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Synthesis and Characterization of Novel Heteroarylacrylonitrile Derivatives Containing Pyrazole Scaffold

Abdullah BİÇER[1]

Öne Çıkanlar:

- Pirazol yapısı içeren yeni heteroarilakrilonitril türevleri (5a-d) sentezlendi
- Potansiyel yeni AChE inhibitörü heteroarilakrilonitril türevleri sentezlendi
- Bileşikler ^{1}H ve ^{13}C NMR ve FTIR spektroskopileri ile karakterize edilmiştir.

ÖZET:

2,3-disübstitüe akrilonitril türevleri, biyoaktiviteleri ve birçok biyoaktif molekül için başlangıç bileşikleri olarak rol oynamaları nedeniyle medisinal kimyadaki en önemli moleküller arasındadır. Birçok heterosiklik yapı AChE enzim inhibitörü olarak araştırılmıştır. Günümüzde, E/Z akrilonitril türevleri yeni AChE inhibitörleri olarak çalışılmaktadır. Bu çalışmada Knoevenagel kondenzasyonu kullanılarak yeni heteroaril-akrilonitril bileşiklerinin sentezlenmesi amaçlanmıştır. Bu kapsamda, pirazol aldehit türevinin (4) çeşitli asetonitril bileşikleri ile reaksiyonlarından 2. ve 3. pozisyonlarda aril ve heteroaril yapılarının olduğu akrilonitril bileşikleri sentezlenmiştir. Pirazol halkası içeren sentezlenen yeni heteroarilakrilonitril türevleri (5a-d) potansiyel AChE inhibitörleridir. Sentezlenen bileşiklerin yapıları FTIR, ^{1}H-NMR ve ^{13}C-NMR spektroskopik teknikleri ile aydınlatılmıştır.

Anahtar Kelimeler:

- Arilakrilonitril
- Knoevenagel
- Pirazol
- AChE inhibitör

Synthesis and Characterization of Novel Heteroarylacrylonitrile Derivatives Containing Pyrazole Scaffold

Highlights:

- Novel heteroarylacrylonitrile derivatives (5a-d) containing pyrazole scaffold synthesized
- Potential new AChE inhibitor heteroarylacrylonitrile derivatives synthesized.
- Compounds have been characterized by ^{1}H and ^{13}C NMR and FTIR spectroscopies

ABSTRACT:

2,3-disubstituted acrylonitriles derivatives are among the most important molecules in medicinal chemistry due to their bioactivity and their role as starting compounds for many bioactive molecules. Many heterocyclic structures have been investigated as AChE enzyme inhibitors. Nowadays, E/Z acrylonitrile derivatives are being studied as new AChE inhibitors. This study aimed to synthesis new heteroaryl-acrylonitrile compounds using Knoevenagel condensation. In this context, acrylonitrile compounds with aryl and heteroaryl structures at positions 2 and 3 (respectively)were synthesized from the reactions of pyrazole aldehyde derivative (4) with various acetonitrile compounds. Synthesized novel heteroarylacrylonitrile derivatives (5a-d) containing pyrazole ring are potential AChE inhibitors. The structures of the synthesized compounds were elucidated by FTIR, ^{1}H-NMR and ^{13}C-NMR spectroscopic techniques.

Keywords:

- Arylacrylonitrile
- Knoevenagel
- Pyrazole
- AChE İnhibitors

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INTRODUCTION

Knoevenagel condensation is one of the most useful methods for the synthesis of methylene active compounds such as 3-aryl-2-heteroaryl compounds. Arylacrylonitriles are important compounds used in the synthesis of many bioactive molecules such as flavonoid pigments and vitamin A (Fringuelli et al., 1994). Heteroaryl acrylonitrile derivatives have a wide range of diverse physical and biological properties (Özen et al., 2016b). Anticancer, antibacterial, antioxidant, antitubercular, antibacterial, antiproliferative activity properties of such compounds have been reported in the literature (Özen et al., 2016b, 2016a; Xavier et al., 2023).

