Synthesis of 4,5-dihydro-1H-pyrazole derivatives based on 3-acetyl-5-nitropyridines

Alena Stalinskaya  
Tyumen State University: Tumenskij gosudarstvennyj universitet

Daria Weber  
Tyumen State University: Tumenskij gosudarstvennyj universitet

Tulegen Seilkhanov  
Sh Ualikhanov Kokshetau State University

Ivan Kulakov (✉ i.v.kulakov@utmn.ru)  
Tyumen State University  https://orcid.org/0000-0001-5772-2096

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Abstract

Claisen-Schmidt-type aldol-crotonic condensation of 3-acetyl-5-nitropyridine derivatives with various aromatic aldehydes was used for the preparation of pyridylchalcones. Cyclization of the latter with hydrazine hydrate in acetic acid afforded the corresponding \( N \)-acetyl derivatives of 4,5-dihydro-1\( H \)-pyrazole.

Introduction

Chalcones are of important practical interest to chemists due to their availability and pronounced pharmacological activity of natural chalcones and their synthetic analogues. For example, it is worth noting their properties such as antibacterial and anti-inflammatory [1], antitumor [2, 3] antiparasitic [4], antimycobacterial [5], and others [6-10]. In addition, chalcone derivatives are valuable synthons in the formation of various heterocycles. For example, reactions of chalcones with binucleophiles are used in preparation of 4,5-dihydro-1\( H \)pyrazoles [11, 12], as well as pyrimidines, pyridines, etc. [13-15]. 4,5-Dihydro-1\( H \)pyrazole derivatives have luminescent properties [16] and also exhibit antibacterial [17], antioxidant [18], analgesic [19], anti-inflammatory [20], and antimycobacterial activity [21]. It should be noted that the pyridine-containing derivatives of 4,5-dihydro-1\( H \)pyrazole have low toxicity, as well as their phenyl-substituted analogs. However, the presence of a pyridine core in the molecule increases bioavailability [22].

Previously, we have synthesized symmetric 3,5-bis-derivatives 2 and 3 containing \( \alpha,\beta \)-unsaturated carbonyl moieties and 4,5-dihydro-1\( H \)pyrazole rings starting from 3,5-diacetyl-2,6-dimethylpyridine 1 (Scheme 1) [23]. According to in vivo biological screening, the synthesized compounds exhibit moderately pronounced analgesic activity.

Polyfunctional pyridines, including 3-acetylpyridines, are of particular interest as versatile objects for chemical modification (for example, in 4,5-dihydro-1\( H \)pyrazoles) and subsequent study of the structure-activity relationship of the obtained compounds.

The presence of a nitro group in the molecule can increase its antibacterial activity. Previously, we have studied the antimicrobial and analgesic activity of \( \alpha,\gamma \)-diketoacid derivatives synthesized from 3-acetyl-5-nitropyridine 4 [24].

Herein, we reported the synthesis of a series of azachalcones based on available 3-acetyl-5-nitropyridines 4 and 5 (Fig. 1) and their cyclization to the corresponding 4,5-dihydro-1\( H \)pyrazole derivatives.

The starting pyridines 4 and 5 were synthesized by the classical Hantzsch reaction, i.e., through the multicomponent synthesis of intermediate 1,4-dihydropyridines (1,4-DHPs) and their further aromatization into respective pyridines [25, 26].

Results And Discussion
In order to obtain pyridylchalcones 6a-6e and 7a-7e the Claisen-Schmidt condensation of 3-acetyl-5-
nitropyridines 4, 5 with various aromatic aldehydes in alkaline aqueous-alcoholic medium was carried out. Due to poor solubility in a water-alcohol medium, the starting 5-nitropyridines were pre-dissolved in a minimum amount of methylene chloride (Scheme 2). Pyridylchalcones 6a-6e were obtained with excellent yields (92-99%) as fine-crystalline solids. Pyridylchalcones 7a-7e were isolated with good yields (59-81%).

In order to introduce a new pharmacophore 1H-pyrazole ring into the molecules of compounds 6a-6e and 7a-7e, a heterocyclization reaction with hydrazine hydrate in the presence of acetic acid was performed (Scheme 2).

In the case of 4,5-dihydro-1H-pyrazole 8b, which contains two acidophobic furan rings, the reaction is accompanied by much tarring. Nevertheless, it was possible to isolate the target product with a yield of 30%. It was purified by silica gel column chromatography. 4,5-Dihydro-1H-pyrazole 9b was also obtained in a low yield (30%), probably for the same reason: low stability of the furan ring when heated in acidic media. 4,5-Dihydro-1H-pyrazole derivatives 8a, 9a and 8c-8e, 9c-9e bearing aromatic substituents were isolated by treating the reaction mixtures with ice water and subsequent recrystallization from an appropriate solvent. Yields of the target compounds varied from 47 to 83% (Table 1).

