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An expedient, one-pot, stepwise sequential approach for the regioselective synthesis of pyrazolines

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Abstract

An efficient approach for the synthesis of pyrazoline/pyrazole-tethered pyridinyl methanones is described via a one-pot, stepwise, sequential methodology using chalcones and pyridine-4-carbohydrazide as substrates through a Michael addition followed by cyclization. The reaction proceeds via a catalyst-, solvent-, work-up-, and column-chromatography-free method under melt conditions to provide the pyrazolines in short reaction times with high atom efficiency.

Keywords

chalcones, domino cyclization, ısoniazid, Michael addition, pyrazoline

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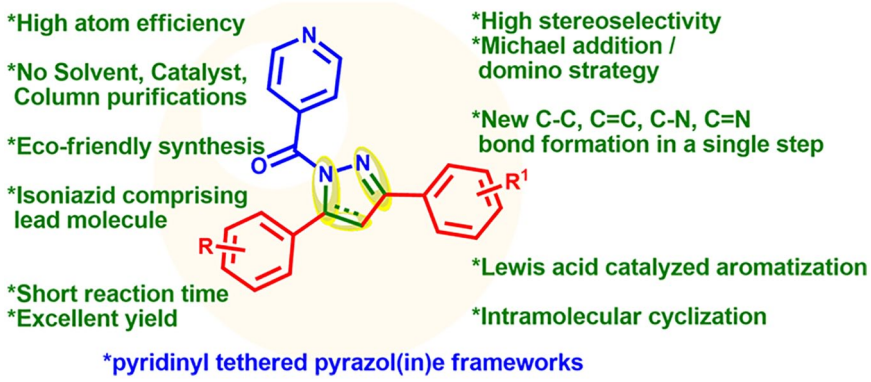
An efficient construction of pyrazoline-based pyridinyl frameworks through Michael addition mediated domino cyclization of chalcones with hydrazides. The two-step procedure generates four new C–C, C=C, C–N, and C=N bonds with regioselectivity and high atom efficiency in excellent yields. Interestingly, the accomplishment of this reaction under melt condition, the catalyst-, solvent-free synthesis in short time provided excellent yields is highly impressive.



Introduction

The synthesis of nitrogen-containing heterocyclic molecules through catalyst-, solvent-, and column-chromatography-free conditions via melt-mediated reactions[1] in the solid state is very useful.[2,3] Chalcones and pyridine-4-carbohydrazide (known as isoniazid) possess significant medicinal properties[4,5] and isoniazid is a valuable drug for tuberculosis (TB).[6] Pyrazoles exhibit a range of potent activities such as antibacterial, antifungal,[7] antidiabetic,[8] and anti-inflammatory[9] behavior, and are also active against many mycobacteria.[10,11] Examples of biologically active chalcones, pyridine-4-carbohydrazides, and pyrazoline/pyrazole motifs[12–15] are shown in Figure 1. α,β-Unsaturated

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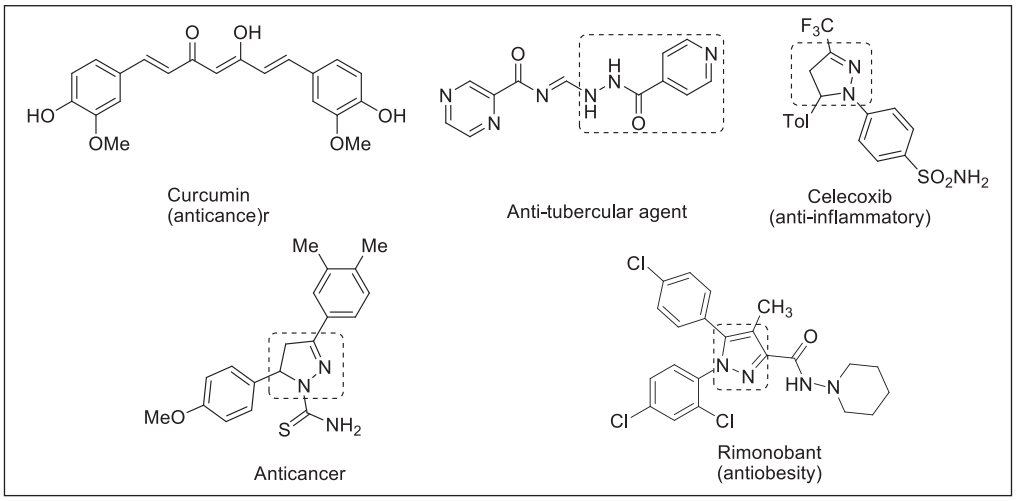


Figure 1. Representative examples of chalcone-, isoniazid-, pyrazoline- and pyrazole unit comprising potential molecules.

carbonyl compounds, such as chalcones, are particularly useful for their medicinal applications due to their easy synthesis and wide-ranging pharmacological applications against many human diseases such as TB,[16] cancer, and HIV.[17,18] Significantly, the design of new drugs containing diverse pharmacophores in a single molecular scaffold may lead to new hybrid compounds with interesting biological profiles. By implementing this strategy, several research groups have developed numerous hybrid molecules by coupling chalcones with various bioactive molecules.[19–22] Based on this approach, we have constructed pyrazolyl-tethered (pyridin-4-yl)methanones that have both pyridinyl and pyrazolyl motifs in a single molecular framework that may have biological significance.[23]

Thus, we envisaged synthesizing the pyrazole-based compounds by a Michael addition initiated domino cyclization. In continuation of our preliminary research studies[24–27] and inspired by the efficient synthetic protocol accomplished by the Bakthadoss Research Group involving a solid-state melt reaction (SSMR),[2,3] we have utilized the aforementioned SSMR protocol for the synthesis of pyrazole-containing molecules.