2,3-disubstituted acrylonitriles containing a heteroaromatic structure at the 2 position have also attracted great interest due to their versatile biological activities (Unsal Tan & Zengin, 2022). These compounds have been shown to have antihyperglycemic, antimalarial, anti-inflammatory, antioxidant and antiviral properties, as well as the ability to inhibit the enzyme acetylcholinesterase (AChE) (De La Torre et al., 2012a; De-la-Torre et al., 2016; Unsal Tan & Zengin, 2022; Takla et al. 2017). Aryl-acrylonitriles are used to produce LEDs (light emitting diodes) (Gómez et al., 1999; Maruyama et al., 1999) . It is also used as a fluorescence probe for the detection of intramolecular thiols (Kwon et al., 2011). The CMONS(Cyano-MethOxy-Nitro-Stilbene) molecule is a chromophore structure and is a luminescent compound under standard UV lamp (Sanz et al., 2001).

Pyrazole derivatives are remarkable molecular structures for the search for new biologically active molecules. By incorporating a pyrazole group into various heterocyclic ring systems, biologically important molecules are synthesized (Abu-Hashem et al., 2010; Siddiqui et al., 2011). Many pyrazole derivatives have a broad spectrum of biological activity (Girisha et al., 2010). Some drugs, such as celecoxib and rimonabant, have a pyrazole ring in their molecular structure (Katritzky et al., 2001).

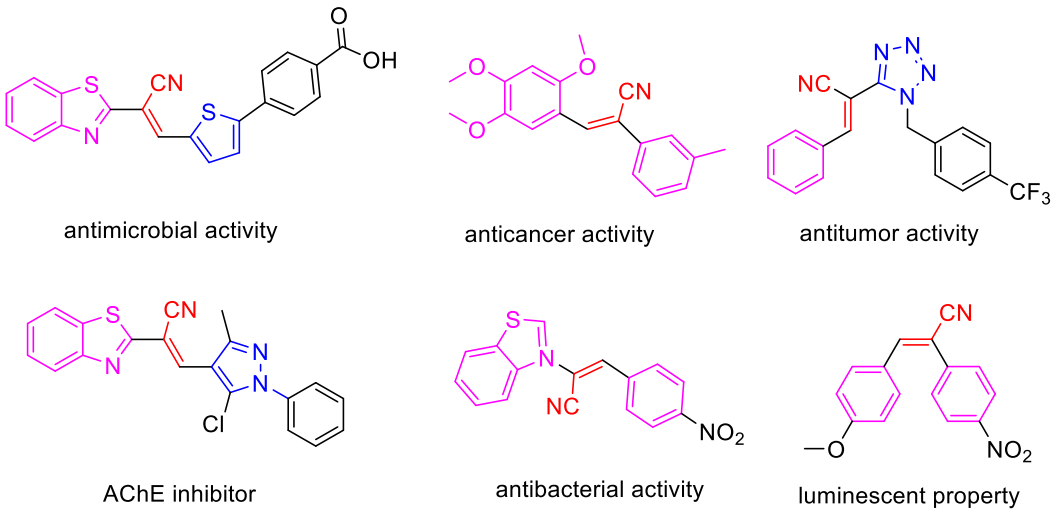

Figure 1. Some bioactive acylonitrile derivatives

Many heterocyclic structures with AChE inhibitory activity have been synthesized so far. Many of these structures have shown bioavailability problems and negative side effects (Mukherjee et al., 2007; Schulz, 2003). Therefore, the synthesis of new molecular structures as AChE inhibitors is always important. The new structures to be synthesized may be used in the treatment of Alzeimer Disease (AD). Today, E/Z acrylonitrile derivatives attract attention as new AChE inhibitors (De La Torre et al., 2012b; Parveen et al., 2014).

Catalysts such as P_2O_5/SiO_2, $ZnCl_2$ and SiO_2Cl are used in the synthesis of aryl acrylonitrile derivatives (Siddiqui et al. 2013; Parveen et al. 2014; Parveen et al. 2019). Arylacrylonitrile derivatives are an attractive molecular scaffold that can be used in the synthesis of new bioactive molecules such as chromenes (Takla et al. 2017; Anas 2022).

In this study, new acrylonitrile derivatives containing pyrazole ring at the 2 position and aryl ring at the 3 position, which are among the heteroarylacrylonitrile derivatives that have an important place in the literature, have been synthesized.

