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Araştırma Makalesi / Research Article

Novel 1,2,3-Triazole Compounds Containing Different Amine Groups: Synthesis, Characterization and *in Silico* Studies on Xanthine Oxidase

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Abstract

In this study, novel 1,2,3-triazole derivatives containing different amine subunits **16**(**a**-**c**) and **17**(**a**-**c**) were synthesized and characterized by FT-IR, HRMS, ^{1}H, and ^{13}C NMR analyses. The interactions with xanthine oxidase (XO) enzyme of these compounds were investigated with molecular docking studies. The obtained results were compared with molecular docking studies of allopurinol and febuxostat, which are the XO inhibitors. All target compounds demonstrated better binding energies than allopurinol in the interaction with the XO. On the other hand, **16a** and **17a** exhibited better binding affinities than febuxostat. The best binding energy values of the target compounds, allopurinol, and febuxostat vary between -6.1 and 9.84 kcal/mol. In this case, the target compounds may show better activity than allopurinol against the XO *in vitro* enzyme-inhibition studies. Additionally, compounds **16a** and **17a** may show better activities than febuxostat, as well. Finally, *in silico* ADME and toxicity studies for all target compounds were performed. The ADME results suggested suitable drug-likeness values for the compounds. Regarding toxicity, the compounds are predicted to be safe in terms of mutagenicity and tumorigenicity.

Keywords
Xanthine oxidase; 1,2,3-Triazole; Allopurinol; Febuxostat; ADMET; Molecular docking

Farklı Amin Grupları İçeren Yeni 1,2,3-Triazol bileşikleri: Sentez, Karakterizasyon ve Ksantin Oksidaz üzerine *in Siliko* Çalışmalar

Öz

Bu çalışmada, farklı amin alt birimleri içeren yeni 1,2,3-triazol türevleri **16**(**a**-**c**) ve **17**(**a**-**c**) sentezlendi ve FT-IR, HRMS, ^{1}H, ve ^{13}C NMR analizleri ile yapıları karakterize edildi. Bu bileşiklerin ksantin oksidaz (XO) enzimi ile etkileşimleri moleküler yerleştirme çalışmaları ile incelendi. Elde edilen sonuçlar, XO inhibitörleri olarak bilinen allopurinol ve febuksostat'in moleküler yerleştirme çalışmaları ile karşılaştırıldı. Hedef bileşikler, XO ile etkileşimlerde allopurinolden daha iyi bağlanma enerjileri gösterdi. Diğer taraftan, **16a** ve **17a** bileşikleri, febuksostat'tan daha iyi bağlanma affiniteleri sergiledi. Hedef bileşikleri, allopurinol ve febuksostatın en iyi bağlanma enerjisi değerleri -6.1 ile 9.84 kcal/mol arasında değişmektedir. Bu durumda, hedef bileşiklerinin *in vitro* enzim inhibisyon çalışmalarında XO'ya karşı allopurinolden daha iyi aktivite göstermesi olasıdır. Ayrıca, **16a** ve **17a** bileşikleri de febuksostattan daha iyi aktivite gösterebilir. Son olarak, tüm hedef bileşikler için *in siliko* ADME ve toksisite çalışmaları yapılmıştır. ADME sonuçları, bileşikler için kabul edilebilir ilaç benzerlik değerleri önerdi. Toksisite ile ilgili olarak, tüm bileşiklerin mutajenite ve tümörijenite açısından güvenli olduğu tahmin edilmektedir.

Anahtar kelimeler
Ksantin oksidaz; 1,2,3-Triazol; Allopurinol, Febuksostat; ADMET; Moleküler yerleştirme

1. Introduction

There are many therapeutic approaches available for the treatment of gout (Pillinger and Mandell 2020). One of them is the use of XO inhibitory drugs. Allopurinol and febuxostat are the most common gout drugs. Febuxostat is known to be more effective against the XO and to be safer than allopurinol. However, both allopurinol and febuxostat have some side effects (Frampton 2015). Therefore, the discovery of new XO inhibitors is inevitable.

1,2,3-Triazole unit is a key structure found in many organic or inorganic compounds (Ganesh *et al*. 2011; Garudachari *et al*. 2014), which show various bioactive properties (Tan 2020). Triazole compounds are resistant to hydrolysis in acidic and basic conditions as well as oxidation and reduction due to their aromatic stability. These compounds can form electrostatic interactions with various receptors (Deshmukh *et al*. 2006). The triazole ring has also been used as a linker structure to obtain many hybrid molecules (Hans *et al*. 2010; Bunders *et al*. 2011). Alkylamine groups, another active group, are quite effective moieties on the structural bioactivity of many organic molecules (Aouad 2017; Deshmukh *et al.* 2019).

To contribute to the discovery of new and alternative XO inhibitors, some novel 1,2,3-triazole derivatives were synthesized and their structures characterized in this study. The inhibitory effects of the compounds on the XO enzyme were investigated with the assist of *in silico* studies and compared with allopurinol and febuxostat data.