Results and discussion

Thus, we combined the substituted chalcone **3** (1 mmol) synthesized from various aldehydes and acetophenones and isoniazid **4a** (1 mmol) through a Michael addition mediated cyclization.

Chalcones **3a–l** and isoniazid **4a** were ground thoroughly in a round-bottom flask and allowed to melt at 160 to 180 °C for 30 to 45 min; this procedure led to the required products **5a–l** in excellent yields (92%–98%). The isolated yields of the products are given in Table 1. In order to extend the substrate scope of the reaction, we also reacted isoniazid (**4a**) in a melt with *o*-benzylated chalcone **3m** at 170 °C for 45 min, which led to the pyrazoline **5m** in 93% yield (Scheme 1).

We then decided to broaden the ring size, so we reacted *o*-phenylenediamine (OPDA) (**4b**) in a melt at 200 °C for 45 min with **3m**. Unfortunately, the reaction was unsuccessful in providing the expected product **7** and the imidazole **6** was obtained instead (Scheme 1). An earlier report[28] revealed that the use of *meta-/para*-substituted chalcones gives benzodiazepines rather than imidazoles.[29] Owing to the presence of the *o*-benzyl unit in chalcone **3m**, steric hindrance may be the reason for the failure to obtain benzodiazepine **7**.

In order to extend the applicability of the reaction, the pyrazolines **5g–l** were treated with $FeCl_3$ in acetic acid which resulted in oxidation leading to the corresponding pyrazoles **8a–f** (Table 2).

The structures of the compounds **5m** and **6** were confirmed by single-crystal X-ray analysis (Figure 2). The spatial orientations of the substituents present on the pyrazole ring were established from the single-crystal X-ray diffraction (XRD) analysis of these pyrazoline and imidazole derivatives (**5m** and **6**), and their Cambridge Crystallographic Data Centre (CCDC) numbers are 1586980 and 1586981, respectively.

Conclusion

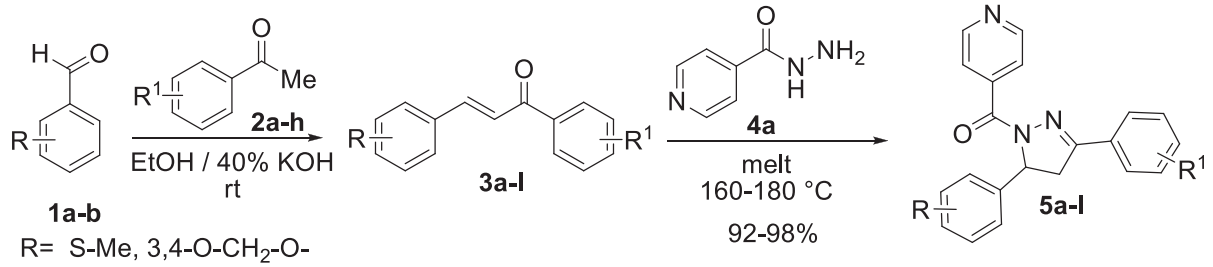
We have successfully constructed pyrazolines and pyrazoles in a one-pot, stepwise approach with high regioselectivity. Some of the notable features are as follows: (1) the reaction creates new C–C, C=C, C–N, and C=N bonds in a unique fashion through a domino process that includes a Michael addition followed by a cyclization; (2) the reactions proceed under eco-friendly, solvent-free reaction conditions via a work-up-, catalyst-, chromatography-free method that provides excellent yields in short reaction times; (3) this protocol provides the opportunity for the synthesis of libraries of trisubstituted pyrazol(in)es with high atom efficiency (>96%); and (4) the structures of the newly synthesized molecules have been characterized by IR, NMR, and mass spectrometry, and by single-crystal X-ray analyses. These pyrazoline/pyrazole products are currently undergoing biological screening.