**Conclusion**

In summary, a series of new potentially biologically active pyridylchalcone and 4,5-dihydro-1H-pyrazole derivatives was synthesized based on poorly studied 3-acetyl-5-nitropyridines 4 and 5. Moreover, it was shown that the presence of an acceptor nitro group in the pyridine nucleus greatly facilitates their chemical modification at the acetyl group. The presence of a furyl ring in the 4-position of 5-nitropyridine 4 leads to an increase in the yields of pyridylchalcones to almost quantitative, but significantly reduces the yields and complicates the subsequent isolation of the corresponding derivatives of 4,5-dihydro-1H-pyrazole. The obtained azachalcones and 4,5-dihydro-1H-pyrazole derivatives can be promising objects for search antibacterial agents. After reduction of the nitro group, the resulting amino derivatives of pyrazoles can exhibit excellent luminescent properties.

**Experimental**

IR spectra were recorded on an Infralum FT-801 spectrometer in KBr pellets. $^1$H and $^{13}$C NMR spectra were acquired on a Bruker DRX400 instrument (400 and 100 MHz, respectively) using CDCl$_3$ or DMSO-d$_6$ the internal standard was TMS or residual solvent signals (7.25 and 77.0 ppm in the case of CDCl$_3$ for $^1$H and $^{13}$C nuclei, respectively; 2.49 and 39.9 ppm $^1$H and for $^{13}$C nuclei in DMSO-d$_6$). Elemental analysis was performed on a Carlo Erba EA 1106 automatic CHN-analyzer. The reaction progress and purity of the obtained compounds were controlled by TLC on Sorbil AF-A-UV plates, visualization in iodine vapor and under UV light. Melting points were determined using a Kofler hot bench.
1-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]ethan-1-one (4) and 1-(2-methyl-5-nitro-6-phenylpyridin-3-yl)-3-phenylprop-2-en-1-one (5) were synthesized according to published procedures [20, 21].

**General procedure for the synthesis of pyridylchalcones 6a-6e,7a-7e**

A solution of 0.2 g KOH (4 mmol) in 3 cm$^3$ H$_2$O and 15 cm$^3$ EtOH was cooled in an ice bath (0-5 °C). Then 3-acetyl-5-nitro-6-phenylpyridine 4 or 5 (4 mmol) in 1 cm$^3$ CH$_2$Cl$_2$ was added, and the constantly stirred mixture was treated by dropwise addition of the appropriate aromatic aldehyde (4 mmol). A precipitate of pyridylchalcone 6a-6e, 7a-7e formed after 10 min. The mixture was stirred at room temperature for additional 3 h. Then the precipitate is filtered, washed with a water-alcohol solution and dried in air. The crude product was purified by recrystallization from an appropriate solvent.

**1-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]ethan-1-one (4, C$_{25}$H$_{18}$N$_2$O$_4$)** White crystals; m.p.: 138-140 °C (2-PrOH); yield: 1.13 g (92%); IR (KBr): = 1668 (C=O), 1530, 1334 (NO$_2$) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.63 (s, 3H, CH$_3$), 6.43 (dd, $J$ = 3.7 Hz, 1.9 Hz, 1H, H-4 furan), 6.73 (d, $J$ = 3.7 Hz, 1H, H-3 furan), 6.82 (d, $J$ = 16.0 Hz, 1H, 2-CH=), 7.30 (d, $J$ = 16.0 Hz, 1H, -CH=), 7.36-7.43 (m, 3H, H-3',4',5' Ph), 7.45-7.52 (m, 6H, H-5 furan, H-3,4,5 Ph, H-2',6' Ph), 7.63-7.66 (m, 2H, H-2,6 Ph) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 23.3 (CH$_3$), 112.5, 114.8, 126.4, 128.0 (2C Ar), 128.6 (2C Ar), 128.97, 129.0 (2C Ph), 130.1, 131.3, 131.6, 133.7, 135.3, 142.2, 143.3, 145.5, 146.8, 150.7, 157.1, 194.8 (C=O) ppm.

**1-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-3-phenylprop-2-en-1-one (5, C$_{21}$H$_{16}$N$_2$O$_3$)** White crystals; m.p.: 155-156 °C (2-PrOH); yield: 992 mg (96%); IR (KBr): = 1665 (C=O), 1505, 1331 (NO$_2$) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.80 (s, 3H, CH$_3$), 7.18 (d, $J$ = 15.3, 1H, 2-CH=), 7.45-7.51 (m, 6H, 3-CH=, H-2',3',4',5',6' Ph), 7.59-7.64 (m, 5H, H-2,3,4,5,6 Ph), 8.29 (s, 1H, H-4 pyridine) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 24.0 (CH$_3$), 124.8, 128.3 (2C Ph), 128.8 (4C Ph), 129.2 (2C Ph), 130.2, 131.6, 132.1, 132.7, 133.7, 135.9, 143.5, 147.9, 153.3, 160.7, 192.0 (C=O) ppm.

