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Synthesis of Novel *N*-Substituted Imidazolecarboxylic Acid Hydrazides as Monoamine Oxidase Inhibitors

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Abstract

Novel 2-alkylsulfanyl-1-benzyl-5-imidazolecarboxylic acid hydrazides (**15a,b**) were synthesized as analogues of isocarboxazide, which is a known nonselective irreversible monoamine oxidase inhibitor and tested for monoamine oxidase A and B inhibitory activity. Neither of the compounds showed any inhibition of MAO B activity up to a high concentration of 100 μM. An MAO A activity was only slowly inhibited at this high concentration after prolonged incubation with either compound. This suggests any observed inhibition is not very specific.

Keywords: Monoamine oxidase; Inhibitors; 5-imidazolecarboxylic acid hydrazides

1. Introduction

An MAO (EC 1.4.3.4) is an outer mitochondrial membrane FAD containing enzyme [1] found in nearly all tissues. On the basis of their substrate and inhibitor specificities, two major isoforms have been described, the MAO-A and the MAO-B [2,3] made up of different polypeptides [4]. The structure of human MAO-B was recently resolved [5], and the molecular determinants required for MAO selectivity were investigated [6,7]. The MAOs are responsible for the major neurotransmitter degrading in the central nervous system (CNS) and peripheral tissues [8]. An MAO-A preferentially catalyzes the oxidative deamination of serotonin (5-HT), adrenaline (A) and noradrenaline (NA) and is selectively inhibited by clorgyline (**1**) and moclobemide (**2**). An MAO-B mainly catalyzes the oxidative deamination of β-phenylethylamine and benzylamine and is selectively inhibited by selegiline (**3**). Both isoforms act either on dopamine (DA) in vitro or on tyramine. In mankind, dopamine is preferentially deaminated by MAO-B. Because of their role in the metabolism of monoamine neurotransmitters, the MAO-A and MAO-B are thought to be involved in psychiatric and neurological disorders such as depression and Parkinson's disease, respectively [9].

The early MAO inhibitors such as isocarboxazid (**4**) and tranylcypromine (**5**) were nonselective and irreversible. Because of their adverse actions, the therapeutic applications of first generation MAO inhibitors have been diminished [10–12]. Today efforts toward the development of monoamine oxidase inhibitors are focused on selective MAO-A or MAO-B inhibitors. Selective MAO-B inhibitors are being examined in the treatment of, for example, schizophrenia, Alzheimer's disease, and Parkinson's disease. The MAO-A inhibitors are effective in the treatment of depression.

Our interest in heterocyclic bioisoestes of CNS agents motivated us toward synthesis novel imidazole-containing analogue of isocarbosazid (**4**) in which imidazole has been replaced for isoxazole moiety in the drug. Our goal was to obtain selective MAO inhibitor from nonselective one. We report here the synthesis of novel *N*-substituted imidazolecarboxylic acid hydrazides (Scheme 1) and their MAO inhibitory activities.

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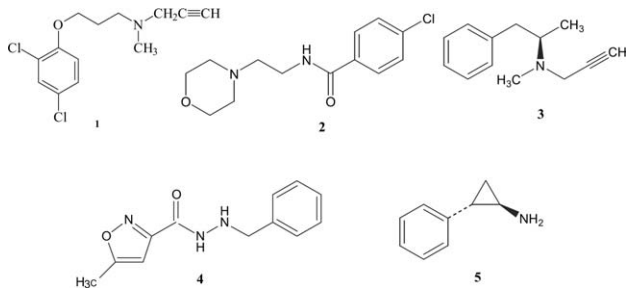


Scheme 1.

2. Experimental procedures

2.1. Chemistry

Melting points were determined on Capillary Electrothermal Apparatus and are uncorrected. The IR spectra were obtained on Perkin-Elmer Model paragon 1000. ^{1}H-NMR spectra were obtained on Bruker Ac-80 spectrophotometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Compounds **7**, **8** and **9** were synthesized as it has been reported previously [13], but compound **10** was prepared through a modified procedure.

