*Scientific paper*

# Design, Synthesis and Biological Screening of Novel 1,5-Diphenyl-3-(4-(trifluoromethyl)phenyl)-2-pyrazoline Derivatives

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## Abstract

1-Phenyl-5-substituted-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole derivatives were synthesized from chalcone derivatives. The structures of compounds were characterized by IR, $^1$H NMR spectroscopic methods and elemental analysis. All compounds were evaluated for their *in vitro* antioxidant activity using DPPH and ABTS methods, anti-inflammatory activity using lipoxygenase inhibitory method and antidiabetic activity using the α-glucosidase inhibitory method. Especially, pyrazoline derivatives exhibited stronger anti-inflammatory activity than the reference drug indomethacin ($IC_{50}$: 50.45 μM) and their $IC_{50}$ values were in the range of 0.68 and 4.45 μM. In addition, the ADME properties of all chalcone and pyrazoline derivatives were calculated by Lipinski's and Veber's rules.

**Keywords**: 2-Pyrazoline; lipoxygenase enzyme; α-glucosidase; ABTS and DPPH

## 1. Introduction

Pyrazoline scaffolds bearing five-membered heterocyclic ring systems are used frequently in organic synthesis and medicinal chemistry because of their broad spectrum of activities.[1] Pyrazoline rings have important pharmacological and biological properties such as antioxidant, anti-inflammatory, analgesic, antimicrobial, antimalarial, antihypertensive, anticonvulsant, antidepressant, anticancer.[2–6] We studied the synthesis and antiproliferative activity of some pyrazoline compounds in our previous study.[7] Pyrazolines exhibited these different activities by interacting with some receptors or enzymes. For example, ElBordiny *et al.* demonstrated in their study that pyrazolines are superior lipoxygenase enzyme inhibitors compared to the reference drug.[8] Furthermore, Chaudhry *et al.* and Sathish *et al.* reported pyrazoline derivatives as alpha-glucosidase inhibitors.[9,10] Additionally, many studies proved different activities of pyrazoline derivatives as receptor tyrosine kinase, topoisomerase 1, carbonic anhydrase and cholinesterase inhibitors. It was found that nitrogen atoms of the pyrazoline ring and at least one substitution with aryl moiety are essential for anti-inflammatory activity (Gawad *et al.*, 2012).[11–15]

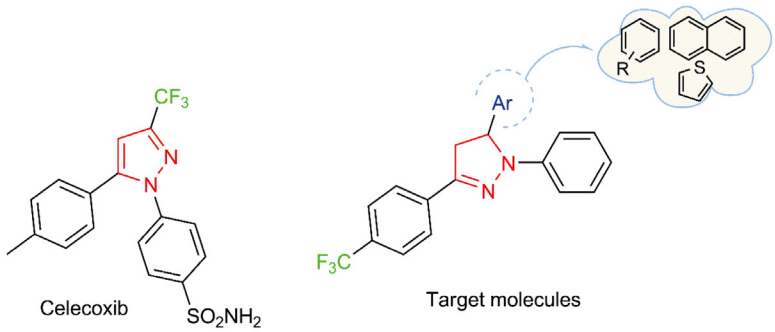



**Figure 1.** Chemical structure of designed compounds and celecoxib

Several drug molecules carrying pyrazole core with different activities are currently available in the market, for example, antipyrine (analgesic), celecoxib (anti-inflammatory), pyrazofurin (antibiotic).[16]

It is known that fluorine substitution increases biological activity and metabolic-chemical stability (compared to C–H bond) in drug research. Furthermore, fluorine alters physicochemical properties and enhances binding affinity to target protein easily.[17–18] We designed new molecules which are carrying pyrazoline core and trifluoromethyl substitution on the aromatic ring (Figure 1).

In this study, we synthesized chalcone derivatives from 4'-(trifluoromethyl)acetophenone in the first step. Then we synthesized new 2-pyrazoline derivatives from chalcones. We aimed to show different biological activities of pyrazoline derivatives. Therefore all synthesized compounds were screened for their antioxidant activity using DPPH and ABTS method, anti-inflammatory activity using lipoxygenase inhibitory method, and antidiabetic activity using α-glucosidase inhibitory methods.

# 2. Experimental

## 2. 1. Synthesis

Chemicals and solvents were obtained from Sigma Aldrich (St. Louis, MO, USA) or Merck (Darmstadt, Germany). The progress of the reaction was monitored *via* thin layer chromatography (TLC), performed on commercially available silica gel (Kieselgel 60, F254) coated aluminum sheets (Merck) by using developing systems: petroleum ether/acetone (60:40 v/v) as a solvent system. The visualization on TLC was done under ultraviolet (UV) light ($\lambda$ = 254 nm). Melting points were determined by Schmelzpunktbestimmer SMP II apparatus. Infrared spectra were recorded on a Shimadzu FTIR 8400S Spectrometer and data was expressed in wavenumber ν ($cm^{-1}$). Proton nuclear magnetic resonance (NMR) (400 MHz) spectra were recorded with a Bruker ACP 200 spectrometer (Bruker Corp., Billerica, MA, USA). Deuterated dimethylsulfoxide (DMSO-$d_6$) was used as the solvent and tetramethylsilane (TMS) as the internal standard. The chemical shift values (δ) were expressed in ppm. Elemental analyses (C, H and N) was performed on a CHNS-Thermo Scientific Flash 2000 (Waltham, MA, USA).