**3-(Furan-2-yl)-1-[4-(furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]prop-2-en-1-one (6b, C$_{23}$H$_{16}$N$_2$O$_5$)** Bright-beige crystals; m.p.: 150-152 °C (2-PrOH); yield: 1.10 g (94%); IR (KBr): = 1623 (C=O), 1543, 1375 (NO$_2$) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.62 (s, 3H, CH$_3$), 6.44 (dd, $J$ = 3.7 Hz, 1.8 Hz, 1H, H-4' furan), 6.50 (dd, $J$ = 3.7 Hz, 1.8 Hz, 1H, H-4 furan), 6.66-6.75 (m, 3H, 2-CH=, H-3 furan, H-3' furan), 7.06 (d, $J$ = 16.0 Hz, 1H, 3-CH=), 7.46-7.50 (m, 4H, H-3,4,5 Ph, H-5' furan), 7.52 (d, $J$ = 1.3 Hz, 1H, H-5 furan), 7.60-7.64 (m, 2H, H-2,6 Ph) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 23.2 (CH$_3$), 112.4, 113.0, 114.9, 117.7, 123.7, 128.0 (3C Ph), 128.9 (3C Ph), 130.0, 131.6, 132.4, 135.4, 134.3, 143.3, 145.5, 146.0, 150.3, 150.7, 157.0, 194.3 (C=O) ppm.

**3-(Furan-2-yl)-1-(2-methyl-5-nitro-6-phenylpyridin-3-yl)prop-2-en-1-one (7b, C$_{19}$H$_{14}$N$_2$O$_4$)** Yellow crystals; m.p.: 160-161 °C (2-PrOH); yield: 712 mg (71%); IR (KBr): = 1657 (C=O), 1504, 1326 (NO$_2$) cm$^{-1}$; $^1$H NMR
(400 MHz, CDCl₃): δ = 2.80 (s, 3H, CH₃), 6.55 (br. s, 1H, H-4 furan), 6.80 (d, J = 3.0 Hz, 1H, H-3 furan), 7.07 (d, J = 15.2 Hz, 1H, 2-CH=), 7.41 (d, J = 15.2 Hz, 1H, 3-CH=), 7.46-7.50 (m, 3H, H-3,4,5 Ph), 7.58 (m, 3H, H-5 furan, H-2,6 Ph), 8.30 (s, 1H, H-4 pyridine) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 24.1 (CH₃), 113.1, 118.2, 121.7, 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 132.1, 132.8, 132.9, 135.9, 143.5, 146.1, 150.7, 153.3, 160.8, 191.0 (C=O) ppm.

1-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-3-(thiophen-2-yl)prop-2-en-1-one (6c, C₂₃H₁₈N₂O₄S) Beige crystals; m.p.: 148-149 °C (2-PrOH); yield: 1.20 g (95%); IR (KBr): = 1643 (C=O), 1530, 1375 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.64 (s, 3H, CH₃), 6.45 (br. s, 1H, H-4 furan), 6.62 (d, J = 16.8 Hz, 1H, 2-CH=), 6.75 (d, J = 3.1 Hz, 1H, H-3 furan), 7.08 (t, J = 4.6 Hz, 1H, H-4 thiophene), 7.30 (d, J = 3.1 Hz, 1H, H-3 thiophene), 7.43 (d, J = 16.8 Hz, 1H, 3-CH=), 7.41-7.52 (m, 6H, H-3,4,5 Ph, H-5 furan, H-5 thiophene), 7.62-7.68 (m, 2H, H-2,6 Ph) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 23.3 (CH₃), 112.4, 114.9, 125.0, 128.0 (2C Ph), 128.6, 128.9 (2C Ph), 128.9, 130.1, 130.4, 131.5, 132.9, 135.3, 139.0, 139.1, 142.2, 143.3, 145.5, 150.7, 157.1, 194.1 (C=O) ppm.

1-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-3-(thiophen-2-yl)prop-2-en-1-one (7c, C₁₉H₁₄N₂O₃S) Bright-yellow crystals; m.p.: 166-168 °C (2-PrOH); yield: 746 mg (71%); IR (KBr): = 1656 (C=O), 1503, 1323 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.79 (s, 3H, CH₃), 6.95 (d, J = 16.8 Hz, 1H, 2-CH=), 7.14 (d, J = 4.6 Hz, 1H, H-4 thiophene), 7.40 (d, J = 3.0 Hz, 1H, H-3 thiophene), 7.47-7.55 (m, 4H, H-5 thiophene, H-3,4,5 Ph), 7.61 (d, J = 4.5 Hz, 2H, H-2,6 Ph), 7.75 (d, J = 15.3, 1H, 3-CH=), 8.28 (s, 1H, H-4 pyridine) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 24.0 (CH₃), 123.3, 128.2 (2C Ph), 128.7, 128.8 (2C Ph), 130.2, 130.7, 132.0, 132.7, 133.4, 135.8, 139.2, 140.0, 143.4, 153.2, 160.6, 191.2 (C=O) ppm.