*2.1.1. 1-Benzyl-2-methylsulfanylimidazole-5-carboxylic acid(**10a**)*

Compound **9a** (2.9 g, 11.78 mmol), sodium hydroxide (1.45 g, 36.25 mmol) and distilled water (100 ml) were heated at 150 °C for 15 min. Then a solution of silver nitrate (2.9 g, 17.05) in water (10 ml) was added. The resulting mixture was refluxed at 100 °C overnight. Then hydrochloric acid (2 N) was added to adjust pH between 3 and 4. The precipitate was filtered to give 0.96 g of 1-benzyl-2-methylsulfanylimidazole-5-carboxylic acid (**10a**), yield 90%; mp 225–227 °C; IR(KBr): ν 1700 cm^{-1}(C=O); ^{1}H-NMR($CDCl_3$): 7.87 (s, 1H, H_4-imidazole), 7.33–7(m, 5H, arom), 5.47(s, 2H, CH_2N), 2.67(s, 3H, CH_3).

*2.1.2. 1-Benzyl-2-ethylsulfanylimidazole-5-carboxylic acid(**10b**)*

It was prepared as described for **10a,** yield 68%; mp 158–160 °C; IR(KBr): ν 1694 cm^{-1}(C=O); ^{1}H-NMR($CDCl_3$): 7.87 (s, 1H, H_4-imidazole), 7.32–7.01(m, 5H, arom), 5.47(s, 2H, CH_2N), 3.14 (q, 2H,CH_2S), 1.28(t, 3H, CH_3).

*2.1.3. 1-Benzyl-2-methylsulfanylimidazole-5-carbonyl chloride(**11a**)*

Compound **10a** (3 g, 12.09 mmol) and thionyl chloride (1.5 ml, 20.29 mmol) were refluxed for 1 h. After evaporating thionyl chloride in vacuum, acid halide **11a** was remained as a viscous liquid, which was used directly in the next step.

*2.1.4. 1-Benzyl-2-ethylsulfanylimidazole-5-carbonyl chloride(**11b**)*

It was prepared from **10b** as described for **11a**.

*2.1.5. 1-Benzyl-2-methylsulfanylimidazole-5-carboxylic acid methyl ester(**12a**)*

To crude viscous liquid **11a** was added dropwise at ice bath, dry methanol (5 ml, 123.8 mmol) and then stirred overnight at room temperature. The resulting mixture was basified by adding saturated solution of sodium bicarbonate and extracted with chloroform (3 × 100 ml). Chloroform was evaporated to give 2.91 g of 1-benzyl-2-methylsulfanylimidazole-5-carboxylic acid methyl ester (**12a**), yield 92%; oily; IR(KBr): ν 1713 cm^{-1}(C=O); ^{1}H-NMR($CDCl_3$): 7.80 (s, 1H, H_4-imidazole), 7.30–7.27(m, 5H, arom), 5.50 (s, 2H, CH_2N), 3.70(s, 3H, CH_3O), 2.67(s, 3H, CH_3).

*2.1.6. 1-Benzyl-2-methylsulfanylimidazole-5-carboxylic acid methyl ester(**12b**)*

It was prepared from **11b** as described for **12a**, yield 94%; oily; IR (KBr): ν 1713 cm^{-1}(C=O); ^{1}H-NMR($CDCl_3$): 7.80 (s, 1H, H_4-imidazole), 7.30–7.27(m, 5H, arom), 5.50 (s, 2H, CH_2N), 3.70(s, 3H, CH_3O), 3.14(q, 2H, CH_2S), 1.28(t, 3H, CH_3).