Experimental

Materials and methods

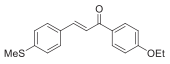
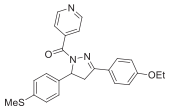
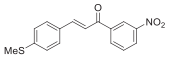
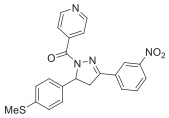
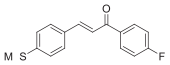
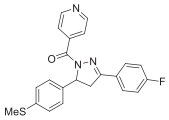
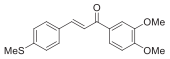
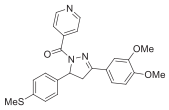
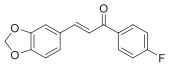
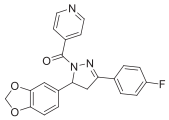
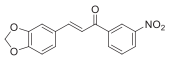
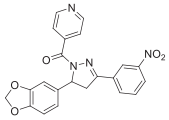
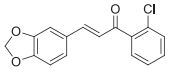
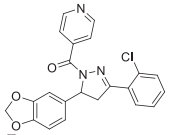
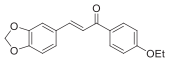
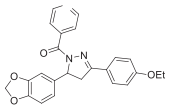
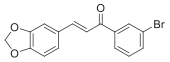
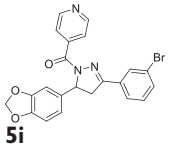
All reagents and chemicals were obtained from Sigma-Aldrich (St. Louis, MO, USA) and Merck (Bangalore, Karnataka, India).

Table 1. Synthesis of pyrazolines **5a–l** from chalcone derivatives **3a–l**.



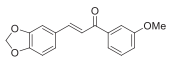
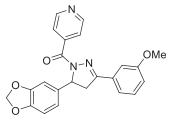
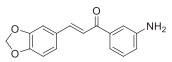
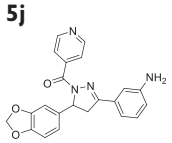
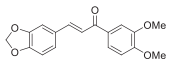
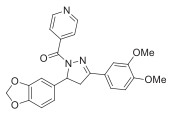
R= S-Me, 3,4-O-CH_2-O-

R_1= 2-Cl, 4-F, 4-NO_2, 3-Br, 3-NH_2, 3-OMe, 4-OEt, 3,4-$(OMe)_2$

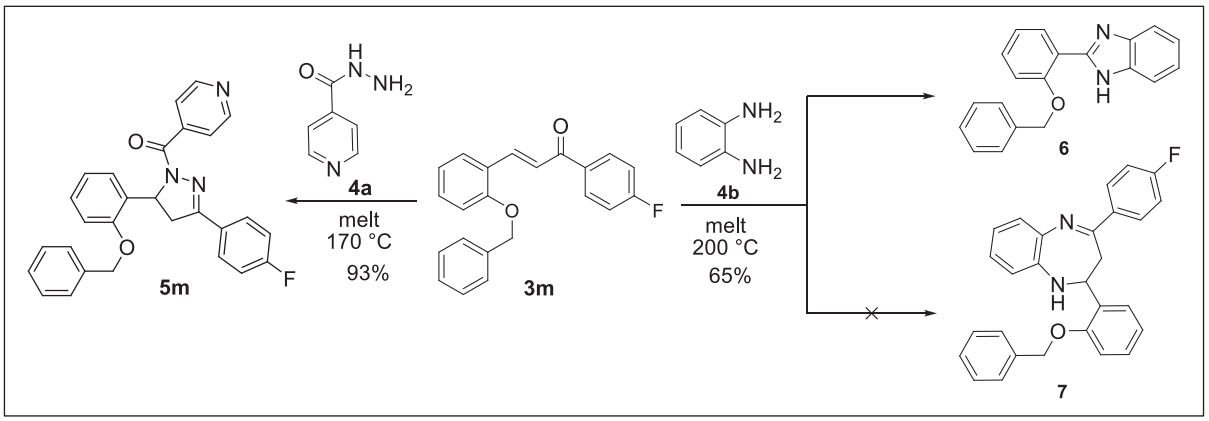
Entry	Chalcone	Pyrazoline product[a]	Yield (%)[b]
1	 **3a**	 **5a**	96
2	 **3b**	 **5b**	92
3	 **3c**	 **5c**	94
4	 **3d**	 **5d**	96
5	 **3e**	 **5e**	92
6	 **3f**	 **5f**	90
7	 **3g**	 **5g**	95
8	 **3h**	 **5h**	97
9	 **3i**	 **5i**	96

(Continued)

Table 1. (Continued)

Entry	Chalcone	Pyrazoline product[a]	Yield (%)[b]
10	 **3j**	 **5j**	95
11	 **3k**	 **5k**	96
12	 **3l**	 **5l**	98

[a]All products were fully characterized by spectroscopic analysis.
[b]Isolated yields of pure products.



Scheme 1. Synthesis of **5m** and **6** from **3m**.

Physical and chemical characterization

A Perkin Elmer fourier transform infrared spectroscopy (FTIR) (4000-400 cm^{-1}) instrument was used to record the IR spectra as KBr pellets. ^{1}H and ^{13}C NMR spectra were obtained at 500 and 125 MHz (BRUKER AV-III, fourier-transform nuclear magnetic resonance (FT-NMR) spectrometer) using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard. The DEPT135 spectrum was recorded in a standard manner ($\theta = 135$ pulse program). Mass spectra were recorded on a Thermo Scientific Orbitrap Elite mass spectrometer. The XRD studies were conducted on a Bruker Kappa APE XII diffractometer. Thin-layer chromatography (TLC) was performed using pre-coated silica gel sheets, and the spots were observed by ultraviolet (UV) and iodine vapor absorption.