1-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-3-(3-nitrophenyl)prop-2-en-1-one (6d, C₂₅H₁₇N₃O₆) Bright-beige crystals; m.p.: 146-148 °C (2-PrOH-CHCl₃); yield: 1.30 g (98%); IR (KBr): = 1656 (C=O), 1530, 1353 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.64 (s, 3H, CH₃), 6.45 (br. s, 1H, H-4 furan), 6.75 (d, J = 3.1 Hz, 1H, H-3 furan), 6.86 (d, J = 16.8 Hz, 1H, 2-CH=), 7.34 (d, J = 16.8 Hz, 1H, 3-CH=), 7.45-7.52 (m, 4H, H-3,4,5 Ph, H-5 furan), 7.58 (t, J = 8.4 Hz, 1H, H-5 Ar), 7.63-7.65 (m, 2H, H-2,6 Ph), 7.76 (d, J = 7.6 Hz, 1H, H-6 Ar), 8.24 (d, J = 9.1 Hz, 1H, H-4 Ar), 8.30 (s, 1H, H-2 Ar) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 23.4 (CH₃), 112.7, 115.0, 122.8, 125.3, 128.0 (2C Ph), 128.6, 128.9 (2C Ph), 129.0, 130.2, 130.3, 131.0, 133.9, 135.2, 135.5, 142.1, 142.9, 143.2, 145.7, 148.6, 151.1, 157.2, 193.9 (C=O) ppm.

1-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-3-(3-nitrophenyl)prop-2-en-1-one (7d, C₂₁H₁₅N₃O₅) White crystals; m.p.: 183-185 °C (2-PrOH-CHCl₃); yield: 689 mg (59%); IR (KBr): = 1669 (C=O), 1605, 1366 (NO₂) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 2.85 (s, 3H, CH₃), 7.33 (d, J = 15.2 Hz, 1H, 2-CH=), 7.50-7.54 (m, 3H, H-3,4,5 Ph), 7.62-7.65 (m, 2H, H-2,6 Ph), 7.67-7.73 (m, 2H, 3-CH=, H-5 Ar), 7.95 (d, J = 7.6 Hz, 1H, H-6 Ar), 8.33 (d, J = 7.6 Hz, 1H, H-4 Ar), 8.36 (s, 1H, H-2 Ar), 8.50 (s, 1H, H-4 pyridine) ppm; ¹³C (100 MHz, CDCl₃): δ = 24.3 (CH₃), 123.0, 125.6, 126.9, 128.3 (2C Ph), 128.9 (2C Ph), 130.3, 130.4, 131.9, 132.3, 134.2, 135.5, 135.7, 134.4, 143.4, 148.7, 153.8, 161.0, 190.8 (C=O) ppm.
3-(4-Fluorophenyl)-1-[4-(furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]prop-2-en-1-one (6e, C_{25}H_{17}FN_{2}O_{4})

Bright-beige crystals; m.p.: 136-138 °C (2-ProH); yield: 1.30 g (99%); IR (KBr): = 1670 (C=O), 1532, 1319 (NO2) cm^{-1}; 1H (400 MHz, CDCl3): δ = 2.63 (s, 3H, CH3), 6.44 (br. s, 1H, H-4 furan), 6.72-6.76 (m, 2H, 2-CH=, H-3 furan), 7.08 (t, J = 8.4 Hz, 2H, H-3,5 Ar), 7.26 (d, J = 15.2 Hz, 1H, 3-CH=), 7.46-7.55 (m, 6H, H-5 furan, H-3,4,5 Ph, H-2,6 Ar), 7.62-7.68 (m, 2H, H-2,6 Ph) ppm; 13C NMR (100 MHz, CDCl3): δ = 23.3 (CH3), 112.5, 114.8, 116.3 (d, 2J_{CF} = 22.1 Hz, 2C Ar), 126.0, 128.0 (2C Ph), 128.9 (2C Ph), 128.95, 130.0, 130.1, 130.6 (d, 3J_{CF} = 8.6 Hz, 2C Ar), 131.5, 135.3, 142.1, 143.3, 145.4, 145.5, 150.8, 157.1, 164.4 (d, 1J_{CF} = 253.1 Hz), 194.6 (C=O) ppm.

3-(4-Fluorophenyl)-1-(2-methyl-5-nitro-6-phenylpyridin-3-yl)prop-2-en-1-one (7e, C_{21}H_{15}FN_{2}O_{3})

White crystals; m.p.: 173-174 °C (2-ProH); yield: 869 mg (80%); IR (KBr): = 1666 (C=O), 1510, 1345 (NO2) cm^{-1}; 1H NMR (400 MHz, CDCl3): δ = 2.79 (s, 3H, CH3), 7.07-7.15 (m, 3H, 2-CH=, H-3,5 Ar), 7.46-7.51 (m, 3H, 3-CH=, H-2,6 Ar), 7.54-7.63 (m, 5H, H-2,3,4,5,6 Ph), 8.28 (s, 1H, H-4 pyridine) ppm; 13C NMR (100 MHz, CDCl3): δ = 24.0 (CH3), 116.5 (d, 2J_{CF} = 22.1 Hz, 2C Ar), 124.4, 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 130.2, 130.8 (d, 3J_{CF} = 8.6 Hz, 2C Ar), 132.1, 132.6, 135.8, 143.5, 146.4, 153.3, 160.7, 164.6 (d, 1J_{CF} = 254.0 Hz), 191.6 (C=O) ppm.

General procedure for the synthesis of 4,5-dihydro-1H-pyrazoles 8a-8e, 9a-9e

A solution of 0.3 cm^3 N_2H_4.H_2O (5 mmol) in 4 cm^3 2-ProOH was constantly stirred and treated by dropwise addition of a solution of the appropriate pyridylchalcone 6a-6e or 7a-7e (0.5 mmol) in 10 cm^3 AcOH. The mixture was refluxed for 20 h, then it was cooled and poured into 50 cm^3 ice-water mixture. The formed precipitate of 4,5-dihydro-1H-pyrazole 8a-8e, 9a-9e was filtered off, washed with H_2O, and air-dried. The crude product was purified by recrystallization or by silica gel column chromatography (compound 8b).

