 per 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), 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 ºC, 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 percloric 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}. 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.

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 18 000 *g* for 20 min. The resulting pellet (P2) is resuspended in fresh 0.25 M sucrose and recentrifuged at 18 000 *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 (*Frankhauser, 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 (14C-5-HT or ^{14}C β-phenylethylamine) at 10 s 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 ml 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 1 000 *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 (Graham-Smith, 1971)**

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 tryptamine HCl freshly dissolved in saline are injected intravenously. Immediately after tryptamine HCl administration, the animals are observed individually for three 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 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.

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 300µl acetonitrile and 40µl phosphoric acid 40% to 100µl plasma or organ homogenate and placing the mixture in a vortex for 5 s. 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. Equipment system with mass spectrometry (API2000, 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/minA mixture of ammonium formate (20 µM) buffer-acetonitrile-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.

3. Results and discussions

Chemistry

In a continuation to our previous work, that leads to synthesis of potent anti-arrhythmic substituted pyrimidine, thiazolopyrimidine, pyrazole, and pyridine derivatives **1-17** (Figs. 1-3) (Mohamed, 2008). Herein we screened these compounds for theirs Monoamine Oxidase A and B Inhibitors activities.

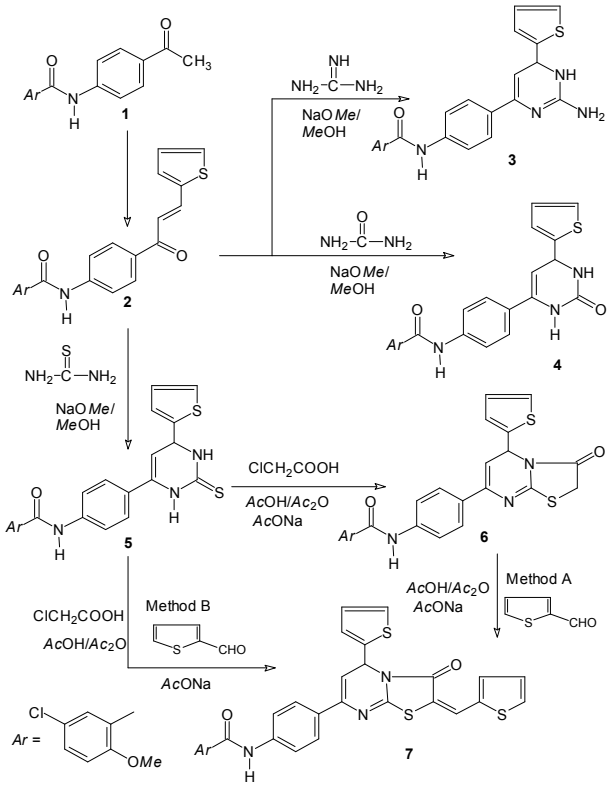

Figure 1. Synthetic pathway of compounds **1-7**

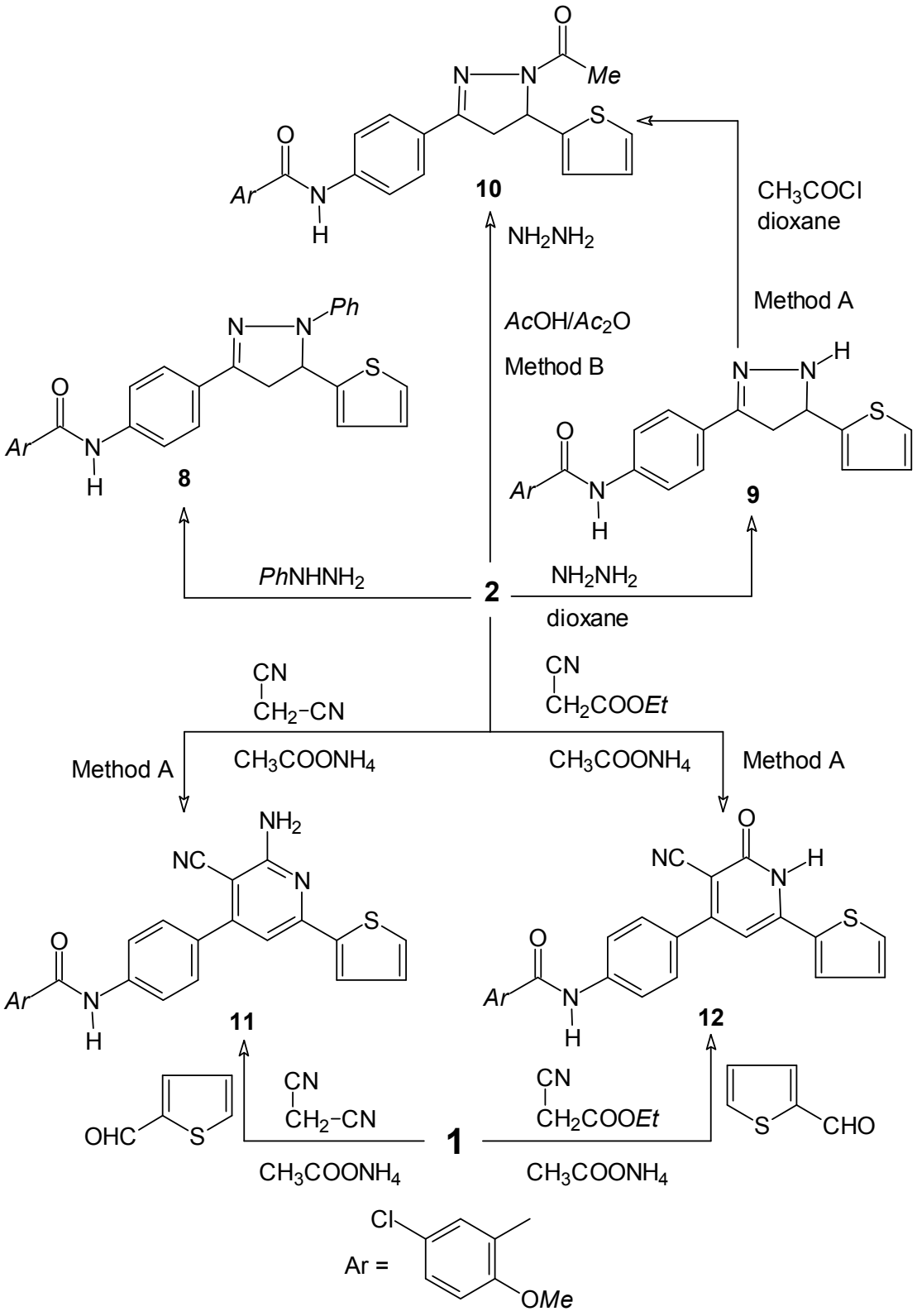

Figure 2. Synthetic pathway of compounds **8-12**

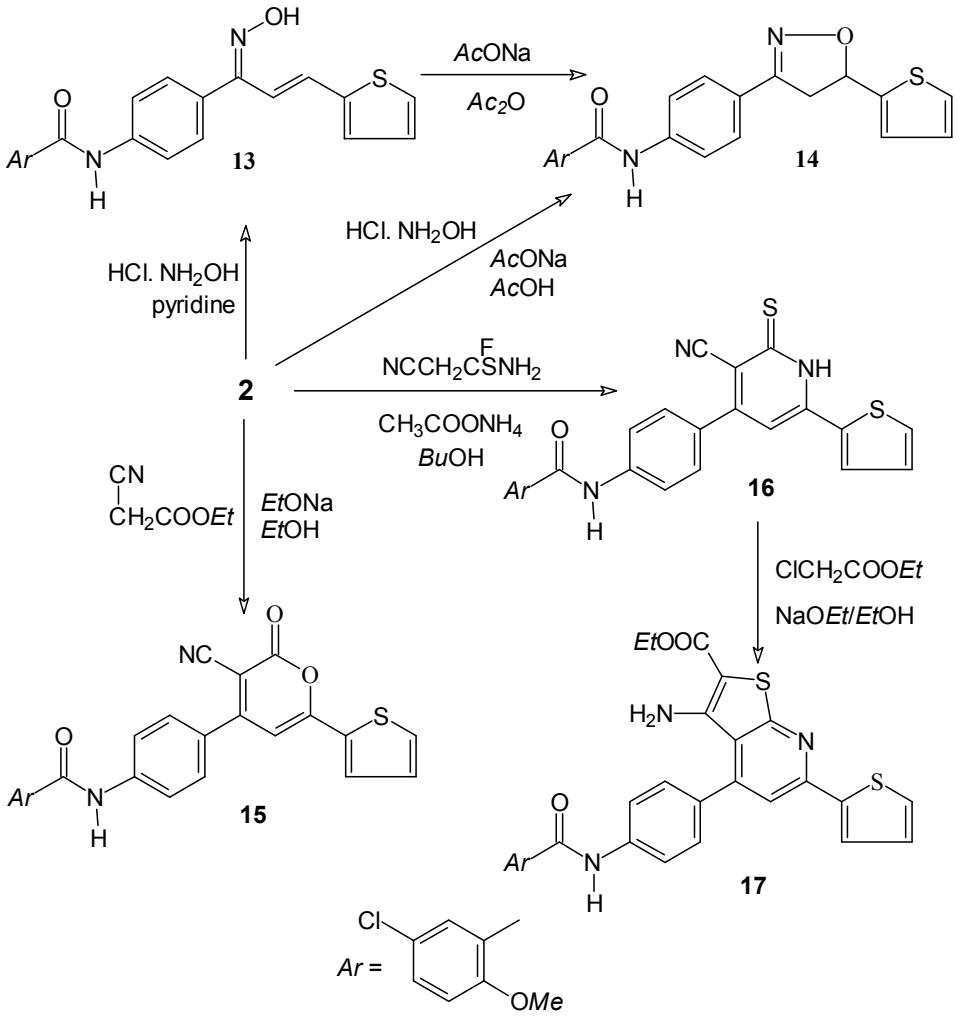

Figure 3. Synthetic pathway of compounds **13-17**

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), 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 µlM for MAO-B) [36].

The inhibitory activities (Ki) and A-selectivity (SI) of the tested compounds are depicted in Table 1. All 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 K_m 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 micromolar concentration, and compounds had Kis in the low nanomolar range. The selectivity indexes (SIs) ranged from 88,478 to 1074.

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 descending order **7, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2,** and **1**. It is worth mentioned that all compunds are more potent than Clorgyline, Moclobemide and Selegiline.

Table 1: MAO-A and B Inhibitory Activities (Ki; pM), and Selectivity (SI) of the Tested Compounds [a]

Comp. No	Ki (μM) MAO-A	Ki (μM) MAO-B	SI[a]
1	0.000985	0.087	88.32487
2	0.000966	0.084	86.95652
3	0.000956	0.083	86.82008
4	0.000866	0.079	91.22402
5	0.000857	0.078	91.01517
6	0.000747	0.077	103.079
7	0.000738	0.066	89.43089
8	0.000649	0.065	100.1541
9	0.000560	0.064	114.2857