2. Materials and Methods

2.1. Chemistry

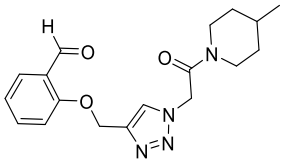
A Perkin Elmer spectrophotometer for the FT-IR spectra, a Bruker NMR for the ^{1}H-NMR (400 MHz), ^{13}C-NMR (100 MHz) spectra, *an Agilent* Technologies 6530 Accurate-Mass LC/Q-TOF/MS for the HR-MS data, and a *Thermo* Scientific for melting points (mp) were used.

9, **12**(**a**-**c**), **13**(**a**-**c**), **14**(**a**-**c**), and **15**(**a**-**c**) compounds were synthesized as described in the literature (Aouad 2017; Bunders *et al*. 2011; Deshmukh *et al*. 2019; Dommerholt *et al*. 2014; Hans *et al.* 2010; Hou *et al*. 2012; Lee *et al.* 2015; Pokhodylo *et al*. 2020**;** Tan 2022)

Synthesis of 16(a-c) and 17(a-c)

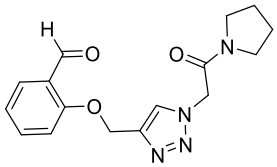
14(**a-c**) (1 equiv.) or **15**(**a-c**) (1 equiv.) were added to a solution of **9** (1 equiv.) in 15 mL of methanol at room temperature (r.t.). A mixture of $CuSO_4.5H_2O$ (0.1 equiv.) and Na-*L*-ascorbate (0.1 equiv.) in 15 mL of water were added, then the reaction mixture was stirred at r.t. for about 2 h. Thereafter, 15 mL of ethyl acetate was added to the medium and the mixture was extracted with water (3×20 mL). The organic part was dried with Na_2SO_4. The pure product was purified by column chromatography technique (Ethyl acetate/Hexane: 60/40) from the crude product.

Compound 16a



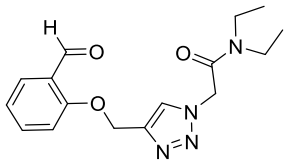
Yield: 85 %; white solid, mp= 96-97 °C, FT-IR (cm^{-1}): 3142, 2950-2864, 2107, 1682, 1650, 1597, 1559, 1479, 1455, 1418. HR-MS ($C_{18}H_{22}N_4O_3$): 343.17661 [*M*+H]$^+$ (calculated: 343.16949). ^{1}H-NMR δ (DMSO-d_6, ppm) 10.34 (*s*, 1H), 8.20 (*s*, 1H), 7.71-7.65 (*m*, 2H), 7.46 (*d*, 1H, *J* = 8.4 Hz), 7.12-7.08 (*m*, 1H), 5.51-5.41 (*m*, 2H), 5.36 (*s*, 2H), 4.27 (*d*, 1H, *J* = 13.2 Hz), 3.85 (*d*, 1H, *J* = 13.2 Hz), 3.04 (*t*, 1H, *J* = 12.4 Hz), 2.59 (*t*, 1H, *J* = 12.4 Hz), 1.67-1.60 (*m*, 3H), 1.16-1.08 (*m*, 1H), 0.96-0.89 (*m*, 4H).^{13}C-NMR δ (DMSO-d_6, ppm) 189.7, 164.1, 160.8, 142.4, 136.8, 128.1, 126.8, 124.9, 121.6, 114.5, 62.5, 51.2, 44.9, 42.4, 40.3, 34.3, 33.7, 30.6, 21.9.

Compound 16b



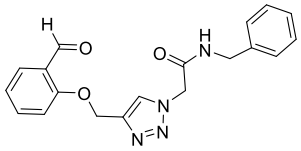
Yield: 70 %; white solid, mp= 134-135 °C, FT-IR (cm^{-1}): 3153, 2982-2878, 1793, 1684, 1654, 1595, 1555, 1446. HR-MS ($C_{16}H_{18}N_4O_3$): 315.14525 [*M*+H]$^+$ (calculated: 315.13777). ^{1}H-NMR δ ($CDCl_3$, ppm) 10.47 (*s*, 1H), 7.94 (*s*, 1H), 7.84 (*d*, 1H, *J* = 7.6 Hz), 7.57 (*t*, 1H, *J* = 7.6 Hz), 7.20 (*t*, 1H, *J* = 8.4 Hz), 7.07 (*t*, 1H, *J* = 7.2 Hz), 5.37 (*s*, 2H), 5.19 (*s*, 2H), 3.58-3.51 (m, 4H), 2.09-2.03 (*m*, 2H), 1.96-1.89 (*m*, 2H).^{13}C-NMR δ ($CDCl_3$, ppm) ^{13}C-NMR δ ($CDCl_3$, ppm) 189.6, 162.9, 160.5, 143.3, 135.9, 128.5, 125.1, 124.9, 121.3, 113.0, 62.4, 51.7, 46.4, 46.2, 26.1, 24.1.

