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ORIGINAL ARTICLE / ÖZGÜN MAKALE

SYNTHESIS AND STRUCTURE ELUCIDATION OF NEW METHYL 1*H*-BENZIMIDAZOLE-5-CARBOXYLATE DERIVATIVES

YENİ METİL 1H-BENZİMİDAZOL-5-KARBOKSİLAT TÜREVLERİNİN SENTEZİ VE YAPILARININ AYDINLATILMASI

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ABSTRACT

Objective: *In this study, in connection with previous works in our department, some methyl 1H-benzimidazole-5-carboxylate derivatives were synthesized for the first time. Compounds were modified by substituting the second position of the benzimidazole ring with 4-methylpiperidinyl groups for increasing antibacterial activity.*
Material and Method: *The targeted methyl 1H-benzimidazole-5-carboxylates were synthesized by the reaction of o-phenylendiamine derivatives with urea. Oxygen at the 2nd position was converted to chlorine in the presence of $POCl_3$. Finally, the resulting products were obtained by the nucleophylic substitution with 4-methylpiperidine. Structures of synthesized compounds were elucidated with ^1H- ^{13}C-NMR and LC-MS techniques.*
Result and Discussion: *Methyl 1H-benzimidazole-5-carboxylate derivatives bearing 4-methyl piperidinyl groups at the 2nd position were synthesized to improve better in vitro antibacterial activity profiles. In vitro antibacterial activity of the synthesized compounds in this study is under investigation.*
Keywords: *^1H-^{13}C-NMR, 1H-benzimidazole, 4-methylpiperidine, methyl 1H-benzimidazole-5-carboxylates*

ÖZ

Amaç: *Bu çalışma kapsamında daha önce bölümümüzde sentezlenen bileşiklere ek olarak bazı yeni metil 1H-benzimidazol-5-karboksilat türevlerinin sentezi gerçekleştirilmiştir. Antibakteriyel aktiviteyi artırmak için benzimidazol halkasının 2. konumu 4-metilpiperidinil grubuyla modifiye edilmiştir.*

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Gereç ve Yöntem: *Tasarlanan metil 1H-benzimidazol-5-karboksilat bileşikleri, o-fenilendiamin türevlerinin üre ile reaksiyonu sonucu sentezlenmiştir. 2. konumda bulunan oksijen atomu $POCl_3$ varlığında klor ile yer değiştirmiştir. Son olarak, 4-metil piperidin ile nükleofilik sübstitüsyonla hedeflenen bileşiklere ulaşılmıştır. Elde edilen bileşiklerin yapıları ^1H-^{13}C-NMR ve LC-MS teknikleriyle aydınlatılmıştır.*

Sonuç ve Tartışma: *Bu çalışmada daha iyi in vitro antibakteriyel aktivite elde etmek için 2. konumda 4-metilpiperidinil grubu taşıyan metil 1H-benzimidazol-5-karboksilat türevleri sentezlenmiştir. Bu çalışmada sentezlenen bileşiklerin in vitro antibakteriyel etkileri araştırılmaktadır.*

Anahtar Kelimeler: *^1H-^{13}C-NMR, 1H-benzimidazol, 4-metilpiperidin, metil 1H-benzimidazol-5-karboksilat*

INTRODUCTION

Benzimidazole is an important pharmacophore and a privileged structure in medicinal chemistry [1]. Many benzimidazole derivatives containing ester groups on the benzene ring have been synthesized for their antimicrobial [2,3], anti-inflammatory [4], antihypertensive [5] and anticancer [6] activities. In addition, antibacterial [7-9] and antifungal [8,9] effects of the compounds that bear 4-methyl piperidine moiety have been reported in various references. Furthermore, our previous work [10] showed that benzimidazoles containing methyl or ethyl ester groups display good antibacterial and antimycotic activity. **13f** and **13h** were found the most active compounds against *Staphylococcus aureus* with MIC values of 0.78 and 1.56 µg/ml and against MRSA with MIC values of 0.78 and 0.39 µg/ml, respectively (Figure 1). Taking into consideration these structural features and the expectation of much better antibacterial activity with 4-methylpiperidine groups, it has been planned to prepare benzimidazoles carrying the ester groups on the benzene ring and with additional substitution at position C-2. And their *in vitro* antibacterial activity studies are planned to test in further analysis.