*2.1.7. 1-Benzyl-2-methylsulfanylimidazole-5-carboxylic acid hydrazide(**13a**)*

To a solution of compound **12a** (3 g, 11.45 mmol) in ethanol (5 ml), hydrazine hydrate (80%, 1.25 ml, 45.02 mmol) was added. After 30 min the precipitate was isolated by filtration and crystallized from ethanol to give **13a** , yield 80%; m.p. 92–95 °C; IR(KBr): ν 3315, 3240 (NH), 1651 cm^{-1}(C=O); ^{1}H-NMR (DMSO-d_6): 7.65(s, 1H, H-C_4 imidazole), 7.32–7.01(m, 5H, arom), 5.54(s, 2H, CH_2N), 2.52 (s, 3H, CH_3).

*2.1.8. 1-Benzyl-2-ethylsulfanylimidazole-5-carboxylic acid hydrazide(**13b**)*

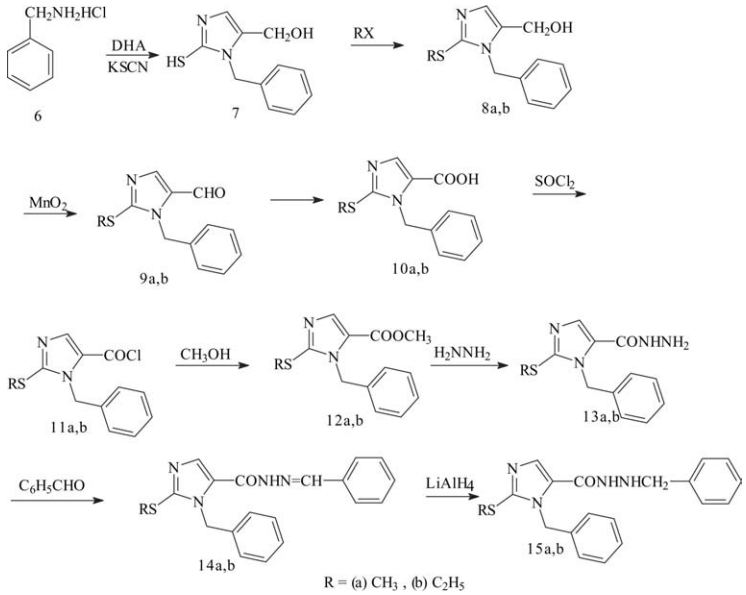
It was prepared from **12b** as described for **13a**, yield 86.7%; m.p. 72–73 °C; IR (KBr): 3320, 3260 (NH), 1653 cm^{-1}(C=O); ^{1}H-NMR (DMSO-d_6): 7.65(s, 1H, H-C_4 imidazole), 7.32–7.01(m, 5H, arom), 5.54(s, 2H, CH_2N), 3.14(q, 2H, CH_2S), 1.28(s, 3H, CH_3).

*2.1.9. 1-Benzylidene-2-(1-benzyl-2-methylsulfanylimidazole-5-carbonyl)hydrazine(**14a**)*

Benzaldehyde (1.6 g, 15 mmol) was added to a solution of 10 ml of ethanol containing **13a** (2.7 g, 10.3 mmol). The solution was stirred for 10 min at which time product began to crystallize. On cooling at 4 °C for 12 h, the solid was filtered off under vacuum and the solid filter cake was washed using 2 ml of cold ethanol in each washing and was recrystallized from ethanol to give **14a,** yield 77%; m.p. 181–184 °C; IR(KBr): ν 3432 (NH), 1648 cm^{-1}(C=O); ^{1}H-NMR (DMSO-d_6): 11.67(s, 1H, N=CH), 8.3(s, 1H, CONH), 7.9(s, 1H, H-C_4 imidazole), 7.8–6.8 (m, 10H, arom), 5.58 (s, 2H, CH_2N), 2.56 (s, 3H, CH_3).

*2.1.10. 1-Benzylidene-2-(1-benzyl-2-ethylsulfanylimidazole-5-carbonyl)hydrazine(**14b**)*

It was prepared from **13b** as described for **14a,** yield 79.75%; m.p. 175–177 °C; IR(KBr): ν 3432 (NH), 1648 cm^{-1}



Scheme 2.