Compound 16c



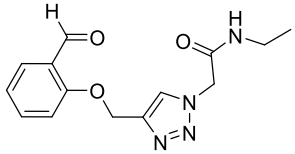
Yield: 80 %; white solid, mp= 75-76 °C, FT-IR (cm^{-1}): 3153, 2970-2871, 1737, 1683, 1654, 1599, 1580, 1480, 1457. HR-MS ($C_{16}H_{20}N_4O_3$): 317.16072 $[M+H]^+$ (calculated: 317.15345). ^{1}H-NMR δ ($CDCl_3$, ppm) 10.47 (*s*, 1H), 7.99 (*s*, 1H), 7.83 (*t*, 1H, *J* = 7.2 Hz), 7.56 (*t*, 1H, *J* = 7.2 Hz), 7.19 (*d*, 1H, *J* = 8.4 Hz), 7.05 (*t*, 1H, *J* = 7.2 Hz), 5.35 (*s*, 2H), 5.25 (*s*, 2H), 3.42 (*q*, 4H, *J* = 6.4 Hz), 1.27 (*t*, 3H, *J* = 6.8 Hz), 1.14 (*t*, 3H, *J* = 6.8 Hz). ^{13}C-NMR δ ($CDCl_3$, ppm) 189.6, 163.7, 160.5, 136.0, 128.5, 125.1, 121.2, 113.0, 62.4, 51.0, 41.9, 41.0, 14.3, 12.8.

Compound 17a



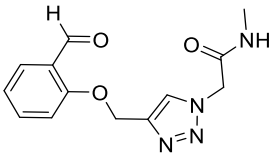
Yield: 85%; white solid, mp= 215-216 °C, FT-IR (cm^{-1}): 3282, 3150, 3107, 3064-2878, 1738, 1689, 1668, 1655, 1597, 1582, 1553, 1485, 1453. HR-MS ($C_{19}H_{18}N_4O_3$): 351.14524 $[M+H]^+$ (calculated: 351.13808).^{1}H-NMR δ (DMSO-d_6, ppm) 10.34 (*s*, 1H), 8.92-8.91 (*m*, 1H), 8.30 (*s*, 1H), 7.71-7.66 (*m*, 2H), 7.46 (*d*, 1H, *J* = 5.2 Hz), 7.33-7.25 (*m*, 5H), 7.12-7.08 (*m*, 1H), 5.36 (*s*, 2H), 5.20 (*s*, 2H), 4.32 (*d*, 2H, *J* = 5.6 Hz). ^{13}C-NMR δ (DMSO-d_6, ppm) 189.6, 165.8, 160.9, 142.5, 139.1, 136.8, 128.8, 128.1, 127.8, 127.4, 126.7, 124.9, 121.5, 114.6, 62.6, 52.1, 42.8.

Compound 17b



Yield: 85%; white solid, mp= 195-196 °C, FT-IR (cm^{-1}): 3271, 3142, 3107, 2978-2875, 1768, 1714, 1684, 1654, 1598, 1582, 1564, 1486, 1452, 1395. HR-MS ($C_{14}H_{16}N_4O_3$): 289.12962 $[M+H]^+$ (calculated: 289.12239). ^{1}H-NMR δ (DMSO-d_6, ppm) 10.34 (*s*, 1H), 8.35 (*s*, 1H), 8.26 (*s*, 1H), 7.71-7.66 (*m*, 2H), 7.46 (*d*, 1H, *J* = 8 Hz), 7.12-7.09 (*m*, 1H), 5.35 (*s*, 2H), 5.08 (*s*, 2H), 3.12-3.10 (*m*, 2H), 1.34 (*t*, 3H, *J* = 7.2 Hz).^{13}C NMR δ (DMSO-d_6, ppm) 189.6, 165.4, 160.8, 142.4, 136.8, 128.1, 126.6, 124.9, 121.6, 114.6, 62.5, 52.1, 34.2, 14.9.

Compound 17c



Yield: 70%; white solid, mp= 193-194 °C, FT-IR (cm^{-1}): 3281, 3142, 3107, 3000-2875, 1686, 1657, 1598, 1579, 1487, 1454. HR-MS ($C_{13}H_{14}N_4O_3$): 275.11393 $[M+H]^+$ (calculated: 275.10661).^{1}H-NMR δ (DMSO-d_6, ppm) 10.34 (*s*, 1H), 8.26 (*s*, 1H), 7.66-7.71 (*m*, 2H), 7.46 (*d*, 1H, *J* = 8.4 Hz), 7.08-7.12 (*m*, 1H), 5.35 (*s*, 2H), 5.09 (*s*, 2H), 2.63 (*d*, 3H, *J* = 4 Hz).^{13}C-NMR δ (DMSO-d_6, ppm) 189.8, 166.2, 160.8, 142.5, 136.9, 128.2, 126.6, 124.9, 121.6, 114.6, 62.4, 52.1, 26.1.