MATERIALS AND METHODS

All chemicals were commercially available and used without further purification. Melting points were determined in a Gallenkamp melting point apparatus. FTIR spectra were recorded on a Bruker Tensor 27 FTIR spectrometer using a KBr disk in the range 4000-400 cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance DPX 400 MHz spectrometer using $CDCl_3$ as solvent.

The pyrazole ring was synthesized by cyclocondensation of acetylacetone and phenyl hydrazine. Then, pyrazole derivative containing formyl group (4) was synthesized by Vilsmeir Haack's formylation of compound (3) using $POCl_3$/DMF (Genin et al., 2000; Biçer et al., 2022; Biçer & Altundaş, 2023). In the last step, the target products (5a-d) molecules were synthesized by using Knoevenagel reaction of compound (4) with aryl-acrylanitrile derivatives (Özen et al., 2016b) (Figure 2 and 3).

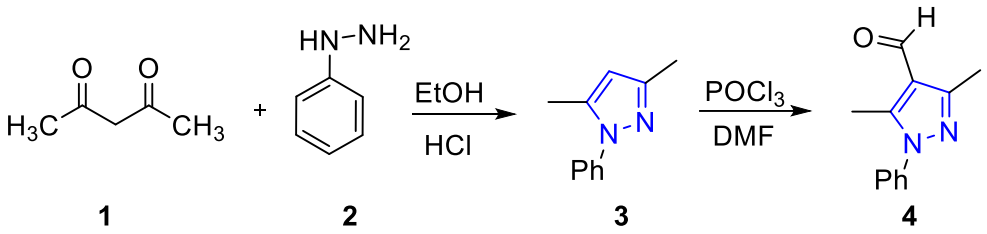

Figure 2. Synthesis Figure of 3,5-dimethyl-1-phenyl-1H-pyrazole-4-carbaldehyde

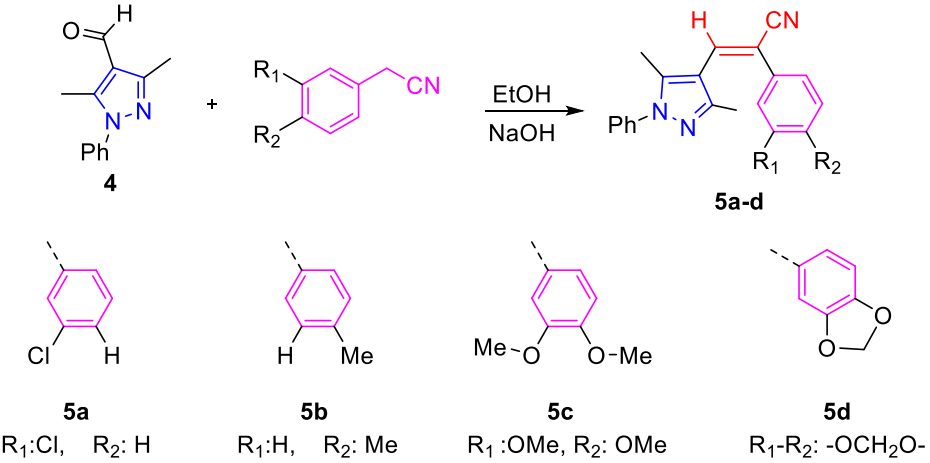

Figure 3. Synthesis of pyrazole-containing acrylonitrile derivatives

RESULTS AND DISCUSSION

New heteroarylacrylonitrile derivatives containing pyrazole ring were synthesized using the synthesis route described in Figure 2 and 3. ^{1}H-NMR and ^{13}C-NMR spectra of the synthesized molecules are given in Figure 4-8. (3) and (4) were synthesized according to the literature (Biçer et al., 2022; Biçer & Altundaş, 2023).

3,5-dimethyl-1-aryl-1H-pyrazole derivatives (3): FTIR (cm^{-1}): 3059 (Ar-CH stretch.), 2924-2868 (Alif.-CH stretch.),1953-1807 (Ph overtone), 1598-1554 (C=C stretch), 775-691(Pyrazole peaks range). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38-7.23 (m, 5H), 5.94 (s, 1H), 2.25 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 148.92, 139.96, 139.34, 128.97, 127.20, 124.72, 106.93, 13.51, 12.36.

