Cascade and multicomponent synthesis of structurally diverse 2-(pyrazol-3-yl)pyridines and polysubstituted pyrazoles

Raquel Barroso, María-Paz Cabal, Azucena Jiménez,* and Carlos Valdés*\textsuperscript{a}

\textsuperscript{a}Departamento de Química Orgánica e Inorgánica and Instituto Universitario de Química Organometálica “Enrique Moles”. Universidad de Oviedo. c/ Julián Clavería 8. Oviedo 33006. Spain. azujp@hotmail.com; acvg@uniovi.es

Contents
1. General considerations.
2. Experimental procedures for the synthesis of compounds 3, 4, 5, and 8.
   2.1. Method 1: General procedure for the synthesis of 2-(pyrazol-3-yl)pyridines 3, 4 and 8 from N-tosylhydrazones 1 and 2-ethynylpyridines 2.
   2.2. Method 2: General procedure for the three-components synthesis of 2-(pyrazol-3-yl)pyridines 3 and trisubstituted pyrazoles 8.
   2.3. Method 3: General procedure for the one-pot/multicomponents synthesis of 2-(pyrazol-3-yl)pyridines from α-bromoketones.
3. Characterization data of compounds 3, 5 and 8.
4. Synthesis of polyheterocycle 10 by click reaction starting from 3s.
5. Copies of the $^1$H and $^{13}$C NMR spectra.
1. General considerations

The reactions were carried out in a RR98030 12 place Carousel Reaction Station™ from Radleys Discovery Technologies, equipped with gas tight threaded caps with a valve, cooling reflux head system, and digital temperature controller, unless otherwise indicated. K₂CO₃ was purchased from Acros, stored in a flask purged with nitrogen and weighted in the air. CH₃CN was dried using the procedures described in D. Perrin, *Purification of Laboratory Chemicals*, Pergamon Press Ltd. 1980, 2nd Ed. NMR spectra were recorded in CDCl₃ at 400 or 300 MHz for ¹H and 75 MHz for ¹³C, with tetramethylsilane as internal standard for ¹H and the residual solvent signals as standard for ¹³C. The data is being reported as s = singlet, bs = broad singlet, d = doublet, dd = double doublet, t = triplet, dt = double triplet, q = quadruplet and m = multiplet or unresolved, chemical shifts in ppm and coupling constant(s) in Hz. HRMS were measured in EI mode, and the mass analyser of the HRMS was TOF. N-Tosylhydrazones were prepared from the corresponding carbonyl compounds and N-tosylhydrazide through previously described methodologies.¹

2. Experimental procedures for the synthesis of compounds 3, 4, 5, and 8.

2.1. Method 1: General procedure for the synthesis of 2-(pyrazol-3-yl)pyridines 3 from N-tosylhydrazones 1 and 2-ethynlypyridines 2.

\[ \text{N-NHHTs} \ + \ \text{H-CH₂CN} \xrightarrow{K₂CO₃, 110 °C} \text{N-NHHTs} \]

2.1.1. Standard procedure
In a carousel tube reactor the corresponding N-tosylhydrazone 1 (0.24 mmol), 2-ethynlypyridine (0.2 mmol) and K₂CO₃ (0.4 mmol, 55 mg) were dissolved in 2 ml of

CH$_3$CN and the mixture was stirred at 110 ºC for 16 h under nitrogen atmosphere. Then, the reaction was allowed to reach room temperature and was treated with 10 mL of CH$_2$Cl$_2$ and 10 mL of NaHCO$_3$ saturated aqueous solution. The layers were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2x5 mL). The organic layers were combined, washed with brine (5 mL), dried over Na$_2$SO$_4$, filtered, and the solvent was removed under reduced pressure. The resulting oily residue was purified by flash chromatography in silica gel to afford the 2-(pyrazol-3-yl)pyridine.

2.1.2 Procedure with slow addition of the N-tosylhydrazone:
In a carousel tube reactor the 2-ethynlypyridine 2 (0.2 mmol) and K$_2$CO$_3$ (0.4 mmol, 55 mg) were mixed in 1 ml of CH$_3$CN under nitrogen atmosphere and the solution was heated to 100 ºC. Then, a solution of the N-tosylhydrazone 1 (0.3 mmol) in 1 ml of CH$_3$CN was slowly added with a syringe pump over a period of 2h. The mixture was stirred for 16 h at 100 ºC. Then, the reaction was allowed to reach room temperature and was treated with 10 mL of CH$_2$Cl$_2$ and 10 mL of NaHCO$_3$ saturated aqueous solution. Then, the workup of the reaction is identical to that described above.