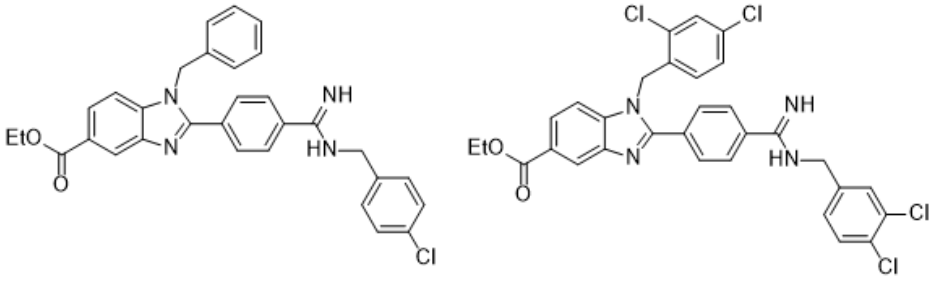


Figure 1. Previously synthesized potent benzimidazoles containing ethyl ester groups **13f** and **13h**, respectively

MATERIAL AND METHOD

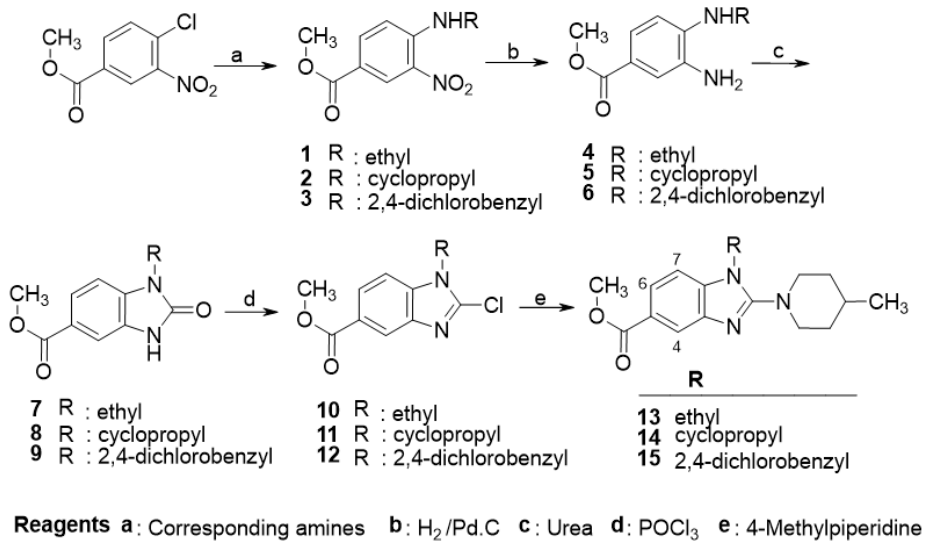
Experimental

Uncorrected melting points were measured on an Büchi B-540 capillary melting point apparatus. ^1H (400 and 500 MHz) and ^{13}C (100 and 125 MHz) NMR spectra were recorded employing a Varian Mercury (AGILENT) 400 MHz and BRUKER AVANCE NEO 500 MHz FT spectrometers, chemical shifts (δ) are in ppm relative to TMS. The samples (5-15 mg) were prepared in 0.75 ml of $CDCl_3$. TMS was used as an internal standard. The liquid chromatography mass spectrometry (LC-MS) spectra were taken on a Waters Micromass ZQ connected with Waters Alliance HPLC (Waters Corporation, Milford, MA, USA), using the ESI (+) method with a C-18 column (XTerra®, 4.6 X 250 mm, 5 µm).

Chemistry

The synthetic pathways for the preparation of targeted compounds are outlined in Scheme 1.

