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RESEARCH ARTICLE

Synthesis of Some Novel Schiff Base Derivative 5-Substituted-4-Amino-1,2,4-Triazole-3-one Compounds with Potential Lipase Inhibition Activity

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Synthesis of Some Novel Schiff Base Derivative 5-Substituted-4-Amino-1,2,4-Triazole-3-one Compounds with Potential Lipase Inhibition Activity

SUMMARY

In this study, 5 new Schiff base compounds containing triazole-imidazole rings were synthesized. Compounds containing this binary system have been realized for heterocyclic imine derivative compounds. According to literature information, these obtained compounds are expected to have potential biological activities such as anticonvulsant and antimicrobial activities. In the first step of the synthesis, iminoster derivative compounds (1a-e) were obtained from aryl/alkyl nitrile compounds by the Pinner method. In the second step, ester ethoxycarbonyl derivative compounds (2a-e) were obtained by the reaction of aryl/alkyl iminoester (1a-e) compounds with ethoxycarbonyl hydrazine compound. The resulting ester ethoxycarbonyl hydrazones were reacted with hydrazine hydrate, and the corresponding triazole-amine (3a-e) compounds were obtained using the method given in the literature. In the original step of the study, the 5-substituted-4-amino-1,2,4-triazol-3-one compounds (3a-e) were reacted with 4-imidazole carboxyaldehyde and five new Schiff bases 4-{[((1H-imidazol-4-yl)methylene]amino}-5-substituted-2,4-dihydro-3H-1,2,4-triazole-3-one compounds (4a-e) were obtained. A series of 5 new 5-substituted-4-{[(1H-imidazol-4-yl)methylene]amino}-2,4-dihydro-3H-1,2,4-triazole-3-one (4a-e) were synthesized, and their physical properties and IR, 1H-NMR, and 13C-NMR spectral analyses were performed to elucidate the structures of the compounds. The pancreatic lipase enzyme inhibition activities of the obtained new Schiff base compounds were investigated. They showed average activity against the positive control "Orlistat".

Key Words: *Iminoester, Schiff base, triazole-imidazole, ester ethoxycarbonyl hydrazones, pancreatic lipase enzyme inhibition*

Potansiyel Lipaz İnhibisyon Aktiviteli Bazı Yeni Schiff Baz Türevi 5-Sübstitüe-4-Amino-1,2,4-Triazol-3-on Bileşiklerinin Sentezi

ÖZ

Bu çalışmada, triazol-imidazol halkaları içeren 5 yeni Schiff bazı bileşiği sentezlenmiştir. Bu ikili sistemi içeren bileşikler, heterosiklik imin türevi bileşiklerdir. Literatür bilgilerine göre, elde edilen bu bileşiklerin antikonvülsan ve antimikrobiyal aktiviteler gibi potansiyel biyolojik aktivitelere sahip olması beklenmektedir. Sentezin birinci basamağında, aril/alkil nitril bileşiklerinden Pinner yöntemi ile iminoster türevi bileşikleri (1a-e) elde edilmiştir. İkinci aşamada, aril/alkil iminoester (1a-e) bileşiklerinin etoksikarbonil hidrazin bileşiği ile reaksiyonu sonucu ester etoksikarbonil türevi bileşikler (2a-e) elde edilmiştir. Ortaya çıkan ester etoksikarbonil hidrazonlar, hidrazin hidrat ile reaksiyona sokularak ve literatürde verilen yöntem kullanılarak karşılık gelen triazol-amin (3a-e) bileşikleri elde edilmiştir. Çalışmanın orijinal basamağında, 5-sübstitüe-4-amino-1,2,4-triazol-3-on bileşikleri (3a-e), 4-imidazol karboksialdehit ve beş yeni Schiff bazı 4-{[((1H-imidazol-4-il)metilen]amino}-5-substitue-2,4-dihidro-3H-1,2,4-triazol-3-on bileşikleri (4a-e) elde edilmiştir. Bu çalışmada, 5 yeni 5- substitue-4-{[(1H-İmidazol-4-il)metilen] amino}-2,4-dihidro-3H-1,2,4-triazol-3-on (4a-e) bileşikleri sentezlenmiş ve fiziksel özellikleri ve yapılarının aydınlatılması için IR, 1H-NMR ve 13C-NMR spektral analizleri yapılmıştır. Elde edilen yeni Schiff bazı bileşiklerinin pankreatik lipaz enzim inhibisyon aktiviteleri incelenmiştir. Pozitif kontrol "Orlistat"a karşı ortalama bir aktivite göstermişlerdir.

