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Synthesis of some novel hydrazone and 2-pyrazoline derivatives: Monoamine oxidase inhibitory activities and docking studies

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ABSTRACT

A novel series of 2-pyrazoline and hydrazone derivatives were synthesized and investigated for their human monoamine oxidase (hMAO) inhibitory activity. All compounds inhibited the hMAO isoforms (MAO-A or MAO-B) competitively and reversibly. With the exception of **5i**, which was a selective MAO-B inhibitor, all derivatives inhibited hMAO-A potently and selectively. According to the experimental K_i values, compounds **6e** and **6h** exhibited the highest inhibitory activity towards the hMAO-A, whereas compound **5j**, which carries a bromine atom at R^4 of the A ring of the pyrazoline, appeared to be the most selective MAO-A inhibitor. Tested compounds were docked computationally into the active site of the hMAO-A and hMAO-B isozymes. The computationally obtained results were in good agreement with the corresponding experimental values.

Monoamine oxidases (MAOs) are flavoenzymes which play an important role in the oxidative catabolism of amine neurotransmitters and dietary amines.[1,2] MAO contains flavin adenine dinucleotide (FAD) as a cofactor and exist in two isoforms in mammals, namely MAO-A and MAO-B.[3] MAO-A preferentially deaminates serotonin and norepinephrine and is selectively inhibited by clorgyline, whereas MAO-B preferentially deaminates -phenylethylamine and benzylamine and is selectively inhibited by l-deprenil.[4,5]

Inhibitors of MAO-A are clinically used as antidepressants and anxiolytics,[6,7] while MAO-B inhibitors are used in the treatment of Parkinson's disease and in the management of symptoms associated with Alzheimer's disease.[8] The availability of the crystal structures of the two isoforms of human MAO facilitates the understanding of the selective interactions between these proteins and their ligands, making it possible to investigate the catalytic mechanism and recognize the pharmacophoric requirements necessary for the rational design of new inhibitors.[8–12]

Substrates and inhibitors of MAO usually carry an amino or imino group, which seems to play an essential role in the orientation and complex formation at the active site of the enzyme. Numerous substituted hydrazines and hydrazides have been studied as MAO inhibitors.[13,14] 2-Pyrazolines can be considered a cyclic hydrazine moiety,[15] and it has been found that they confer MAO inhibitory and antidepressant activity.[1,15–23] Acetyl substitution of the 2-pyrazoline ring on N1 has been found to favor inhibitory activity on MAO isoforms. This substitution increases the positive charge of N1 of the heterocycle which strengthens the charge-transfer bond with the isoalloxazine nucleus of FAD and reduces the steric hindrance of the molecules.[24–26]

Most currently used MAO inhibitors produce side effects due to a lack of affinity and selectivity towards one of the isoforms. For this reason, it is necessary to design more potent, reversible and selective inhibitors of MAO-A and MAO-B. A series of chalcones have been found to exhibit MAO inhibitory activity.[27] It is also known that pyrazoline and hydrazone derivatives inhibit MAO.[28,29] In this study, we have synthesized new hydrazone and 2-pyrazoline derivatives and evaluated their MAO inhibitory activities.

Chalcone derivatives were prepared by the reaction of acetophenone and benzaldehyde derivatives, **1** and **2**, in KOH/MeOH. The ensuing chalcone derivatives **3a**–**3h** were then reacted with hydrazide compounds to furnish hydrazone and 2-pyrazoline derivatives, **5a**–**5j** and **6a**–**6i** (Scheme 1). Structures, physicochemical and spectral characterization of the synthesized compounds are given in Supplementary data.

Hydrazone formation is dependent on the Schiff base reaction, and thus the optimization of the pH value affects the product yield. In these reactions, 2-pyrazoline and hydrazone derivatives are

