Organic & Biomolecular Chemistry

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DOI: 10.1039/C9OB00701F

ARTICLE

Synthesis of pyrazolylvinyl ketones from furan derivatives

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

A new protocol for the synthesis of pyrazol-5-ylvinyl ketones, e. g. pyrazole-chalcones, employing furfuryl ketones as a triketone equivalent, has been developed. The reaction occurs under mild conditions and does not require the use of expensive materials. Other important benefits include simplicity and atom efficiency of this approach.

Introduction

The pyrazole ring is an important structural subunit in various bioactive compounds including many marketed drugs.[1] Pyrazole derivatives demonstrate potent anticancer activity by the inhibition of topoisomerase II,[2] tubulin,[3] mTOR,[4] proto-oncogene B-RAF,[5] cyclin-dependent kinases (CDK),[6] phosphatidylinositide 3-kinases (PI3K),[7] anaplastic lymphoma kinases (ALK),[8] and other pharmacologically relevant targets.[9] On the other hand, heterocyclic chalcones turned out to be privileged scaffolds with a great pharmacological potential in medicinal chemistry.[10] For example, pyrazole-chalcones bearing a pyrazole ring instead of phenyl B-ring and an α,β-unsaturated ketone motif, represent promising anticancer[11] and antitumor agents (Figure 1).[12] Furthermore, they can serve as precursors of valuable linked pyrazoles.[11b,13]

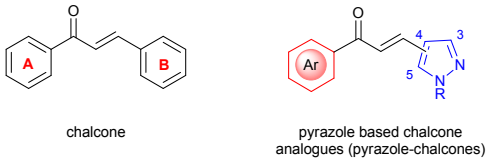

Fig. 1 Structure of chalcone and pyrazole-chalcones.

A common route for the synthesis of pyrazole-chalcones is the Claisen–Schmidt condensation of corresponding pyrazole aldehydes.[14,15] However, the application of this method for the preparation of pyrazol-5-yl derivatives has been a long time limited due to the synthetic inaccessibility of pyrazol-5-yl carbaldehydes. In 2017, the first pyrazol-5-ylvinyl ketones, including chalcone analogues, were reported by Kamal et al. (Figure 2). These compounds induced cell cycle arrest, mitochondrial membrane depolarization and apoptosis in a human breast cancer cell line (MCF-7) in a nanomolar range and can be considered as potential lead structures in the development of tailored cancer therapeutics.[16]

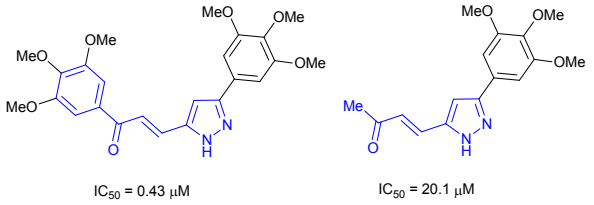

Fig. 2 Pyrazol-5-ylvinyl ketones possessing strong activity against breast cancer cell line MCF-7.

The reported synthetic sequence included the Knorr pyrazole synthesis, reduction of 1*H*-pyrazole-5-carboxylates to give pyrazol-5-yl methanols, their oxidation to corresponding aldehydes, and the subsequent Claisen–Schmidt condensation (Scheme 1a). The products were obtained in 23-40% yields over 5 steps. We supposed that readily available furfuryl ketones[17] can be considered as a triketone equivalent and might serve as efficient precursors of the desired molecules (Scheme 1b). Herein, we report a new simple method for the synthesis of pyrazol-5-ylvinyl ketones, e.g. pyrazole-chalcones, from furan derivatives.