Synthesis of chalcones **3a**

The aldehyde (1 mmol) and substituted acetophenone (1 mmol) were dissolved in ethanol (20 mL) in the presence of 40% NaOH. The reaction mixture was stirred at room temperature for 4 h and neutralized with 1N HCl. The resulting precipitate was filtered, and the crude sample was washed with hot ethanol and dried.[24,25]

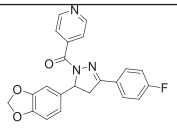
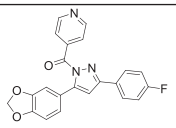
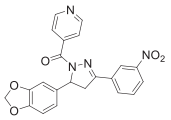
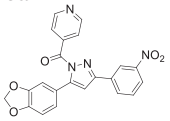
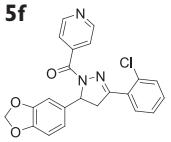
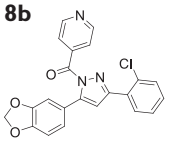
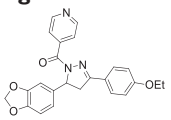
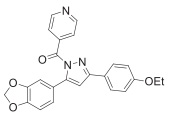
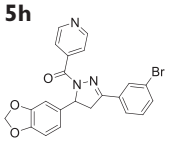
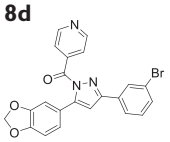
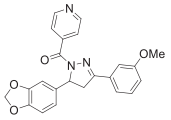
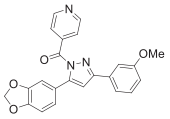
Synthesis of isoniazid-containing pyrazoline **5a***:* Typical procedure

A mixture of substituted chalcone **3a** (0.298 g, 1 mmole) and pyridine-4-carboxylic acid hydrazide **4** (0.137 g, 1 mmol) in a round-bottomed flask was ground thoroughly to make a homogeneous solid that was allowed to melt at 160 °C for 30 min. After cooling, the crude mass was washed with EtOAc/hexane mixture (1:3) to give the product **5a** in 96% yield.[30]

Synthesis of isoniazid-containing pyrazole **8a**

A solution of the pyrazoline **5e** (1 mmol), ferric chloride (0.2 mmol, 2 mol%), and acetic acid (10 mL) was stirred at room temperature. The formation of the pyrazole was monitored by TLC, and the reaction mixture was quenched with aqueous $NaHCO_3$ (30 mL). The reaction mixture was then extracted with $CHCl_3$. The organic phase was dried and

Table 2. Synthesis of pyrazole derivatives **8a–f** from pyrazolines **5e–j**.

Entry	Pyrazoline	Pyrazole product[a]	Time (h)	Yield (%)[b]
1	 **5e**	 **8a**	4	81
2	 **5f**	 **8b**	4	82
3	 **5g**	 **8c**	3	82
4	 **5h**	 **8d**	2	85
5	 **5i**	 **8e**	3	83
6	 **5j**	 **8f**	2	85

[a]All products were fully characterized by spectroscopic analysis.
[b]Isolated yields of pure products.

concentrated under reduced pressure to provide the pyrazole[31] **8a** in good yield.

*(3-(4-ethoxyphenyl)-5-(4-(methylthio)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (***5a***).* Mp = 145–146 °C; R_f = 0.40 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3042, 2974, 2924, 1649; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 6.1 Hz, 2H), 7.86 (d, *J* = 6.0 Hz, 2H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 9.8 Hz, 2H), 7.26 (d, *J* = 2.2 Hz, 2H), 6.97 – 6.92 (m, 2H), 5.75 (dd, $J_{1,2}$ = 11.6, 4.7 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.80 (dd, $J_{1,2}$ = 17.6, 11.6 Hz, 1H), 3.23 (dd, $J_{1,2}$ = 14.0, 3.6 Hz, 1H), 2.48 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.17, 156.74, 149.67, 141.81, 138.26, 138.06, 128.52, 127.19, 126.35, 123.75, 122.53, 117.82, 114.76, 63.71, 60.76, 41.68, 15.94, 14.69; HRMS (ESI): m/z $[M]^+$ calculated for $C_{24}H_{23}N_3O_2S$: 417.1511; found: 417.1540.

*(5-(4-(methylthio)phenyl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (***5b***).* Mp = 153–154 °C; R_f = 0.27 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3043, 2919, 1663, 1532; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, *J* = 6.0 Hz, 2H), 8.44 (t, *J* = 1.8 Hz, 1H), 8.32 (ddd, $J_{1,2,3}$ = 8.2, 2.1, 0.8 Hz, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 5.7 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 9.6 Hz, 4H), 5.84 (dd, $J_{1,2}$ = 11.8, 5.0 Hz, 1H), 3.91 (dd, $J_{1,2}$ = 17.9, 11.8 Hz, 1H), 3.33 (dd, $J_{1,2}$ = 17.9, 5.1 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.08, 154.03, 148.62, 142.54, 138.99, 137.18, 132.53, 132.21, 130.14, 130.06, 127.19, 126.25, 125.26, 124.02, 121.71, 61.32, 41.59, 15.71; HRMS (ESI): m/z $[M]+^1$ calculated for $C_{22}H_{18}N_4O_3S$: 418.1100; found: 419.1187.

