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Synthesis of Imine Congeners of Resveratrol and Evaluation of Their Anti-Platelet Activity

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Abstract: Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is a cardioprotective phytochemical occurring in many plant products. In this study, a new series of imine congeners of resveratrol has been synthesized in which the imine moiety replaced the double bond in the structure of resveratrol. In addition, the in vitro antiplatelet activity of these resveratrol derivatives has been evaluated against adenosine diphosphate (ADP), arachidonic acid (AA), and collagen as platelet aggregation inducers. In general, the synthesized compounds were active as antiplatelet agents, and, therefore, the imine functional group may be considered as an effective replacement for a double bond in resveratrol for developing new and promising antiplatelet drugs.

Keywords: stilbenes; cardioprotection; antiplatelet drugs; polyphenols

1. Introduction

Cardiovascular diseases (CVDs) are recognized as the first global cause of death. It has been reported by the World Health Organization (WHO) that 17.7 million people died from CVDs in 2015 [1,2]. Platelet aggregation plays an essential role in the process of blood clotting and CVDs. However, many antiplatelet drugs such as aspirin and clopidogrel, which are available in clinics, are associated with some side effects such as bleeding and drug resistance that limit their usage [3,4]. Therefore, the search for new antiplatelet agents with fewer side effects and higher efficacy is among the priorities of medicinal chemists.

Natural products with various chemical structures have an important role in drug discovery and development [5–9]. Although chemical diversity of the natural products is pivotal in finding useful lead compounds, usually chemical modifications are needed to improve their potency and physicochemical properties [10–12]. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) (**1**) (Figure 1) is one of these lead compounds. This stilbene is found in many natural sources such as grapes,

apples, and berries [13–15]. Various biological activities of resveratrol have been reported such as anticancer, anti-inflammatory, antioxidant, and antiplatelet [13,16,17]. Orsini et al. synthesized and evaluated the antiplatelet aggregation activity of resveratrol 3-*O*-β-D-glucopyranoside and related hyroxystilbenes [18]. Dutra et al. synthesized new resveratrol and resveratrol-furoxan hybrids as antiplatelet and antithrombotic agents [19].

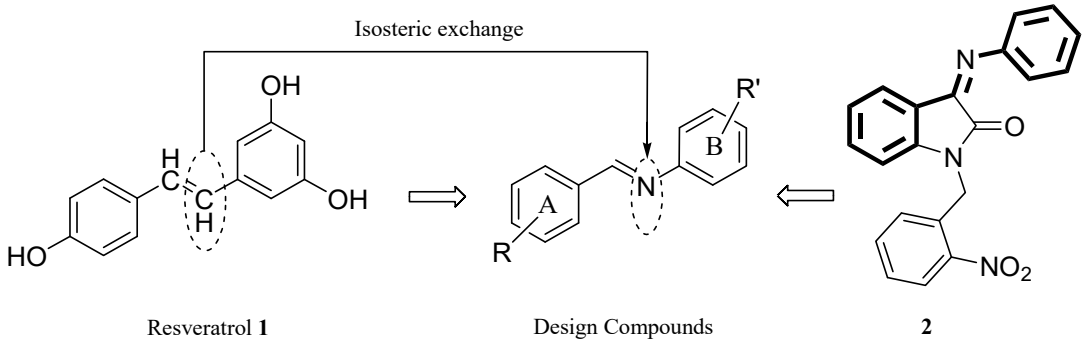


Figure 1. Design of imine resveratrol derivatives.

A literature review revealed that C=N moiety is present in many structures with antiplatelet activity. Tehrani et al. synthesized a series of Schiff bases derived from 2-hydrazinyl-1,3,4-thiadiazole with high antiplatelet activity [20]. Akhlaghi et al. reported 3-(arylimino)indolin-2-one and 1-(aryl)-3-(phenylimino)indolin-2-one derivatives as antiplatelet agents [21]. Among their synthesized derivatives, compound (2) exhibited high antiplatelet activity against arachidonic acid (AA) as a platelet aggregation inducer (IC_{50} = 3.4 μM) [21]. Furthermore, antiplatelet activity of *N*′-benzylidene-carbohydrazide-1*H*-pyrazolo[3,4-*b*]pyridine derivatives have been reported [22]. A variety of indole hydrazone derivatives such as indole *N*-acylhydrazones [23,24], indole-3-carboxaldehyde phenylhydrazones [25], *N*-1 substituted indolehydrazones [26], indole-3-carbaldehyde, and indole-2-carbaldehayde hydrazones [27] have been previously synthesized in our research group. Some of these reported derivatives exhibited remarkable antiplatelet activity.