1-[3-{4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl}ethan-1-one (8a, C_{27}H_{22}N_{4}O_{4})

Beige crystals; m.p.: 198-200 °C (2-ProH); yield: 137 mg (59%); IR (KBr): = 1670 (C=O), 1536, 1350 (NO2) cm^{-1}; 1H (400 MHz, CDCl3): δ = 2.40 (s, 3H, COCH3), 2.55 (dd, 2J = 16.8 Hz, 3J = 4.6 Hz, 1H, 4-CH2 pyrazole), 2.74 (s, 3H, CH3), 3.29 (dd, 2J = 18.4 Hz, 3J = 12.3 Hz, 1H, 4-CH2 pyrazole), 5.62 (dd, 3J = 10.7 Hz, 3J = 4.6 Hz, 1H, 5-CH pyrazole), 6.36 (br. s, 1H, H-4 furan), 6.64 (d, J = 3.1 Hz, 1H, H-3 furan), 7.17 (br. s, 3H, H-3’,4’,5’ Ph), 7.27-7.32 (m, 1H, H-4 Ph), 7.33-7.39 (m, 2H, H-2’,6’ Ph), 7.48 (s, 3H, H-3,5 Ph, H-5 furan), 7.60 (d, J = 7.6 Hz, 2H, H-2’,6’ Ph) ppm; 13C NMR (100 MHz, CDCl3): δ = 21.9 (CH3), 24.2 (COCH3), 45.5 (4-CH2 pyrazole), 59.6 (5-CH pyrazole), 112.1, 114.4, 124.7, 125.3 (2C Ph), 127.7, 127.9 (3C Ph), 128.9 (4C Ph), 130.1, 131.0, 135.2, 140.9, 143.3, 145.3, 150.4, 152.1, 159.2, 169.0 (COCH3) ppm.

1-[3-{2-Methyl-5-nitro-6-phenylpyridin-3-yl]-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl}ethan-1-one (9a, C_{23}H_{20}N_{4}O_{3})

Yellow crystals; m.p.: 191-193 °C (2-ProH); yield: 96 mg (48%); IR (KBr): = 1670 (C=O), 1536, 1350 (NO2) cm^{-1}; 1H (400 MHz, CDCl3): δ = 2.45 (s, 3H, COCH3), 3.05 (s, 3H, CH3), 3.26 (dd, 2J = 16.8 Hz,
$^3J = 4.6 \text{ Hz}, 1\text{H}, 4-\text{CH}_2\text{pyrazole}$, $3.87 \text{ (dd, } ^2J = 16.8 \text{ Hz, } ^3J = 12.2 \text{ Hz}, 1\text{H}, 4-\text{CH}_2\text{pyrazole})$, $5.64 \text{ (dd, } ^3J = 12.2 \text{ Hz, } ^2J = 4.6 \text{ Hz}, 1\text{H}, 5-\text{CHpyrazole})$, $7.22-7.36 \text{ (m, 5H, H-2',3',4',5',6' Ph)}$, $7.49 \text{ (m, 3H, H-3,4,5 Ph)}$, $7.59 \text{ (d, } J = 7.63 \text{ Hz, 2H, H-2,6 Ph})$, $8.10 \text{ (s, 1H, H-4 pyridine ppm)}$; $^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta = 22.1 \text{ (CH}_3\text{), 27.2 (COCH}_3\text{), 43.9 (4-CHpyrazole), 59.6 (5-CHpyrazole), 125.1, 125.4 (2C Ph), 128.0, 128.3 (2C Ph), 128.8 (2C Ph), 129.1 (2C Ph), 130.1, 131.9, 135.8, 141.0, 143.7, 150.2, 151.4, 161.1, 169.0 (COCH}_3\text{)} ppm.

1-[5-(Furan-2-yl)-3-[4-(furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-4,5-dihydro-1Hpyrazol-1-yl]ethan-1-one (8b, C$_{29}$H$_{20}$N$_4$O$_5$) Beige crystals; m.p.: 176-178 °C (SiO$_2$, EtOAc-hexane (1:3)); yield: 68 mg (30%); IR (KBr): = 1665 (C=O), 1542, 1358 (NO$_2$) cm$^{-1}$; $^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 2.32 \text{ (s, 3H, COCH}_3\text{), 2.77 (s, 3H, CH}_3\text{), 2.97 (dd, } ^2J = 18.3 \text{ Hz, } ^3J = 6.1 \text{ Hz, 1H, 4-CH}_2\text{pyrazole), 3.11 (dd, } ^2J = 18.3 \text{ Hz, } ^3J = 12.2 \text{ Hz, 1H, 4-CH}_2\text{pyrazole), 5.66 (dd, } ^3J = 12.2 \text{ Hz, } ^2J = 4.6 \text{ Hz, 1H, 5-CHpyrazole), 6.33 (d, } ^3J = 4.6 \text{ Hz, 1H, H-4' furan), 6.36 (d, } ^3J = 3.1 \text{ Hz, 1H, H-3' furan), 6.50 (br. s, 1H, H-4 furan), 6.71 (d, } J = 3.1 \text{ Hz, 1H, H-3 furan), 7.34 (br. s, 1H, H-5' furan), 7.45-7.54 \text{ (m, 4H, H-3,4,5 Ph, H-5 furan), 7.60-7.62 (m, 2H, H-2,6 Ph) ppm}; ^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta = 22.0 \text{ (CH}_3\text{), 24.0 (COCH}_3\text{), 41.2 (4-CH}_2\text{pyrazole), 53.3 (5-CHpyrazole), 107.9, 110.7, 112.3, 114.7, 124.5, 128.0 (2C Ph), 128.9 (2C Ph), 130.2, 130.9, 135.3, 142.0, 143.0, 143.5, 145.5, 150.7, 151.3, 152.4, 159.4, 169.2 (COCH}_3\text{)} ppm.