### 2. 1. 1. General Procedure for the Synthesis of Chalcone

1 mmol of 4'-(trifluoromethyl)acetophenone and equimolar quantities of substituted aromatic aldehydes were dissolved in methanol, then NaOH (50% water solution) was added to the reaction mixture. It was stirred at room temperature for 16 h and then poured into ice-cold water. The precipitated product was washed with water, filtered and recrystallized from methanol.[19]

### 2. 1. 2. General Procedure for the Synthesis of Pyrazoline

10 mmol of chalcone derivatives, 10 mmol of phenylhydrazine hydrochloride and 10 mL of glacial acetic acid were put in a reaction flask. The content was refluxed and stirred for 12 h. Then, it was neutralized with dilute ammonia solution. The precipitate was washed with water, filtered and recrystallized from ethanol.[20]

**3-(2,6-Dimethylphenyl)-1-(4-(trifluoromethyl)phenyl) prop-2-en-1-one (1a)**

White powder, yield 77%, mp 74.3–74.5 °C. IR (KBr) ν 3064, 2978, 2912, 1696, 1606, 1591, 1573, 1510, 1408, 1315, 1213, 1161, 1064, 835 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 2.38 (s, 6H, $2CH_3$), 7.12–7.87 (m, 5H, Ar-H and CH=CH), 7.92 (d, $J$ = 8.4 Hz, 2H, Ar-H) 8.27 (d, $J$ = 8.4 Hz, 2H, Ar-H). Anal. Calcd for $C_{18}H_{15}F_3O$: C, 71.04; H, 4.97. Found: C, 70.82; H, 4.86%.

**3-(2,6-Dichlorophenyl)-1-(4-(trifluoromethyl)phenyl) prop-2-en-1-one (1b)**

Yellow powder, yield 65%, mp 62.3–62.7 °C. IR (KBr) ν 3072, 1696, 1606, 1573, 1508, 1467, 1408, 1305, 1213, 1161, 1064, 835 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.41–8.24 (m, 9H, Ar-H and CH=CH). Anal. Calcd for $C_{16}H_9Cl_2F_3O$: C, 55.68; H, 2.63. Found: C, 55.48; H, 2.78.

**3-*o*-Tolyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (1c)**

Yellow powder, yield 75%, mp 89.0–89.8 °C. IR (KBr) ν 3053, 2978, 2897, 1683, 1595, 1510, 1462, 1410, 1317, 1211, 1161, 1064, 833 $cm^{-1}$. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 2.42 (s, 3H, CH), 7.26–8.32 (m, 10H, Ar-H and CH=CH). Anal. Calcd for $C_{17}H_{13}F_3O$: C, 70.34; H, 4.51. Found: C, 70.56; H, 4.55.

**3-(4-Isopropylphenyl)-1-(4-(trifluoromethyl)phenyl) prop-2-en-1-one (1d)**

White powder, yield 81%, mp 84.7–85.3 °C. IR (KBr) ν 3053, 2960, 2928, 1660, 1600, 1579, 1510, 1408, 1319, 1215, 1165, 1066, 821 $cm^{-1}$. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 1.23 (d, $J$ = 7.2 Hz, 6H, $CH_3$), 2.94 (m, 1H, CH), 7.35–8.33 (m, 10H, Ar-H and CH=CH). Anal. Calcd for $C_{19}H_{17}F_3O$: C, 71.69; H, 5.38. Found: C, 71.44; H, 5.46.

**3-Phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (1e)**

White powder, yield 75%, mp 113.7–114.3 °C. IR (KBr) ν 3063, 1664, 1600, 1573, 1510, 1410, 1317, 1217, 1159, 1064, 839 $cm^{-1}$. $^1$H NMR (600 MHz, DMSO-$d_6$) δ 7.44–8.35 (m, 11H, Ar-H and CH=CH). Anal. Calcd for

$C_{16}H_{11}F_3O$: C, 69.56; H, 4.01. Found: C, 69.78; H, 4.07 (CAS Number: 62056-10-4).[21]

**3-(4-Chlorophenyl)-1-(4-(trifluoromethyl)phenyl) prop-2-en-1-one (1f)**

White powder, yield 69%, mp 125.2–125.7 °C (CAS Number: 57076-98-9).[22]

**3-*p*-Tolyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (1g)**

White powder, yield 72%, mp 147.8–148.4 °C (CAS Number: 1551606-21-3).[23]

**3-*m*-Tolyl-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (1h)**

White powder, yield 82%, mp 92.0–92.5 °C. IR (KBr) ν 3061, 2978, 2922, 1662, 1600, 1573, 1510, 1450, 1410, 1317, 1217, 1159, 1064, 837 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 2.34 (s, 3H, CH), 7.26–8.31 (m, 10H, Ar-H and CH=CH). Anal. Calcd for $C_{17}H_{13}F_3O$: C, 70.34; H, 4.51. Found: C, 70.47; H, 4.44.

**3-(Thiophen-2-yl)-1-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (1i)**

White powder, yield 65%, mp 135.4–135.9 °C (CAS Number: 1372376-05-0).[24]

**3-(4-(Dimethylamino)phenyl)-1-(4-(trifluoromethyl) phenyl)prop-2-en-1-one (1j)**

White powder, yield 75%, mp 140.5–141.2 °C (CAS Number: 1940174-93-5).[25]

**3-(Naphthalen-1-yl)-1-(4-(trifluoromethyl)phenyl) prop-2-en-1-one (1k)**

Yellow powder, yield 74%, mp 92.0–92.5 °C. IR (KBr) ν 3078, 2980, 1660, 1593, 1573, 1435, 1408, 1319, 1215, 1163, 1064, 839 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 7.59–8.64 (m, 13H, Ar-H and CH=CH). Anal. Calcd for $C_{20}H_{13}F_3O$: C, 73.61; H, 4.12. Found: C, 73.87; H, 4.22.

