NEW THIAZOLYLHYDRAZONE DERIVATIVES AS POTENT MONOAMINE OXIDASE AND AROMATASE INHIBITORS

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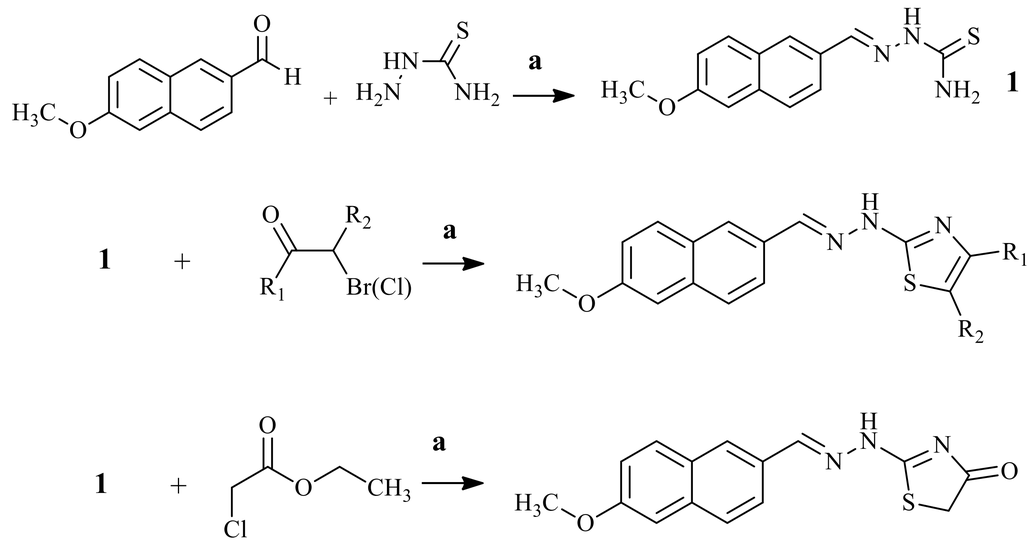
Abstract: 2-Thiazolylhydrazone nucleus carrying various structures have been known with inhibitory effects on monoamine oxidase (MAO) enzymes. In this study, twenty-one novel 2-(2-((6-methoxynaphthalen-2-yl)methylene)hydrazinyl)thiazole derivatives (**2a-u**) were synthesized and investigated for their MAO and aromatase inhibitory effects. As a result of the study, compound **2j** carrying 3-nitrophenyl residue on the thiazole ring extremely inhibited MAO-A, and compound **2t** carrying phenyl and methyl on thiazole ring was found to inhibit MAO-A both very strongly and selectively. Compounds **2k** and 2q exhibited selective and high inhibitory potential on MAO-B. Compounds **2q** and **2u** showed satisfying inhibition on aromatase enzyme. Molecular docking and molecular dynamic simulation studies were carried out with the aforementioned compounds and MAO and aromatase enzymes , and findings were correlated with the experimental results.

Keywords : 2-Thiazolylhydrazones; aromatase inhibition; molecular docking; molecular dynamic simulation; monoamine oxidase inhibition

Introduction:

2-Thiazolylhydrazones were defined as a new pharmacophore group in terms of monoamine oxidase inhibition activity by Chimenti and his working group, and derivatives containing different groups were reported in many studies [1-3]. In addition, thiazole-bearing compounds are in a group of non-steroidal aromatase inhibitor drugs since they are in azole structure [4,5]. In the light of reported data, in this study, new thiazolylhydrazone derivatives bearing 6-methoxynaphtalene ring were synthesized and their enzyme inhibitory effects were investigated on MAO-A, MAO-B and aromatase. The synthetic protocol was given below in **Scheme 1**. The structures of all twenty-one compounds were elucidated with spectroscopic data.