5-dimethyl-1-phenyl-1H-pyrazole-4-carbaldehyde (4): M.P. 127-130 ºC. FTIR (cm^{-1}): 3061 (Ar-CH stretch.), 2927 (Alif-CH stretch.), 2851-2771(CHO stretch.), 1671(C=O stretch.), 1597-1544 (C=C stretch.), 818-701 (Pyrazole peaks range). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.05 (s, 1H, CHO), 7.47-7.32 (m, 5H), 2.49 (s, 3H), 2.46 (s, 3H).

General synthesis of (*E*)-3-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-(aryl)acrylonitrile derivatives (5a-d): A solution of 3,5-dimethyl-1-phenyl-1H-pyrazol-4-carbaldehyde (4) (0.1 mmol) and arylacetonitrile derivative (1 mmol) in ethyl alcohol (20 mL) was heated to 70 ºC for 20 min and then 20% NaOH solution was added dropwise to the reaction medium until cloudy and refluxed for another hour. The reaction mixture was then poured into ice water and the solids were filtered off and washed with plenty of water (Özen et al., 2016b).

(*E*)-2-(3-chlorophenyl)-3-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)acrylonitrile (5a): yellow solid, 50% yield, M.P. 80-82 ºC. FTIR (cm^{-1}): 3061(Ar-CH stretch.), 2930-2854 (Alif.-CH stretch.), 2211 (CN stretch.) 1550-1500 (C=C stretch.), 817-669 (Pyrazole peaks range). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, *J* = 8 Hz, 1H), 7.52-7,48 (m, 7H), 7.47 (s, 1H, C=CH), 7.44 (d, *J* = 8 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H), ^{13}C-NMR (101 MHz, $CDCl_3$) δ: 149.01, 139.18, 139.05, 134.98, 134.88, 132.77, 129.25, 128.15, 127.06, 125.02, 117.82, 115.52, 111.98, 14.04, 13,14.

(*E*)-3-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)-2-(*p*-tolyl)acrylonitrile (5b): White solid, 15% yield. FTIR (cm^{1}): 3066 (Ar-CH stretch.), 2919 (Alif.-CH stretch.), 2154 (CN stretch.), 1588 (C=C stretch.), 837-695 (Pyrazole peaks range). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.47 (d, *J* =8 Hz, 2H), 7.43-7.30 (m, 6H), 6.40 (d, *J* = 4 Hz, 2H), 2.45 (s, 3H, Me), 2.43 (s, 3H), 2.41 (s, 3H).

(*E*)-2-(3,4-dimethoxyphenyl)-3-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)acrylonitrile (5c): yellow solid, 36% yield, M.P. 88-90 ºC. FTIR (cm^{-1}): 3062-3011(Ar-CH stretch.), 2936 (Alif.-CH stretch.), 2213 (CN stretch.), 1580 (C=C stretch.), 810-667 (Pyrazole peaks range). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.45-7.40 (m, 5H), 7.18 (s, 1H, C=CH), 7.17 (dd, *J* = 8 Hz, *J* = 4 Hz, 1H), 7.07 (d, *J* =4 Hz, 1H), 6.85 (d, *J* =8 Hz, 1H), 3.90 (s, 3H, OMe), 3.87 (s, 3H, OMe), 2.43 (s, 3H), 2,41 (s, 3H).

(*E*)-2-(benzo[d][1,3]dioxol-5-yl)-3-(3,5-dimethyl-1-phenyl-1H-pyrazol-4-yl)acrylonitrile (5d): yellow solid, 26% yield, M.P. 160-162 ºC. FTIR (cm^{-1}): 3019 (Ar-CH stretch.), 2966 (Alif.-CH stretch.), 2215 (CN stretch.) 1551-1502 (C=C stretch.), 810-697 (Pyrazole peaks range). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.53-7.50 (m, 5H), 7.34 (s, 1H,,C=CH), 7.20 (dd, *J* = 8 Hz, *J* = 4 Hz, 1H), 7.15 (d, *J* = 4 Hz, 1H), 6.90 (d, *J* = 8 Hz, 1H), 2.42 (s, 3H), 2.40 (s, 3H).^{13}C-NMR (101 MHz, $CDCl_3$) δ: 148.82, 147.47, 139.13, 138.87, 132.81, 129.22, 128.53, 128.08, 124.98, 120.41, 118.15, 115.64, 113.16, 108.64, 105.83, 101.67, 13.93, 13.08.