1-[5-(Furan-2-yl)-3-(2-methyl-5-nitro-6-phenylpyridin-3-yl)-4,5-dihydro-1Hpyrazol-1-yl]ethan-1-one (9b, C$_{27}$H$_{18}$N$_4$O$_4$) Bright-yellow crystals; m.p.: 141-142 °C (CHCl$_3$-hexane); yield: 59 mg (30%); IR (KBr): = 1667 (C=O), 1545, 1347 (NO$_2$) cm$^{-1}$; $^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 2.42 \text{ (s, 3H, -COCH}_3\text{), 3.04 (s, 3H, CH}_3\text{), 3.56 (dd, } ^2J = 16.7 \text{ Hz, } ^3J = 4.6 \text{ Hz, 1H, 4-CH}_2\text{pyrazole), 3.70 (dd, } ^2J = 18.4 \text{ Hz, } ^3J = 10.6 \text{ Hz, 1H, 4-CH}_2\text{pyrazole), 5.74 (dd, } ^3J = 10.6 \text{ Hz, } ^2J = 4.6 \text{ Hz, 1H, 5-CHpyrazole), 6.36 \text{ (br. s, 1H, H-4 furan), 6.40 (br. s, 1H, H-3 furan), 7.33 (br. s, 1H, H-5 furan), 7.47-7.52 \text{ (m, 3H, H-3,4,5 Ph), 7.59-7.64 \text{ (m, 2H, H-2,6 Ph), 8.17 (s, 1H, H-4 pyridine ppm); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta = 22.1 \text{ (CH}_3\text{), 27.1 (COCH}_3\text{), 39.6 (4-CH}_2\text{pyrazole), 53.0 (5-CHpyrazole), 108.3, 110.7, 125.0, 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 132.0, 135.9, 142.2, 143.7, 150.4, 151.1, 151.4, 161.2, 169.1 (COCH}_3\text{)} ppm.

1-[3-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-5-(thiophen-2-yl)-4,5-dihydro-1Hpyrazol-1-yl]ethan-1-one (8c, C$_{25}$H$_{18}$N$_4$O$_4$S) Beige crystals; m.p.: 189-190 °C (2-PrOH); yield: 111 mg (47%); IR (KBr): = 1676 (C=O), 1534, 1349 (NO$_2$) cm$^{-1}$; $^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 2.35 \text{ (s, 3H, -COCH}_3\text{), 2.75 (s, 3H, CH}_3\text{), 2.81 (dd, } ^2J = 18.4 \text{ Hz, } ^3J = 4.6 \text{ Hz, 1H, 4-CH}_2\text{pyrazole), 3.23 (dd, } ^2J = 18.4 \text{ Hz, } ^3J = 12.2 \text{ Hz, 1H, 4-CH}_2\text{pyrazole), 5.87 (dd, } ^3J = 10.6 \text{ Hz, } ^2J = 4.6 \text{ Hz, 1H, 5-CHpyrazole), 6.44 \text{ (br. s, 1H, H-4 furan), 6.66 (d, } J = 4.6 \text{ Hz, 1H, H-3 furan), 6.94-6.96 \text{ (m, 2H, H-3,4 thiophene), 7.23 (d, } J = 4.5 \text{ Hz, 1H, H-5 thiophene), 7.33 \text{ (br. s, 1H, H-5 furan), 7.42-7.51 \text{ (m, 3H, H-3,4,5 Ph), 7.57-7.65 \text{ (m, 2H, H-2,6 Ph) ppm)); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{): } \delta = 22.0 \text{ (CH}_3\text{), 24.2 (COCH}_3\text{), 45.3 (4-CH}_2\text{pyrazole), 55.3 (5-CHpyrazole), 112.3, 114.6, 124.5, 124.66, 124.69, 126.9, 127.9 (2C Ph), 128.9 (2C Ph), 130.2, 131.0, 135.2, 143.1, 143.4, 143.9, 145.4, 150.6, 152.0, 159.2, 169.2 (COCH}_3\text{)} ppm.
1-[3-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-5-(thiophen-2-yl)-4,5-dihydro-1Hpyrazol-1-yl]ethan-1-one (9c, C$_{21}$H$_{18}$N$_4$O$_3$S) Beige crystals; m.p.: 174-175 °C (2-PrOH); yield: 169 mg (83%); IR (KBr): = 1676 (C=O), 1534, 1349 (NO$_2$) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.43 (s, 3H, COCH$_3$), 3.04 (s, 3H, CH$_3$), 3.43 (dd, $^2$J = 16.7 Hz, $^3$J = 4.6 Hz, 1H, 4-CH$_2$ pyrazole), 3.84 (dd, $^2$J = 16.8 Hz, $^3$J = 12.2 Hz, 1H, 4-CH$_2$ pyrazole), 5.96 (dd, $^3$J = 12.2 Hz, $^3$J = 3.1 Hz, 1H, 5-CH pyrazole), 6.96 (dd, $^2$J = 4.6 Hz, 3.1 Hz, 1H, H-4 thiophene), 7.06 (d, $^2$J = 3.1 Hz, 1H, H-3 thiophene), 7.23 (d, $^2$J = 4.6 Hz, 1H, H-5 thiophene), 7.44-7.54 (m, 3H, H-3,5 Ph), 7.56-7.65 (m, 2H, H-2,6 Ph), 8.14 (s, 1H, H-4 pyridine) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 21.1 (CH$_3$), 27.0 (COCH$_3$), 43.6 (4-CH$_2$ pyrazole), 55.0 (5-CH pyrazole), 124.8, 125.0, 125.1, 127.0, 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 131.9, 135.8, 143.4, 143.7, 150.2, 151.5, 161.1, 169.1 (COCH$_3$) ppm.