10	0.000530	0.059	111.3208
11	0.000519	0.058	111.7534
12	0.000458	0.057	124.4541
13	0.000447	0.047	105.1454
14	0.000436	0.046	105.5046
15	0.000335	0.045	134.3284
16	0.000324	0.044	135.8025
17	0.000223	0.043	192.8251
Clorgyline[b]	0.054	58	1074.1
Moclobemide[b]	11.5	>100	>87
Selegiline[b]	3.8	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%. bSI (selectivity index) = Ki (MAO-B)/Ki (MAO-A) ratio. [b] Lit. 8.

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-phenylethylamine 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. 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 MAO-A inhibitors activity were more potent than the MAO-B inhibitors activity. The compounds are arranged in the following descending order **7, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2**, and **1**. It is worth mentioned that all compunds are more potent than depranyl.

Table 2: IC_{50}-values of compounds against type A and type B monoamine oxidase activities in rat brain synaptosomes

Comp. No	IC_{50}-values (μM) of against MAO-A	IC_{50}-values of (μM) against MAO-B
1	33.57×10^{-16}	18.63×10^{-9}
2	29.97×10^{-16}	17.43×10^{-9}
3	29.76×10^{-16}	16.83×10^{-9}
4	28.75×10^{-16}	15.94×10^{-9}
5	27.64×10^{-16}	14.54×10^{-9}
6	26.43×10^{-16}	13.65×10^{-9}
7	23.82×10^{-16}	12.86×10^{-9}
8	21.73×10^{-16}	11.79×10^{-9}
9	18.43×10^{-16}	9.38×10^{-9}
10	17.64×10^{-16}	8.27×10^{-9}
11	16.55×10^{-16}	7.36×10^{-9}
12	15.78×10^{-16}	6.45×10^{-9}
13	13.57×10^{-16}	4.54×10^{-9}
14	11.36×10^{-16}	3.65×10^{-9}
15	9.45×10^{-16}	2.76×10^{-9}
16	8.24×10^{-16}	1.87×10^{-9}
17	7.23×10^{-16}	0.98×10^{-9}
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%.