*(3-(4-fluorophenyl)-5-(4-(methylthio)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (***5c***).* Mp = 156–157 °C; R_f = 0.44 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}):

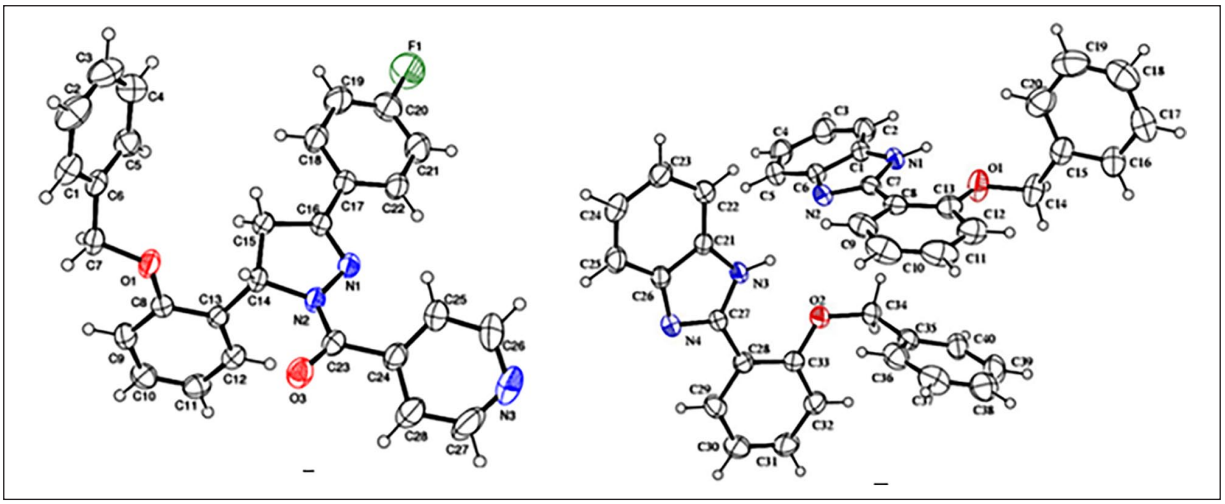


Figure 2. ORTEP diagrams of compounds **5m** and **6**.

3034, 2993, 2946, 2921, 1644, 1328; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 5.8 Hz, 2H), 7.86 (d, J = 5.8 Hz, 2H), 7.73 – 7.68 (m, 2H), 7.29 – 7.23 (m, 4H), 7.16 – 7.11 (m, 2H), 5.77 (dd, $J_{1,2}$ = 11.7, 4.9 Hz, 1H), 3.82 (dd, $J_{1,2}$ = 17.8, 11.7 Hz, 1H), 3.24 (dd, $J_{1,2}$ = 17.8, 4.9 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.28 ($^1J_{C-F}$ = 253.2 Hz), 163.98, 163.28, 155.11, 149.07, 142.30, 138.59, 137.75, 128.93 ($^3J_{C-F}$ = 8.8 Hz),127.16, 127.05 ($^4J_{C-F}$ = 2.52 Hz), 126.31, 123.89, 116.12 ($^2J_{C-F}$ = 22.6 Hz), 116.03, 60.99, 41.72; HRMS (ESI): m/z $[M]^+$ calculated for $C_{22}H_{18}FN_3OS$: 391.1155; found: 391.1180.