Anahtar Kelimeler: *İminoester, Schiff bazı, triazol-imidazol, ester etoksikarbonil hidrazon, pankreatik lipaz enzim inhibisyonu*

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INTRODUCTION

Obesity occurs as a result of the energy taken into the body by food being more than the energy spent (Altunkaynak & Özbek, 2006). Obesity is one of the most important health problems in developed and developing countries in terms of mortality and morbidity rates. Obesity and many diseases, such as diabetes, hypertension, cardiovascular diseases, and cancer, which are directly related to obesity, cause high levels of health problems and economic losses on a global scale (Jack et al., 2017; Blüher, 2019; Sener et al., 2023). Supplying the energy balance of the body is very important in the treatment and control of obesity. Also, reducing the fat in the diet reduces the risk of developing obesity.

Lipases, included in the hydrolase class, are important enzymes that play a role in the digestion of fats and are target molecules in the treatment of obesity. Orlistat is known to be a potent gastric and pancreatic lipase inhibitor (Sener et al., 2021). Today, studies on the search for new treatment agents continue due to the side effects of existing drugs used in the treatment of obesity.

Heterocycles having 1,2,4-triazole skeletons are widely studied compounds with important biological properties as an antifungal, antiviral, antimigraine, antidepressant, and antitumoral (Figure 1) (Strzelecka & Swiatek, 2021).

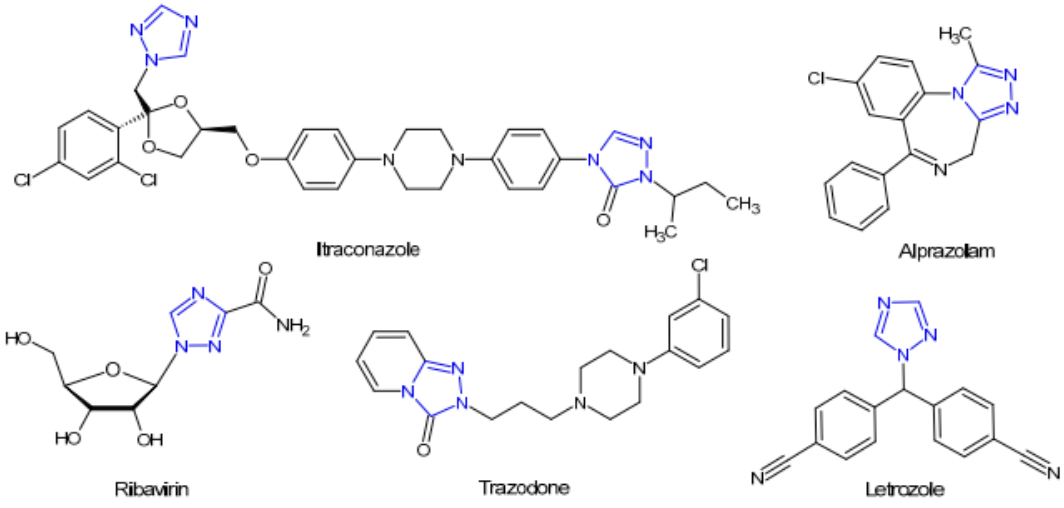


Figure 1. Some biologically active compounds with 1,2,4-triazole skeletons

Schiff bases attract attention by taking part in the structure of many compounds, providing a diversity of biological activities such as muscle relaxants, antibiotics, anti-tuberculosis, etc.) (Figure 2) (Hassan et al., 2015).

