Süleyman Demirel Üniversitesi
Sağlık Bilimleri Dergisi
Cilt 12, Sayı 2, 184 - 191, 2021

Suleyman Demirel University
Journal of Health Sciences
Volume 12, Issue 2, 184 - 191, 2021

In Silico ADME Screening and Evaluation of Antimicrobial and Antimycobacterial Activities of 3,5-Diphenyl Pyrazoline Derivatives

3,5 Difenil Pirazolin Türevlerinin İn Siliko ADME Taraması ve Antimikrobiyal ve Antimikobakteriyel Etkilerinin Değerlendirilmesi

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ÖZET

Amaç: Antibiyotiklerin biliçsiz bir şekilde yaygın kullanımı antibiyotiklere karşı direnç gelişimine neden olmaktadır. Bir antibiyotiğe karşı direnç gelişimi oluştuğunda, artık o antibiyotik tedavi dozunda ya daha düşük etkinlik gösterecek ya da etkisini tamamen kaybedecektir. Antibiyotiklere direnç gelişimi hızla artarken, her geçen gün yeni antibiyotik geliştirme ihtiyacı da artmaktadır. Bu amaçla, bu çalışmada pirazolin yapısındaki bazı bileşiklerin antimikrobiyal ve antitüberküloz etkileri araştırılmıştır. Bileşiklerin fizikokimyasal özellikleri ve ilaç özelliklerine benzerliği, bir bileşiğin ilaç olarak kullanılıp kullanılamayacağını belirlemek için oldukça önemlidir. Sentezlenen bileşiklerin fizikokimyasal özellikleri, ilaç özelliklerine benzerliği ve Lipinski kurallarına uygunluğu belirlendi. Materyal-Metod: Sentezlenen bileşiklerin ilaç özelliklerine benzerliği çevrimiçi İsviçre ADME aracı kullanılarak belirlendi. Antitüberküloz aktivite, mikroplaka alamar mavisi deneyi ile saptandı. Antimikrobiyal aktivite mikrodilüsyon yöntemi ile test edildi. Bulgular: Tüm bileşikler, bazıları hiç ihlal olmadan, bazıları da bir ihlalle Lipinski kurallarına uydu. B7, B10 ve B11 bileşikleri Lipinski'nin kurallarını bir ihlal ile sağlamıştır. Diğer bileşikler, Lipinski'nin kurallarının tamamını ihlalsiz olarak sağlamıştır. Tüm bileşiklerin yüksek gastrointestinal absorbsiyona sahip olduğu tahmin edildi. Bileşikler genel olarak yüksek lipofilisiteye sahip olduğundan, B12 dışındaki tüm bileşiklerin kan beyin bariyerini geçebileceği tahmin edildi. Sonuç: Sentezlenen bileşiklerin çoğunlukla *Enterococcus faecalis*, *Enterococcus faecalis* izolatı ve *Candida albicans*'a karşı daha etkili olduğu bulunmuştur. Bileşik B10, 16µg/mL MIC değeri ile *Enterococcus faecalis* izolatına karşı en iyi antimikrobiyal aktiviteyi sergilemiştir.

Anahtar Kelimeler: Pirazolin, antimikobakteriyel, antimikrobiyal, in siliko ADME

Alınış / Received: 01.02.2021 Kabul / Accepted: 25.03.2021 Online Yayınlanma / Published Online: 15.08.2021