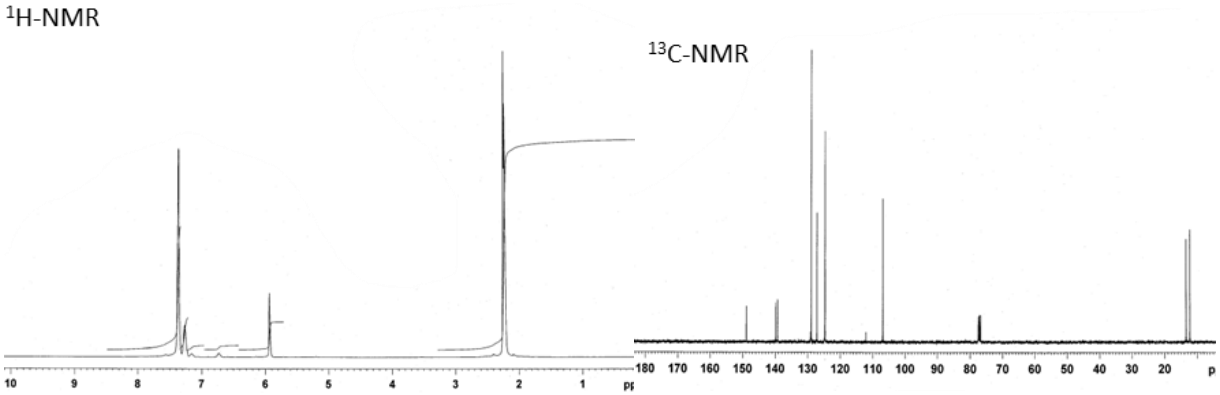

Figure 4. ^{1}H-NMR and ^{13}C-NMR spectrums of compound (3)

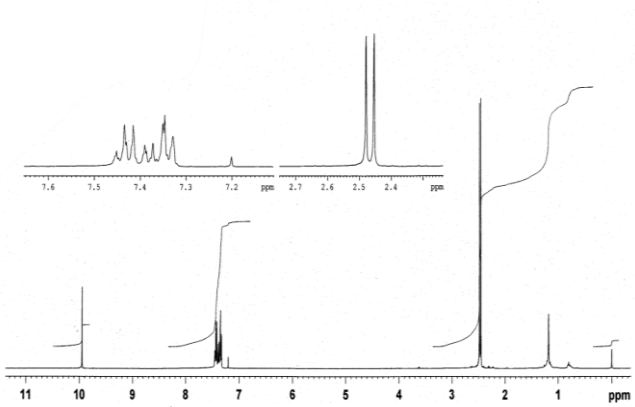

Figure 5. ^{1}H-NMR spectrum of compound (4)

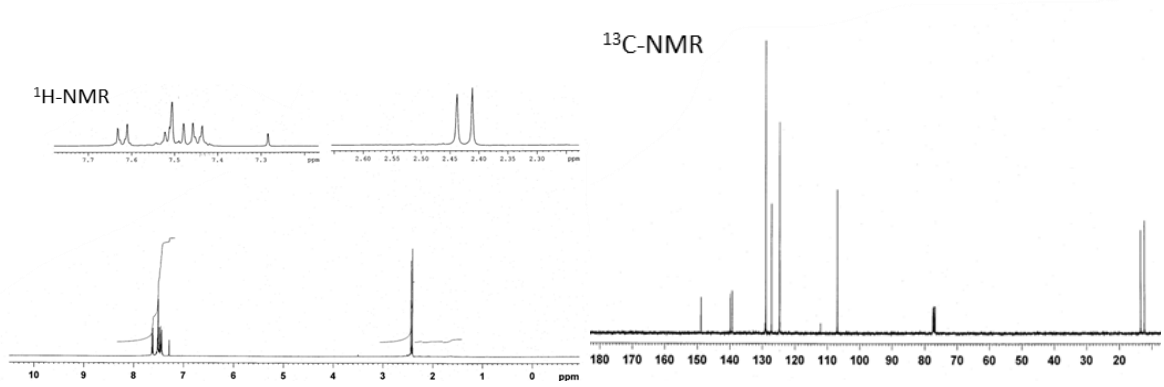

Figure 6. ^{1}H-NMR and ^{13}C-NMR spectrums of compound (5a)