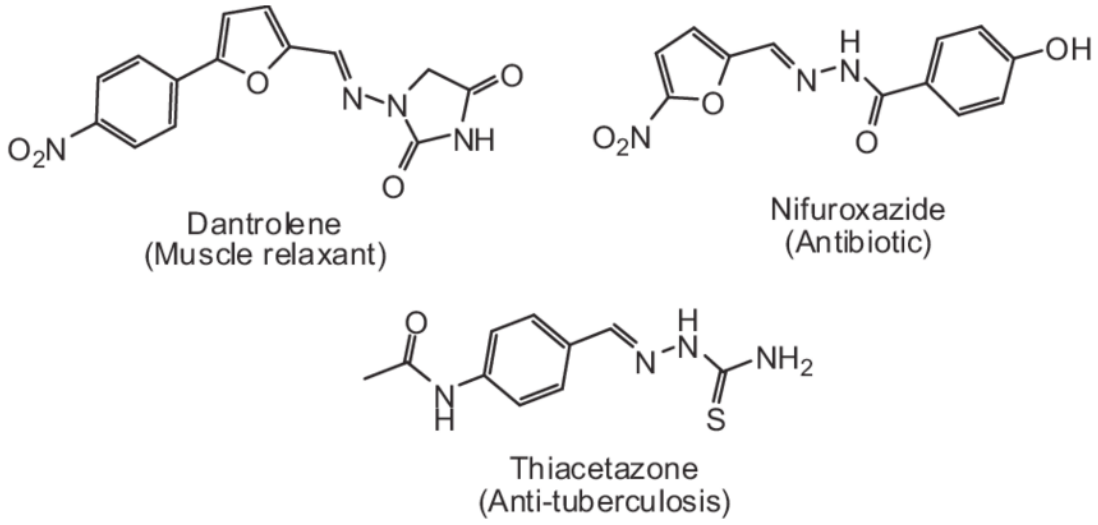


Figure 2. Some biologically active compounds with Schiff base group

1,2,4-triazol-amine compounds (Figure 3) related to systems used to obtain imine derivatives. In literature, it has been reported that triazole-amine compounds also show anticonvulsant and antimicrobial activities (Kahveci et al., 2012; El-Sayed et al., 2013; Kahveci et al., 2014).

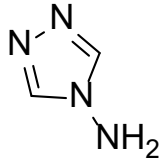


Figure 3. 4-Amino-1,2,4-triazole

Amongst azoles, the imidazole system has attracted much attention because of its potential to generate new chemotherapeutic agents (Rekha et al., 2019; Kahveci, 2005). Some imidazole-based drugs, alosetron, etomidate, clotrimazole, and eprosartan are shown in Figure 4 (Campos & Berteina-Raboin, 2020).