2.2. Molecular docking

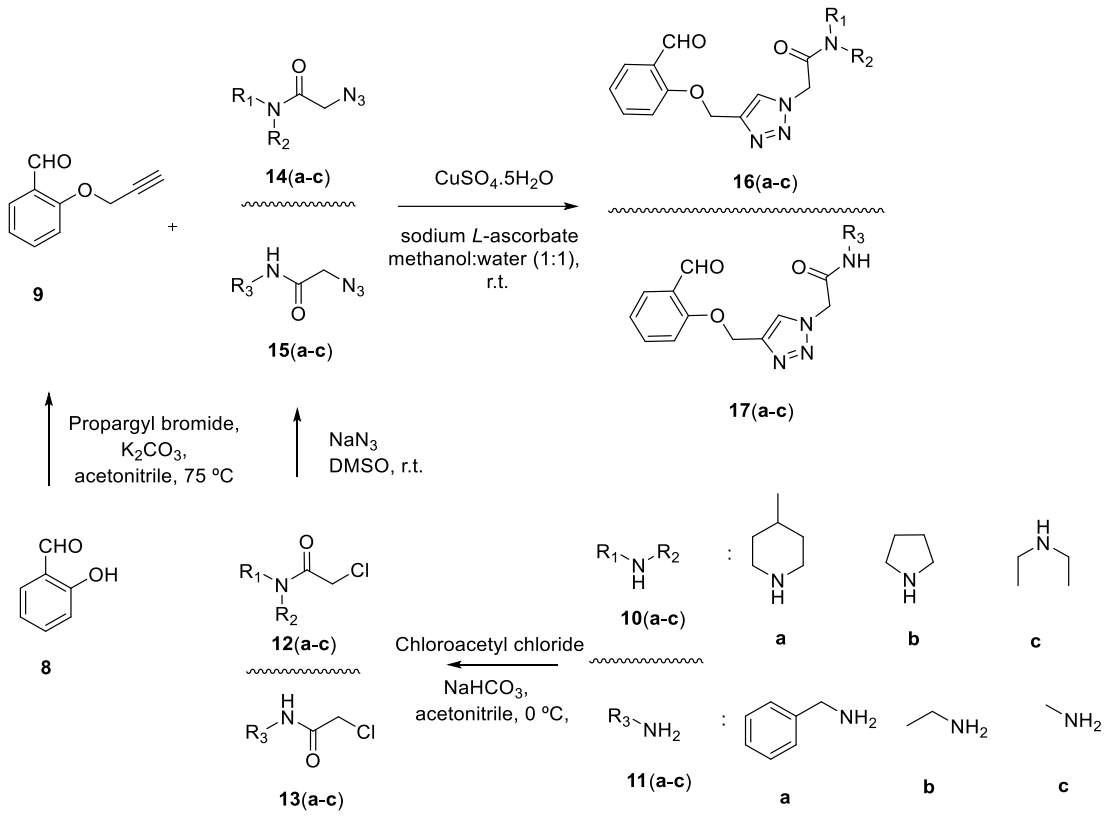
PDB ID: 3NVY, the three-dimensional structure of the XO enzyme, was retrieved from the Protein Data Bank website (https://www.rcsb.org/). The two-dimensional structures of all compounds were drawn on ChemDraw (Pr.16.0). The docking studies were performed *via* AutoDock 4.2 (Morris *et al*. 2009). The grid box centers were coordinated as X: 39.268 Å, Y: 21.834 Å, Z: 20.368 Å and the box sizes were set at 40x40x40 $Å^3$. The two-dimensional and three-dimensional visualization were performed with Discovery Studio Visualizer 2021 (Biovia 2021).

3. Results and Discussions

3.1. Chemistry

Compounds **16**(**a-c**) and **17**(**a-c**) containing an aromatic ring and various alkylamine groups, the target compounds, were synthesized from compound **8** (Scheme 1). Initially, **8** was reacted with firstly K_2CO_3 and later propargyl bromide in acetonitrile, and **9** (Hans *et al*. 2010) was obtained. Compound **9** was purified by crystallization from diethyl ether at room temperature. The organic azido compounds are known in the literature. **14**(**a-c**) (Aouad 2017; Deshmukh *et al*. 2019; Hou *et al*. 2012) and **15**(**a-c**) (Bunders *et al*. 2011; Dommerholt *et al*. 2014; Lee *et al.* 2015; Pokhodylo *et al.* 2020)