ABSTRACT

Objective: The unconscious widespread use of antibiotics leads to the development of resistance to antibiotics. When resistance to an antibiotic develops, it now either shows less efficacy or loses its effect completely at that antibiotic treatment dose. While the development of resistance to antibiotics increases rapidly, the need for the development of new antibiotics rises every day. For this purpose, in this study, antimicrobial and antitubercular effects of some compounds in the pyrazoline structure were investigated. The physicochemical properties and drug-likeness of the compounds are quite important for determining whether a compound can be used as a drug or not. Physicochemical properties and drug-likeness of the synthesized compounds were evaluated and the relevance for Lipinski's rules was determined. Material-Method: Drug-likeness properties of the synthesized compounds were determined using online Swiss ADME tool. Antitubercular activity is detected by microplate alamar blue assay. Antimicrobial activity is tested by microdilution method. Results: All compounds obeyed the Lipinski's rules, some of with no violation, some of with one violation. Compounds B7, B10 and B11 provided Lipinski's rules with one violation. Other compounds ensured Lipinski's rules with no violation. All compounds were predicted to have high gastrointestinal absorption. As the compounds generally have high lipophilicity, it was predicted that all compounds except B12 can cross the blood brain barrier. Conclusion: Synthesized compounds were mostly found to be more effective against *Enterococcus faecalis*, *Enterococcus faecalis* isolate and *Candida albicans*. Compound B10 demonstrated the best antimicrobial activity against *Enterococcus faecalis* isolate with a 16µg/mL MIC value.

Keywords: Pyrazoline, antimycobacterial, antimicrobial, in silico ADME

DOI:10.22312/sdusbed.872130
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1. Introduction

Unconscious use of antibiotics is causing resistance development (1). The resistance is an important risk that threats the lives of millions of people, as it destroys the effectiveness of antibiotics. Bacteria develop resistance by horizontal gene transfer, reducing cell permeability and pumping the antibiotic out of the cell, synthesizing enzymes that break down the antibiotic or modifying drug targets, or by mutation (2). Many antibiotics lost their effectiveness as a result of resistance development. This makes it necessary to develop new effective antibiotics.

Enterococcus faecalis is a Gram-positive bacterium that occur naturally in the gastrointestinal tract of humans and other animals. However, by the frequent use of antibiotics, these bacteria have turned into a dangerous pathogen that can cause many infections such as urinary tract infections, endocarditis, bacteremia, intra-abdominal and pelvic infections, wound and soft tissue infections, meningitis and neonatal sepsis. In addition to being resistant to many antibiotics intrinsically, developing new resistance mechanisms through plasmids and transposons makes these bacteria dangerous (3,4).

According to WHO's data, tuberculosis is one of the uppermost ten causes of death and one million people died from tuberculosis in 2018. Nowadays, there is a Covid-19 pandemia all over the world, and it is seen that the patients who have weakened lungs due to tuberculosis are at very high risk (5).
Prediction of bioavailability, pharmacokinetic and drug-likeness properties of compounds is very valuable for evaluating whether a compound can be a drug or not. Some pharmaceutical companies developed some filters to describe the drug likeness properties of the compounds. Swiss ADME program determines the drug likeness properties of compounds according to these filters (6).

The pyrazoline structure obtained by saturating one of the double bonds in the pyrazole ring has three tautomers of which the most stable one is 2-pyrazolines (7). 2-Pyrazolines attract the attention of researchers due to their different pharmacological activities. Antimicrobial (8), antituberculous (9), antifungal (10), antiinflammatory (11), analgesic (12) and antidepressant (13) activities are some of the activities of this ring system. The development of new antibiotics has gained importance due to the rapidly increasing resistance against antibiotics. In addition, people with other accompanying diseases often die because of outbreaks such as the Covid-19. The lives of people with long-term illnesses, such as tuberculosis, are at a very high risk during such epidemic periods. This reveals the importance of the discovery of new antibiotics. For this purpose, we synthesized pyrazoline derivative compounds (14,15), a ring system that draws attention with its antimicrobial, antifungal and antituberculosis activities. Then we examined the antimicrobial and antifungal activities of these compounds by microdilution method while antitubercular activities were tested by microplate alamar blue assay (MABA).