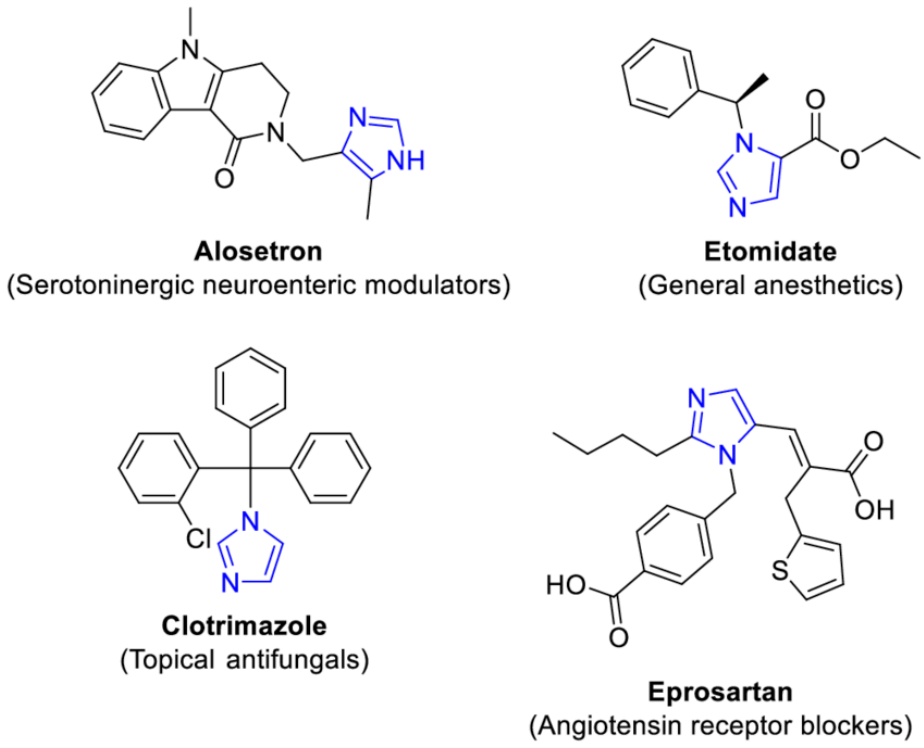
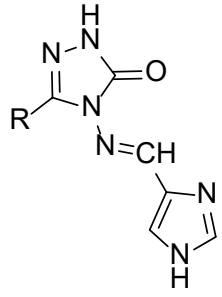


Figure 4. Some imidazole-based drugs

In view of the above-mentioned biological importance of triazole, imidazole, and Schiff bases and as a continuation of our interest in the synthesis of novel compounds with expected biological activities, this study deals with the design and synthesis of a series of the novel "Schiff base compounds containing triazole-imidazole rings" (compounds **4a-e**) (Figure 5) which have promising ***Lipase enzyme inhibition activities*** compared with "orlistat".



R: -CH_3, -C_6H_5,-CH_2-C_6H_5, -CH_2-(4-CH_3-C_6H_4), -CH_2-(4-Cl-C_6H_4)

Figure 5. The newly synthesized Compounds **4a-e**

MATERIAL AND METHODS

1. Chemistry

All chemicals were supplied by Merck. Melting points were determined on a Thomas Hoover capillary melting point apparatus (Philadelphia, PA, USA) and are uncorrected. The IR spectra were recorded on a Bruker Vector 22 IR (Beaconsfield, UK) (KBr disc). ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Bruker 400 MHz NMR spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C), using TMS as an internal standard, DMSO-d_6 were used as NMR solvents. All chemical shift values were recorded as δ (ppm). The purity of the compounds was checked by thin-layer chromatography (silica gel, HF254, type 60, 0,25 mm, Merck). Elemental analysis data were performed on a Leco CHNS932 analyzer.

1.1. Synthesis of Iminoester HCl derivatives (Compound 1a-e)

The Iminoester HCl derivative compounds (**1a-e**) were synthesized using the *Pinner method* (Pinner, 1892). In this method, appropriate aryl/alkyl nitrile derivatives and ethanol were reacted with HCl (g) at 0-5°C in anhydrous ether to obtain the corresponding iminoester hydrochloride. In order to obtain HCl gas, H_2SO_4 and NH_4Cl were reacted, and the resulting HCl gas was passed into the reaction medium with the Kip device**.**

1.2. Synthesis of ester ethoxycarbonyl hydrazones (Compound 2a-e)

Ester ethoxycarbonyl derivative compounds (**2a-e**) were obtained by the reaction of aryl/alkyl iminoester (**1a-e**) compounds with ethoxycarbonyl hydrazine compound. The equivalent amount (0.03 mol) of aryl/alkyl iminoester hydrochloride derivatives (**1a-e**) and ethoxycarbonyl hydrazine were dissolved in absolute ethanol (50 mL). The reaction is stirred in an ice bath for 6 hours, and the precipitated ammonium chloride is filtered off from the reaction medium. The filtrate is evaporated and crystallized with petroleum ether (İkizler et al., 1996).