**5-(2,6-Dimethylphenyl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole (2a)**

Yellow powder, yield 75%, mp 133.3–133.8 °C. IR (KBr) ν 3068, 2974, 2912, 1616, 1593, 1510, 1408, 1319, 1215, 1163, 1064, 839 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 2.04 and 2.55 (2s, 6H, $2CH_3$), 3.16 (dd, *Jax* = 6.33 Hz, *Jab* = 17.88 Hz, 1H, Ha), 4.02 (dd, *Jbx* = 13.75 Hz, *Jab* = 17.88 Hz, 1H, Hb), 5.75 (dd, *Jax* = 6.33 Hz, *Jbx* = 13.76 Hz, 1H, Hx), 6.72–7.17 (m, 8H, Ar-H), 7.77 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.92 (d, *J* = 8.1 Hz, 2H, Ar-H). Anal. Calcd for $C_{24}H_{21}F_3N_2$: C, 73.08; H, 5.37; N, 7.10. Found: C, 73.55; H, 5.27; N, 7.35.

**5-(2,6-Dichlorophenyl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole (2b)**

Yellow powder, yield 65%, mp 142.2–142.9 °C. IR (KBr) ν 3055, 1618, 1587, 1521, 1498, 1321, 1247, 1118, 1064, 839 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 3.24 (dd, *Jax* = 6.12 Hz, *Jab* = 17.44 Hz, 1H, Ha), 3.96 (dd, *Jbx* = 13.96 Hz, *Jab* = 17.44 Hz, 1H, Hb), 6.14 (dd, *Jax* = 6.12 Hz, *Jbx* = 13.96 Hz, 1H, Hx), 6.72–7.92 (m, 12H, Ar-H). Anal. Calcd for $C_{22}H_{15}Cl_2F_3N_2$: C, 60.71; H, 3.47; N, 6.44. Found: C, 60.22; H, 3.37; N, 6.66.

**1-Phenyl-5-*o*-tolyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole (2c)**

Yellow powder, yield 77%, mp 119.6–120.1 °C. IR (KBr) ν 3059, 2980, 2916, 1616, 1587, 1521, 1495, 1319, 1217, 1163, 1064, 839 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 2.43 (s, 3H, $CH_3$), 3.04 (dd, *Jax* = 6.55 Hz, *Jab* = 17.52 Hz, 1H, Ha), 3.99 (dd, *Jbx* = 13.60 Hz, *Jab* = 17.52 Hz, 1H, Hb), 5.64 (dd, *Jax* = 6.56 Hz, *Jbx* = 13.60 Hz, 1H, Hx), 6.72–7.25 (m, 9H, Ar-H), 7.74 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.91 (d, *J* = 8.4 Hz, 2H, Ar-H). Anal. Calcd for $C_{23}H_{19}F_3N_2$: C, 72.62; H, 5.03; N, 7.36. Found: C, 72.32; H, 5.17; N, 7.47.

**5-(4-Isopropylphenyl)-1-phenyl-3-(4-(trifluoromethyl) phenyl)-4,5-dihydro-1*H*-pyrazole (2d)**

Orange powder, yield 81%, mp 89.1–89.4 °C. IR (KBr) ν 3051, 2960, 2899, 1618, 1595, 1556, 1498, 1319, 1249, 1163, 1064, 839 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 0.97 and 1.55 (2d, 6H, $2CH_3$), 2.79 (m, 1H, CH), 3.14 (dd, *Jax* = 6.24 Hz, *Jab* = 17.28 Hz, 1H, Ha), 3.95 (dd, *Jbx* = 13.45 Hz, *Jab* = 17.27 Hz, 1H, Hb), 5.56 (dd, *Jax* = 6.24 Hz, *Jbx* = 13.44 Hz, 1H, Hx), 6.72–7.52 (m, 9H, Ar-H), 7.73 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.93 (d, *J* = 8.1 Hz, 2H, Ar-H). Anal. Calcd for $C_{25}H_{23}F_3N_2$: C, 73.51; H, 5.68; N, 6.86. Found: C, 73.77; H, 5.49; N, 6.75.

**1,5-Diphenyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*- pyrazole (2e)**

Yellow powder, yield 73%, mp 108.2–108.4 °C. IR (KBr) ν 3064, 1618, 1595, 1554, 1496, 1321, 1249, 1163, 1064, 837 $cm^{-1}$. $^1H$ NMR (600 MHz, DMSO-$d_6$) δ 3.17 (dd, *Jax* = 6.66 Hz, *Jab* = 17.46 Hz, 1H, Ha), 3.96 (dd, *Jbx* = 12.49 Hz, *Jab* = 17.44 Hz, 1H, Hb), 5.58 (dd, *Jax* = 6.66 Hz, *Jbx* = 12.49 Hz, 1H, Hx), 6.74–7.51 (m, 10H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.94 (d, *J* = 8.4 Hz, 2H, Ar-H). Anal. Calcd for $C_{22}H_{17}F_3N_2$: C, 72.12; H, 4.68; N, 7.65. Found: C, 72.31; H, 4.63; N, 7.77.

**5-(4-Chlorophenyl)-1-phenyl-3-(4-(trifluoromethyl) phenyl)-4,5-dihydro-1*H*-pyrazole (2f)**

Orange powder, yield 66%, mp 79.1–79.3 °C. IR (KBr) ν 3055, 1618, 1597, 1554, 1496, 1319, 1249, 1163, 1064, 839 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 3.16 (dd, *Jax* = 6.24 Hz, *Jab* = 17.28 Hz, 1H, Ha), 3.96 (dd, *Jbx* = 12.40 Hz, *Jab* = 17.28 Hz, 1H, Hb), 5.60 (dd, *Jax* = 6.23 Hz, *Jbx* = 12.41 Hz, 1H, Hx), 6.74–7.51 (m, 9H, Ar-H), 7.75 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.91 (d, *J* = 8.4 Hz, 2H, Ar-H). Anal. Calcd for $C_{22}H_{16}ClF_3N_2$: C, 65.92; H, 4.02; N, 6.99. Found: C, 65.75; H, 3.88; N, 6.72.