Compounds **1,2,4,5** [10,11], **7,8** [11], and **11** [12] were synthesized according to the lit. method. Reduction of the nitro groups of **1-3** afforded **4-6**. These compounds were fused with urea for obtaining **7-9.** Treatment of **7-9** with $POCl_3$ gave **10-12**. Final compounds **13-15** were prepared by the nucleophilic substitution reaction of **10-12** with 4-methylpiperidine.



Scheme 1. Synthesis of targeted benzimidazoles

General Procedure for Synthesis of 1-3

To a solution of methyl 4-chloro-3-nitrobenzoate (4.6 mmol) in DMF (1.5 ml), the corresponding amines (9.3 mmol) were added and the mixture was heated for 3-8 h at 80°C. The mixture was allowed to cool, and water was added. The resultant precipitate was filtered off and crystallized from the mixture of ethanol-water.

General Procedure for Synthesis of 4-6

Compounds **1-3** (3.4 mmol) in ethanol (75 ml) were reduced by hydrogenation using 40 psi of H_2 and 10% Pd-C (40 mg) until the cessation of H_2 uptake. The catalyst was filtered on a bed of Celite, washed with ethanol and the filtrate was concentrated in vacuo. The crude amines were used for further steps without crystallization [13].

General Procedure for Synthesis of 7-9

A mixture of **4-6** (2 mmol) and urea (11.9 mmol) was heated at 150°C for 5 h. Water was added, the precipitate was collected and recrystallized from toluene [13].

General Procedure for Synthesis of 10-12

A mixture of **10-12** (1.92 mmol) and $POCl_3$ (80 mmol) was refluxed with stirring for 7 h and dry HCl gas was passed through the refluxing liquid during the first 4 h, then $POCl_3$ was evaporated, the reaction mixture was poured into ice-cold water, 4N NaOH was added and the mixture was extracted with EtOAc. The extract was washed with water, dried over Na_2SO_4 and evaporated. Recrystallization of the mixture from EtOAc: *n*-hexane gave **10-12** [13].

General Procedure for Synthesis of 13-15

A mixture of **10-12** (1.7 mmol) and 4-methylpiperidine (2 mmol) in DMF (0.5 ml) was heated for 8 h at 110°C, water was added and the mixture was extracted with EtOAc. The extract was washed with water, dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography ($CHCl_3$:isopropanol 10:1) to give **13-15** [13].

Methyl 4-((2,4-dichlorobenzyl)amino)-3-nitrobenzoate (3)

Yield: 65%. m.p. 132-133°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 3.89 (s, 3H, OC*H*$_3$), 4.65 (d, 2H, J=6Hz, C*H*$_2$), 6.73, (d, 1H, J=8.8Hz), 7.225-7.228 (m, 2H), 7.45 (s, 1H) , 8.01 (dd, 1H, J=8.8 & 2Hz), 8.72 (br.s, 1H, N*H*), 8.90 (d, 1H, J=2.4Hz) ; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm : 165.4, 147.1, 136.5, 134.5, 133.9, 132.5, 131.95, 129.85, 129.4, 129.2, 127.6, 118.3, 113.7, 52.2, 44.4. $C_{15}H_{12}Cl_2N_2O_4$.

Methyl 1-ethyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-5-carboxylate (7)

Yield: 65%. m.p. 198-200°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 1.37 (t, 3H, J=7.6Hz, C*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 3.98 (q, 2H, J=7.6Hz, C*H*$_2$), 7.02 (d, 1H, J=8Hz), 7.83-7.87 (m, 2H), 10.61 (br.s, 1H, N*H*) ; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm : 167.1, 155.8, 133.7, 127.9, 123.8, 123.5, 111.0, 107.1, 52.0, 35.9, 13.6. **MS** m/z (ESI+) : 221 [M+H] (68%) for $C_{11}H_{12}N_2O_3$.