1.3. Synthesis of triazole amine (Compounds 3a-e)

General procedure for the preparation of 3-substituted-4-amino-4,5-dihydro-1H-1,2,4-triazole-5-ones.

The resulting ester ethoxycarbonyl hydrazones (compound **2a-e)** (0.01 mol) were refluxed for 5 hours with a solution of hydrazine hydrate (1.25 mL) in water (60 mL). The solution was crystallized by cooling to obtain the crude product (compound **3a-e**). The solid material thus obtained was filtered off and recrystallized from ethanol (Milcent et al., 1980; Kahveci, 2005).

Melting points for compounds **1a-e, 2a-e, and 3a-e** are consistent with literature data (Kahveci, 2005; Kahveci et al., 2014).

1.4. Synthesis pathway for Compounds 4a-e

In the original step of the study, the 5-substituted-4-amino-1,2,4-triazole-3-one compounds (**3a-e**) were reacted with 4-imidazole carboxaldehyde and five new Schiff bases 4-{[(1*H*-imidazol-4-yl)methylene] amino}-5-substituted-2,4-dihydro-3*H*-1,2,4-triazole-3-one compounds (**4a-e**) were obtained. For this reaction, anhydrous ethanol was used as a solvent, and 3 drops of acetic acid as a catalyst, and a boiling process was carried out under reflux under these conditions for 3-4 hours (the completion of the reaction was checked by thin layer chromatography). Afterward, the reaction mixture was cooled, and the precipitated product was filtered, purified by ethanol-water crystallization, and dried. The melting point was checked, and spectroscopy studies were carried out to elucidate the structure**.**

Compound 4a: 4-{[(1*H*-Imidazol-4-yl)methylen]amino}-5-methyl-2,4-dihidro-3*H*-1,2,4-triazol-3-one

Yield: 89 %, **M.p.:** 284-285 °C, **IR (vmax/cm^{-1}):** 3426, 3200 (NH, NH), 1691 (C=O), 1608 (C=N). **^{1}H-NMR (DMSO-d6),** δ, ppm: 1.20 (3H, s, CH_3), 7.74 (1H, s, Ar-H), 7.82 (1H, s, Ar-H), 9.52 (1H, s, CH), 11.70 (1H, s, NH, triazole), 12.56 (1H, s, NH,

imidazole). **^{13}C-NMR (DMSO-d6),** δ, ppm: 11.263 (CH_3), 127.54, 142.53 (C-imidazole), 144.56 (C=N, imidazole), 151.87 (C=O, triazole), 152.01 (C=N), 156.69 (CH=N). **Anal. Calcd for $C_7H_8N_6O$**: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.95; H, 4.54; N, 43.98.

Compound 4b: 4-{[(1*H*-Imidazol-4-yl)methylen]amino}-5-phenyl-2,4-dihidro-3*H*-1,2,4-triazol-3-one

Yield: 87 %, **M.p.:** 236-238 °C, **IR (vmax/cm^{-1})**: 3144 (NH), 1706 (C=O), 1604 (C=N). **^{1}H-NMR (DMSO-d6),** δ, ppm: 7.47-7.48 (2H, m, ArH), 7.75-7.92 (3H, m, ArH), 7.74 (1H, s, Ar-H), 7.82 (1H, s, Ar-H), 9.38 ve 9.73 (1H, s, CH), 11.66 (1H, s, NH, triazole), 12.27 ve 12.61 (1H, s, NH, imidazole). **^{13}C-NMR (DMSO-d_6)**, δ, ppm: 125.17, 127.20, 127.30, 128.18, 128.93, 129.33, 130.37, (ArC), 142.56 (C-imidazole), 144.71 (C=N, imidazole), 145.46 (C=N, triazole), 152.01 (C=O, triazole), 156.77 (C=N). **Anal. Calcd for $C_{12}H_{10}N_6O$**: C, 56.69; H, 3.96; N, 33.05. Found: C, 56.85; H, 4.02; N, 33.10.