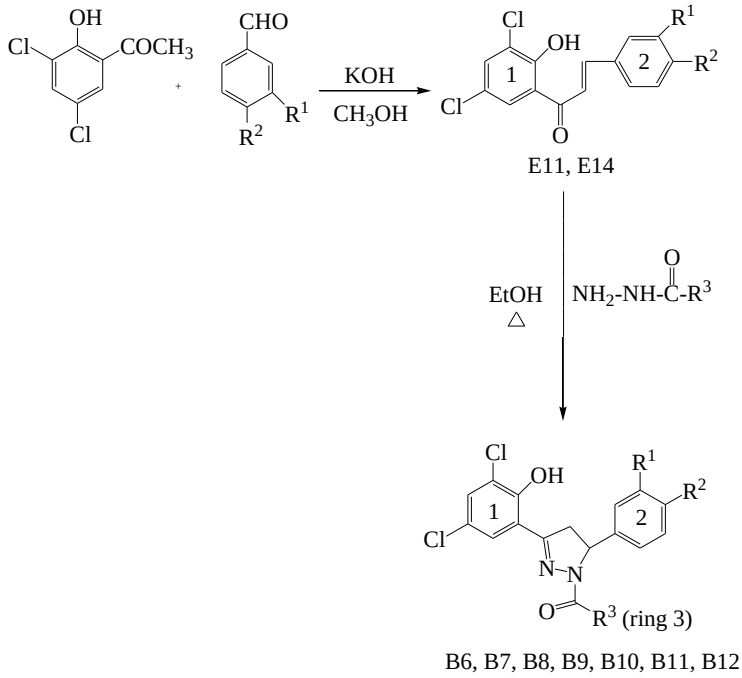
2. Material-Method

Experimental part of our study was realized in Pharmaceutical Chemistry Laboratory of Ankara University Faculty of Pharmacy and Pharmaceutical Microbiology Laboratory of Gazi University Faculty of Pharmacy.

Synthesis

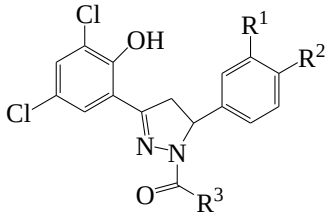
Chalcone derivatives (**E11**, **E14**) were obtained by the reaction of equimolar amounts of acetophenone and benzaldehyde derivatives via Claisen Schmidt condensation. Then, corresponding hydrazides reacted with chalcones to give pyrazolines (Figure 1). Reaction and product details have been previously published (14, 15). Formula of compounds were exhibited in Table 1.

Figure 1. Synthesis of compounds **E11**, **E14**, **B6-B12**



B6, B7, B8, B9, B10, B11, B12

Table 1. Formula of compounds



Compound	R1	R2	R3
B6	-H	- CH_3	Pyridine-4-yl
B7	-H	- CH_3	4-Methoxyphenyl
B8	- CH_3	- H	Pyridine-4-yl
B9	- CH_3	- H	Furan-2-yl
B10	- CH_3	- H	Phenyl
B11	- CH_3	- H	4-Methoxyphenyl
B12	- CH_3	- H	4-Methyl-1,2,3-thiadiazole-5-yl
E11	-H	- CH_3	-
E14	- CH_3	- H	-

Antibacterial and antifungal activity

Antibacterial and antifungal susceptibility were tested according to CLSI-M100-S16 guidelines (16) and M27-A3 (17) standards, respectively. Antibacterial activities of compounds were determined against *E. coli* ATCC 25922 [**K**], *E. coli* ATCC 35218 [**L**], *E. coli* isolate (ESBL) [**M**], *Pseudomonas aeruginosa* ATCC 27853 [**N**], *P. aeruginosa* isolate (gentamicin resistant) [**O**], *Staphylococcus aureus* ATCC 29213 [**P**], *S. aureus* isolate (MRSA) [**Q**] *Enterococcus faecalis* ATCC 29212 [**R**], *E. faecalis* isolate (VRE) [**S**], and

antifungal activities against *Candida albicans* ATCC 10231 [**T**] and *C. krusei* ATCC 6258 [**U**] strains. *E. coli* isolate produces extended spectrum beta lactamase enzyme and was used as the ESBL strain. *S. aureus* isolate is resistant to methicillin and all beta lactam antibiotics (MRSA). *E. faecalis* isolate is resistant to vancomycin (VRE). *C. krusei* ATCC 6258 strain was used because it is resistant to fluconazole naturally. MICs were determined as the lowest concentrations inhibiting macroscopic growth. Details of the method can be found in our previous publication (18).