2.1.3 Synthesis of 3j through a one pot procedure from the ketone and tosylhydrazide
In a carousel tube reactor the corresponding α-substituted ketone (0.2 mmol), N-tosylhydrazide (0.22 mmol) and CH$_3$CN (1.5 ml) were added. After 6 h at 60 ºC, 2-ethynlypyridine (0.4 mmol, 42 μl), K$_2$CO$_3$ (0.4 mmol, 55 mg) and 1.5 ml of CH$_3$CN were added to the mixture. The reaction was stirred at 110 ºC for 16 h under nitrogen atmosphere. Then, the reaction was allowed to reach room temperature and was treated with 10 mL of CH$_2$Cl$_2$ and 10 mL of NaHCO$_3$ saturated aqueous solution. Then, the workup of the reaction is identical to that described above.

2.1.4 Procedure for the synthesis of NH-free 2-(pyrazol-3-yl)pyridines 4.
The procedure is identical to that described above for 2-(pyrazol-3-yl)pyridines 3, employing in this case N-tosylhydrazone 1h.

2.1.5. General procedure for the synthesis of 2,6-bis(pyrazolyl)pyridines 5 by reaction of N-tosylhydrazones 1 with 2,6-diethynlypyridine
The procedure is identical to that described above for 2-(pyrazol-3-yl)pyridines 3 but employing 0.2 mmol of 2,6-diethynlypyridine 2e, 0.8 mmol of N-tosylhydrazone and 0.8 mmol (110 mg) of K$_2$CO$_3$. 
2.2. Method 2: General procedure for the three-components synthesis of 2-(pyrazol-3-yl)pyridines 3 and trisubstituted pyrazoles 8

In a carousel tube reactor the α-bromo-N-tosylhydrazone 6 (0.2 mmol), 2-ethynlypyridine 2 (0.2 mmol), the corresponding NH-azole (0.1 mmol) and K$_2$CO$_3$ (0.5 mmol, 76 mg) were dissolved in 3 ml of CH$_3$CN and the mixture was stirred at 110 ºC for 16 h under nitrogen atmosphere. Then, the reaction was allowed to reach room temperature and was treated with 10 mL of CH$_2$Cl$_2$ and 10 mL of NaHCO$_3$ saturated aqueous solution. Then, the workup of the reaction is identical to that described for Method 1.

2.3. Method 3: General procedure for the one-pot/multi-components synthesis of 2-(pyrazol-3-yl)pyridines from α-bromoketones.

In carousel tube reactor, the corresponding α-bromoketone 9 (0.2 mmol) and N-tosylhydrazide (0.22 mmol) were mixed with 1.5 mL of CH$_3$CN, and the mixture was stirred at 60 ºC for 6 h. Then, the 2-ethynlypyridine (0.2 mmol), the corresponding heterocycle (0.1 mmol), K$_2$CO$_3$ (0.5 mmol, 70 mg) and 2.5 ml of CH$_3$CN were added to the mixture. The reaction was stirred at 110 ºC for 16 h under nitrogen atmosphere. Then, the reaction was allowed to reach room temperature and was treated with 10 mL of CH$_2$Cl$_2$ and 10 mL of NaHCO$_3$ saturated aqueous solution. Then, the workup of the reaction is identical to that described for method 1.
3. Characterization data of compounds 3, 4, 5, and 8

2-(1-Benzyl-5-phenyl-1H-pyrazol-3-yl)pyridine (3a)

Following Method 1 (standard procedure), from 2-ethynylpyridine (0.1 mmol, 10 μl) and N'-(1,2-diphenylethyldiene)-4-methylbenzenesulfonohydrazide (0.12 mmol, 43.7 mg), were obtained 13.5 mg of 3a (44 % isolated yield) as a yellowish oil. Rf = 0.59 (Hexane/EtOAc, 2:1).