Compound 4c: 4-{[(1*H*-Imidazol-4-yl)methylen]amino}-5-benzyl-2,4-dihidro-3*H*-1,2,4-triazol-3-one

Yield: 85 %, **M.p.:** 240-241 °C, **IR (vmax/cm^{-1}):** 3268, 3147 (NH), 1710 (C=O), 1612, 1600 (C=N). **^{1}H-NMR (DMSO-d_6),** δ, ppm: 4.10 (2H, s, CH_2), 7.14-7.30 (5H, m, ArH), 7.75 (1H, s, Ar-H), 7.83 (1H, s, Ar-H), 9.53 (1H, s, CH), 11.72 (1H, s, NH, triazole), 12.73 (1H, s, NH, imidazole). **^{13}C-NMR (DMSO-d_6),** δ, ppm: 30.84 (CH_2), 127.04, 127.40, 128.87, 129.25, 136.65, 137.65 (ArC), 144.80 (C=N, imidazole), 150.12 (C=N, triazole), 153.94 (C=O, triazole), 156.74 (HC=N). **Anal. Calcd for $C_{13}H_{12}N_6O$**: C, 58.20; H, 4.51; N, 31.33. Found: C, 58.45; H, 4.55; N, 31.38.

Compound 4d: 4-{[(1*H*-Imidazol-4-yl)methylen]amino}-5-(4-methylbenzyl)-2,4-dihidro-3*H*-1,2,4-triazol-3-one

Yield: 90%, **M.p.:** 252-253 °C, **IR (vmax/cm^{-1}):** 3158, 3123 (NH), 1718, 1693 (C=O), 1610, 1580 (C=N). **^{1}H-NMR (DMSO-d_6),** δ, ppm: 1.89 (3H, s, CH_3), 3.92 (2H, s, CH_2), 7.07 (2H, d, J= 6.8 Hz, ArH), 7.18 (2H, d, J= 6.8 Hz, ArH), 7.66 (1H, s, Ar-H), 7.84 (1H, s, Ar-H), 9.50 (1H, s, CH), 11.83 (1H, s, NH, triazole), 12.55 (1H, s, NH, imidazole). **^{13}C-NMR (DMSO-d_6),** δ, ppm: 21.05 (CH_3), 30.85 (CH_2), 127.23, 129.25, 129.37, 133.22, 136.14 (ArC), 144.75 (C=N, imidazole), 146.27 (C=N, triazole), 151.82 (C=O, triazole), 156.70 (HC=N). **Anal. Calcd for $C_{14}H_{14}N_6O$**: C, 59.56; H, 5.00; N, 29.77. Found: C, 59.59; H, 5.02; N, 29.80.

Compound 4e: 4-{[(1*H*-Imidazol-4-yl)methylen]amino}-5-(4-chlorobenzyl)-2,4-dihidro-3*H*-1,2,4-triazol-3-one

Yield: % 91**, M.p.:** 213-214 °C, **IR (vmax/cm^{-1}):** 3166, 3124 (NH), 1694 (C=O), 1609, 1577 (C=N). **^{1}H-NMR (DMSO-d_6),** δ, ppm: 3.98 (2H, s, CH_2), 7.33-7.37 (4H, m, ArH), 7.74 (1H, s, Ar-H), 7.82 (1H, s, Ar-H), 9.51 (1H, s, CH), 11.87 (1H, s, NH, triazole), 12.56 (1H, s, NH, imidazole). **^{13}C-NMR (DMSO-d_6),** δ, ppm: 30.75 (CH_2), 120.62, 127.33, 128.75, 131.07, 131.33, 131.83, 135.27 (ArC), 142.37 (C=N, imidazole), 146.27 (C=N, triazole), 151.81 (C=O, triazole), 156.70 (HC=N).). **Anal. Calcd for $C_{13}H_{11}ClN_6O$**: C, 51.58; H, 3.66; N, 27.76. Found: C, 52.02; H, 3.69; N, 27.80.