Antimycobacterial activity

To detect the antimycobacterial activity *Mycobacterium tuberculosis* H37RV (ATCC 27294) strain [**V**] was used. To evaluate the antimycobacterial activity, MABA method was used (19). According to this method 1:1 mixture of 10X Alamar Blue reagent were added to wells. A blue color or a pink color formation indicated no proliferation and proliferation, respectively. The MIC (µg/mL) was determined as the lowest drug concentration preventing formation of pink color. Details of the method were reported in our previous publication (18).

In silico absorbtion, distrubution, metabolism and elimination (ADME) determination

Bioavailibility, pharmacokinetic and drug-likeness properties of compounds were determined by using Swiss ADME online tool. This tool includes Lipinski, Ghose, Veber, Egan, Muegge filters and bioavailability score to detect the drug-likeness. Leading pharmaceutical companies developed these filters to detect the drug-likeness (6).

3. Results

Antimicrobial and antimycobacterial test results were shown in Table 2.

Table 2. Antimicrobial and antimycobacterial test results

	MIC value (µg/mL)											
Compounds	**K**	**L**	**M**	**N**	**O**	**P**	**Q**	**R**	**S**	**T**	**U**	**V**
B6	64	128	128	64	64	128	64	32	64	64	64	64
B7	64	128	128	64	128	128	64	64	64	64	64	64
B8	64	128	128	128	128	128	64	64	64	64	64	64
B9	64	128	128	64	128	128	64	64	64	64	64	64
B10	64	128	128	64	128	128	64	32	16	32	64	64
B11	64	128	128	128	64	128	64	64	64	64	64	64
B12	64	128	128	64	64	128	64	64	64	64	64	64
E11	128	128	128	128	128	64	64	128	128	128	64	64
E14	128	128	128	128	128	64	64	128	128	128	64	64
Ampicilin	2	-	>1024	-	-	0.5	-	0.5	0.5	-	-	-
Gentamicin	0.25	-	256	1	64	0.5	128	8	8	-	-	-
Ofloxacin	0.015	-	16	1	1	0.125	0.5	1	4	-	-	-
Meropenem	0.008	-	0.015	0.25	0.015	0.03	-	4	8	-	-	-
Vancomycin	-	-	-	-	-	0.5	1	1	8	-	-	-
Ampicilin/ sulbactam (1/1)	-	16	-	-	-	-	-	-	-	-	-	-

Amoxicilin/ clavulonic acid (2/1)	-	16	-	-	-	-	-	-	-	-	-	-
Fluconazole	-	-	-	-	-	-	-	-	-	0.0625	32	-
Amphotericin B	-	-	-	-	-	-	-	-	-	<0.03	0.5	-
Ethambuthol												4
Isoniazid												0.125

Our compound's physicochemical and pharmacokinetic properties were given in Table 3. Some abbreviations were used as Molecular weight (MW), Hidrogen Bond Acceptors (HBA), Hidrogen Bond Donors (HBD), Number of Rotatable Bonds (NRB), Molar Refractivity (MR), Topological Polar Surface Area (TPSA), Gastrointestinal Absorbtion (GIA), Blood Brain Barrier Permeant (BBBP), Lipinski Violations (LV) in Table 3. iLogP and mLogP are the descriptors of lipophilicity. Log *Kp* is the indicator of skin permeation. As the negativity of log Kp (with Kp in cm/s), increases, skin permeability of molecules decreases (6).