**1-Phenyl-5-*p*-tolyl-3-(4-(trifluoromethyl)phenyl)- 4,5-dihydro-1*H*-pyrazole (2g)**

Yellow powder, yield 80%, mp 123.4–123.7 °C. IR (KBr) ν 3007, 2924, 2852, 1614, 1597, 1552, 1498, 1321, 1244, 1168, 1064, 835 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 2.25 (s, 3H, $CH_3$), 3.16 (dd, *Jax* = 6.30 Hz, *Jab* = 17.91 Hz, 1H, Ha), 3.93 (dd, *Jbx* = 12.42 Hz, *Jab* = 17.91 Hz, 1H, Hb), 5.56 (dd, *Jax* = 6.31 Hz, *Jbx* = 12.40 Hz, 1H, Hx), 6.72–7.19 (m, 9H, Ar-H), 7.77 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.94 (d, *J* = 8.1 Hz, 2H, Ar-H). Anal. Calcd for $C_{23}H_{19}F_3N_2$: C, 72.62; H, 5.03; N, 7.36. Found: C, 72.35; H, 5.20; N, 7.57.

**1-Phenyl-5-*m*-tolyl-3-(4-(trifluoromethyl)phenyl)- 4,5-dihydro-1*H*-pyrazole (2h)**

Yellow powder, yield 75%, mp 145.9–146.3 °C. IR (KBr) ν 3028, 2926, 1614, 1585, 1552, 1498, 1321, 1244, 1155, 1064, 835 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 2.24 (s, 3H, $CH_3$), 3.14 (dd, *Jax* = 6.61 Hz, *Jab* = 17.57 Hz, 1H, Ha), 3.95 (dd, *Jbx* = 12.24 Hz, *Jab* = 17.56 Hz, 1H, Hb), 5.50 (dd, *Jax* = 6.60 Hz, *Jbx* = 12.24 Hz, 1H, Hx), 6.71–7.22 (m, 9H, Ar-H), 7.75 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.91 (d, *J* = 8.4 Hz, 2H, Ar-H). Anal. Calcd for $C_{23}H_{19}F_3N_2$: C, 72.62; H, 5.03; N, 7.36. Found: C, 72.47; H, 4.89; N, 7.56.

**1-Phenyl-5-(thiophen-2-yl)-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazole (2i)**

Orange powder, yield 65%, mp 127.0–127.5 °C. IR (KBr) ν 3097, 1618, 1591, 1529, 1479, 1315, 1220, 1166, 1064, 825 $cm^{-1}$. $^1H$ NMR (300 MHz, DMSO-$d_6$) δ 3.25 (dd, *Jax* = 6.56 Hz, *Jab* = 17.61 Hz, 1H, Ha), 3.93 (dd, *Jbx* = 12.33 Hz, *Jab* = 17.61 Hz, 1H, Hb), 5.96 (dd, *Jax* = 6.57 Hz, *Jbx* = 12.33 Hz, 1H, Hx), 6.77–7.38 (m, 8H, Ar-H), 7.76 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.96 (d, *J* = 8.1 Hz, 2H, Ar-H). Anal. Calcd for $C_{20}H_{15}F_3N_2S$: C, 64.50; H, 4.06; N, 7.52. Found: C, 64.14; H, 4.13; N, 7.47.

***N,N*-Dimethyl-4-(1-phenyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1*H*-pyrazol-5-yl)aniline (2j)**

Yellow powder, yield 77%, mp 128.8–129.4 °C. IR (KBr) ν 3070, 2955, 2845, 1614, 1587, 1519, 1492, 1320, 1240, 1163, 1055, 806 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 2.81 (s, 6H, $2CH_3$), 3.10 (dd, *Jax* = 6.35 Hz, *Jab* = 17.46 Hz, 1H, Ha), 3.86 (dd, *Jbx* = 12.33 Hz, *Jab* = 17.47 Hz, 1H, Hb), 5.44 (dd, *Jax* = 6.32 Hz, *Jbx* = 12.31 Hz, 1H, Hx), 6.63–7.17 (m, 9H, Ar-H), 7.72 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.91 (d, *J* = 8.4 Hz, 2H, Ar-H). Anal. Calcd for $C_{24}H_{22}F_3N_3$: C, 70.40; H, 5.42; N, 10.26. Found: C, 70.56; H, 5.35; N, 10.43.

**5-(Naphthalen-1-yl)-1-phenyl-3-(4-(trifluoromethyl) phenyl)-4,5-dihydro-1*H*-pyrazole (2k)**

Orange powder, yield 79%, mp 94.4–94.6 °C. IR (KBr) ν 3059, 1635, 1591, 1533, 1483, 1321, 1259, 1168, 1064, 835 $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$) δ 3.12 (dd, *Jax* = 6.56 Hz, *Jab* = 17.40 Hz, 1H, Ha), 4.01 (dd, *Jbx* = 12.81 Hz, *Jab* = 17.39 Hz, 1H, Hb), 6.26 (dd, *Jax* = 6.56 Hz, *Jbx* = 12.80 Hz, 1H, Hx), 6.71–8.00 (m, 16H, Ar-H). Anal. Calcd for $C_{26}H_{19}F_3N_2$: C, 74.99; H, 4.60; N, 6.73. Found: C, 75.43; H, 4.49; N, 6.56.