2. Biological Activity

Measurement of pancreatic lipase inhibitory activity in vitro

Lipase enzyme inhibition was performed with a modified method using p-nitro phenylbutyrate as a substrate (Bustanji et al., 2011; Jo et al., 2017). All samples were buffered (0.1 M Tris-HCl buffer, pH=8.0) with final concentrations of 25, 50, 100, 200, and 400 µg/mL; Orlistat, which was used as a standard, was prepared with a buffer solution (0.1 M Tris-HCl buffer, pH=8.0) with final concentrations of 6.25, 12.5, 25, 50 and 100 µg/mL.

For each sample, the microplate was prepared to contain 3 negative control wells (A), 3 negative control blanks (B), 3 sample wells (C), and 3 blank wells (D). 5 µL of buffer was pipetted into wells A and B,

and 5 µL of test solution into wells C and D. 90 µL of lipase enzyme solution (200 U/mL) was pipetted into all wells and incubated at 37 °C for 15 minutes. After incubation, 5 µL of substrate solution (10 mM p-nitro phenyl butyrate acetonitrile solution) was pipetted into wells A and C, and 5 µL of buffer into wells B and D. Next, the microplate was incubated at 37°C for 10 min. After incubation, absorbance at 405 nm was read with a spectrophotometer (SpetrostarNano-BMG LABTECH), and % inhibition values were calculated using the formula below.

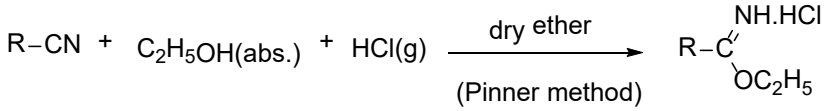
RESULTS AND DISCUSSION

Chemistry

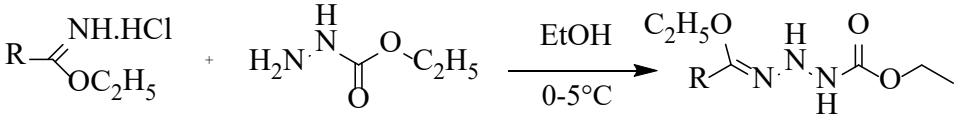
In this study, five new Schiff base compounds (compound **4a-e**) were synthesized and their pancreatic lipase enzyme inhibitor activities were examined. The 5 new compounds **4a-e** were obtained by reacting triazole amine derivatives (Compounds **3a–e**) with 4-imidazole carboxaldehyde with a synthesis method used for the first time.

Within the scope of this study, 5 new imine compounds containing triazole-imidazole rings were synthesized, and IR, ^{1}H-NMR, and ^{13}C-NMR spectral analysis were performed to elucidate the structures of the compounds and evaluated for pancreatic lipase enzyme inhibition activities.

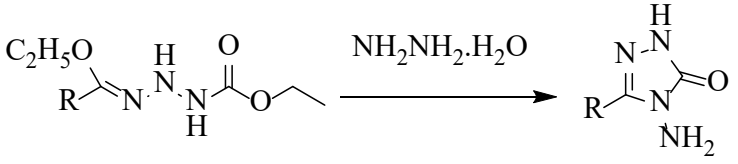
The general synthesis pathway for compounds was given in Scheme 1.



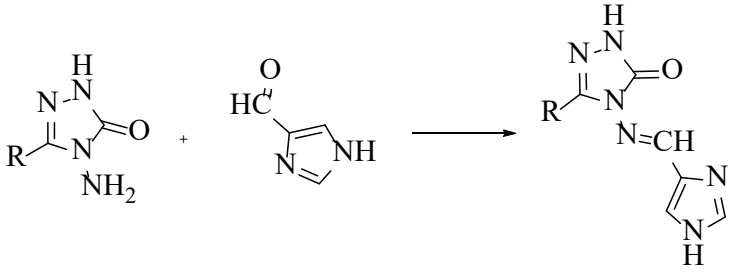
Compound 1a-e



Compound 2a-e



Compound 3a-e



Compound 4a-e

R: -CH_3, -C_6H_5,-CH_2-C_6H_5, -CH_2-(4-CH_3-C_6H_4), -CH_2-(4-Cl-C_6H_4)