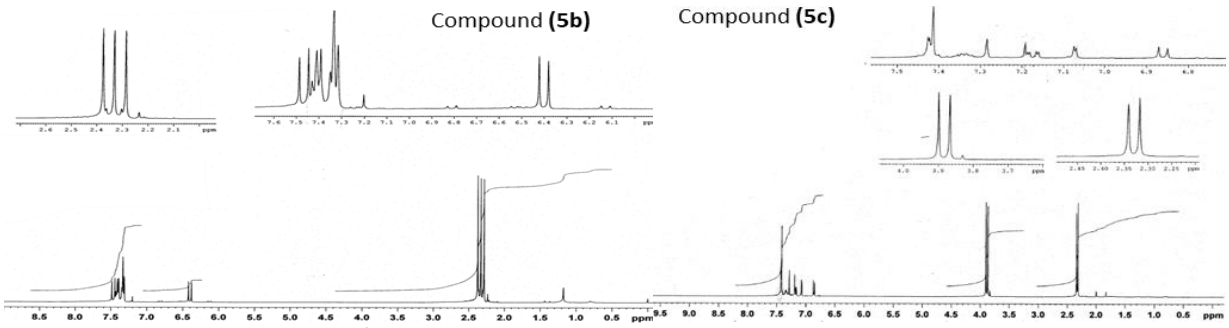

Figure 7. ^{1}H-NMR spectrum of compound (5b) and compound (5c)

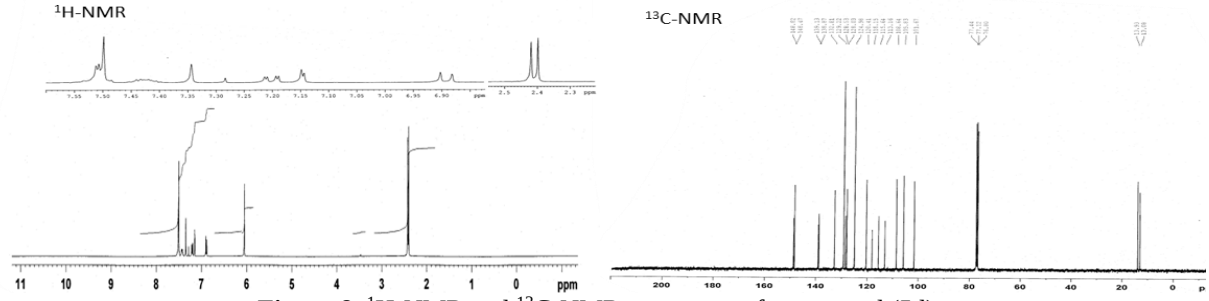

Figure 8. ^{1}H-NMR and ^{13}C-NMR spectrums of compound (5d)

Also, in the reaction with 2-(4-nitrophenyl)acetonitrile derivative, a large number of product mixtures were formed. Trace amounts of product formation were observed in the reactions with 2-(2-methylphenyl)acetonitrile and 2-(4-trifluoromethylphenyl)acetonitrile derivatives.

CONCLUSION

In this study, 2,3-disubstituted acrylonitriles (5a-d) containing a pyrazole ring at the 2 position and an aryl ring at the 3 position were synthesized by Knoevenagel condensation reaction. The heteroaryl acrylonitrile

derivatives containing thiazole ring synthesized in this preliminary study have potential AChE enzyme inhibition properties. By increasing the number of these derivatives and investigating their AChE inhibition properties by establishing a structure-activity relationship, it is predicted that a drug active substance that can be used in the treatment of diseases such as Alzeimer Disease (AD) can be found. If the bioactivities of such molecules are investigated, important gains will be provided to the literature.

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Conflict of Interest

The article author declares that there is no conflict of interest.

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