(C=O); ^{1}H-NMR (DMSO-d_6): 11.2 (s, 1H, N=CH), 8.3(S, 1H, CONH), 7.9(s, 1H, H-C_4 imidazole), 7.8–6.8 (m, 10H, arom), 5.5 (s, 2H, CH_2N), 3.1(q, 2H, CH_2S), 1.2 (t, 3H, CH_3).

*2.1.11. 1-Benzyl-2-(1-benzyl-2-methylsulfanylimidazole-5-carbonyl)hydrazine(**15a**)*

Compound **14a** was added portionwise to 5 ml of anhydrous tetrahydrofuran containing lithium aluminum hydride (63 mg, 1.66 mmol). The reaction mixture was stirred overnight. The excess lithium aluminum hydride was decomposed with 0.86 ml of ethyl acetate. Then 0.5 ml of water was added to decompose the complex. The solid was separated by filtration and the tetrahydrofuran was evaporated in vacuum until a solid remained. The residue was recrystallized from methanol to give the title **15a** yield 627%; m.p. 135–138 °C; IR(KBr): ν 3432 (NH), 1648 cm^{-1}(C=O); ^{1}H-NMR (DMSO-d_6): 8.23(s, 1H, CONH), 7.67(s, 1H, H-C_4 imidazole), 7.6–6.9 (m, 10H, arom), 5.5 (s, 2H, CH_2N), 3.6–2.9 (m, 3H, NH, CH_2N), 2.5 (s, 3H, CH_3).

*2.1.12. 1-Benzyl-2-(1-benzyl-2-ethylsulfanylimidazole-5-carbonyl)hydrazine(**15b**)*

It was prepared from **14b** as described for **15a,** yield 59.7%; m.p. 126–128 °C; IR(KBr): ν 3432 (NH), 1648 cm^{-1}(C=O); ^{1}H-NMR (DMSO-d_6): 8.29(s, 1H, CONH), 7.93 (s, 1H, H-C_4 imidazole), 7.8–6.8 (m, 10H, arom), 5.6 (s, 2H, CH_2N), 3.7–2.9 (m, 5H, NH, CH_2N, CH_2S), 1.3 (t, 3H, CH_3).

3. Results and Discussion

3.1. Chemistry

Compounds **7–9** and **13** were synthesized as it has been previously reported [13], but compounds **10** and **12** were synthesized again through a new method. Benzylamine hydrochloride (**6**) was stirred with 1,3-dihydroxyacetone dimmer and potassium thiocyanate to give 5-hydroxymethyl-2-mercapto-1-benzylimidazole (**7**). Subsequent alkylation of compound **7** with alkyl halides afforded 2-alkylsulfanyl-1-benzyl-5-hydroxymethylimidazole (**8**). Oxidation of **8** with manganese dioxide gave **9**, which was further oxidized by boiling in alkaline solution of silver nitrate to give 2-alkylsulfanyl-1-benzylimidazole-5-carboxylic acid (**10**).

Compound 10 was converted to its acid halide (**11**), which was then reacted with methanol to give its methyl ester (**12**). Addition of hydrazine hydrate to **12** gave the corresponding hydrazide (**13**). Condensation of **13** with benzaldehyde afforded **14** which was later reduced by lithium aluminum hydride to give title 1-benzyl-2-alkylsulfanylimidazole-5-carboxylic acid *N*'-benzyl-hydrazide (**15**). Scheme 2

3.2. Biology

Title compounds (**15a,b**) were sent to the Department of Biochemistry of Emory University and tested on recombinant human MAO A and MAO B for their inhibitory activities [14]. Neither of the compounds showed any inhibition of MAO B activity up to a high concentration of 100 μM. An MAO A activity was only slowly inhibited at this high concentration after prolonged incubation with either compound. This suggests any observed inhibition is not very specific.

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