Table 3. Some physicochemical and pharmacokinetic properties of synthesized compounds

Compound	**MW (g/mol)**	**HBA**	**HBD**	**NRB**	**iLogP**	**mLogP**	**Log *Kp* (cm/s)**	**MR**	**TPSA (Å²)**	**GIA**	**BBBP**	**LV**
E11	307.17	2	1	3	3.17	4.05	-4.26	83.26	37.30	High	Yes	0
E14	307.17	2	1	3	3.18	4.05	-4.26	83.26	37.30	High	Yes	0
B6	426.30	4	1	4	3.41	3.68	-5.67	121.74	65.79	High	Yes	0
B7	455.33	4	1	5	4.11	4.36	-5.10	130.43	62.13	High	Yes	1
B8	426.30	4	1	4	3.44	3.68	-5.67	121.74	65.79	High	Yes	0
B9	415.27	4	4	4	3.52	3.51	-5.27	116.21	66.04	High	Yes	0
B10	425.31	3	1	4	3.71	4.72	-4.90	123.94	52.90	High	Yes	1
B11	455.33	4	1	5	4.06	4.36	-5.10	130.43	62.13	High	Yes	1
B12	447.34	5	1	4	3.62	3.29	-5.56	122.37	106.92	High	No	0

4. Discussion

Both pyrazolines and chalcones displayed the same activity against *E. coli* [**L**], ESBL, MRSA, *C. krusei* and *Mycobacterium tuberculosis*. Pyrazoline structure was found to be more effective against *E. coli* [**K**], *Enterococcus faecalis* [**R**], VRE, *Candida albicans* compared to chalcone structure. Ring closure has a positive effect on these bacteria and fungi. Only against *Staphylococcus aureus* [**P**], chalcones were found to be more effective than 2-pyrazolines.

Compound **B10** exhibited the best activity against *E. faecalis* [**R**], VRE and *C. albicans*. Compounds **B6**, **B11** and **B12** showed the same effect as gentamicin against *P. aeruginosa* isolate. However, the *P. aeruginosa* isolate is resistant to gentamicin, already.

Compound **B10**, which contains 2-hydroxy-3,5-dichloro in the ring 1, methyl in the ring 2 and phenyl in the ring 3, had half the effect of vancomycin, meropenem and gentamicin against *E. faecalis* isolate. All compounds were found to be more effective than ampicilin and gentamicin against ESBL.

Compounds **B6**, **B7**, **B9**, **B10** and **B12** were found to be more effective than other pyrazoline compounds against *P. aeruginosa* [**N**]. Although the presence of methyl in the meta position of the 2nd ring reduces the activity, the use of furan-2-yl, phenyl and 4-methyl-1,2,3-thiadiazol-5-yl rings simultaneously with the m-methyl substitution in the 2nd ring increased the activity.

B6 and **B10** showed the best activity against *Enterococcus faecalis* [**R**] with 32 µg/mL MIC value. Since the 1st ring of all compounds is the same, when we compare the effects of the 2nd and 3rd rings on activity, the activity increased when the 2nd ring contains methyl in the para position, while the 3rd ring is

pyridine. The presence of the 4-methoxyphenyl structure in the third ring also increased the activity while the second ring contained methyl in meta position.