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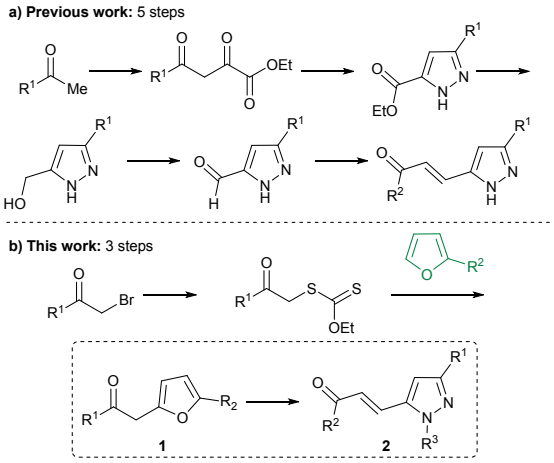
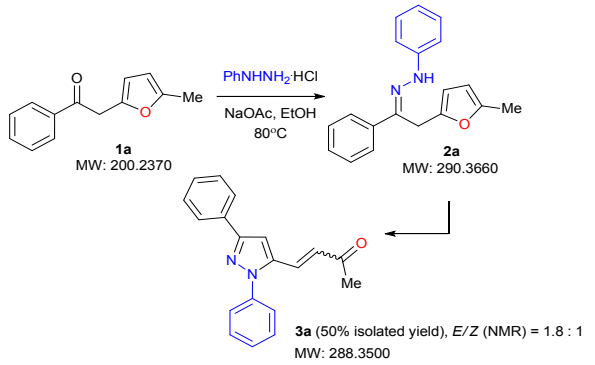
† Electronic Supplementary Information (ESI) available: complete compound characterisation data, copies of the ^{1}H and ^{13}C NMR spectra, copies of the HMBC, HSQC, COSY, and NOESY spectra, complete LC-MS data, X-Ray data. CCDC 1877820 contains the supplementary crystallographic data for this paper. See DOI: 10.1039/x0xx00000x



Scheme 1 Synthesis of pyrazol-5-ylvinyl ketones: previous approach and this work.

Results and discussion

First, we studied the reaction of easily available furfuryl ketone **1a**[17c] with phenyl hydrazine hydrochloride (Scheme 2). The solution of furfuryl ketone **1a**, phenyl hydrazine hydrochloride, and sodium acetate in ethanol was stirred at room temperature. Surprisingly, the LC-MS data of the reaction mixture in 5 min did not only indicate hydrazone **2a** along with the starting compound, but some traces of the target pyrazole **3a** as well (Figure 3a. For complete data, see SI).



Scheme 2 Model reaction. Conditions: 2 mmol of furfuryl ketone, 2 mmol of phenyl hydrazine hydrochloride, 4 mmol of sodium acetate, 5 mL of EtOH.

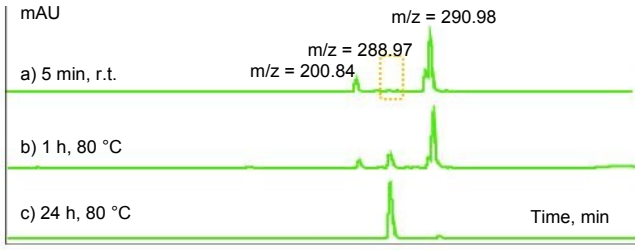


Fig. 3 LC-MS control of the reaction **1a**→**3a**: UV chromatograms (254 nm).

We supposed that the second reaction of the domino sequence **1a**→**2a**→**3a** could be affected by temperature. At 80 °C, the product **3a** was apparently formed in higher yield (Figure 3b). In 24 h, we observed the full conversion of **1a** and the formation of **3a** as a main product (Figure 3c). The use of 2 equiv of phenyl hydrazine hydrochloride did not improve the outcome of the reaction. In both experiments, with 1 equiv or 2 equiv of $PhNHNH_2{\cdot}HCl$, the yield of **3a** was 50%. Pyrazole **3a** was obtained as a mixture of (*E*)- and (*Z*)-isomers. Nevertheless, it did not require further separation, while it was quantitatively converted into the pure (*E*)-isomer under heating with iodine (Scheme 3).[18] Complete characterization was performed for the desired product (*E*)-**3a**, the overall yield of which was 50%.