1-[3-[4-(Furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-5-(3-nitrophenyl)-4,5-dihydro-1Hpyrazol-1-yl]ethan-1-one (8d, C$_{27}$H$_{21}$N$_5$O$_6$) Beige crystals; m.p.: 165-168 °C (CH$_2$Cl$_2$-hexane); yield: 128 mg (50%); IR (KBr): = 1679 (C=O), 1534, 1345 (NO$_2$) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.41 (s, 3H, COCH$_3$), 2.56 (dd, $^2$J = 18.3 Hz, $^3$J = 6.1 Hz, 1H, 4-CH$_2$ pyrazole), 2.77 (s, 3H, CH$_3$), 3.36 (dd, $^2$J = 18.3 Hz, $^3$J = 12.2 Hz, 1H, 4-CH$_2$ pyrazole), 5.64 (dd, $^3$J = 12.2 Hz, $^3$J = 6.1 Hz, 1H, 5-CH pyrazole), 6.43 (d, $^2$J = 3.0 Hz, 1H, H-4 furan), 6.69 (d, $^2$J = 3.1 Hz, 1H, H-3 furan), 7.35 (br. s, 1H, H-5 furan), 7.45-7.51 (m, 3H, H-3,4,5 Ph), 7.54-7.58 (m, 2H, H-5,6 Ar), 7.62 (d, $^2$J = 7.6 Hz, 2H, H-2,6 Ph), 8.06 (s, 1H, H-2 Ar), 8.18 (dd, $^2$J = 6.1 Hz, 3.1 Hz, 1H, H-4 Ar) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 21.9 (CH$_3$), 24.2 (COCH$_3$), 45.3 (4-CH$_2$ pyrazole), 59.2 (5-CH pyrazole), 112.4, 114.5, 120.5, 122.9, 124.3, 127.9 (2C Ph), 128.9 (2C Ph), 130.0, 130.3, 131.1, 132.0, 135.1, 143.2, 143.3, 143.4, 145.3, 148.6, 150.7, 151.8, 159.1, 169.4 (COCH$_3$) ppm.

1-[3-(2-Methyl-5-nitro-6-phenylpyridin-3-yl)-5-(3-nitrophenyl)-4,5-dihydro-1Hpyrazol-1-yl]ethan-1-one (9d, C$_{23}$H$_{19}$N$_5$O$_6$) Beige crystals; m.p.: 181-182 °C (2-PrOH); yield: 171 mg (77%); IR (KBr): = 1679 (C=O), 1534, 1345 (NO$_2$) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.48 (s, 3H, COCH$_3$), 3.06 (s, 3H, CH$_3$), 3.29 (dd, $^2$J = 16.8 Hz, $^3$J = 6.1 Hz, 1H, 4-CH$_2$ pyrazole), 3.96 (dd, $^2$J = 18.3 Hz, $^3$J = 12.2 Hz, 1H, 4-CH$_2$ pyrazole), 5.71 (dd, $^3$J = 12.2 Hz, $^3$J = 6.1 Hz, 1H, 5-CH pyrazole), 7.47-7.54 (m, 3H, H-3,4,5 Ph), 7.54-7.64 (m, 4H, H-2,6 Ph, H-5,6 Ar), 8.10 (br. s, 2H, H-2 Ar, H-4 pyridine), 8.18 (d, $^2$J = 7.6 Hz, 1H, H-4 Ar) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 22.0 (CH$_3$), 27.2 (COCH$_3$), 43.6 (4-CH$_2$ pyrazole), 59.0 (5-CH pyrazole), 120.6, 123.1, 124.5, 128.3 (2C Ph), 128.8 (2C Ph), 130.2 (2C Ar), 132.0 (2C Ar), 135.7, 143.0, 143.6, 148.7, 150.1, 151.7, 161.2, 169.3 (COCH$_3$) ppm.