(3-(3,4-dimethoxyphenyl)-5-(4-(methylthio)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5d**). Mp = 140–141 °C; R_f = 0.18 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3063, 2922, 1733, 1647; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, J = 4.8 Hz, 2H), 8.01 (d, J = 5.5 Hz, 2H), 7.28 (dd, $J_{1,2}$ = 7.1, 3.9 Hz, 5H), 7.20 (dd, $J_{1,2}$ = 8.3, 1.9 Hz, 1H), 6.91 (dd, $J_{1,2}$ = 8.4, 2.0 Hz, 1H), 5.76 (dd, $J_{1,2}$ = 11.6, 4.7 Hz, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.84 (dd, $J_{1,2}$ = 17.7, 11.6 Hz, 1H), 3.27 (dd, $J_{1,2}$ = 17.7, 4.7 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.93, 157.74, 151.83, 149.34, 148.99, 142.66, 141.22, 137.69, 127.16, 126.36, 124.72, 123.35, 120.99, 110.84, 108.90, 60.94, 55.99, 55.95, 41.78, 15.76; HRMS (ESI): m/z $[M]^+$ calculated for $C_{24}H_{23}N_3O_3S$: 433.1460; found: 433.1490.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5e**). Mp = 143–144 °C; R_f = 0.46 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3065, 3043, 2945, 2922, 1749, 1646, 1332; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, J = 5.4 Hz, 2H), 7.83 (d, J = 5.8 Hz, 2H), 7.69 (dd, $J_{1,2}$ = 8.7, 5.3 Hz, 2H), 7.12 (t, J = 8.5 Hz, 2H), 6.83 (dd, $J_{1,2}$ = 8.0, 1.1 Hz, 1H), 6.78 (d, J = 7.9 Hz, 2H), 5.93 (s, 2H), 5.72 (dd, $J_{1,2}$ = 11.6, 4.8 Hz, 1H), 3.78 (dd, $J_{1,2}$ = 17.8, 11.7 Hz, 1H), 3.21 (dd, $J_{1,2}$ = 17.8, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.24 ($^1J_{C-F}$ = 253.2 Hz), 164.19, 155.00, 149.49, 148.29, 147.38, 141.90, 135.05, 128.91 ($^3J_{C-F}$ = 8.8 Hz), 127.12 ($^4J_{C-F}$ = 2.5 Hz), 123.72, 119.36, 116.26, 116.08 ($^2J_{C-F}$ = 22.6 Hz), 108.65, 106.00, 101.26, 61.18, 41.85; HRMS (ESI): m/z $[M]+^1$ calculated for $C_{22}H_{16}FN_3O_3$: 389.1176; found: 390.1251.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5f**). Mp = 132–133 °C; R_f = 0.29 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3055, 3028, 2928, 1770, 1644, 1527; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, J = 5.5 Hz, 2H), 8.43 (s, 1H), 8.35 – 8.30 (m, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 5.0 Hz, 2H), 7.66 (t, J = 8.0 Hz, 1H), 6.87 – 6.76 (m, 3H), 5.97 (s, 2H), 5.80 (dd, $J_{1,2}$ = 11.7, 4.9 Hz, 1H), 3.89 (dd, $J_{1,2}$ = 17.9, 11.8 Hz, 1H), 3.32 (dd, $J_{1,2}$ = 17.9, 5.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.10, 154.00, 148.62, 148.43, 147.62, 142.58, 134.40, 132.55, 132.19, 130.25, 130.05, 125.25, 124.02, 121.71, 119.41, 108.78, 105.91, 101.36, 61.53, 41.74; HRMS (ESI): m/z $[M]+^1$ calculated for $C_{22}H_{16}N_4O_5$: 416.1121; found: 417.1198.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5g**). Mp = 124–125 °C; R_f = 0.46 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3031, 2919, 1713, 1644; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (d, J = 4.7 Hz, 2H), 7.88 (d, J = 5.8 Hz, 2H), 7.65 (d, J = 7.7 Hz, 1H), 7.44 (dd, $J_{1,2}$ = 7.9, 1.2 Hz, 1H), 7.35 (td, J = 7.7, 1.8 Hz, 1H), 7.33 – 7.28 (m, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.81 – 6.77 (m, 2H), 5.93 (s, 2H), 5.71 (dd, $J_{1,2}$ = 11.6, 4.6 Hz, 1H), 3.98 (dd, $J_{1,2}$ = 18.3, 11.7 Hz, 1H), 3.39 (dd, $J_{1,2}$ = 18.3, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.18, 155.64, 148.76, 148.27, 147.40, 142.22, 134.82, 133.04, 131.33, 131.16, 130.44, 129.86, 127.12, 124.08, 119.44, 108.64, 106.07, 101.25, 61.29, 44.52; HRMS (ESI): m/z $[M]^+$ calculated for $C_{22}H_{16}ClN_3O_3$: 405.0880; found: 405.0910.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(4-ethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5h**). Mp = 129–130 °C; R_f = 0.30 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3065, 3045, 2977, 2918, 1647; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 5.9 Hz, 2H), 7.92 (d, J = 5.6 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 6.85 (dd, $J_{1,2}$

= 8.0, 1.6 Hz, 1H), 6.81 – 6.77 (m, 2H), 5.95 (s, 2H), 5.70 (dd, $J_{1,2}$ = 11.5, 4.6 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.78 (dd, $J_{1,2}$ = 17.7, 11.6 Hz, 1H), 3.22 (dd, $J_{1,2}$ = 17.7, 4.7 Hz, 1H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.55, 161.23, 156.09, 148.67, 148.26, 147.32, 142.85, 135.17, 128.54, 124.15, 123.10, 119.42, 114.77, 108.63, 106.06, 101.23, 63.71, 61.00, 41.85, 14.68; HRMS (ESI): m/z [M]+^{1} calculated for $C_{24}H_{21}N_3O_4$: 415.1532; found: 416.1612.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(3-bromophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5i**). Mp = 167–168 °C; R_f = 0.38 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3027, 3055, 2918, 1778, 1645; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (d, J = 5.6 Hz, 2H), 7.90 (d, J = 5.6 Hz, 2H), 7.81 (s, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.60 (ddd, $J_{1,2,3}$ = 7.9, 1.8, 0.8 Hz, 1H), 7.33 (t, J = 7.9 Hz, 1H), 6.86 – 6.76 (m, 3H), 5.96 (s, 2H), 5.74 (dd, $J_{1,2}$ = 11.7, 4.8 Hz, 1H), 3.80 (dd, $J_{1,2}$ = 17.9, 11.7 Hz, 1H), 3.23 (dd, $J_{1,2}$ = 17.9, 4.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.88, 154.88, 148.51, 148.36, 147.50, 142.79, 134.68, 133.80, 132.75, 130.42, 129.78, 125.37, 124.11, 123.06, 119.40, 108.71, 105.97, 101.30, 61.26, 41.71; HRMS (ESI): m/z [M]+^{1} calculated for $C_{22}H_{16}BrN_3O_3$: 449.0375; found: 450.0454.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(3-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5j**). Mp = 141–142 °C; R_f = 0.29 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3063, 2912, 1731, 1643; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, J = 5.9 Hz, 2H), 7.86 (d, J = 6.0 Hz, 2H), 7.35 (t, J = 7.9 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.01 (dd, $J_{1,2}$ = 8.1, 2.5 Hz, 1H), 6.84 (dd, $J_{1,2}$ = 8.0, 1.3 Hz, 1H), 6.81 – 6.77 (m, 2H), 5.94 (s, 2H), 5.71 (dd, $J_{1,2}$ = 11.6, 4.7 Hz, 1H), 3.84 (s, 3H), 3.79 (dd, $J_{1,2}$ = 17.8, 11.7 Hz, 1H), 3.22 (dd, $J_{1,2}$ = 17.8, 4.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.13, 159.83, 156.03, 149.27, 148.27, 147.36, 142.05, 135.08, 132.11, 129.94, 123.88, 123.10, 119.46, 116.44, 112.18, 108.64, 106.05, 101.24, 61.14, 55.37, 41.87; HRMS (ESI): m/z [M]$^+$ calculated for $C_{23}H_{19}N_3O_4$: 401.1376; found: 401.1405.