To illustrate the scope of the reaction, a series of furfuryl ketones has been synthesized and subjected to the optimized reaction conditions with phenyl hydrazine hydrochloride (Scheme 3). Each product **3** was prepared in a pure (*E*)-form through *E/Z* isomerization and fully characterized (Figure 4).

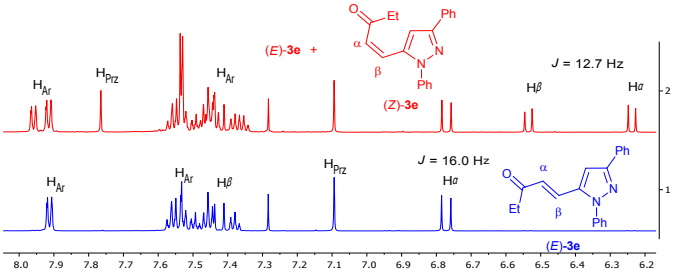


Fig. 4 Monitoring of *E/Z* Isomerization: selected sections of the ^1H NMR spectra of (*E*)-**3e** [1] and (*E,Z*)-**3e** [2] in $CDCl_3$.

The yields of pyrazoles **3** were moderate to good (37-68%) when R^2 was a phenyl group bearing a halogen or electron-neutral H atom. When R^2 was methyl or methoxy-substituted phenyl group, the corresponding pyrazoles **3d** and **3f** were obtained in 42 and 32%, respectively. Obviously, electron donating substituents reduce the electrophilicity of the carbonyl that leads to lower yields of pyrazoles **3d** and **3f**.

In respect of R^1, alkyl groups are generally more favored, but their electronic effect does not play crucial role, leading to pyrazoles **3** in comparable yields. Thus, the reaction worked well for furfuryl ketones bearing methyl, ethyl, and butyl groups. When R^1 was an aromatic phenyl group, pyrazole-chalcone **3i** was isolated in low 37%. Importantly, the reaction **1**→**3** could be performed on gram scale without detriment to the yield. The structure of the product (*E*)-**3h** was confirmed by the single-crystal X-Ray diffraction (Figure 5).

Next, the scope of hydrazines was investigated. The reaction with hydrochlorides of phenyl hydrazine, *p*-tolyl hydrazine, and *p*-methoxy phenyl hydrazine, afforded pyrazoles **3** in good yields (52-53%). The pyrazole-chalcone **3m** (R^1 = Ph) was isolated in 24% yield as a (*E*)-isomer. Interestingly, an experiment with 2-bromophenyl hydrazine hydrochloride provided hydrazone **2n** instead of an expected pyrazole, because of reduced nucleophilicity of the nitrogen and