Therefore, the present research was aimed at the synthesis of a new series of imine congeners of resveratrol in which the imine moiety replaced the double bond in the structure of resveratrol (Figure 1) [28], and the evaluation of their in vitro antiplatelet activity against adenosine diphosphate (ADP), arachidonic acid (AA), and collagen as platelet aggregation inducers.

2. Results and Discussion

2.1. Chemistry

The designed compounds were synthesized by the reaction of different aniline derivatives with appropriate aldehydes in water as a green solvent without any catalyst (Figure 2). The synthesized derivatives (**3a**–**3r**) were obtained with high yields (>89%). Structure of the synthesized compounds was characterized by LC-MS ^{1}H-NMR and ^{13}C-NMR. The ^{1}H-NMR spectra of the synthesized compounds exhibited a singlet peak for the CH=N proton between 8.51 and 8.96 ppm.

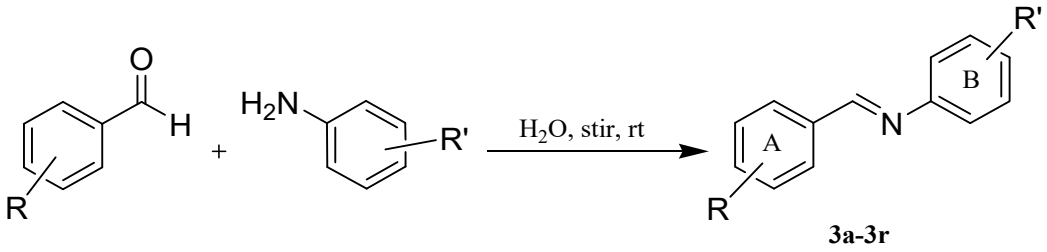
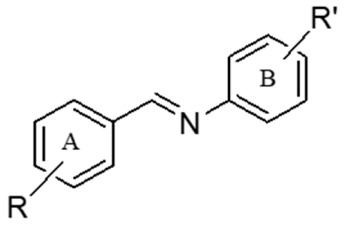


Figure 2. Synthesis of resveratrol derivatives.

2.2. Anti-Platelet Activity

The anti-platelet activity of the synthesized derivatives against ADP, AA, and collagen as platelet aggregation inducers were evaluated, according to the Born method [29,30]. The obtained data are presented in Table 1.

Table 1. Anti-platelet activity of the synthesized derivatives. Adenosine diphosphate (ADP), arachidonic acid (AA), and collagen were used as a platelet aggregation inducer at a final concentration of 5 μM, 1.35 μM, and 2.5 μg·mL^{-1}, respectively. The results are expressed as the mean ± standard error of mean (SEM) from three independent experiments.



Compound	R	R′	AA [a] Inhibition (%)	AA (IC_{50} μM)	ADP [a] Inhibition (%)	Collagen [a] Inhibition (%)
3a	4-OCH_3	-	74.7 ± 2.5	301.0 ± 8.7	43.2 ± 3.3	15.9 ± 1.5
3b	3-OCH_3, 4-OH	-	100	180.2 ± 5.4	52.1 ± 2.2	39.0 ± 8.8
3c	2-OH	4′-OCH_3	100	86.1 ± 6.6	30.2 ± 5.3	46.8 ± 4.3
3d	4-OCH_3	4′-OCH_3	100	155.5 ± 4.3	41.4 ± 6.4	29.1 ± 1.9
3e	3,4-dimethoxy	4′-OCH_3	100	73.6 ± 3.4	63.2 ± 3.1	80.7 ± 1.4
3f	4-CH_3	4′-OCH_3	100	143.3 ± 6.2	33.6 ± 1.4	60.0 ± 4.1
3g	3-OCH_3, 4-OH	4′-OCH_3	94.9 ± 0.7	179.2 ± 7.1	34.4 ± 5.6	41.0 ± 6.6
3h	3-OCH_3	4′-OH	100	69.1 ± 5.4	77.4 ± 1.9	73.1 ± 2.1
3i	2-OH	4′-OH	100	29.9 ± 1.1	36.3 ± 3.9	70.8 ± 1.3
3j	4-OCH_3	4′-OH	100	68.3 ± 1.4	44.1 ± 3.6	67.2 ± 3.2
3k	4-CH_3	4′-OH	100	65.4 ± 3.4	45.8 ± 3.3	59.03 ± 6.2
3l	3,4-dimethoxy	4′-OH	93.7 ± 5.6	65.3 ± 2.0	53.5 ± 2.7	67.8 ± 3.5
3m	3,4,5-trimethoxy	4′-OH	88.0 ± 3.1	65.2 ± 3.4	84.6 ± 1.1	93.4 ± 0.9
3n	3-OH	4′-OH	100	62.3 ± 7.1	33.4 ± 3.5	80.5 ± 1.4
3o	2-OCH_3	4′-OH	92.4 ± 2.1	130.7 ± 5.1	43.8 ± 1.6	74.9 ± 3.4
3p	2-OH	2′-OH	95.1 ± 3.0	65.5 ± 4.3	41.1 ± 3.7	70.2 ± 2.5
3q	3-OH	2′-OH	100	30.7 ± 1.2	38.4 ± 3.9	36.1 ± 3.5
3r	4-CH_3	2′-OH	100	19.8 ± 1.1	39.8 ± 3.2	63.5 ± 1.3
Indomethacin				1.67 ± 0.67	42.0 ± 1.1	
Acetyl salicylic acid (ASA)				0.24 ± 0.05	21.0 ± 0.6	