## 2. 2. Biological Studies

### 2. 2. 1. Antioxidant Activity

#### 2. 2. 1. 1. DPPH Radical Scavenging Activity

Free radical scavenging capacity of chalcone and pyrazoline derivatives was carried out according to the methods described previously.[26,27] Briefly, 1 mg of the compound was dissolved in DMSO and four different concentrations (0.250–0.048 µg/mL, approximately) were prepared. 190 µL methanol solution of DPPH (0.1 mM) was added on this mixture in a well of 96-well plate. The mixture was allowed to stand in the dark at room temperature for 30 min. Absorbance readings were carried out at 517 nm. The DPPH stock solution without compounds was taken as the negative control. The percentage of inhibition was calculated according to the following:

$$\text{DPPH scavenging effect (\%)} = \frac{A_{\text{control}} - A_{\text{compound}}}{A_{\text{control}}} \cdot 100 \quad (1)$$

$A_{\text{control}}$: Absorbance of the control (containing all reagents except the synthesized compounds).

$A_{\text{compound}}$: Absorbance of the synthesized compounds.

Tests were repeated in quadruplicate. Ascorbic acid was used as the positive control.

#### 2. 2. 1. 2. ABTS Radical Scavenging Activity

ABTS radical cations were prepared by dissolving 7 mM ABTS and 4.9 mM potassium persulfate, allowing them to react for 16 h at room temperature in the dark. Then, the ABTS radical solution was diluted with 96% ethanol to an absorbance recorded at 734 nm. Four different concentrations of the analyzed compounds were prepared according to the above method, DPPH radical scavenging activity.[27] Absorbance readings were recorded at 734 nm. The percentage of inhibition was calculated according to the following:

$$\text{ABTS scavenging effect (\%)} = \frac{A_{\text{control}} - A_{\text{compound}}}{A_{\text{control}}} \cdot 100 \quad (2)$$

Tests were repeated in quadruplicate. Trolox was used as the positive control.

### 2. 2. 2. Anti-Inflammatory Activity

The anti-lipoxygenase activity was evaluated as described by Phosrithong and Nuchtavorn with slight modifications described by Yıldırım *et al.*[28,29] Four different concentrations of chalcone and pyrazoline derivatives

were added to 250 µL of 0.1 M borate buffer pH 9.0, followed by the addition of 250 µL of type V soybean lipoxygenase solution in a buffer (20.000 U/mL). The mixture was incubated at 25 °C for 5 min and 1000 µL of 0.6 mM linoleic acid solution was added, mixed well and the change in absorbance at 234 nm was measured for 6 min. The percentage of inhibition was calculated from the following equation:

$$\% \text{ inhibition} = \frac{A_{\text{control}} - A_{\text{compound}}}{A_{\text{control}}} \cdot 100 \qquad (3)$$

Tests were repeated in quadruplicate. Indomethacin was used as the positive control. The $IC_{50}$ values were determined as the concentration of the synthesized compounds required to inhibit lipoxygenase enzyme activity by 50%.

### 2. 2. 3. Antidiabetic Activity

#### 2. 2. 3. 1. α-Glucosidase Inhibitory Assay

The α-glucosidase inhibitor activity was evaluated as described by Ramakrishna *et al.* with slight modifications described by Sen *et al.*[30,31] 40 µL of 0.1 M sodium phosphate buffer (pH 6.8) was mixed with 10 µL of the synthesized compound at 37 °C. The mixtures were incubated at 25 °C for 10 minutes with 100 µL of α-glucosidase which was obtained from *Saccharomyces cerevisiae.* Then, 50 µL of 5 mM *p*-nitrophenyl-α-D-glucopyranoside (pNPG) which was prepared in the buffer, was added to the mixture. The resulting solution was incubated at 25 °C for 5 minutes again, and absorbance was recorded before and after incubation at 405 nm.

The percentage of inhibition was calculated from the following equation:

$$\% \text{ inhibition} = \frac{A_{\text{control}} - A_{\text{compound}}}{A_{\text{control}}} \cdot 100 \qquad (4)$$

Tests were repeated in quadruplicate. Acarbose was used as the positive control. The $IC_{50}$ values were determined as the concentration of the synthesized compounds required to inhibit α-glucosidase enzyme activity by 50%.

### 2. 2. 4. Statistical Analysis

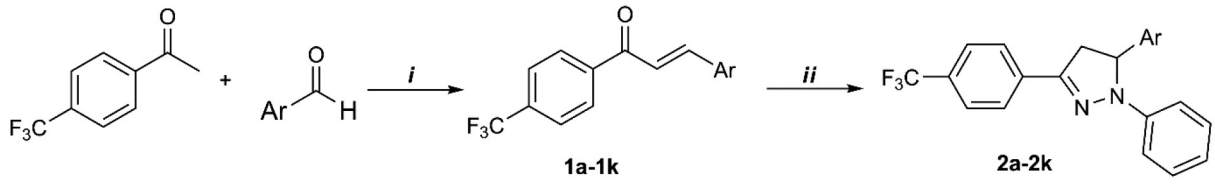
The data were given as means ± standard deviations and analyzed by one-way analysis of variance (ANOVA) followed by the Tukey's multiple comparison tests using GraphPad Prism 5. Differences between means at $p < 0.05$ level were considered significant.