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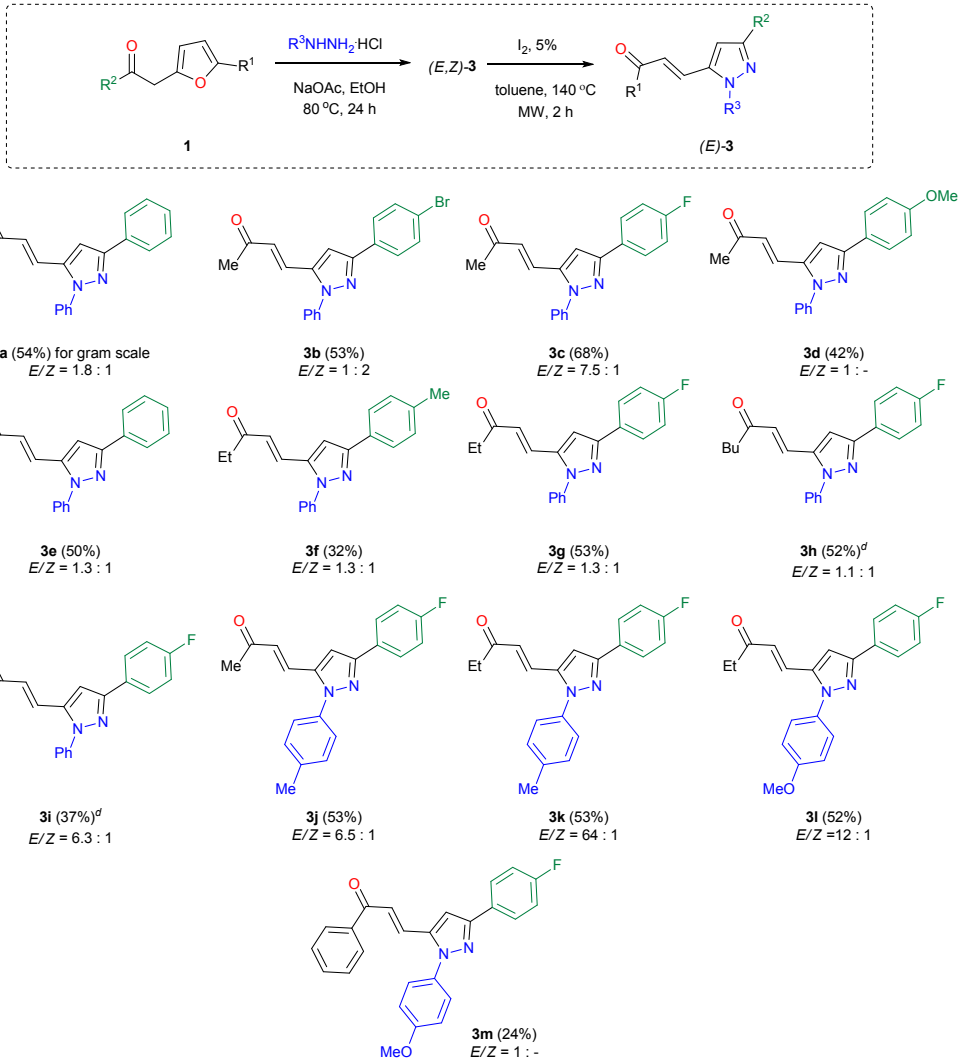
additionally, the steric hindrance (Fig. 6). No further cyclization was observed at higher temperature, using *i*-PrOH as a solvent, or under microwave irradiation. When the reaction was performed with unprotected hydrazine dihydrochloride, azine **2o** was obtained in low yield. The prolongation of the reaction time and the use of an excess of hydrazine dihydrochloride failed to produce any product.



Scheme 3 Reaction scope.[a,b,c]

[a]2 mmol scale. [b]Isolated yields. [c]The ratio (*E/Z*) was determined according the NMR data. [d]*E/Z* Isomerization was performed in 6 h.

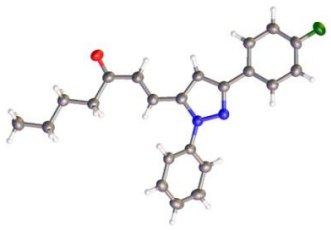


Fig. 5 Structure of (*E*)-**3h**.

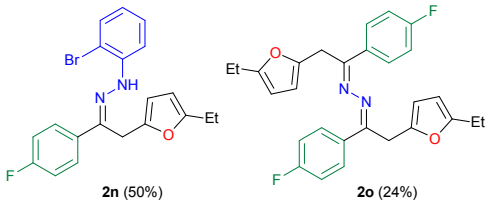
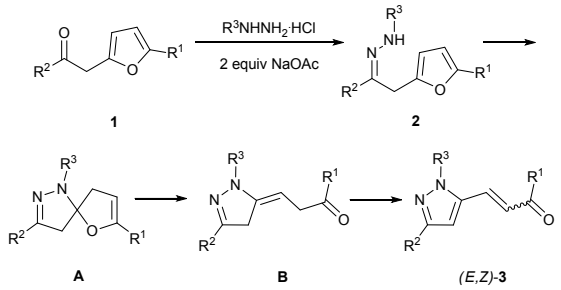