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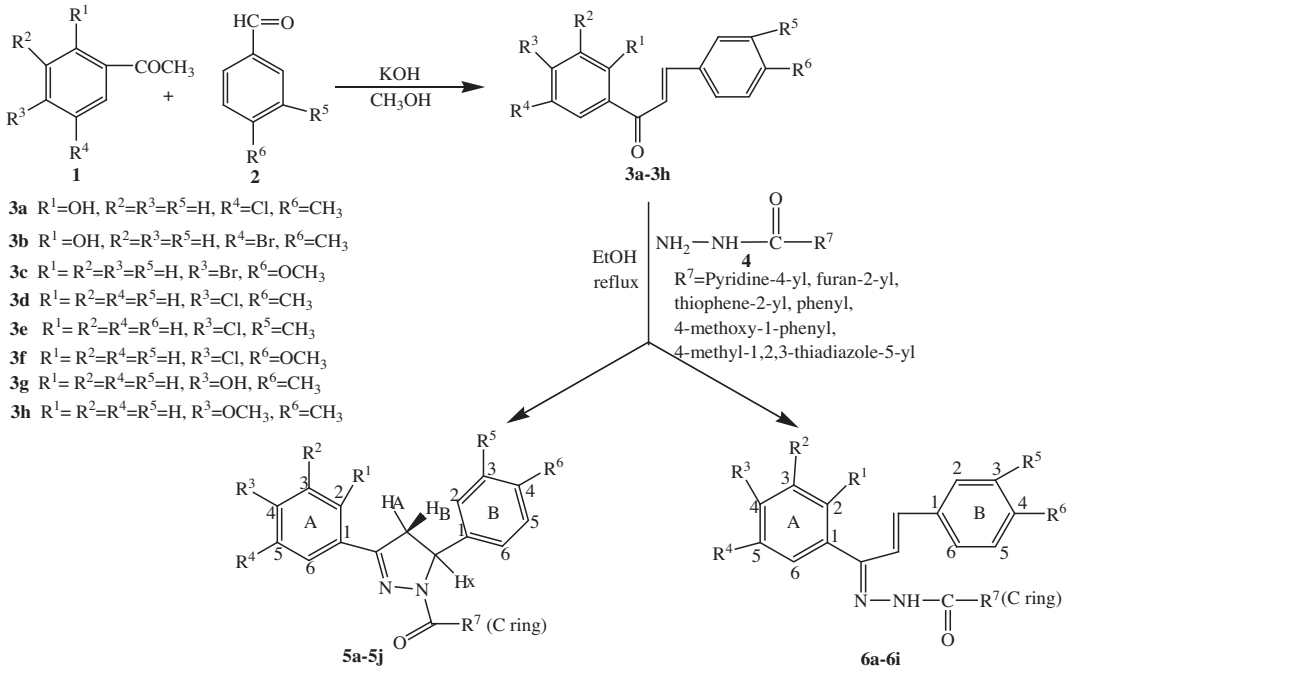

3a R^1=OH, R^2=R^3=R^5=H, R^4=Cl, R^6=CH_3
3b R^1 =OH, R^2=R^3=R^5=H, R^4=Br, R^6=CH_3
3c R^1= R^2=R^3=R^5=H, R^3=Br, R^6=OCH_3
3d R^1= R^2=R^4=R^5=H, R^3=Cl, R^6=CH_3
3e R^1= R^2=R^4=R^6=H, R^3=Cl, R^5=CH_3
3f R^1= R^2=R^4=R^5=H, R^3=Cl, R^6=OCH_3
3g R^1= R^2=R^4=R^5=H, R^3=OH, R^6=CH_3
3h R^1= R^2=R^4=R^5=H, R^3=OCH_3, R^6=CH_3

5a R^1=OH, R^2=R^3=R^5=H, R^4=Cl, R^6=CH_3, R^7=pyridine-4-yl
5b R^1=OH, R^2=R^3=R^5=H, R^4=Cl, R^6=CH_3, R^7=furan-2-yl
5c R^1=OH, R^2=R^3=R^5=H, R^4=Cl, R^6=CH_3, R^7=phenyl
5d R^1=OH, R^2=R^3=R^5=H, R^4=Cl, R^6=CH_3, R^7=4-methoxy-1-phenyl
5e R^1=OH, R^2=R^3=R_5=H, R^4=Cl, R^6=CH_3, R^7=4-methyl-1,2,3-thiadiazole-5-yl
5f R^1=OH, R^2=R^3=R^5=H, R^4=Br, R^6=CH_3, R^7=pyridine-4-yl
5g R^1=OH, R^2=R^3=R^5=H, R^4=Br, R^6=CH_3, R^7=furan-2-yl
5h R^1=OH, R^2=R^3=R^5=H, R^4=Br, R^6=CH_3, R^7=phenyl
5i R^1=OH, R^2=R^3=R^5=H, R^4=Br, R^6=CH_3, R^7=4-methoxy-1-phenyl
5j R^1=OH, R^2=R^3=R^5=H, R^4=Br, R^6=CH_3, R^7=thiophene-2-yl