Methyl 1-cyclopropyl-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-5-carboxylate (8)

Yield: 70%. m.p. 225-227°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 1.04-1.07 (m, 2H, C*H*$_2$), 1.15-1.18 (m, 2H, C*H*$_2$), 2.91-2.94 (m, 1H, C*H*), 3.90 (s, 3H, OC*H*$_3$), 7.22 (d, 1H, J=8.4Hz, H-7), 7.81 (d, 1H, J=1.6Hz, H-4), 7.85 (dd, 1H, J=8 & 1.6Hz, H-6), 10.32 (br.s, 1H, N*H*) ; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm : 167.1, 156.4, 135.0, 127.4, 123.8, 123.7, 110.8, 108.2, 52.05, 22.5, 6.1. **MS** m/z (ESI+) : 233 [M+H] (100%) for $C_{12}H_{12}N_2O_3$.

Methyl 1-(2,4-dichlorobenzyl)-2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazole-5-carboxylate (9)

Yield: 60%. m.p. 219-221°C. **^{1}H-NMR** (500 MHz, $CDCl_3$) δ ppm : 3.92 (s, 3H, C*H*$_3$), 5.21 (s, 2H, C*H*$_2$), 6.91 (d, 1H, J=8.3Hz, H-7), 7.05 (d, 1H, J=8.35Hz, H-6'), 7.19 (dd, 1H, J=8.35 & 2.05Hz, H-5'), 7.47 (d, 1H, J=2.05Hz, H-3'), 7.82 (dd, 1H, J=8.3 & 1.55Hz, H-6), 7.85 (d, 1H, J=1.2Hz, H-4), 10.04 (s, 1H, N*H*) ; **COSY** ($CDCl_3$) δ ppm: [H-6 : H-7], [H-5' : H-6'] ; **^{13}C-NMR** (125 MHz, $CDCl_3$) δ ppm : 166.8, 155.8, 134.4, 133.5, 131.6, 129.65, 129.2, 127.7, 127.6, 124.33, 124.26, 111.1, 107.9, 52.2, 41.7. **MS** m/z (ESI+) : 351 [M+H] (68%), 353 [M+H+2] (31%), 355 [M+H+4] (8%) for $C_{16}H_{12}Cl_2N_2O_3$.

Methyl 2-chloro-1-ethyl-1*H*-benzo[*d*]imidazole-5-carboxylate (10)

Yield: 40%. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 1.46 (t, 3H, J=7.2Hz, C*H*$_3$), 3.95 (s, 3H, OC*H*$_3$), 4.28 (q, 2H, J=7.6Hz, C*H*$_2$), 7.35 (d, 1H, J=8.4Hz, H-7), 8.04 (dd, 1H, J=8.4 & 1.2Hz, H-6), 8.40 (d, 1H, J=1.2Hz, H-4) ; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm : 167.2, 141.9, 141.1, 137.6, 125.05, 124.8, 121.6, 109.05, 52.2, 39.75, 14.6. **MS** m/z (ESI+) : 239 [M+H] (100%), 241 [M+H+2] (31%), for $C_{11}H_{11}ClN_2O_2$.

Methyl 2-chloro-1-cyclopropyl-1*H*-benzo[*d*]imidazole-5-carboxylate (11)

Yield: 45%. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 1.14-1.32 (m, 4H, C*H*$_2$-C*H*$_2$), 3.23-3.25 (m, 1H, C*H*), 3.93 (s, 3H, OC*H*$_3$), 7.52 (d, 1H, J=8.4Hz, H-7), 8.01 (dd, 1H, J=8.4 & 1.6Hz, H-6), 8.34 (d, 1H, J=1.6Hz, H-4) ; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm : 167.5, 144.4, 141.05, 139.6, 125.2, 124.95, 121.8, 110.2, 52.4, 25.6, 7.5. **MS** m/z (ESI+) : 251 [M+H] (100%), 253 [M+H+2] (31%) for $C_{12}H_{11}ClN_2O_2$.