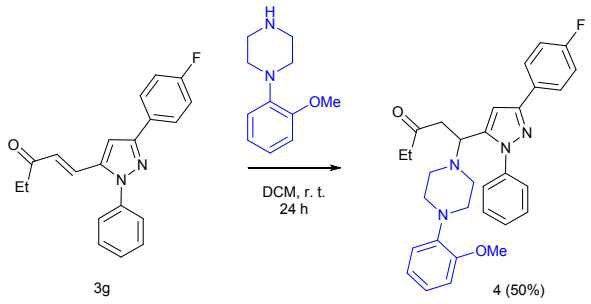
Fig. 6 Isolated hydrazone **2n** and azine **2o**.

A plausible mechanism for the reaction **1** → **3** is presented at Scheme 4. It starts with the formation of hydrazone **2**. The subsequent nucleophilic attack of nitrogen on the C(2) atom of the furan ring affords spyrocyclic intermediate A. The ring opening of **A** results in the formation of intermediate B which undergoes further aromatization to give the final compounds **3**.



Scheme 5 Proposed mechanism.

Importantly, an active enone fragment, one of the key structural benefits of compounds **3**, can be utilized for further functionalization of products, leading to the great structural diversity.[19] Thus, the reaction of **3g** with 1-(2-methoxyphenyl)piperazine produced a product of aza-Michael addition in 50% yield (Scheme 6). This simple experiment illustrates that various functionalities can be easily incorporated into the reported scaffold *via* standard chemical transformations to affect pharmacological properties.



Scheme 6 Aza-Michael addition.

Conclusions

In summary, we have described a novel synthetic route to pyrazol-5-ylvinyl ketones, employing furfuryl ketones as a triketone equivalent. The method shows a wide substrate scope, working especially well for furfuryl ketones bearing an alkyl group at the furan ring. Due to the availability of starting compounds, simplicity of the protocol, and atom efficiency of our approach, the developed procedure represents a valuable alternative to the known 5 step strategy. Further exploration of the reaction scope, in particular, the use of removable protecting groups, is underway in our laboratory.

Experimental

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General remarks

All commercial products and solvents were used without further purification. All reactions were run under the air unless noted otherwise.

The reactions under microwave irradiation were conducted in Microwave Synthesis Reactor «Biotage® Robot Eight» using sealed microwave reaction vessels. TLC analyses were performed on Merck 60 F254 aluminum plates in combination with UV detection (254 nm). Flash chromatography was performed on silica gel 200-300 mesh using mixture EtOAc/*i*-hexane as eluents. Melting points were determined on a Mel-Temp II Laboratory Devices apparatus; the values are uncorrected. NMR spectra were recorded on a Bruker AV-600 (^{1}H NMR at 600 MHz and ^{13}C NMR at 151 MHz) and Bruker AV-400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 101 MHz) spectrometers. Proton chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets), coupling constants (*J*) and integration. Coupling constants (*J*) are reported in Hertz (Hz). Carbon chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ δ = 77.16 ppm).

IR spectra were measured on PerkinElmer Spectrum BX spectrophotometer (KBr and NaCl plates). HRMS-ESI spectra were recorded at the Chair of Organic Chemistry, Friedrich Alexander University of Erlangen-Nuremberg. LC-MS data were obtained on a BRUKER ESQUIRE 2000 using electrospray ionization (ESI), DAD detector, and a Kinetex C8 analytical column (2.1 mm x 75 mm, 2.6 μm).

General procedure for the synthesis of pyrazoles 3

Hydrazine hydrochloride (2 mmol) and anhydrous NaOAc (4 mmol) were added to a solution of furfuryl ketone **1** (2 mmol) in ethanol (5 mL), and the mixture was stirred for 24 hours at 80 °C (TLC and LC-MS control). Then, the reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (4 × 25 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting crude product was purified by flash chromatography using EtOAc/*i*-Hex as eluents to give a mixture of (*E,Z*)-isomers which was isomerized to give (*E*)-**3**.