were synthesized starting from various secondary and primary amines **10**(**a**-**c**) and **11**(**a**-**c**). The amines **10**(**a**-**c**) and **11**(**a**-**c**) were treated with firstly $NaHCO_3$, later chloroacetyl chloride in acetonitrile to obtain compounds **12**(**a**-**c**) and **13**(**a**-**c**). Then, the acetamide derivatives were reacted with NaN_3 in DMSO and the corresponding **14**(**a**-**c**) and **15**(**a**-**c**) were obtained. In the last step, copper (I)-catalyzed click chemistry reactions (Himo *et al.* 2005) were used to synthesize **16**(**a-c**) and **17**(**a-c**) For this, compounds **14**(**a**-**c**) or **15**(**a**-**c**) in methanol were reacted with the corresponding alkyne compound (**9**), later added the mixture of $CuSO_4.5H_2O$ and sodium *L*-ascorbate in water to the reaction medium. **16**(**a-c**) and **17**(**a-c**) compounds were obtained.



Scheme 1. Synthesis stages of **16**(**a**-**c**) and **17**(**a**-**c**)

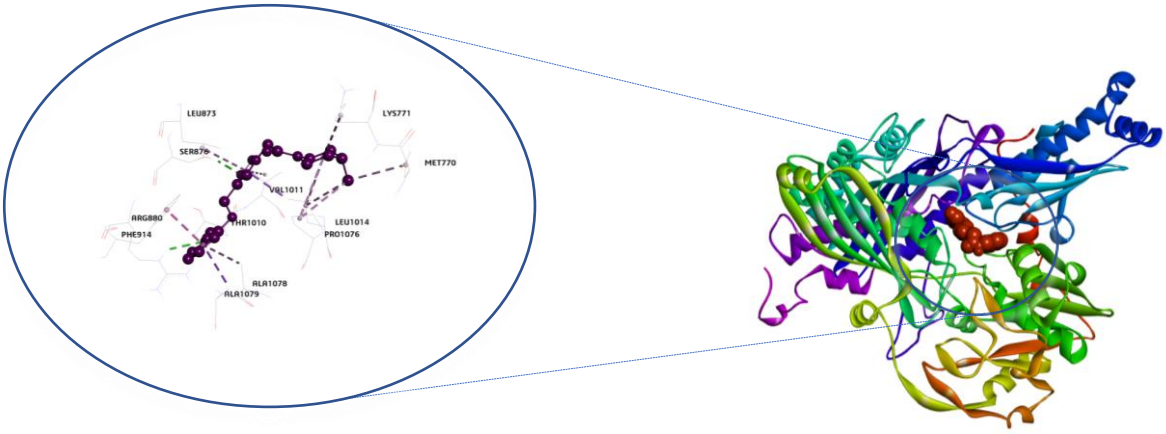
3.2. Molecular docking studies

To investigate enzyme-compound interactions, the docking studies were applied to the three-dimensional crystal structure of the XO (PDB ID: 3NVY). 3NVY PDB file contains quercetin as a ligand. Therefore, the docking mode for 3NVY was arranged according to quercetin. All compounds were similarly docked. The predicted inhibition activities, best binding energies, ligand efficiencies, intermolecular energies, and VDW-H bond desolvation energy values belonging to these compounds are given in Table 1. In our previous studies (Tan 2020; Tan 2021), we found that the best binding energy value of allopurinol in the interactions with the XO was 6.1 kcal/mol in the docking studies. According to this, compounds **16**(**a-c**) and **17**(**a-c**) showed better binding affinities than allopurinol. At the same time, the docking results of the target compounds were also compared with febuxostat. **16a** and **17a** among these compounds showed better binding affinities than febuxostat. Compounds **16a** and **17a** gave the lowest binding energy values (-9.84 kcal/mol and -9.36 kcal/mol). The three-dimensional interaction and the best binding pose of compound **16a** are shown in Figure 1. The two-dimensional interactions of all compounds and febuxostat are shown in Figures 2 and 3.

Table 1: The docking results of febuxostat, **16**(**a-c**), and **17**(**a-c**).

Compounds	B.E. (kcal/mol)	I.E. (kcal/mol)	L.E. (kcal/mol)	V.B.D.E. (kcal/mol)	I.A. (µM)
16a	**-9.84**	-11.63	-0.10	-11.52	**0.061**
16b	-8.60	-10.39	-0.28	-10.11	0.496
16c	-8.61	-11.00	-0.23	-10.76	0.487
17a	**-9.36**	-11.75	-0.15	-11.60	**0.136**
17b	-7.95	-10.04	-0.25	-9.78	1.49
17c	-7.60	-9.39	0.26	-9.13	2.68
Febuxostat	**-9.07**	-10.86	-1.07	-9.78	**0.225**

B.E: Binding Energy**, I.E.:** Intermolecular Energy**, L.E.:**Ligand Efficiency, **V.B.D.E.:** VDW-H Bond Desolvation Energy, **I.A.:** Inhibition Activity



a **b**

Figure 1. The three-dimensional interactions (a) and the best binding pose (b) of **16a** with the XO.