\[^1\text{H}\text{NMR (300 MHz, CDCl}_3\text{)} \delta (\text{ppm}) = 8.67 (\text{ddd, } J = 4.9, 1.8, 0.9 \text{ Hz, } 1\text{H, CH}), 8.04 (\text{dt, } J = 8.0, 1.0 \text{ Hz, } 1\text{H, CH}), 7.65 (\text{td, } J = 7.6, 1.8 \text{ Hz, } 1\text{H, CH}), 7.41 (\text{m, } 5\text{H, CH}), 7.31 (\text{m, } 2\text{H, CH}), 7.23 (\text{m, } 2\text{H, CH}), 7.13 (\text{m, } 2\text{H, CH}), 7.03 (\text{s, } 1\text{H, CH}), 5.46 (\text{s, } 2\text{H, CH}_2).\]

\[^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta (\text{ppm}) = 152.3 (\text{C}), 151.2 (\text{C}), 149.4 (\text{CH}), 145.7 (\text{C}), 137.5 (\text{C}), 136.5 (\text{CH}), 130.5 (\text{C}), 128.9 (\text{CH}), 128.7 (2\text{CH}), 128.6 (2\text{CH}), 128.5 (\text{CH}), 127.8 (\text{CH}), 127.5 (\text{CH}), 126.7 (2\text{CH}), 122.4 (\text{CH}), 120.2 (\text{CH}), 105.1 (\text{CH}), 53.5 (\text{CH}_2).\]

EI HRMS: calcd. For C\text{21}H\text{18}N\text{3}[M+1]^+ : 312.1497, found: 312.1495

2-(1-benzyl-5-phenyl-1H-pyrazol-3-yl)-6-bromopyridine (3b)

Following Method 1 (slow addition), from 2-bromo-6-ethynlypyridine (0.3 mmol, 89 mg) and N'-(1,2-diphenylethyldiene)-4-methylbenzenesulfonohydrazide (0.36 mmol, 0.13 g), were obtained 17.2 mg of 3b (49 % isolated yield) as a colorless oil. Rf = 0.47 (Hexane/EtOAc, 2:1).

\[^1\text{H NMR (300 MHz, CDCl}_3\text{)} \delta (\text{ppm}) = 8.02 (\text{dd, } J = 7.7, 0.9 \text{ Hz, } 1\text{H, CH}), 7.59 (\text{t, } J = 7.8 \text{ Hz, } 1\text{H, CH}), 7.48 – 7.35 (\text{m, } 6\text{H, CH}), 7.30 (\text{d, } J = 5.4 \text{ Hz, } 3\text{H, CH}), 7.08 (\text{dd, } J = 8.1, 2.0 \text{ Hz, } 2\text{H, CH}), 7.05 (\text{s, } 1\text{H, CH}), 5.43 (\text{s, } 2\text{H, CH}_2).\]
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 153.6 (C), 150.0 (C), 145.8 (C), 141.7 (C), 138.8 (CH), 137.3 (C), 130.3 (C), 128.8 (2CH), 128.8 (CH), 128.7 (2CH), 128.6 (2CH), 127.5 (CH), 126.7 (CH), 126.5 (CH), 118.7 (CH), 105.8 (CH), 53.5 (CH$_2$).

EI HRMS: calcd. for C$_{21}$H$_{17}$BrN$_3$ [M+1]$^+$: 390.0597; found 390.0600.

2-(1-(Methoxymethyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (3c)

Following **Method 1** (slow addition), from 2-ethynylpyridine (0.1 mmol, 10$\mu$l) and N'-[(2-methoxy-1-phenylethylidene)-4-methylbenzenesulfonyl]hydrazide (0.12 mmol, 38.2 mg), were obtained 11.7 mg of 3c (44% isolated yield) as a yellowish oil. Rf = 0.58 (Hexane/EtOAc, 2:1).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.68 (d, $J = 4.0$, 1H, CH), 8.05 (d, $J = 7.9$ Hz, 1H, CH), 7.77 (td, $J = 7.8$, 1.7 Hz, 1H, CH), 7.67 (dd, $J = 8.0$, 1.5 Hz, 2H, CH), 7.49 (m, 3H, CH), 7.26 (m, 1H, CH), 7.09 (s, 1H, CH), 5.48 (s, 2H, CH$_2$), 3.55 (s, 3H, OCH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 151.9 (C), 151.1 (C), 149.2 (CH), 146.3 (C), 136.8 (CH), 130.0 (CH), 128.9 (2CH), 128.8 (CH), 127.9 (CH), 122.7 (CH), 120.4 (CH), 105.6 (CH), 79.9 (CH$_2$), 56.8 (OCH$_3$).

EI HRMS: calcd. for C$_{16}$H$_{16}$N$_3$O [M+1]$^+$: 266.1287; found 266.1288.