Molecule code	R_1	R_2
2a	phenyl	H
2b	4-methylphenyl	H
2c	3-methoxyphenyl	H
2d	4-methoxyphenyl	H
2e	3-chlorophenyl	H
2f	4-chlorophenyl	H
2g	3-fluorophenyl	H
2h	4-fluorophenyl	H
2i	4-cyanophenyl	H
2j	3-nitrophenyl	H
2k	4-nitrophenyl	H
2l	4-(methylsulfonyl)phenyl	H
2m	(1,1'-biphenyl)-4-yl	H
2n	naphthalen-2-yl	H
2o	3,4-dichlorophenyl	H
2p	benzofuran-2-yl	H
2q	$-CH_2COOEt$	H
2r	CH_3	CH_3
2s	CH_3	-COOEt
2t	phenyl	CH_3
2u	-	-

Scheme 1. The synthesis and derivatives of the compounds **(2a-2u)**

Biological results : The enzyme inhibition potencies of the compounds on monoamine oxidase A and B enzyme were studies at 10^{-3} and 10^{-4} M concentrations. The inhibition concentrations (IC_{50}) were calculated for appropriate compounds and were represented in **Table 1**. Compounds **2j** and **2t** exhibited magnificient inhibitory activity on the MAO-A enzyme, nearly 100 times higher than standard drug. Compounds **2j, 2k** and **2q** acquired to inhibit MAO-B, with very close or half the potency of selegiline. Compounds **2q** and **2u** displayed high aromatase inhibition which was very close to letrozole. Molecular docking and molecular dynamic simulations studies were done for active compounds. Only, **2q**-MAO-B docking pose was given in this poster as **Figure 1**. The interaction with Gln206 was observed for compound **2q**, which is an important residue for the MAO-B selectivity that supports in-vitro results. Compounds **2q** and **2u** were determined to interact HEM protein with π-π bonds which is a necessary for aromatase inhibition. Molecular dynamic simulation and docking studies were determined to support *in vitro* activity results.

Table 1. IC_{50} values of compounds **2j, 2k, 2q, 2t, 2u**, moclobemide, selegiline and letrazole against MAO-A, MAO-B, and aromatase enzymes.

	IC_{50} (μM)		
Compounds	**MAO-A**	**MAO-B**	**Aromatase**
2j	0.068±0.002	0.046±0.002	-
2k	-	0.082±0.003	-
2t	0.072±0.003	-	-
2q	-	0.039±0.001	0.031±0.001
2u	-	-	0.042±0.001
Moclobemide	6.061±0.262	-	-
Selegiline	-	0.036±0.001	-
Letrazole	-	-	0.026±0.001

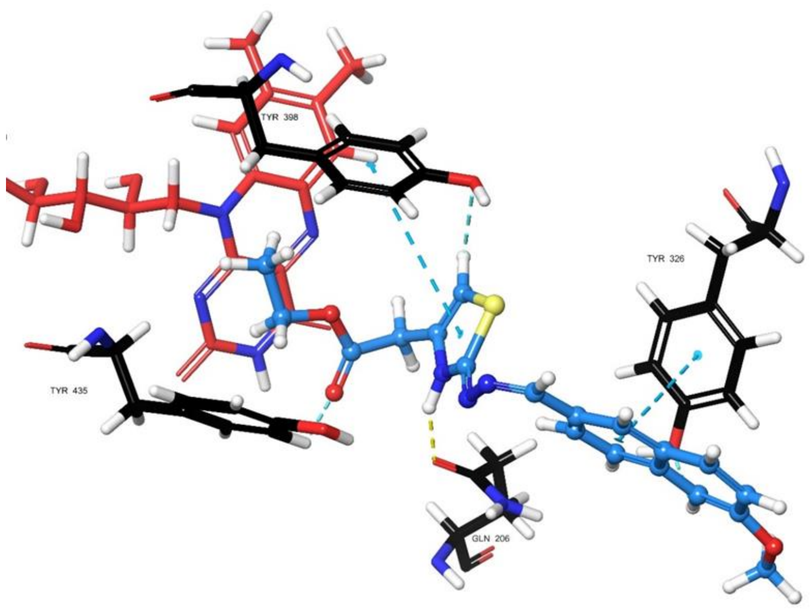


Figure 1. The aspect of **2q**-MAO-B enzyme complex as 3D (PDBID: 2V5Z)

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