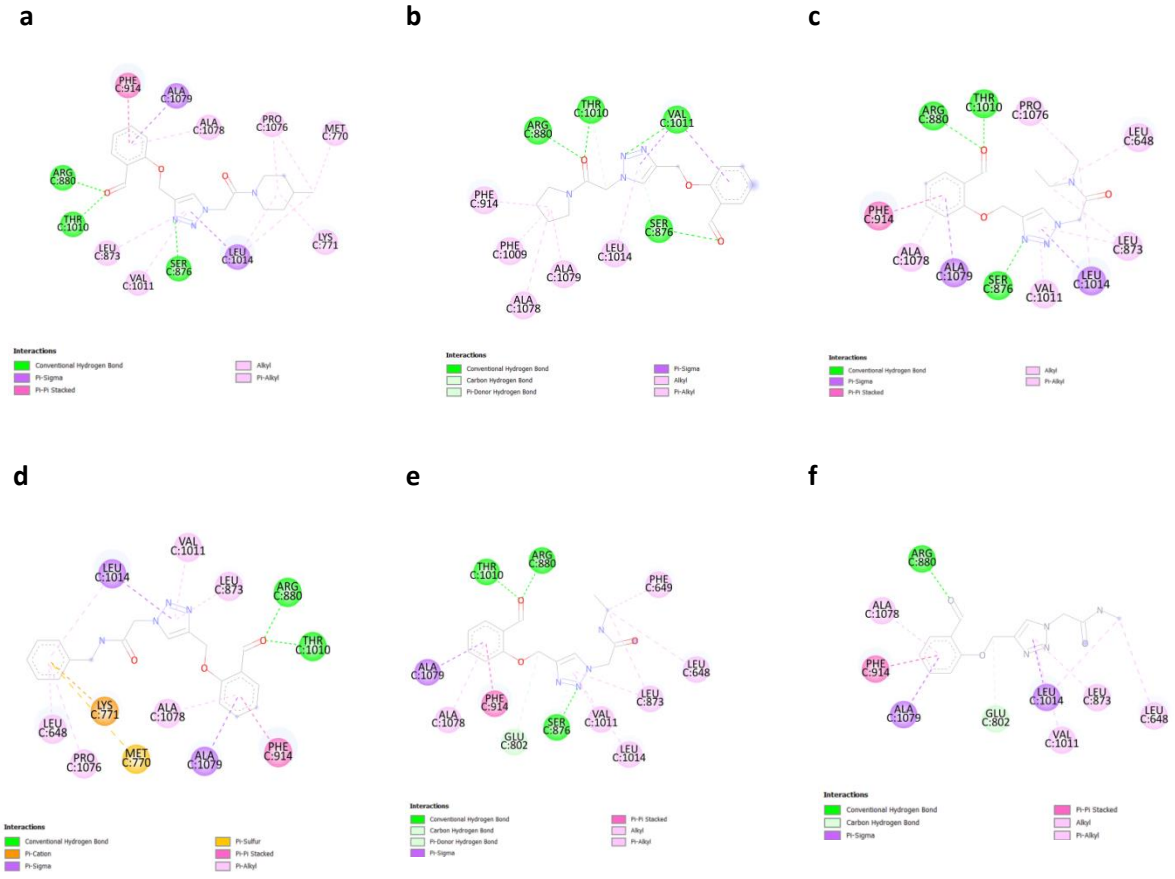


Figure 2. The two-dimensional interactions of compounds **16a** (a), **16b** (b), **16c** (c), **17a** (d), **17b** (e), and **17c** (f) with the XO

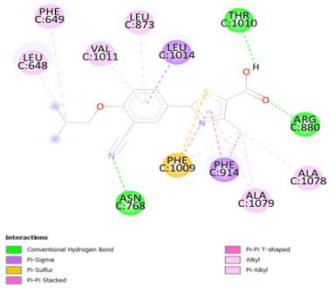


Figure 3. The two-dimensional interactions with the XO of febuxostat.

3.4. In silico ADMET studies

The predicted ADME properties of **16**(**a-c**) and **17**(**a-c**) were investigated *via* the SwissADME website (http://www.swissadme.ch/). According to the website, the target compounds except for **17a** and **17c** are suitable in terms of drug-likeness values and bioavailability (Figure 4 and Table 2). **17a** and **17c** among all compounds showed a bit slip in the saturation part (Figure 4). The compounds have high gastrointestinal absorption (GI) and no blood-brain barrier (BBB) permeant. All compounds except **16b** are not substrates of P-glycoprotein (P-gp). The bioavailability scores of the compounds were 0.55. Log S (ESOL) values of the compounds range from -2.90 to -1.55. All compounds are soluble in the water, but compound **17a** is moderately soluble. Log Kp values of the compounds are -7.28, -7.67, -7.51, -7.31,-7.73, -7.90 cm/s. Finally, the predicted toxicity properties of the compounds were investigated *via* OSIRIS property Explorer (https://www.organic-chemistry.org/prog/peo/). According to the Osiris, the compounds are predicted to be safe in terms of mutagenicity and tumorigenicity. However, the compounds may be indicated medium risk in point of irritant effect, and also, they may indicate toxicity risk in terms of reproductive effect.