8-Methoxy-2-(pyridin-2-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine (3d)

Following **Method 1** (slow addition), from 2-ethynlypyridine (0.1 mmol, 10$\mu$l) and N'-(2-methoxycyclohexylidene)-4-methylbenzenesulfonylhydrazide (0.12 mmol, 35.6 mg), were obtained 17.5 mg of 3d (72% isolated yield) as a colorless oil. Rf = 0.23 (Hexane/EtOAc, 3:1).
$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 8.65 (bs, 1H, CH), 7.91 (d, $J = 7.9$ Hz, 1H, CH), 7.73 (td, $J = 7.8$, 1.6 Hz, 1H, CH), 7.22 (d, $J = 5.6$ Hz, 1H, CH), 6.68 (s, 1H, CH), 5.61 (d, $J = 3.8$ Hz, 1H, CH), 3.26 (s, 3H, OCH$_3$), 2.97 (dd, $J = 15.0$, 5.4 Hz, 1H, CH), 2.79 (t, $J = 13.4$ Hz, 1H, CH), 2.32 (m, 1H, CH$_2$), 2.23 (m, 2H, CH$_2$), 1.83 (m, 2H, CH$_2$), 1.46 (t, $J = 13.1$ Hz, 1H, CH$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 152.3 (C), 149.2 (CH), 145.7 (C), 136.7 (CH), 122.2 (CH), 120.1 (CH), 105.2 (CH), 92.0 (CH), 55.7 (CH$_3$), 32.5 (CH$_2$), 27.4 (CH$_2$), 25.8 (CH$_2$), 23.1 (CH$_2$).

EI HRMS: calcd. for C$_{14}$H$_{18}$N$_3$O [M+1]$^+$ : 244.1449; found 244.1444.

(R)-8-Methoxy-2-(6-methylpyridin-2-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine (3e)

Following Method 1 (slow addition), from 2-ethynyl-6-methylpyridine (0.16 mmol, 22.3 mg) and $N^\prime$-(2-methoxycyclohexylidene)-4-methylbenzenesulfonohydrazide (0.19 mmol, 56.3 mg), were obtained 21.4 mg of 3e (52% isolated yield) as a colorless oil. Rf = 0.37 (Hexane/EtOAc, 1:1).

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.65 (d, $J = 7.7$ Hz, 1H, CH), 7.60 (t, $J = 7.7$ Hz, 1H, CH), 7.05 (d, $J = 7.4$ Hz, 1H, CH), 6.66 (s, 1H, CH), 5.60 (d, $J = 3.6$ Hz, 1H, CH), 3.24 (s, 3H, OCH$_3$), 2.96 (dd, $J = 14.7$, 5.6 Hz, 1H, CH$_2$), 2.78 (t, $J = 13.1$ Hz, 1H, CH$_2$), 2.62 (s, 3H, CH$_3$), 2.29 (m, 1H, CH$_2$), 2.10 (m, 2H, CH$_2$), 1.73 (m, 2H, CH$_2$), 1.43 (q, $J = 13.0$ Hz, 1H, CH$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 158.2 (C), 151.9 (C), 149.9 (C), 145.5 (C), 136.7 (CH), 121.8 (CH), 117.2 (CH), 105.3 (CH), 91.8 (CH), 55.6 (CH$_3$), 32.5 (CH$_2$), 27.4 (CH$_2$), 25.8 (CH$_2$), 24.7 (CH$_3$), 23.1 (CH$_2$).

EI HRMS: calcd. for C$_{15}$H$_{20}$N$_3$O [M+1]$^+$ : 258.1601; found 258.1601.
(R)-2-(6-Bromopyridin-2-yl)-8-methoxy-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine (3f)

Following **Method 1** (slow addition), from 2-bromo-6-ethynylpyridine (0.3 mmol, 89 mg) and N’-(2-methoxycyclohexylidene)-4-methylbenzenesulfonohydrazide (0.19 mmol, 56.3 mg), were obtained 53 mg of 3f (55% isolated yield) as a yellow oil. Rf = 0.5 (Hexane/EtOAc, 2:1).

1H NMR (300 MHz, CDCl₃) δ (ppm) = 1H NMR (300 MHz, CDCl₃) δ (ppm) = 7.90 (dd, J = 7.7, 0.9 Hz, 1H, CH), 7.56 (t, J = 7.8 Hz, 1H, CH), 7.38 (dd, J = 7.8, 0.9 Hz, 1H, CH), 6.71 (s, 1H, CH), 5.57 (d, J = 3.3 Hz, 1H, CH), 3.24 (s, 3H, OCH₃), 2.93 (m, 1H, CH), 2.77 (t, J = 12.8 Hz, 1H, CH₂), 2.45 (m, 2H, CH₂), 2.13 (d, J = 13.8 Hz, 1H, CH₂), 2.03 (d, J = 14.3 Hz, 1H, CH₂), 1.83 (dd, J = 8.5, 6.8 Hz, 1H, CH₂).