Isomerization (*E,Z*)-3 → (*E*)-3

Microwave reaction vessel was charged with (*E,Z*)-**3** (0.2 mmol), I_2 (0.0034 g, 0.013 mmol) and toluene (5 mL). The reaction mixture was stirred at 140 °C in a microwave reactor for 2-6 hours. After completion of the reaction, toluene and iodine were removed under reduced pressure to afford pure (*E*)-**3**.

For compounds with R^1=Me the isomerization might be achieved by heating of the reaction mixture with iodine at 80 °C.

DOI: 10.1039/C9OB00704F

Characterization data of representative compounds (*E*)-3

(*E*)-(4-(1,3-Diphenyl-1*H*-pyrazol-5-yl)but-3-en-2-one ((*E*)-3a). Yield 0.29 g (50%). Yellow solid. M. p. 110–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.91 (m, 2H), 7.58–7.35 (m, 9H), 7.09 (s, 1H), 6.74 (dd, *J* = 16.1, 1.4 Hz, 1H), 2.32 (d, *J* = 1.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 196.9, 151.9, 139.3, 138.4, 131.9, 129.0, 128.5, 128.3, 128.3, 128.2, 127.9, 125.3, 125.1, 103.1, 27.6 ppm. IR (NaCl): 1691 (C=O), 1608, 1502, 1348, 1241, 943 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{19}H_{16}N_2O$ $[M+H]^+$: 289.1341; found: 289.1335.

(*E*)-4-(3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazol-5-yl)but-3-en-2-one ((*E*)-3b). Yield 0.38 g (53%). Yellow solid. M. p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.65 (m, 2H), 7.48–7.40 (m, 7H), 7.25 (d, *J* = 16.1 Hz, 1H), 6.95 (s, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 2.22 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.4, 151.3, 140.0, 138.8, 131.9, 131.9, 129.6, 129.0, 128.9, 128.8, 127.4, 125.6, 122.4, 103.5, 28.2 ppm. IR (NaCl): 1736 (C=O), 1604, 1503, 1447, 1349, 1246, 1145, 983 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{19}H_{15}BrN_2O$ $[M+H]^+$: 367.0446; found: 367.0441.

(*E*)-4-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl)but-3-en-2-one ((*E*)-3c). Yield 0.42 g (68%). Yellow solid. M. p. 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2H), 7.46–7.38 (m, 5H), 7.26 (d, *J* = 16.1 Hz, 1H), 7.07–7.01 (m, 2H), 6.93 (s, 1H), 6.63 (d, *J* = 16.1 Hz, 1H), 2.22 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.4, 164.2, 161.7, 151.5, 140.0, 138.8, 129.5, 128.9, 128.9, 127.6, 127.5, 125.6, 115.8, 115.6, 103.4, 28.1 ppm. IR (NaCl): 1741 (C=O), 1622, 1507, 1487, 1377, 1236, 982, 956 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{19}H_{15}FN_2O$ $[M+H]^+$: 307.1247; found: 307.1241.

(*E*)-4-(3-(4-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-5-yl)but-3-en-2-one ((*E*)-3d). Yield 0.27 g (42%). Beige solid. M. p. 125–127 °C (EtOAc/Hex = 1:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.83 (m, 2H), 7.58–7.47 (m, 5H), 7.34 (d, *J* = 16.1 Hz, 1H), 7.02–6.98 (m, 3H), 6.73 (d, *J* = 16.1 Hz, 1H), 3.87 (s, 3H), 2.33 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.6, 159.8, 152.2, 139.7, 138.9, 129.5, 129.2, 128.7, 128.6, 127.1, 125.6, 125.1, 114.1, 103.1, 55.4, 28.1 ppm. IR (NaCl): 1667 (C=O), 1652, 1613, 15919, 1498, 1452, 1438, 1426, 1361, 1243, 1179. HRMS (ESI): *m/z* calcd. for $C_{20}H_{18}N_2O_2$ $[M+Na]^+$: 341.1266; found: 341.1255.