1-[5-(4-Fluorophenyl)-3-[4-(furan-2-yl)-2-methyl-5-nitro-6-phenylpyridin-3-yl]-4,5-dihydro-1Hpyrazol-1-yl]ethan-1-one (8e, C$_{27}$H$_{21}$FN$_4$O$_4$) Beige crystals; m.p.: 181-183 °C (2-PrOH); yield: 157 mg (65%); IR (KBr): = 1667 (C=O), 1535, 1345 (NO$_2$) cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 2.38 (s, 3H, COCH$_3$), 2.53 (dd, $^2$J = 18.3 Hz, $^3$J = 4.5 Hz, 1H, 4-CH$_2$ pyrazole), 2.73 (s, 3H, CH$_3$), 3.27 (dd, $^2$J = 18.3 Hz, $^3$J = 12.2 Hz, 1H, 4-CH$_2$ pyrazole), 5.56 (dd, $^3$J = 12.2 Hz, $^3$J = 4.5 Hz, 1H, 5-CH pyrazole), 6.40 (br. s, 1H, H-4 furan), 6.64 (d, $^2$J = 4.5 Hz, 1H, H-3 furan), 7.04 (t, $^2$J = 9.1 Hz, 2H, H-3,5 Ar), 7.11-7.15 (m, 2H, H-2,6 Ar), 7.26 (br. s, 1H, H-5 furan), 7.43-7.48 (m, 3H, H-3,4,5 Ph), 7.58-7.63 (m, 2H, H-2,6 Ph) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 21.9 (CH$_3$),
24.2 (CO\textsubscript{3}), 45.5 (4-CH\textsubscript{2} pyrazole), 59.0 (5-CH pyrazole), 112.2, 114.4, 115.8 (d, \(J_{C\text{-}F} = 22.1\) Hz, 2C Ar), 124.7, 127.1 (d, \(J_{C\text{-}F} = 8.6\) Hz, 2C Ar), 128.0 (2C Ph), 128.9 (2C Ph), 130.2, 131.0, 135.2, 136.8, 143.3, 143.4, 145.2, 150.5, 151.9, 159.1, 162.1 (d, \(J_{C\text{-}F} = 246.3\) Hz), 169.1 (CO\textsubscript{3}) ppm.

1-[5-(4-Fluorophenyl)-3-(2-methyl-5-nitro-6-phenylpyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl]ethan-1-one (9e, C\textsubscript{22}H\textsubscript{19}FN\textsubscript{4}O\textsubscript{3}) Yellow crystals; m.p.: 196-198 °C (2-PrOH); yield: 82 mg (39%); IR (KBr): = 1667 (C=O), 1511, 1409 (NO\textsubscript{2}) cm\textsuperscript{-1}; \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 2.42\) (s, 3H, COCH\textsubscript{3}), 3.03 (s, 3H, CH\textsubscript{3}), 3.21 (dd, \(J = 17.9\) Hz, \(J = 4.6\) Hz, 1H, 4-CH\textsubscript{2} pyrazole), 3.84 (dd, \(J = 17.9\) Hz, \(J = 11.9\) Hz, 1H, 4-CH\textsubscript{2} pyrazole), 5.59 (dd, \(J = 11.9\) Hz, \(J = 4.6\) Hz, 1H, 5-CH pyrazole), 6.97-7.09 (m, 2H, H-3,5 Ar), 7.15-7.23 (m, 2H, H-2,6 Ar), 7.42-7.51 (m, 3H, H-3,4,5 Ph), 7.54-7.62 (m, 2H, H-2,6 Ph), 8.07 (s, 1H, H-4 pyridine) ppm; \(^13\)C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 22.1\) (CH\textsubscript{3}), 27.1 (CO\textsubscript{3}), 43.8 (4-CH\textsubscript{2} pyrazole), 59.0 (5-CH pyrazole), 116.0 (d, \(J_{C\text{-}F} = 22.0\) Hz, 2C Ar), 124.9, 127.3 (d, \(J_{C\text{-}F} = 7.6\) Hz, 2C Ar), 128.3 (2C Ph), 128.8 (2C Ph), 130.1, 131.9, 135.8, 136.9, 143.7, 150.2, 151.5, 161.1, 162.3 (d, \(J_{C\text{-}F} = 244.4\) Hz), 169.1 (CO\textsubscript{3}) ppm.

**Declarations**

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Table

Table 1 Yields of compounds 6-9
| Comp. | Ar | 6, R = H | 7, R = H | 8, R = H | 9, R = H | Yield (%) |
|-------|----|----------|----------|----------|----------|-----------|
| a     | ![Ar](image) | 92       | 96       | 59       | 48       |
| b     | ![Ar](image) | 94       | 71       | 30       | 30       |
| c     | ![Ar](image) | 95       | 71       | 47       | 83       |
| d     | ![Ar](image) | 98       | 59       | 50       | 77       |
| e     | ![Ar](image) | 99       | 80       | 65       | 39       |