13C NMR (75 MHz, CDCl₃) δ (ppm) = 153.8 (C), 148.4 (C), 145.8 (C), 141.7 (C), 138.7 (CH), 126.3 (CH), 118.5 (CH), 105.8 (CH), 92.0 (CH), 55.7 (OCH₃), 32.5 (CH₂), 27.3 (CH₂), 25.8 (CH₂), 23.1 (CH₂).


2-[1-[(3,5-Dimethyl-1H-pyrazol-1-yl)methyl]-5-phenyl-1H-pyrazol-3-yl]pyridine (3g)

Following **Method 1**, from 2-ethynlypyridine (0.17 mmol, 17 µl) and (E)-N’-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.20 mmol, 75 mg) were obtained 25.8 mg of 3g (47 % isolated yield). Additionally, when product 3g was obtained employing 1 mmol of the corresponding tosylhydrazone and following the general method 1, the isolated yield was increased to 61 %.
Following **Method 2** (slow addition), from 2-ethynylpyridine (0.17 mmol, 17 µl) and (E)-N′-(2-bromo-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.16 mmol, 60 mg), were obtained 22.2 mg of **3g** (82% isolated yield).

Following **Method 3** from 2-ethynylpyridine (0.16 mmol, 16.6 µl), 2-bromo-1-phenylethan-1-one (0.16 mmol, 33.3 mg), 3,5-dimethyl-1H-pyrazole (0.082 mmol, 8 mg) and 4-methylbenzenesulfonohydrazide (0.18 mmol, 33.6 mg) were obtained 11.3 mg of **3g** (42% isolated yield).

**Compound 3g** is obtained as a white solid. m.p. = 123 – 124 °C. Rf = 0.19 (Hexane/EtOAc, 2:1).

\[ \text{EI HRMS: calcd. for } C_{20}H_{20}N_{5}[M+1]^+ : 330.1712, \text{ found: } 330.1713. \]

2-(1-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-6-methoxypyridine (**3h**)

Following **Method 1** (slow addition), from 2-ethynyl-6-methoxypyridine (0.09 mmol, 14.2 mg) and (E)-N′-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.11 mmol, 42.4 mg), were obtained 17.1 mg of **3h** (53% isolated yield) as a colorless oil. Rf = 0.52 (Hexane/EtOAc, 2:1).
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.82 (d, $J$ = 7.4 Hz, 2H, CH), 7.57-7.51 (m, 5H, CH), 6.97 (s, 1H, CH), 6.67 (dd, $J$ = 6.4, 2.0 Hz, 1H, CH), 6.18 (s, 2H, CH$_2$), 5.83 (s, 1H, CH), 4.01 (s, 3H, OCH$_3$), 2.50 (s, 3H, CH$_3$), 2.19 (s, 3H, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 163.7 (C), 152.0 (C), 149.5 (C), 148.7 (C), 145.8 (C), 141.0 (C), 139.0 (CH), 129.8 (C), 129.7 (2CH), 128.8 (CH), 128.7 (2CH), 112.5 (CH), 109.5 (CH), 106.3 (CH), 105.6 (CH), 60.2 (CH$_2$), 53.2 (OCH$_3$), 13.6 (CH$_3$), 11.3 (CH$_3$).

EI HRMS: calcd. for C$_{21}$H$_{22}$N$_5$O [M+1]$^+$: 360.1818, found : 360.1819.

1-[(5-Phenyl-3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl]-1H-indole (3i)