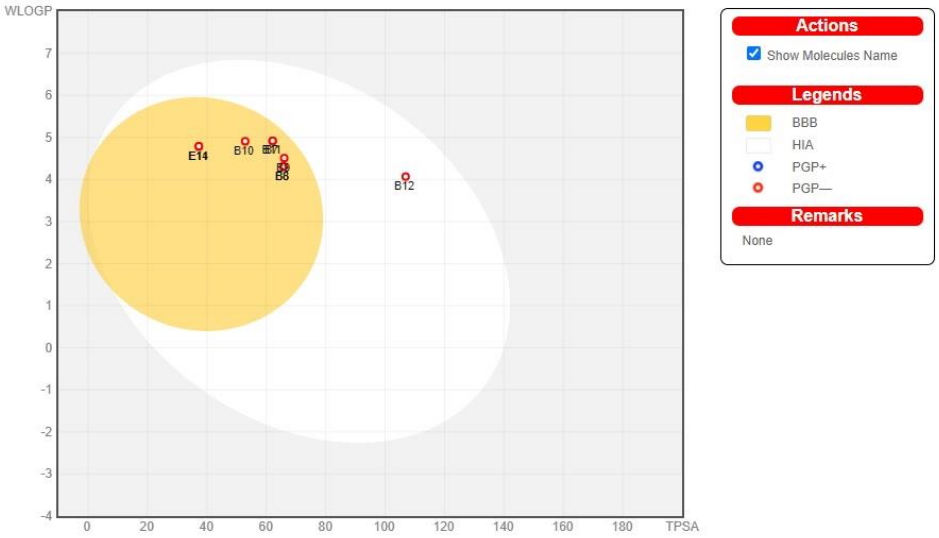
For prediction of being an orally active drug in humans, obeying Lipinski's rules such as MW<500; mLogP<4.15; HBA<10; and HBD<5 is important. According to these rules, an orally active drug should not have more than one violation (20). For drug-likeness prediction, all compounds, except **B7**, **B10**, **B11**, obeyed the Lipinski's rules with no violation. Compounds **B7**, **B10** and **B11** provided Lipinski's rules with one violation. Compounds **B6**, **B8** and **B9** were found appropriate for Lipinski (20), Ghose (21), Veber (22), Egan (23) and Muegge (24) filters.

Topological Polar Surface Area (TPSA) describes the polarity of the molecules and expected to be between 20 and 130 $Å^2$. Number of rotatable bonds shouldn't be more than 9 for flexibility (25). All compounds obeyed the TPSA and rotatable bonds value. Molar refractivity (MR) describes polarizability. Molar refractivity should be between 40-130 (21,25).

P-glycoprotein (P-gp) is the most widely recognized efflux transporter. Substrates of P-gp have increased excretion, reduced distribution to protected tissues and reduced absorption. High passive diffusion can dominate the P-gp efflux. So, when the passive diffusion is low, effect of P-gp efflux increases. Efflux by P-gp causes attenuated delivery of the compound to the therapeutic target. So, it brings along problems for the drug discovery (26). None of our compounds is P-gp substrate. According to BOILED- Egg (Figure 2), all compounds except **B12**, are in the yolk (highly probable blood brain barier permenant regio).

Compound **B12** takes part in white regio (highly probable passive gastrointestinal absorbtion (HIA) regio). All compounds exhibited high gastrointestinal absorbtion. Prediction of bioavailability and drug-likeness were found 0.55 for all of the compounds. Compounds **B6**, **B7**, **B8**, **B11** and **B12** are predicted to inhibit CYP2C19, CYP2C9, CYP3A4, compounds **B9**, **E11** and **E14** inhibit CYP1A2, CYP2C19, CYP2C9, CYP3A4, compound **B10** inhibit CYP2C19, CYP2C9. All of the compounds were predicted to inhibit CYP enzymes meaning that there may be interactions with the drugs that are metabolized through these cytochrome enzymes.

Figure 2. BOILED- Egg to map our compounds. Since B6 with B8, B7 with B11 and E11 with E14 are isomers to each other, they appear in the same position.



5. Conclusion

Consequently, synthesized compounds were mostly found to be more effective against *Enterococcus faecalis*, *E. faecalis* isolate and *Candida albicans*. The most active compound was found to be **B10**. Most of the compounds did not violate the Lipinski's rules, while the three compounds (**B7**, **B10**, **B11**) provided with one violation. According to the Lipinski's rules, all compounds were found suitable for oral use. All compounds were predicted to inhibit the cytochrome P450 enzymes, CYP2C19 and CYP2C9. Except compound **B12**, all compounds were predicted to cross the blood brain barrier.

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