Methyl 2-chloro-1-(2,4-dichlorobenzyl)-1*H*-benzo[*d*]imidazole-5-carboxylate (12)

Yield: 44%. m.p. 132-134°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 3.94 (s, 3H, OC*H*$_3$), 5.47 (s, 2H, C*H*$_2$), 6.54 (d, 1H, J=8.8Hz, H-7), 7.12 (dd, 1H, J=8.4 & 2Hz, H-5'), 7.18 (d, 1H, J=8.4Hz, H-6'), 7.48 (d, 1H, J=2Hz, H-3'), 7.98 (dd, 1H, J=8.8 & 1.6Hz, H-6), 8.43 (d, 1H, J=0.8Hz, H-4). **MS** m/z (ESI+) : 369 [M+H] (68%), 371 [M+H+2] (67%), 373 [M+H+4] (23%), 375 [M+H+6] (3%) for $C_{16}H_{11}Cl_3N_2O_2$.

Methyl 1-ethyl-2-(4-methylpiperidin-1-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate (13)

Yield: 30%. m.p. 113-115°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 0.99 (d, 3H, J=6.8Hz, C*H*$_3$), 1.33-1.45 (m, 5H), 1.58-1.6 (m, 1H), 1.75-1.78 (m, 2H), 2.99-3.06 (m, 2H), 3.52-3.55 (m, 2H), 3.88 (s, 3H, OC*H*$_3$), 4.02 (q, 2H, J=7.6Hz, C*H*$_2$), 7.19 (d, 1H, J=8.8Hz, H-7), 7.87 (dd, 1H, J=8.8 & 1.6Hz, H-6), 8.28 (d, 1H, J=1.2Hz, H-4) ; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm : 167.9, 159.2, 140.6, 138.2, 124.0,

123.4, 119.8, 108.6, 52.2, 51.5, 39.6, 34.2, 30.9, 22.05, 14.5. **MS** m/z (ESI+) : 302 [M+H] (100%) for $C_{17}H_{23}N_3O_2$.

Methyl 1-cyclopropyl-2-(4-methylpiperidin-1-yl)-1*H*-benzo[*d*]imidazole-5-carboxylate (14)

Yield: 35%. m.p. 132-133°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 0.99 (d, 3H, J=6.8Hz, C*H*$_3$), 1.02-1.04 (m, 2H), 1.08-1.16 (m, 2H), 1.32-1.41 (m, 2H), 1.57-1.62 (m, 1H), 1.75-1.78 (m, 2H), 2.94-3.00 (m, 2H), 3.13-3.16 (m, 1H), 3.87 (s, 3H, OC*H*$_3$), 3.93-3.96 (m, 2H), 7.27 (d, 1H, J=8.4Hz, H-7), 7.82 (dd, 1H, J=8.4 & 1.2Hz, H-6), 8.17 (d, 1H, J=1.2Hz, H-4) ; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm : 168.2, 159.15, 140.7, 139.9, 123.8, 122.7, 119.1, 109.2, 52.1, 49.9, 34.15, 30.9, 26.2, 22.1, 7.9. **MS** m/z (ESI+) : 314 [M+H] (100%), for $C_{18}H_{23}N_3O_2$.

Methyl 1-(2,4-dichlorobenzyl)-2-(4-methylpiperidin-1-yl)-1*H*-benzo[d]imidazole-5-carboxylate (15)

Yield: 33%. m.p. 181-183°C. **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm : 0.96 (d, 3H, J=6.4Hz, C*H*$_3$), 1.31-137 (m, 2H), 1.55 (m, 1H), 1.67-1.70 (m, 2H), 2.92-2.99 (m, 2H), 3.39-3.42 (m, 2H), 3.89 (s, 3H, OC*H*$_3$), 5.17 (s, 2H, benzylic C*H*$_2$), 6.74 (d, 1H, J=8.8Hz, H-7), 6.90 (d, 1H, J=8Hz, H-6'), 7.13 (dd, 1H, J=8.4 & 2Hz, H-5'), 7.47 (d, 1H, J=1.6Hz, H-3'), 7.80 (dd, 1H, J=8 & 1.6Hz, H-6), 8.30 (d, 1H, J=1.2Hz, H-4) ; **^{13}C-NMR** (100 MHz, $CDCl_3$) δ ppm : 167.65, 159.9, 141.5, 138.8, 134.3, 133.1, 132.1, 129.7, 127.84, 127.76, 124.4, 123.4, 119.9, 108.3, 51.9, 50.9, 45.7, 33.8, 30.6, 21.8. **MS** m/z (ESI+) : 432 [M+H] (100%), 334 [M+H+2] (61%), 436 [M+H+4] (12%) for $C_{22}H_{23}Cl_2N_3O_2$.