Table 2. Some *in silico* ADME properties of **16**(**a-c**), and **17**(**a-c**).

Some ADME properties	**Compounds**					
	16a	**16b**	**16c**	**17a**	**17b**	**17c**
Molecular weight (g/mol)	342.39	314.34	316.36	350.37	288.30	274.28
Rotatable bonds	7	7	9	9	8	7
H-bond donors	0	0	0	1	1	1
H-bond acceptors	5	5	5	5	5	5
Fraction Csp3	0.44	0.38	0.38	0.16	0.29	0.23
TPSA ($Å^2$)	77.32	77.32	77.32	86.11	86.11	86.11
Log $P_{o/w}$ (XLOGP3)	1.56	0.77	1.01	1.59	0.46	0.1
Log Kp (cm/s)	-7.28	-7.67	-7.51	-7.31	-7.73	-7.90
Log S (ESOL)	-2.32	-2.17	-2.20	-2.90	-1.78	-1.55
Druglikeness (Lipinski)	Yes	Yes	Yes	Yes	Yes	Yes

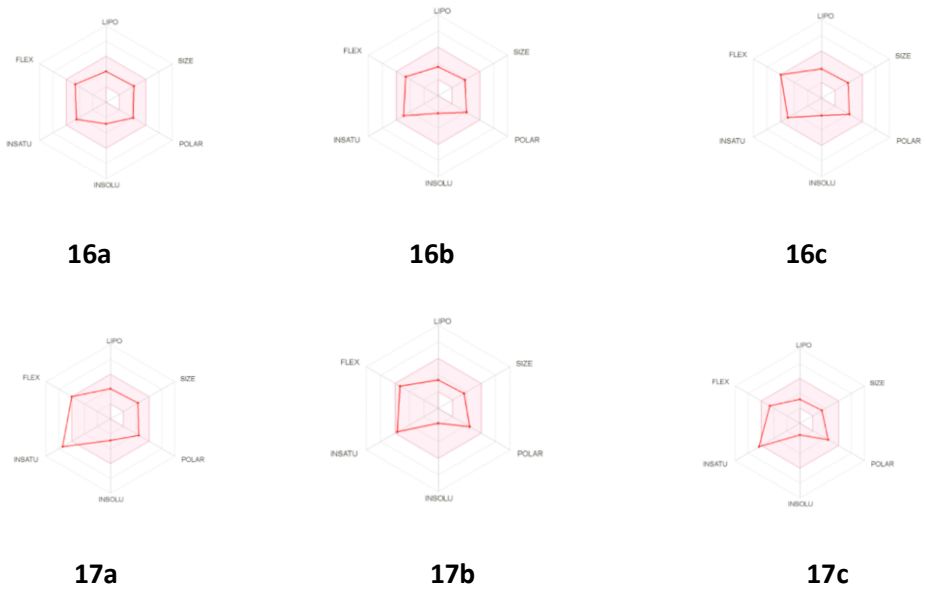


Figure 4. Bioavailability radar images of **16**(**a-c**) and **17**(**a-c**)

4. Conclusions

The interactions with the XO enzyme of compounds **16**(**a-c**) and **17**(**a-c**) synthesized *via* the CuAAC method were investigated *via* molecular docking studies by comparing with allopurinol and febuxostat. The triazole compounds showed better binding affinities than allopurinol in the interactions with the XO. **16a** and **17a** in these compounds showed better binding affinities than febuxostat. In this case, the target compounds may show better activity than allopurinol against the XO in the enzyme-inhibition studies, while **16a** and **17a** may show better activities than febuxostat, as well. The *in silico* ADMET studies of the compounds were performed to determine physicochemical, medicinal chemistry, water-solubility, pharmacokinetics, drug-likeness, lipophilicity, and toxicity properties. The predicted results suggested acceptable ADME scores for the target compounds. Regarding toxicity, while all compounds appear to be safe in terms of mutagenicity, and tumorigenicity, they may be toxic in terms of irritant and reproductive effect. Consequently, **16**(**a-c**) and **17**(**a-c**) may be considered new inhibitor candidates against the XO enzyme.

5. Acknowledgment

The author thanks to Mus Alparslan University (Grand no: BAP-21-TBMY-4901-01)

6. References

Aouad, M.R., 2017. Click Synthesis and antimicrobial screening of novel isatin-1, 2, 3-triazoles with piperidine, morpholine, or piperazine moieties. *Organic Preparations and Procedures International,* **49(3)**, 216-227.

Biovia, D. S. (2021). Discovery Studio, version 21.1. 0. San Diego: *Dassault Systèmes*.