[a] Inhibition of platelet aggregation was assessed at 1 mM concentration.

2.3. Structure Activity Relationship

The data reported in Table 1 show that all the compounds (**3a**–**3r**) at the concentration of 1 mM inhibited platelet aggregation induced by ADP, AA, and collagen. The inhibition range for ADP and collagen were 30%–84.6% and 15.9%–93.4%, respectively. When AA was used as a platelet aggregation inducer, the inhibition was increased and ranged from 74.7% to 100%.

Compound **3m** with three-methoxy group on ring A inhibited platelet aggregation induced by all the three platelet inducers above 85%.

Since all compounds at concentration of 1 mM were able to completely inhibit platelet aggregation induced by AA, the IC_{50} values for these compounds were calculated (Table 1).

As shown in Table 1, all the compounds with hydroxyl substituent on the B ring show high activity (IC_{50} < 69.1 μM) except **3o**. The results demonstrated that all the compounds with Schiff base and phenolic hydroxyl groups at the ortho position of ring A or B show IC_{50} values ranging between 19.8 μM and 30.7 μM except for **3c** and **3p**. Compounds **3i** and **3q** exhibited satisfactory activity with IC_{50} values of 29.9 μM and 30.7 μM, respectively. Compound **3r** with IC_{50} value of 19.8 μM was the most active compound.

3. Materials and Methods

3.1. General Procedure for the Preparation of **3a**–**3r**

The mixture of aromatic amine (1 mmol) and aldehyde (1 mmol) in water was stirred at room temperature. After completion of the reaction indicated by TLC (thin-layer chromatography), the obtained precipitate was filtered off and washed with water. The obtained precipitate was recrystallized from the appropriate solvent.

(E)-1-(4-Methoxyphenyl)-N-phenylmethanimine (**3a**). Yield 95%; m.p. 48–50 °C (m.p. 49–50 °C [31]). ESI-MS *m*/*z*: 212 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO$: C 79.59, H 6.20, N 6.63, found C 79.57, H 6.21, N 6.64.

(E)-2-Methoxy-4-[(phenylimino)methyl]phenol (**3b**). Yield 89%. m.p. 159–162 °C (m.p. 158–160 °C [32]). ESI-MS *m*/*z*: 228 $[M + H]^+$; Anal. Calcd for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16, found C 73.97, H 5.76, N 6.15.

(E)-2-{[(4-Methoxyphenyl)imino]methyl}phenol (**3c**). Yield 94%. m.p. 76–77 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.32 (s, 1H, OH), 8.94 (s, 1H, HC=N), 7.61 (m, 1H, Ar-H), 7.42 (m, 3H, Ar-H), 6.96 (m, 4H, Ar-H), 3.79 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 161.72, 160.62, 158.99, 141.19, 133.25, 132.80, 123.09, 119.85, 119.53, 116.97, 115.13, 55.86; ESI-MS *m*/*z*: 228 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16, found C 73.95, H 5.76, N 6.17.

(E)-N,1-bis(4-Methoxyphenyl)methanimine (**3d**). Yield 89%. m.p. 154–155 °C (m.p. 154 °C [33]). ESI-MS *m*/*z*: 242 $[M + H]^+$. Anal. Calcd for $C_{15}H_{15}NO_2$: C 74.67, H 6.27, N 5.81, found C 74.68, H 6.28, N 5.79.