Scheme 1. General synthesis method

The cream-colored compounds were obtained in yields of 85-94%. In the FT-IR spectra of newly synthesized compounds **4a-e**, the characteristic bands appeared for C=O bands between 1691-1718 cm^{-1} for triazole-3-on and the C=N bands between 1604-1612 cm^{-1} for imine, approximately. In the ^{1}H-NMR spectra, the signals of NH protons and imine –N=CH- protons verified the structure of Schiff base imine derivative compounds **4a-e**. The ^{13}C-NMR spectra also support the expected structures. The protons and carbons in the structure were observed at expected chemical shifts and integral values.

2. Biological evaluation

Lipase Enzyme Inhibition Results

All the newly synthesized compounds were screened for their pancreatic lipase enzyme inhibition activities compared with "orlistat".

The lipase enzyme inhibition results of the compounds and "orlistat" used as a standard are given as the IC50 value (Table 1). The IC50 value of Orlistat was found to be 20.190 ± 0.933 μg/mL. When the compounds were compared among themselves, the highest lipase enzyme inhibition was observed in compound **4a** (115.026 ± 2.48). All newly synthesized compounds showed weak activity compared to "orlistat".

According to these activity results, the compound with the highest activity is the 4a compound with the methyl substituent. In other compounds where the aromatic ring is substituted, it is seen that the activity decreases. These results suggest that when the aromatic ring comes into the structure, it creates a steric hindrance in enzyme inhibition. However, the compound that gave the lowest IC50 value after the methyl substituent was **4e** containing the chlorobenzyl substituent. The effect of the chlorine substituent of the compound is noteworthy.

Table 1. Results of lipase enzyme inhibition of compounds **4a-e**

Compounds	Lipase enzyme inhibition (IC_{50} (μg/mL) ± S**D**)
4a	115.026 ± 2.48
4b	283.917 ± 6.202
4c	221.606 ± 2.604
4d	200.277 ± 4.462
4e	131.469 ± 1.615
Orlistat	20.190 ± 0.933

CONCLUSION

5 new 5-substitued-4-{[(1*H*-imidazol-4-yl)methylen]amino}-2,4-dihydro-3*H*-1,2,4-triazol-3-one derivatives (Compound **4a-e**) were synthesized and characterized by using IR, ^{1}H-NMR, ^{13}C-NMR spectral analysis.

These new Schiff bases (compound **4a-e**) containing imine function were obtained by reacting 4-amino 1,2,4-triazole 3-one compounds with 4-imidazole carboxaldehyde. In this study, new heterocyclic imine compounds containing these triazole and imidazole ring systems together were obtained. All the newly synthesized compounds were screened for their pancreatic lipase enzyme inhibition activities compared with "orlistat". All of the compounds showed weak activity against "orlistat".

According to the activity results, the effect of the chlorobenzyl substituent is similar to the methyl substituent. The effect of the electrophilic property of the chlorine atom attracts attention. In this context, in order to examine the effect of electrophilic groups on the activity, it is planned to evaluate the structure-activity with the synthesis of new compounds bearing different substituents.

ACKNOWLEDGEMENTS

This study was orally presented at the 5th International Eurasian Conference on Biological and Chemical Sciences (EurasianBioChem, 2022) with the title

"Synthesis of some novel Schiff base derivative 5-substituted-4-amino-1,2,4-triazole 3-one compounds with potential biological activity" (Paper ID:275).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Compounds were designed by İ.S.D. and B.K. Compounds were synthesized by Y.K., İ.S.D., and B.K. Then structures were determined by İ.S.D. and B.K. Pancreatic lipase enzyme inhibition activity by microdilution method was made by Ş.K. Finally, manuscript preparation was realized by İ.S.D. and B.K. and Ş.K.

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