Bunders, C., Cavanagh, J., and Melander, C., 2011. Flustramine inspired synthesis and biological evaluation of pyrroloindoline triazole amides as novel inhibitors of bacterial biofilms. *Organic & biomolecular chemistry,* **9(15)**, 5476-5481.

Deshmukh, T.R., Khare, S.P., Krishna, V.S., Sriram, D., Sangshetti, J.N., Bhusnure, O., Shingate, B. B., 2019. Design and Synthesis of New Aryloxy-linked Dimeric 1, 2, 3-Triazoles via Click Chemistry Approach: Biological Evaluation and Molecular Docking Study. *Journal of Heterocyclic Chemistry,* **56(8)**, 2144-2162.

Dommerholt, J., Van Rooijen, O., Borrmann, A., Guerra, C.F., Bickelhaupt, F.M., and Van Delft, F.L., 2014. Highly accelerated inverse electron-demand cycloaddition of electron-deficient azides with aliphatic cyclooctynes. *Nature Communications,* **5(1)**, 1-7.

Frampton, J.E., 2015. Febuxostat: a review of its use in the treatment of hyperuricaemia in patients with gout. *Drugs,* **75(4)**, 427-438.

Ganesh, V., Sudhir, V.S., Kundu, T., and Chandrasekaran, S., 2011. 10 years of click chemistry: synthesis and applications of ferrocene-derived triazoles. *Chemistry–An Asian Journal,* **6(10)**, 2670-2694.

Garudachari, B., Isloor, A.M., Satyanarayana, M., Fun, H.K., and Hegde, G., 2014. Click chemistry approach: Regioselective one-pot synthesis of some new 8-trifluoromethylquinoline based 1, 2, 3-triazoles as potent antimicrobial agents. *European journal of medicinal chemistry,* **74**, 324-332.

Hans, R.H., Guantai, E.M., Lategan, C., Smith, P.J., Wan, B., Franzblau, S. G.,Chibale, K., 2010. Synthesis, antimalarial and antitubercular activity of acetylenic chalcones. *Bioorganic & medicinal chemistry letters,* **20(3)**, 942-944 (and therein).

Himo, F., Lovell, T., Hilgraf, R., Rostovtsev, V.V., Noodleman, L., Sharpless, K.B., & Fokin, V.V., 2005. Copper (I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates. *Journal of the American chemical society,* **127(1)**, 210-216.

Hou, D.R., Hung, M.S., Liao, C.C., and Lin, C.C., 2012. 1, 2, 3-Triazole derivatives as new cannabinoid-1 receptor antagonists. In: Google Patents.

Lee, D., Kim, D., Lee, S., Kim, T., Kim, J., Kim, S., Song, K.S., 2015. Efficient syntheses of 1, 2, 3-Triazoloamide derivatives using solid-and solution-phase synthetic approaches. *Molecules,* **20(11)**, 19984-20013.

Morris, G.M., Huey, R., Lindstrom, W., Sanner, M.F., Belew, R.K., Goodsell, D.S., and Olson, A.J., 2009. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry,* **30(16)**, 2785-2791.

Pillinger, M.H., and Mandell, B. F. (2020). Therapeutic approaches in the treatment of gout. In *Seminars in Arthritis and Rheumatism*, **50(3)**, 24-S30. WB Saunders.

Pokhodylo, N., Savka, R., and Obushak, M., 2020. Synthesis of (1 H-1, 2, 3-Triazol-1-yl) acetic Acid Derivatives. *Russian Journal of Organic Chemistry,* **56(8)**, 1421-1431.

Tan, A., 2020. Novel 1, 2, 3-triazole compounds: Synthesis, In vitro xanthine oxidase inhibitory activity, and molecular docking studies. *Journal of Molecular Structure,* **1211**, 128060.

Tan, A. 2021. Ksantin Oksidaz İnhibitörü Yeni 1, 2, 3-triazol Türevlerinin Sentezi, Karakterizasyonu ve Moleküler Doking Çalışmaları. *Bitlis Eren Üniversitesi Fen Bilimleri Dergisi*, **9(2)**, 644-654.

Tan, A. 2022. Synthesis, spectroscopic characterization of novel phthalimides derivatives bearing a 1, 2, 3-triazole unit and examination as potential SARS-CoV-2 inhibitors via in silico studies. *Journal of Molecular Structure*, **1261**, 132915.

Whiting, M., Muldoon, J., Lin, Y.C., Silverman, S.M., Lindstrom, W., Olson, A.J., Elder, J.H., 2006. Inhibitors of HIV-1 protease by using in situ click chemistry. *Angewandte Chemie,* **118(9)**, 1463-1467.

Internet Resources

1. http://www.swissadme.ch/, (01.04.2022)
2. https://www.rcsb.org/,(01.04.2022)
3. https://www.organicchemistry.org/prog/peo/, (01.04.2022)