6a R^1=R^2=R^4=R^5=H, R^3=Br, R^6=OCH_3, R^7=4-methoxy-1-phenyl
6b R^1=R^2=R^4=R^5=H, R^3=Br, R^6=OCH_3, R^7=furan-2-yl
6c R^1=R^2=R^4=R^5=H, R^3=Cl, R^6=CH_3, R^7=thiophene-2-yl
6d R^1=R^2=R^4=R^5=H, R^3=Cl, R^6=CH_3, R^7=4-methyl-1,2,3-thiadiazole-5-yl
6e R^1=R^2=R^4=R^6=H, R^3=Cl, R^5=CH_3, R^7=4-methyl-1,2,3-thiadiazole-5-yl
6f R^1=R^2=R^4=R^5=H, R^3=Cl, R^6=OCH_3, R^7=4-methyl-1,2,3-thiadiazole-5-yl
6g R^1=R^2=R^4=R^5=H, R^3=Cl, R^6=OCH_3, R^7=4-methoxy-1-phenyl
6h R^1=R^2=R^4=R^5=H, R^3=OH, R^6=CH_3, R^7=4-methyl-1,2,3-thiadiazole-5-yl
6i R^1=R^2=R^4=R^5=H, R^3=OCH_3, R^6=CH_3, R^7=4-methyl-1,2,3-thiadiazole-5-yl

Scheme 1. General synthesis of compounds **3a**–**3h**, **5a**–**5j**, and **6a**–**6i**.

formed together. At the end of the reaction, only one of the products—either the hydrazone or the 2-pyrazoline derivative—can be isolated. For this Letter, hydrazones were obtained (15–25.7% yield) in an ethanol solution with the reaction of chalcone and acylhydrazines at 78 °C during a period of 40–50 h. When we used chalcones having a 2′-OH group as the starting compound, only 2-pyrazolines were produced, but with chalcones not having a hydroxy group at position 2′, only hydrazones were generated. Generally, 2-pyrazoline derivatives were obtained with a higher yield than hydrazones. The highest yield was achieved with 2′-hydroxy-5′-chloro chalcone derivatives (27.33–74.48%).

Structures of the synthesized hydrazone and 2-pyrazoline derivatives were elucidated by IR, ^{1}H NMR, ^{13}C NMR, mass spectral data, and elemental analyses. The IR spectra of the compounds showed OH bonds at 3178–3446 cm^{-1}, C=O stretching bonds at 1665–1626 cm^{-1}, and C=N stretching bonds at 1605–1546 cm^{-1}. In the ^{1}H NMR spectrum of compounds **5a**–**5j**, the CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ_H 2.88–2.92 ppm and δ_H 3.43–3.52 ppm. The CH proton appeared as a doublet of doublets at δ_H 5.24–5.30 ppm. In the ^{1}H NMR spectrum of compounds **6a**–**6i**, ethylenic protons were observed at δ_H 6.51–7.90 ppm. The protons belonging to the aromatic ring and the other aliphatic groups were observed with the expected chemical shifts and integral values. ^{13}C NMR spectrum of compounds **3b**, **5a**, **5d**, **5g**, **5i**, **6d**, **6e**, **6i** were given in Supplementary data. Mass spectral analysis of the compounds was performed using the ESI (+) or ESI (−) method, and the characteristic peaks were observed in the mass spectra. Molecular ion peaks ([M]+) provided the molecular formula of all synthesized compounds **5a**–**5j**/**6a**–**6i**. Characteristic [M+2] isotope peaks were observed in the mass spectra of the compounds having a halogen atom. All compounds provided satisfactory elemental analyses.

The MAO-A and MAO-B inhibitory activities of the newly synthesized 2-pyrazoline and hydrazone derivatives were determined using the respective hMAO isoforms. Except compound **5i**, all tested compounds were found to inhibit MAO-A selectively and competitively (Table 1). These novel compounds were reversible inhibitors of hMAO-A, since the enzyme activity was restored after the centrifugation-ultrafiltration steps. Compound **5i** showed selectivity towards the MAO-B isoform.

Among compounds **5a**–**5j**, which are 2-pyrazoline derivatives carrying a chloride substitution on the A ring at position 5, compound **5c**, which carries a unsubstituted phenyl ring (C ring), was found to be the most potent MAO-A inhibitor according to its lowest K_i value for hMAO-A (Table 1). However, compound **5j**, which carries a bromide atom at R^4 of the A ring of pyrazoline, appeared as the most selective MAO-A inhibitor in the pyrazoline series according to its highest selectivity index (*SI*) value. *SI* was calculated as K_i (MAO-B)/K_i (MAO-A); the experimental SI value calculated for a compound increases as the selectivity to MAO-A isoform also increases whereas the experimental SI value calculated for a compound decreases, the selectivity to MAO-B increases. For this group of compounds, chloride substitution at R^4 of the phenyl ring was identified as favorable in terms of MAO-A inhibitory potency, whereas bromide substitution at R^4 of the phenyl ring increased the selectivity towards hMAO-A. Compound **5i**, which has a