(3-(3-aminophenyl)-5-(benzo[d][1,3]dioxol-5-yl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5k**). Mp = 181–182 °C; R_f = 0.11 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3327, 3027, 2987, 2922, 1649; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, J = 5.9 Hz, 2H), 7.85 (d, J = 5.5 Hz, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.84 (dd, $J_{1,2}$ = 8.0, 1.5 Hz, 1H), 6.80 – 6.77 (m, 3H), 5.95 (s, 2H), 5.69 (dd, $J_{1,2}$ = 11.6, 4.7 Hz, 1H), 3.76 (dd, $J_{1,2}$ = 17.8, 11.6 Hz, 1H), 3.28 (s, 2H), 3.20 (dd, $J_{1,2}$ = 17.8, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.11, 156.38, 149.40, 148.25, 147.32, 146.79, 142.09, 135.16, 131.73, 129.77, 123.83, 119.39, 117.72, 117.44, 112.51, 108.62, 106.06, 101.23, 61.03, 41.88; HRMS (ESI): m/z [M]$^+$ calculated for $C_{22}H_{18}N_4O_3$: 386.1379; found: 386.1408.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5l**). Mp = 122–123 °C; R_f = 0.14 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3003, 2955, 2925, 1638, 1332; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, J = 5.9 Hz, 2H), 7.99 (d, J = 6.0 Hz, 2H), 7.29 (s, 1H), 7.19 (dd, J = 8.3, 2.0 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.86 (dd, $J_{1,2}$ = 8.0, 1.6 Hz, 1H), 6.81 (s, 1H), 6.80 – 6.78 (m, 1H), 5.96 (s, 1H), 5.72 (dd, $J_{1,2}$ = 11.5, 4.6 Hz, 1H), 3.95 (s, 1H), 3.91 (s, 1H), 3.81 (dd, $J_{1,2}$ = 17.7, 11.6 Hz, 1H), 3.25 (dd, $J_{1,2}$ = 17.7, 4.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.02, 156.50, 151.80, 149.32, 148.32, 147.43, 147.35, 144.18, 134.90, 124.64, 123.40, 120.97, 119.47, 110.83, 108.89, 108.67, 106.03, 101.28, 77.28, 77.02, 76.77, 61.14, 56.04, 55.98, 41.92; m/z [M]$^+$ calculated for $C_{24}H_{21}N_3O_5$: 431.1481; found: 431.1512.

(5-(2-(benzyloxy)phenyl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**5m**). Mp = 148–149 °C; R_f = 0.45 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3057, 2983, 2919, 1725, 1607; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 5.9 Hz, 2H), 7.68 (dd, $J_{1,2}$ = 4.5, 1.6 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.29 – 7.26 (m, 2H), 7.24 – 7.16 (m, 5H), 7.02 – 6.87 (m, 4H), 5.92 (dd, $J_{1,2}$ = 11.8, 5.5 Hz, 1H), 5.01 (s, 2H), 3.63 (dd, $J_{1,2}$ = 17.6, 11.9 Hz, 1H), 3.13 (dd, $J_{1,2}$ = 17.6, 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.18, 163.01 ($^1J_{C-F}$ = 252.5 Hz), 154.60, 154.29, 148.60, 140.90, 135.43, 128.15, 127.73 ($^3J_{C-F}$ = 8.0 Hz), 127.48, 127.32, 127.09, 126.67, 126.43, 126.37 ($^4J_{C-F}$ = 6.0 Hz), 122.72, 120.04, 114.79 ($^2J_{C-F}$ = 22.2 Hz), 111.22, 69.29, 57.34, 39.51; HRMS (ESI): m/z [M]$^+$ calculated for $C_{28}H_{22}FN_3O_2$: 451.1696; found: 451.1422.