(E)-1-(3,4-Dimethoxyphenyl)-N-(4-methoxyphenyl)methanimine (**3e**). Yield 85%. m.p. 126–128 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H, HC=N), 6.96–7.54 (m, 7H, Ar-H), 3.77–3.83 (m, 9H, OCH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 158.46, 158.05, 151.97, 149.45, 144.89, 129.77, 124.08, 122.66, 115.46, 114.95, 114.85, 111.74, 109.68, 56.07, 55.88, 55.73. ESI-MS *m*/*z*: 272 $[M + H]^+$. Anal. Calcd for $C_{16}H_{17}NO_3$: C 70.83, H 6.32, N 5.16, found C 70.81, H 6.31, N 5.17.

(E)-N-(4-Methoxyphenyl)-1-(p-tolyl)methanimine (**3f**). Yield 96%. m.p. 87–88 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H, HC=N), 7.70-7.81 (m, 2H, Ar-H), 7.31-7.42 (m, 4H, Ar-H), 6.98 (m, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 2.38 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 158.2, 157.8, 144.2, 141.0, 133.8, 129.85, 128.88, 122.79, 114.87, 55.76, 21.1. ESI-MS *m*/*z*: 226 $[M + H]^+$. Anal. Calcd for $C_{15}H_{15}NO$: C 79.97, H 6.71, N 6.22, found C 79.95, H 6.70, N 6.23.

(*E)-2-Methoxy-4-{[(4-methoxyphenyl)imino]methyl}phenol* (**3g**). Yield 94%. m.p. 154–155 °C (m.p. 154 °C [34]). ESI-MS *m*/*z*: 258 $[M + H]^+$. Anal. Calcd for $C_{15}H_{15}NO_3$: C 70.02, H 5.88, N 5.44, found C 70.01, H 5.89, N 5.43.

(E)-4-[(3-Methoxybenzylidene)amino]phenol (**3h**). Yield 94%. m.p. 165–167 °C (m.p. 167 °C [35]). ESI-MS *m*/*z*: 228 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16, found C 73.97, H 5.76, N 6.15.

(E)-2-{[(4-Hydroxyphenyl)imino]methyl}phenol (**3i**). Yield 98%. m.p. 140–143 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.44 (s, 1H, OH), 9.72 (s, 1H, OH), 8.94 (s, 1H, HC=N), 7.58 (m, 1H, Ar-H), 7.31–7.37 (m,

3H, Ar-H), 6.84–6.95 (m, 4H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 160.67, 160.60, 157.41, 139.65, 133.00, 132.67, 123.12, 119.89, 119.46, 116.92, 116.43, 116.01, 115.85. ESI-MS m/z: 214 $[M + H]^+$. Anal. Calcd for $C_{13}H_{11}NO_2$: C 73.23, H 5.20, N 6.57, found C 73.21, H 5.21, N 6.56.

(E)-4-[(4-Methoxybenzylidene)amino]phenol (**3j**). Yield 95%. m.p. 187–188 °C (m.p. 189 °C [36]). ESI-MS m/z: 228 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16, found C 74.20, H 5.77, N 6.15.

(E)-4-[(4-Methylbenzylidene)amino]phenol (**3k**). Yield 94%. m.p. 152–153 °C; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.51 (s, 1H, OH), 8.55 (s, 1H, HC=N), 7.78 (m, 2H, Ar-H), 7.18–7.30 (m, 4H, Ar-H), 6.80 (m, 2H, Ar-H), 2.36 (s, 3H, CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 157.51, 156.57, 143.19, 141.24, 134.36, 129.82, 128.73, 122.86, 116.15, 21.59; ESI-MS m/z: 212 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO$: C 79.59, H 6.20, N 6.63, found C 79.45, H 6.19, N 6.62.

(E)-4-[(3,4-Dimethoxybenzylidene)amino]phenol (**3l**). Yield 92%. m.p. 155–156 °C (m.p. 155 °C [37]). ESI-MS m/z: 258 $[M + H]^+$. Anal. Calcd for $C_{15}H_{15}NO_3$: C 70.02, H 5.88, N 5.44, found C 70.10, H 5.87, N 5.45.

(E)-4-[(3,4,5-Trimethoxybenzylidene)amino]phenol (**3m**). Yield 96%. m.p. 140–142 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H, OH), 8.51 (s, 1H, HC=N), 7.18–7.23 (m, 4H, Ar-H), 6.81 (m, 2H, Ar-H), 3.85 (s, 6H, OCH_3), 3.73 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 157.42, 156.60, 153.58, 143.06, 140.31, 132.44, 122.85, 116.19, 115.87, 107.19, 105.88, 60.61, 56.50, 56.36; ESI-MS m/z: 288 $[M + H]^+$. Anal. Calcd for $C_{16}H_{17}NO_4$: C 66.89, H 5.96, N 4.88, found C 66.84, H 5.95, N 4.88.