## 3. Results and Discussion

### 3. 1. Chemistry

Pyrazoline derivatives were synthesized as depicted in Figure 2. Firstly, chalcone derivatives were obtained from 4'-(trifluoromethyl)acetophenone according to Claisen–Schmidt condensation reaction. Then, 2-pyrazoline derivatives were obtained from synthesized chalcones by refluxing in the presence of acidic medium (Figure 2). The structures of the compounds were confirmed by IR, $^1$H NMR spectroscopic methods and elemental analysis. Physicochemical and spectroscopic characterization of the chalcone derivatives **1e**,**f**,**g**,**i**,**j** have been previously described.[21–25]

IR spectra of pyrazoline derivatives afforded aromatic C–H (3097–3007 cm$^{-1}$) stretching, pyrazoline C=N stretching (1635–1614 cm$^{-1}$) and C–F stretching (1168–1118 cm$^{-1}$) bands. When $^1$H NMR spectra of pyrazoline derivatives were examined, three different characteristic signals belonging to the methylene group at position 4 (Ha and Hb) and the methine group at position 5 (Hx) of the pyrazoline ring were determined. These signals appeared as doublet of doublets due to ABX spin system in the structures (Figure 3). The Ha, Hb and Hx protons resonated at 3.04–3.25 ppm ($J_{ab}$ = 17.28–17.91 Hz), 3.86–4.02 ppm ($J_{ax}$ = 6.12–6.66 Hz) and 5.44–6.26 ppm ($J_{bx}$ = 12.24–13.96 Hz), respectively. Aromatic CH protons were seen at 6.63–8.00 as multiplet. Especially *ortho* protons belonging to ar-




**1a** and **2a**: Ar=2,6-dimethylphenyl,
**1b** and **2b**: Ar=2,6-dichlorophenyl,
**1c** and **2c**: Ar=2-methylphenyl,
**1d** and **2d**: Ar=4-isopropylphenyl,
**1e** and **2e**: Ar=phenyl,
**1f** and **2f**: Ar=4-chloro,
**1g** and **2g**: Ar=4-methylphenyl,
**1h** and **2h**: Ar=3-methylphenyl,
**1i** and **2i**: Ar=thiophen-2-yl,
**1j** and **2j**: Ar=4-dimethylaminophenyl,
**1k** and **2k**: Ar=naphthalen-1-yl

**Figure 2.** The synthetic pathway for compounds **1a-1k** and **2a-2k**. Reagents and conditions: (***i***) methanol, NaOH, 10 h; (***ii***) phenylhydrazine hydrochloride, acetic acid, reflux, 12 h.

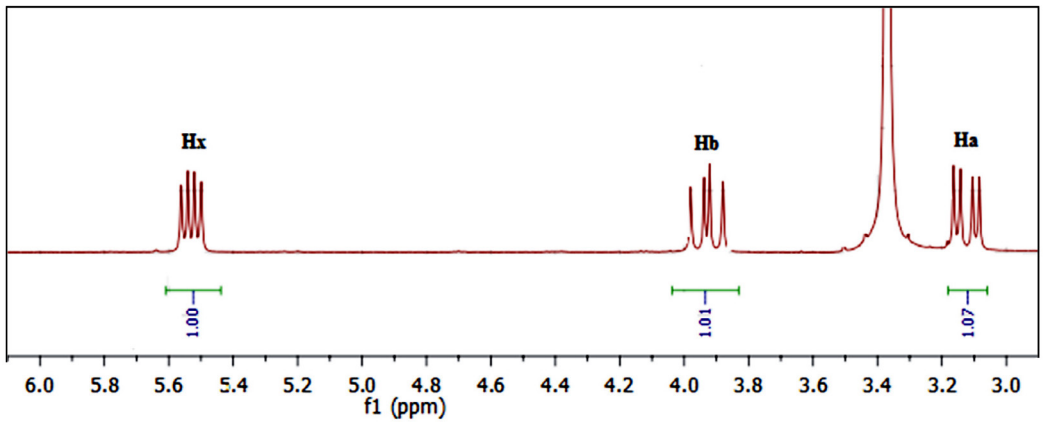



**Figure 3.** Esxample $^1$H NMR spectrum of pyrazoline protons (Ha, Hb and Hx).

omatic ring (bearing trifluoromethyl substituent) were observed as doublet ($J$ = 8.1–8.4 Hz) at 7.72–7.96 ppm.

## 3. 2. Biological Evaluation

All chalcone and pyrazoline derivatives were screened for *in vitro* antioxidant activity with DPPH and ABTS assays, anti-inflammatory activity with lipoxygenase (LOX) inhibition assay and antidiabetic activity with α-glucosidase inhibition assay. All $IC_{50}$ values of compounds against reference standards were given as Table 1. Results demonstrated that all pyrazoline derivatives had a very strong anti-inflammatory activity with $IC_{50}$ values between 0.68 ± 0.07 and 4.45 ± 0.25 μM when compared to