2-(2-(benzyloxy)phenyl)-1H-benzo[d]imidazole (**6**). Mp = 142–144 °C; R_f = 0.35 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 1346, 1680, 2998, 3174; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.20 (s, 2H), 7.04 – 8.61 (m, 13H), 10.63 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 71.37, 112.96, 118.31, 122.09, 122.56, 127.84, 128.87, 129.11, 130.23, 131.22, 135.99, 149.79, 156.13; HRMS (ESI): m/z [M]+^{1} calculated for $C_{20}H_{16}N_2O$: 300.1263; found: 301.1408.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**8a**). Mp = 112–113 °C; R_f = 0.28 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3034, 2922, 1734, 1635; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 – 6.77 (m, 12H), 5.93 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.31 ($^1J_{C-F}$ = 254.5 Hz), 164.21, 155.14, 149.58, 148.40, 147.45, 145.51, 142.01, 135.16, 128.93 ($^3J_{C-F}$ = 8.8 Hz), 127.13 ($^4J_{C-F}$ = 3.7 Hz), 123.91, 119.49, 116.08 ($^1J_{C-F}$ = 21.4 Hz), 108.87, 106.19, 103.71, 101.49; HRMS (ESI): m/z [M]$^+$ calculated for $C_{22}H_{14}FN_3O_3$: 387.1019; found: 387.1009.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(3-nitrophenyl)-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**8b**). Mp = 126–127 °C; R_f = 0.24 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3212, 3116, 3036, 2922, 2854, 1649, 1595; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 – 6.93 (m, 12H), 5.97 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.47, 154.66, 148.99, 148.51, 147.85, 144.93, 142.79, 132.68, 134.52, 132.30, 130.25, 125.46, 124.28, 123.47, 121.87, 119.64, 109.23, 106.65, 104.06, 101.96; HRMS (ESI): m/z [M]$^+$ calculated for $C_{22}H_{14}N_4O_5$: 414.0964; found: 414.0904.

(5-(benzo[d][1,3]dioxol-5-yl)-3-(2-chlorophenyl)-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (**8c**). Mp = 130–131 °C; R_f = 0.24 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3058, 3020,

2959, 2923, 1724, 1642; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 – 7.05 (m, 12H), 5.93 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.37, 155.82, 148.90, 148.35, 147.48, 145.97, 142.30, 134.70, 133.20, 131.44, 131.22, 130.53, 129.92, 127.46, 124.30, 119.64, 108.79, 106.21, 104.04, 101.36; HRMS (ESI): m/z $[M]^+$ calculated for $C_{22}H_{14}ClN_3O_3$: 403.0724; found: 403.2350.

*(5-(benzo[d][1,3]dioxol-5-yl)-3-(4-ethoxyphenyl)-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (***8d***).* Mp = 116–117 °C; R_f = 0.45 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3236, 3064, 3033, 2919, 2851, 1782, 1611; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 – 6.91 (m, 12H), 5.95 (s, 2H), 4.10 (q, J = 10.0 Hz, 2H), 1.46 (t, J = 5.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.51, 161.23, 156.21, 148.92, 148.15, 147.49, 145.39, 142.69, 135.17, 128.79, 124.33, 123.29, 119.65, 115.02, 108.91, 106.34, 104.16, 101.42, 64.08, 15.17; HRMS (ESI): m/z $[M]^+$ calculated for $C_{24}H_{19}N_3O_4$: 413.1376; found: 413.2657.

*(5-(benzo[d][1,3]dioxol-5-yl)-3-(3-bromophenyl)-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (***8e***).* Mp = 135–136 °C; R_f = 0.41 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3063, 2957, 2922, 1684, 1611; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 – 6.87 (m, 12H), 5.96 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.10, 155.07, 148.62, 148.43, 147.46, 144.92, 142.85, 134.90, 133.92, 132.94, 130.62, 129.57, 125.51, 124.22, 123.25, 119.58, 108.84, 106.23, 104.48, 101.47; HRMS (ESI): m/z $[M]^+$ calculated for $C_{22}H_{14}BrN_3O_3$: 447.0219; found: 448.1430.

*(5-(benzo[d][1,3]dioxol-5-yl)-3-(3-methoxyphenyl)-1H-pyrazol-1-yl)(pyridin-4-yl)methanone (***8f***).* Mp = 108–109 °C; R_f = 0.30 (hexane/EtOAc, 1:1); IR (KBr, cm^{-1}): 3062, 2947, 2928, 1681, 1614; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 – 6.85 (m, 12H), 5.94 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.21, 159.90, 156.13, 149.32, 148.36, 147.42, 145.26, 142.13, 135.13, 132.20, 130.00, 123.99, 119.56, 119.34, 116.54, 112.29, 108.74, 106.16, 104.27, 101.36, 55.37; HRMS (ESI): m/z $[M]^+$ calculated for $C_{23}H_{17}N_3O_4$: 399.1219; found: 399.1418. The ^{1}H and ^{13}C NMR spectra, MS data for **5a**-**m**, **6**, **8a**-**f** and ORTEP diagrams of **5m** and **6** can be presented in supplemental material respectively.

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Supplemental material

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