***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 descending order **7, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2,** and **1** Tables 3 and 4.

4. Conclusion

All compounds showed potent inhibitors activity against MAO A&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 descending order **7, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2**, and **1**. Compound **1** showed potent MAOI activity and when it converted to its thiophene aldol condensed product **2** the activity increased. Derivative **2** reacted with guanidine, urea and thiourea and yielded derivatives **3, 4** and **5** that showed more potent a MAO inhibitors activity than their starting derivative 2, but **5** is the most potent one. Fusion of extra saturated thiophrne -3one to derivative **5** leaded to compound **6** increased the MAO inhibitors activity. Further fusion of extra thiophene moiety onto compound 7 converted it to compound **7** increased the MAO inhibitors activity. Treating **2** with hydrazine/dioxan, hydrazine/acetic acid and phenyl hydrazine gives the pyrazoline deriveties **9, 10** and **8** respectively. Derivative **10** showed more potent MAO inhibitors activity than derivative **9**, where derivative **9** showed more potent MAO inhibitors activity than derivative **8**. Treating derivative **2** with oxime yielded the oxazole derivative **14** which showed more potent MAO inhibitors activity more than the pyrazoline derivatives. Fusion of one hetero 6-member heterocyclic ring system made via treating derivative **2** with malononitril /ammonium acetat, ethyl cyanoacetate /ammonium acetat, ethyl cyanoacetate / ethoxide and thiocyano acetamide/ammonium acetat yielded derivatives **11,12,15** and **16** respectively.the descending order of MAO inhibitors activity is **16, 15, 12** and **11**. Fusion of extra thiophen moitey to compound **16** yielded compound **17** with increased the MAO inhibitors activity.

Table 3. *ED*50 (µM) of the tested compounds as *In vivo* Tryptamine seizure potentiation in rats

Comp. No	*ED*50(µM)
1	0.99
2	0.96
3	0.85
4	0.84
5	0.79
6	0.78
7	0.77
8	0.66
9	0.64
10	0.59
11	0.57
12	0.46
13	0.38
14	0.27
15	0.16
16	0.14
17	0.12

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 newly synthesized agents were evaluated in at the end of Experiment in {µM}.

Comp. No.	Plasma Drug Conc in Male Wistar rats experiment 3-2 µM	Plasma Drug Conc in Male Wistar rats experiment 3-3 µM
6	12.34 X10 $^{-9}$	43.33 X10 $^{-9}$
7	5.0 X10 $^{-9}$	6.8 X10 $^{-9}$
8	6.9 X10 $^{-9}$	7.7 X10 $^{-9}$
9	7.8 X10 $^{-9}$	8.6 X10 $^{-9}$
10	8.7 X10 $^{-9}$	6.5 X10 $^{-9}$
14a	5.6 X10 $^{-9}$	5.8 X10 $^{-9}$
14b	4.3 X10 $^{-9}$	4.7 X10 $^{-9}$
14c	3.4 X10 $^{-9}$	7.1 X10 $^{-9}$
16	4.5 X10 $^{-9}$	6.2 X10 $^{-9}$
17	5.6 X10 $^{-9}$	5.3 X10 $^{-9}$

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

5. Structure activity relationships (SAR)

- Fusion of thiophene or extra thiophen moities increased the MAOI activities.
- Fusion of extra cyclic ring to form poly heterocyclic ring systems sharply increased the activities.
- Fusion of polycyclic ring system with 6 membered heterocyclic ring systems either with one or two hetrocyclic ring systems increased the MAOI activities more than those builded with five membered hetrocyclic subunits exscept the oxazole one that is the most potent .
- It was mentioned that fusion of polycyclic ring system with 6 membered heterocyclic ring systems of one heteroatom increasing the activity more than those withone heteroatom.

Acknowledgement

The Authors extend their appreciation to the Deanship of Scientific Research at King Saud University for funding the work through the research group project No. RGP-VPP-099.

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9/22/2013