**Table 1**. Antioxidant, anti-inflammatory and antidiabetic activities of synthesized compounds*

| Compound | $IC_{50}$ (μM) Antioxidant activity DPPH activity | ABTS activity | Anti-inflammatory activity Anti-lipoxgenase activity | Antidiabetic activity α-glucosidase inhibitory activity |
|---|---|---|---|---|
| **1a** | >1000 | >1000 | 128.40 ± 3.92$^{f}$ | 381.20 ± 9.29$^{c,d}$ |
| **1b** | >1000 | 852.80 ± 51.42$^{c}$ | 48.47 ± 2.29$^{c}$ | 460.50 ± 3.89$^{d,e}$ |
| **1c** | 211.60 ± 3.48$^{b}$ | 869.00 ± 64.4$^{c}$ | 121.50 ± 4.77$^{f}$ | 746.10 ± 20.95$^{h,i,j}$ |
| **1d** | 389.50 ± 2.22$^{c,d,e,f}$ | 807.00 ± 16.88$^{c}$ | 79.35 ± 0.93$^{d}$ | 338.60 ± 29.32$^{c}$ |
| **1e** | 282.10 ± 15.92$^{b,c}$ | >1000 | 304.60 ± 1.61$^{h}$ | >1000 |
| **1f** | >1000 | >1000 | 50.97 ± 2.75$^{c}$ | 377.40 ± 4.35$^{c,d}$ |
| **1g** | 286.10 ± 19.48$^{b,c}$ | 635.80 ± 11.45$^{b,c}$ | 105.90 ± 0.02$^{e}$ | >1000 |
| **1h** | 321.30 ± 9.96$^{b,c}$ | >1000 | 38.42 ± 3.02$^{b}$ | >1000 |
| **1i** | >1000 | 907.40 ± 26.80$^{c}$ | 85.13 ± 1.56$^{d}$ | >1000 |
| **1j** | 494.00 ± 10.41$^{e,f,g,h,i}$ | 204.40 ± 4.29$^{a,b}$ | 193.60 ± 0.33$^{g}$ | >1000 |
| **1k** | >1000 | >1000 | 83.07 ± 2.31$^{d}$ | 823.8 ± 0.43$^{j}$ |
| **2a** | 534.40 ± 5.02$^{h,i,j}$ | 136.30 ± 3.97$^{a}$ | 0.68 ± 0.07$^{a}$ | 81.09 ± 0.70$^{a,b}$ |
| **2b** | 586.10 ± 44.19$^{i,j}$ | 117.40 ± 0.18$^{a}$ | 0.76 ± 0.09$^{a}$ | 463.40 ± 6.50$^{d,e}$ |
| **2c** | 505.80 ± 23.04$^{f,g,h,i}$ | 127.00 ± 0.90$^{a}$ | 1.56 ± 0.08$^{a}$ | 613.80 ± 14.13$^{f,g}$ |
| **2d** | 342.90 ± 3.29$^{b,c,d}$ | 108.00 ± 2.92$^{a}$ | 2.15 ± 0.13$^{a}$ | 596.90 ± 18.00$^{f,g}$ |
| **2e** | 645.00 ± 22.0$^{j}$ | 130.10 ± 2.00$^{a}$ | 1.73 ± 0.04$^{a}$ | 519.50 ± 18.72$^{e,f}$ |
| **2f** | 524.20 ± 20.82$^{g,h,i,j}$ | 92.62 ± 5.45$^{a}$ | 3.11 ± 0.05$^{a}$ | 451.30 ± 13.76$^{c,d,e}$ |
| **2g** | 898.90 ± 5.76$^{k}$ | 112.20 ± 2.12$^{a}$ | 4.45 ± 0.25$^{a}$ | 637.90 ± 1.67$^{f,g}$ |
| **2h** | >1000 | 150.90 ± 0.57$^{a}$ | 2.14 ± 0.11$^{a}$ | 657.30 ± 14.68$^{g,h}$ |
| **2i** | 855.60 ± 19.93$^{k}$ | 136.40 ± 0.15$^{a}$ | 4.41 ± 0.02$^{a}$ | 812.70 ± 5.13$^{i,j}$ |
| **2j** | >1000 | 57.13 ± 0.03$^{a}$ | 1.19 ± 0.05$^{a}$ | 201.10 ± 5.22$^{b}$ |
| **2k** | 464.80 ± 11.38$^{d,e,f,g}$ | 94.24 ± 0.86$^{a}$ | 1.22 ± 0.07$^{a}$ | 417.60 ± 10.53$^{c,d,e}$ |
| Ascorbic acid | 14.56 ± 0.60$^{a}$ | | | |
| Trolox | | 12.67 ± 0.28$^{a}$ | | |
| Indomethacin | | | 50.45 ± 0.20$^{c}$ | |
| Acarbose | | | | 62.04 ± 3.32$^{a}$ |

* Each value in the table is represented as mean ± SD ($n$ = 4). Different letter superscripts in the same column indicate significant differences ($p$ < 0.05).

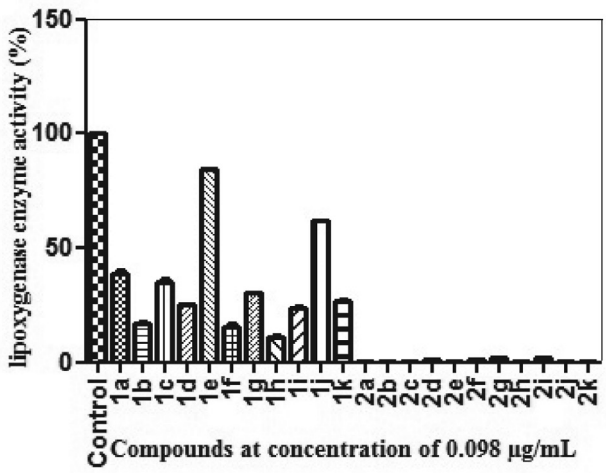



**Figure 4.** Anti-lipoxygenase activity of chalcone and pyrazoline derivatives.

reference standard indomethacin ($IC_{50}$ = 50.45 ± 0.20 µM). Additionally, compound **2a** inhibited 5-lipoxygenase activity by 99.73% at a concentration of 0.098 µg/mL. Chalcone derivatives **1a**–**k** at a concentration of 0.098 µg/mL inhibited lipoxygenase enzyme activity with the inhibition rate of 88.85–15.83% compared to the control (Figure 4).

Synthesized compounds exhibited low antioxidant activity. Only compound **2j** showed the best antioxidant activity according to ABTS assay with $IC_{50}$ value of 57.13 ± 0.03 µM compared to the reference standard trolox (12.67 ± 0.28 µM).