(E)-3-{[(4-Hydroxyphenyl)imino]methyl}phenol (**3n**). Yield 94%. m.p. 191–193 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.69 (s, 1H, OH), 9.55 (s, 1H, OH), 8.51 (s, 1H, HC=N), 7.19–7.37 (m, 5H, Ar-H), 6.83–6.91 (m, 3H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 158.10, 157.66, 156.70, 143.04, 138.29, 130.23, 122.95, 120.44, 118.64, 116.19, 115.90, 114.35; ESI-MS m/z: 214 $[M + H]^+$. Anal. Calcd for $C_{13}H_{11}NO_2$: C 73.23, H 5.20, N 6.57, found C 73.21, H 5.21, N 6.58.

(E)-4-[(2-Methoxybenzylidene)amino]phenol (**3o**). Yield 92%. m.p. 168–169 °C (m.p. 168 °C [35]). ESI-MS m/z: 228 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO_2$: C 73.99, H 5.77, N 6.16, found C 73.94, H 5.78, N 6.15.

(E)-2-[(2-Hydroxybenzylidene)amino]phenol (**3p**). Yield 98%. m.p. 141–143 °C. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.81 (s, 1H, OH), 9.77 (s, 1H, OH), 8.96 (s, 1H, HC=N), 7.13–7.61 (m, 4H, Ar-H), 6.89–6.95 (m, 4H, Ar-H). ^{13}C-NMR (100 MHz, DMSO-d_6) δ 162.13, 161.20, 151.56, 135.40, 133.31, 132.78, 128.53, 120.09, 120.04, 119.96, 119.21, 117.16, 116.98. ESI-MS m/z: 214 $[M + H]^+$. Anal. Calcd for $C_{13}H_{11}NO_2$: C 73.23, H 5.20, N 6.57, found C 73.24, H 5.19, N 6.56.

(E)-2-[(3-Hydroxybenzylidene)amino]phenol (**3q**). Yield 99%. m.p. 122–124 °C (m.p. 122.5–123.5 °C [38]). ESI-MS m/z: 214 $[M + H]^+$. Anal. Calcd for $C_{13}H_{11}NO_2$: C 73.23, H 5.20, N 6.57, found C 73.24, H 5.19, N 6.55.

(E)-2-[(4-Methylbenzylidene)amino]phenol (**3r**). Yield 98%. m.p. 107–108 °C (m.p. 108.5 °C [39]). ESI-MS m/z: 212 $[M + H]^+$. Anal. Calcd for $C_{14}H_{13}NO$: C 79.59, H 6.20, N 6.63, found C 79.58, H 6.19, N 6.64.

3.2. Anti-Platelet Assay

The anti-platelet aggregation activity of the synthesized compounds was evaluated on an APACT 4004 aggregometer (LABiTec, Ahrensburg, Germany), according to the method described before [29,40,41]. Compounds (**3a**–**3r**) were added to platelet-rich plasma (PRP) and were incubated for 5 min at 37 °C. Adenosine diphosphate (ADP), arachidonic acid, and collagen were added separately as platelet aggregation inducers at a final concentration of 5 μM, 1.35 μM, and 2.5 $\mu g \cdot mL^{-1}$, respectively. The aggregation procedure was monitored for 5 min. Compounds were screened at a concentration of 1 mM in DMSO. The IC_{50} values against AA were determined for the synthesized compounds. Each experiment was carried out in triplicate and the results are shown as a mean ± standard error of mean (SEM).

4. Conclusions

In the present study, a series of resveratrol derivatives was synthesized and their antiplatelet activity was evaluated against ADP, AA, and collagen as platelet aggregation inducers. Compound **3r** was the most active agent against AA and, therefore, possesses the potential to be considered a lead compound for future studies and further investigations. Lastly, the imine functional group may be qualified as an effective replacement for the double bond in resveratrol for anti-platelet aggregation pharmacophore.

Supplementary Materials: The following are available online http://www.mdpi.com/1422-8599/2019/1/M1039/s1, Figure S1: Qualitative data analysis report.

Author Contributions: M.B., M.S., M.E., and F.K. carried out the experiments, analyzed the results, and wrote the manuscript. S.V., M.I., and J.S.-R. contributed to the discussion of results and critically reviewed the manuscript. All the authors read and approved the final manuscript.

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