(*E*)-1-(1,3-Diphenyl-1*H*-pyrazol-5-yl)pent-1-en-3-one ((*E*)-3e). Yield 0.15 g (50%). Yellow solid. M. p. 98–101 °C**.** ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.89–7.88 (m, 2H), 7.55–7.35 (m, 9H), 7.07 (s, 1H), 6.76 (d, *J* = 16.0 Hz, 1H), 2.62 (q, *J* = 7.3 Hz, 2H), 1.14 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 200.1, 152.3, 140.0, 139.0, 132.4, 129.5, 128.7, 128.6, 128.6, 128.3, 128.1, 127.8, 125.8, 125.6, 103.4, 34.7, 8.0 ppm. IR (NaCl): 1691 (C=O), 1613, 1498, 765 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{18}N_2O$ $[M+H]^+$: 303.1497, found: 303.1494.

(*E*)-1-(1-Phenyl-3-(*p*-tolyl)-1*H*-pyrazol-5-yl)pent-1-en-3-one ((*E*)-3f). Yield 0.2 g (32%). Yellow solid. M. p. 129–132 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.78–7.77 (m, 2H), 7.54–7.45 (m, 5H), 7.39 (d, *J* = 16.0 Hz, 1H), 7.26–7.23 (m, 2H), 7.04 (s, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 2.61 (q, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 1.14 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 204.1, 156.4, 143.9, 143.0, 142.2, 133.6, 133.4, 133.4, 132.6, 132.1, 131.7, 129.7, 129.6, 107.3, 38.7, 25.3, 12.0 ppm. IR (NaCl): 1691 (C=O), 1611, 1499, 1443, 1352, 1234, 1185, 956 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{21}H_{20}N_2O$ $[M+H]^+$: 317.1654; found: 317.1657.

(*E*)-1-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl)pent-1-en-3-one ((*E*)-3g). Yield 0.34 g (53%). Yellow solid. M. p. 111–113 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.87–7.84 (m, 2H), 7.55–7.46 (m, 5H), 7.39 (d, *J* = 16.0 Hz, 1H), 7.14–7.10 (m, 2H), 7.01 (s, 1H), 6.74 (d, *J* = 16.0 Hz, 1H), 2.62 (q, *J* = 7.3 Hz, 2H), 1.14 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 200.2, 164.2, 161.7, 151.4, 140.2, 138.8, 129.6, 128.0, 128.0, 127.6, 127.6, 125.6, 115.8, 115.6, 103.3, 34.8, 8.1 ppm. IR (NaCl): 1669 (C=O), 1609, 1499, 1446, 1231, 1156, 763 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{17}FN_2O$ $[M+H]^+$: 321.1403; found: 321.1392.

(*E*)-1-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl)hept-1-en-3-one ((*E*)-3h). Yield 0.36 g (52%). White solid. M. p. 121–123 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.77 (m, 2H), 7.47–7.41 (m, 5H), 7.30 (d, *J* = 16.0 Hz, 1H), 7.07–7.03 (m, 2H), 6.95 (s, 1H), 6.67 (d, *J* = 16.0 Hz, 1H), 2.51 (t, *J* = 7.4 Hz, 2H), 1.59–1.50 (m, 2H), 1.29–1.25 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 198.8, 162.7, 161.1, 150.4, 139.1, 137.9, 128.5, 127.7, 127.1, 127.0, 126.5, 126.5, 124.6, 114.7, 114.6, 102.2, 40.3, 25.3, 21.4, 12.8 ppm. IR (NaCl): 1660 (C=O), 1608, 1498, 1447, 1224, 1157, 956 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{22}H_{21}FN_2O$ $[M+H]^+$: 349.1716; found: 349.1703.