Antidiabetic activity of all compounds was evaluated by the α-glucosidase inhibition assay. These results showed that compound **2a** showed maximum α-glucosidase inhibitory activity with the $IC_{50}$ value of 81.09 ± 0.70 µM ($IC_{50}$ for acarbose 62.04 ± 3.32 µM).

## 3. 3. ADME Calculations

The prediction of ADME properties of the compounds is a very important development of new drug candidates. Therefore the druglike molecule was carried out by using the Lipinski rule of five and Veber rule.[32–34] Calculations were performed using molinspiration online server. The screening results were presented in Table 2.

The molecular weights varied from 276.25 to 435.27 for the synthesized compounds which are lower than the maximum molecular weight of 500. All the compounds are having logP in the range of 3.48–6.22. The number of hydrogen bond acceptors of all compounds is 4 which is less than the maximum value of ten. On the other hand, all the compounds have zero hydrogen bond donors which must be less than the maximum value of five. Furthermore, the number of rotatable bonds is in the range of 4–5 which is lower than the maximum value of 10. Similarly the polar

**Table 2**. Predicted ADME, Lipinski and Veber parameters of the synthesized compounds.

| Compound | Lipinski rule of five | | | | Veber rule | |
|---|---|---|---|---|---|---|
| | MW | Log P | *n*-ON | *n*-OHNH | *n*-ROTB | TPSA |
| **1a** | 304.31 | 4.78 | 4 | 0 | 4 | 17.07 |
| **1b** | 345.14 | 5.32 | 4 | 0 | 4 | 17.07 |
| **1c** | 290.28 | 4.55 | 4 | 0 | 4 | 17.07 |
| **1d** | 318.33 | 5.01 | 4 | 0 | 5 | 17.07 |
| **1e** | 276.25 | 4.32 | 4 | 0 | 4 | 17.07 |
| **1f** | 310.70 | 4.82 | 4 | 0 | 4 | 17.07 |
| **1g** | 290.28 | 4.55 | 4 | 0 | 4 | 17.07 |
| **1h** | 290.28 | 4.55 | 4 | 0 | 4 | 17.07 |
| **1i** | 282.28 | 3.48 | 4 | 0 | 4 | 45.31 |
| **1j** | 319.32 | 4.12 | 4 | 0 | 5 | 20.31 |
| **1k** | 326.31 | 5.04 | 4 | 0 | 4 | 17.07 |
| **2a** | 394.43 | 5.69 | 4 | 0 | 4 | 15.60 |
| **2b** | 435.27 | 6.22 | 4 | 0 | 4 | 15.60 |
| **2c** | 380.41 | 5.48 | 4 | 0 | 4 | 15.60 |
| **2d** | 408.46 | 5.89 | 4 | 0 | 5 | 15.60 |
| **2e** | 366.38 | 5.27 | 4 | 0 | 4 | 15.60 |
| **2f** | 400.82 | 5.75 | 4 | 0 | 4 | 15.60 |
| **2g** | 380.41 | 5.48 | 4 | 0 | 4 | 15.60 |
| **2h** | 380.41 | 5.48 | 4 | 0 | 4 | 15.60 |
| **2i** | 372.41 | 4.88 | 4 | 0 | 4 | 43.84 |
| **2j** | 409.45 | 5.07 | 4 | 0 | 5 | 18.84 |
| **2k** | 416.44 | 5.91 | 4 | 0 | 4 | 15.60 |

TPSA: Topological polar surface area, *n*-ON: number of hydrogen bond acceptors, *n*-OHNH: number of hydrogen bond donors, *n*-ROTB: number of rotatable bonds. Calculations were performed using Molinspiration online property calculation toolkit (http://www.molinspiration.com).

surface area of all synthesized compounds is indicated to be in the range of 15.60–45.31 Å$^2$ which is less than the maximum value of 140 Å$^2$. These values demonstrate that none of the synthesized compounds are violating the Lipinski and Veber rules.

## 4. Conclusion

New pyrazoline derivatives were synthesized from chalcone derivatives and the designed molecules were investigated for their drug-likeness properties which were defined as Lipinski and Veber rules. All compounds were tested for their antioxidant (DPPH and ABTS), anti-lipoxygenase and α-glucosidase inhibitory activities. These results showed that pyrazoline derivatives exhibited better activity than chalcone derivatives. Especially pyrazoline derivatives **2a–k** showed very strong anti-lipoxygenase activity each with greater activity than reference drug indomethacin. Also, compounds **2j** and **2a** demonstrated good antioxidant and α-glucosidase inhibitory activity, respectively. These findings revealed that the pyrazoline core could lead to considerably active molecules.

**Conflict of Interest**

Authors declare no conflict of interest.

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## Povzetek

Iz halkonskih derivatov smo sintetizirali serijo 1-fenil-5-substituiranih-3-(4-(trifluorometil)fenil)-4,5-dihidro-1*H*-pirazolov. Strukture spojin smo določili s pomočjo IR ter $^1$H NMR spektroskopskih metod in z elementno analizo. Za vse spojine smo določili *in vitro* antioksidativno aktivnost s pomočjo DPPH in ABTS metod, antiinflamatorno aktivnost s pomočjo metode inhibicije lipooksigenaze ter antidiabetično aktivnost s pomočjo metode inhibicije α-glukozidaze. Še zlasti pirazolinski derivati so izkazali visoke antiinflamatorne aktivnosti, celo večje kot referenčna učinkovina indometacin ($IC_{50}$: 50.45 μM) z $IC_{50}$ vrednostmi v območju od 0.68 do 4.45 μM. V nadaljevanju smo določili še ADME lastnosti vseh halkonskih in pirazolinskih derivatov skladno s pravili Lipinskega in Vebra.