RESULT AND DISCUSSION

As shown in Scheme 1, nitro group of **1-3** was reduced to **4-6**. Cyclization of these compounds with urea under heat afforded **7-9.** Treatment of **7-9** with $POCl_3$ gave **10-12**. By the nucleophilic substitution reaction of **10-12** with 4-methylpiperidine gave the targeted compounds **13-15**. The structures of novel compounds were determined by ^{1}H-^{13}C-NMR and LC-MS. To clarify aromatic protons of **9**, the COSY (Correlated Spectroscopy-2D-NMR technique) spectrum was recorded. Analysis of the COSY spectrum, shown in Figure 2, confirms the assignment of the resonances H-6/H-7 and H-5'/H-6' as neighboring hydrogens.

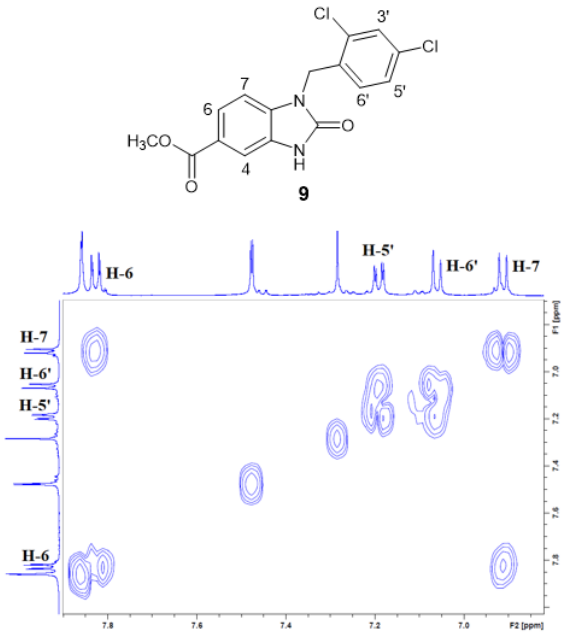


Figure 2. COSY spectrum of compound **9**

In this study, five new intermediate compounds and three new methyl 1*H*-benzimidazole-5-carboxylate derivatives were designed and synthesized, their structures were elucidated with NMR techniques. The ADME parameters of compounds **13-15** in Table 1 are presented. According to theoretical calculations, compound **15** complies with Lipinski's rules by causing one violation. Other ADME parameters of the compounds are within suitable limits. Antibacterial activity studies are under investigation.

Table 1. Calculated ADME parameters of **13-15**.

Compounds	LogP	TPSA	nON	nOHNH	MV	Vio
13	3.59	47.37	5	0	289.68	0
14	3.58	47.37	5	0	295.90	0
15	6.09	47.37	5	0	371.60	1

Log P: log octanol/water partition coefficient; TPSA: Total Polar Surface Area; nON: number of Hydrogen acceptors; nOHNH: number of Hydrogen donors and MV: Molecular Volume were calculated using Molinspiration Calculation of Molecular Properties toolkit. Vio: Violation number of Lipinski's rule.

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AUTHOR CONTRIBUTIONS

Concept: F.D.; Design: F.D.; Control: F.D.; Sources: F.D.; Materials: F.D.; Data Collection and/or Processing: F.D.; Analysis and/or Interpretation: F.D.; Literature Review: F.D.; Manuscript Writing: F.D.; Critical Review: F.D.; Other: -

CONFLICT OF INTEREST

The author declares that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The author declares that ethics committee approval is not required for this study.

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