(1-(2-Bromophenyl)-2-(2-(5-ethylfuran-2-yl)-1-(4-fluorophenyl)ethylidene)-hydrazine (2n). Yield 0.4 g (50%). Yellow solid. M. p. 76–78 °C (EtOAc/*i*-Hex = 1:7). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.36 (s, 1H), 7.87–7.84 (m, 2H), 7.62–7.60 (m, 1H), 7.44–7.43 (m, 1H), 7.29–7.26 (m, 1H), 7.11–7.06 (m, 2H), 6.76–6.73 (m, 1H), 6.12 (d, *J* = 3.1 Hz, 1H), 5.89 (d, *J* = 3.1 Hz, 1H), 4.07 (s, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.2, 161.8, 157.8, 146.3, 142.7, 142.7, 142.2, 132.3, 128.5, 127.8, 127.7, 120.9, 115.5, 115.3, 114.7, 108.0, 104.8, 27.1, 21.5, 12.2 ppm. IR (NaCl): 2974, 1602, 1508, 1232, 1158, 1012, 843 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{20}H_{18}BrFN_2O$ $[M+H]^+$: 401.0665; found: 401.0631.

1,2-Bis(2-(5-ethylfuran-2-yl)-1-(4-fluorophenyl)ethylidene)hydrazine (2o). Yield 0.22 g (24%). Yellow solid. M. p. 76–78 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.96–7.94 (m, 2H), 7.09–7.06 (m, 2H), 5.77–5.74 (m, 2H), 4.22 (s, 2H), 2.52 (q, *J* = 7.5 Hz, 2H), 1.13 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.7, 163.0, 158.0, 156.5, 148.2, 133.4, 129.4, 129.3, 115.4, 115.2, 107.3, 104.7, 28.3, 21.3, 12.1 ppm. IR (NaCl): 1592, 1504, 1458, 1232, 1153, 1020, 840 cm^{-1}. HRMS (ESI): *m/z* calcd. for $C_{28}H_{26}F_2N_2O_2$ $[M+H]^+$: 461.2041; found: 461.2025.

1-(3-(4-Fluorophenyl)-1-phenyl-1*H*-pyrazol-5-yl)-1-(4-(2-methoxyphenyl)piperazin-1-yl)pentan-3-one (4)

Pyrazolylvinyl ketone **3g** (0.045 g, 0.14 mmol) and 1-(2-methoxyphenyl)piperazine (0.028 mL, 0.16 mmol) were mixed in 4 mL of DCM. Sodium triacetoxyborohydride (0.038 g, 0.18 mmol) was added to the above solution and the mixture was stirred at room temperature under nitrogen for 24 h. The solution was washed with brine, dried over anhydrous Na_2SO_4,

filtered, and evaporated under reduced pressure. The resulting crude product was purified by flash chromatography using EtOAc/*i*-Hex as eluents to give **4**. Yield 0.036 g (50%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.75 (m, 4H), 7.52–7.40 (m, 3H), 7.12– 6.81 (m, 6H), 6.52 (s, 1H), 4.56–5.53 (m, 1H), 3.82 (s, 3H), 3.15–2.91 (m, 6H), 2.56–2.44 (m, 6H), 1.04 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 208.69, 150.13, 142.82, 140.99, 129.03, 128.22, 127.47, 127.39, 126.34, 125.62, 123.06, 120.89, 118.14, 115.59, 115.38, 110.94, 102.74, 55.30, 54.80, 50.89, 48.83, 42.99, 36.70, 7.68 ppm. HRMS (ESI): *m/z* calcd. for $C_{31}H_{33}FN_4O_2$ $[M+H]^+$: 513.2666; found: 513.2657.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank Prof. Dr. Vladimir Abaev (K. L. Khetagurov North-Ossetian State University) and Dr. Jürgen Einsiedel (Department of Chemistry and Pharmacy, Institute of Medicinal Chemistry, University of Erlangen-Nuremberg) for helpful discussion.

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