Following Method 1 (slow addition), from 2-ethynlypyridine (0.05 mmol, 5.5µl) and (E)-$N'$-(2-(1H-indol-1-yl)-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.19 mmol, 75 mg), were obtained 19.3 mg of 3i (47% isolated yield) as a yellow oil. Rf = 0.36 (Hexane/EtOAc, 2:1).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.64 (d, $J$ = 4.3 Hz, 1H, CH), 8.06 (d, $J$ = 7.9 Hz, 1H, CH), 7.77 (td, $J$ = 7.8, 1.8 Hz, 1H, CH), 7.51 (m, 4H, CH), 7.38 (m, 2H, CH), 7.20 (m, 2H, CH), 7.10 (m, 2H, CH), 6.95 (s, 1H, CH), 6.94 (d, $J$ = 3.3 Hz, 1H, CH), 6.42 (d, $J$ = 0.6 Hz, 1H, CH), 6.39 (s, 2H, CH$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 152.0 (C), 151.7 (C), 149.2 (C), 145.5 (C), 136.8 (CH), 135.6 (CH), 130.2 (C), 129.6 (CH), 129.4 (2CH), 129.3 (2CH), 129.0 (C), 127.4 (CH), 122.7 (CH), 122.0 (CH), 120.8 (CH), 120.3 (CH), 120.1 (CH), 110.0 (CH), 106.2 (CH), 103.0 (CH), 59.1 (CH$_2$).

EI HRMS: calcd. for C$_{23}$H$_{19}$N$_4$ [M+1]$^+$: 351.1603, found : 351.1604.
2-(1-((4-(4-Fluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (3j)

Modified procedure of **Method 1**: In a carousel tube reactor, the ketone (0.2 mmol) and N-tosylhydrazide (0.22 mmol) were mixed with 1.5 mL of CH\textsubscript{3}CN, and the mixture was stirred at 60 °C for 6 h. Then, the 2-ethynylpyridine (0.2 mmol), K\textsubscript{2}CO\textsubscript{3} (0.5 mmol, 70 mg) and 2.5 ml of CH\textsubscript{3}CN were added to the mixture. The reaction was stirred at 110 °C for 16 h under nitrogen atmosphere. Then, the reaction was allowed to reach room temperature and was treated with 10 mL of CH\textsubscript{2}Cl\textsubscript{2} and 10 mL of NaHCO\textsubscript{3} saturated aqueous solution. Then, the workup of the reaction is identical to that described for method 1 to obtain 11.9 mg of 3j (30% isolated yield) as a white solid. m.p. = 145 – 147 °C. Rf = 0.29 (Hexane/EtOAc, 1:1).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) $\delta$ (ppm) = 8.70 (d, $J = 5.1$ Hz, 1H, CH), 8.22 (s, 1H, CH), 7.79 (d, $J = 1.7$ Hz, 1H, CH), 7.79 (dt, $J = 7.6$, 1.7 Hz, 1H, CH), 7.57 (m, 7H, CH), 7.40 (m, 1H, CH), 7.30 (m, 1H, CH), 7.06 (m, 1H, CH), 7.02 (s, 1H, CH), 6.64 (s, 2H, CH\textsubscript{2}).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) $\delta$ (ppm) = 163.3 (d, $J_{CF} = 247.2$ Hz, C), 153.3 (C), 151.3 (C), 149.7 (CH), 147.5 (d, $J_{CF} = 2.5$ Hz, C), 146.7 (C), 136.7 (CH), 132.4 (d, $J_{CF} = 8.6$ Hz, CH), 130.6 (d, $J_{CF} = 8.6$ Hz, CH), 129.6 (C), 129.5 (2CH), 129.4 (2CH), 128.8 (C), 123.2 (CH), 121.5 (CH), 120.5 (CH), 120.4 (CH), 115.4 (d, $J_{CF} = 22.1$ Hz, CH), 113.0, (d, $J_{CF} = 22.1$ Hz, CH), 106.2 (CH), 61.4 (CH\textsubscript{2}).

\textsuperscript{19}F NMR (282 MHz, CDCl\textsubscript{3}) $\delta$ (ppm) = -112.6.

EI HRMS: calcd. for C\textsubscript{23}H\textsubscript{18}FN\textsubscript{6} [M+1]$: 397.1570, found : 397.1571.
**tert-Butyl** \((S)-2-(5-methyl-3-(pyridin-2-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate\) (mixture of rotamers, 1:1.2) \(3k\)

![3k]

Following **Method 1** (slow addition), from 2-ethynylpyridine (0.10 mmol, 10 µl) and \(\text{tert-butyl-2-(1-(2-tosylhydrazineylidene)ethyl)pyrrolidine-1-carboxylate}\) (0.10 mmol, 38.2 mg), were obtained 16.8 mg of \(3k\) (50% isolated yield) as a colorless oil. \(\text{Rf} = 0.16\) (Hexane/EtOAc, 3:1).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 8.60 (bs, 1H, CH), 8.0 (bs, 1H, CH), 7.72 (bs, 1H, CH), 7.19 (bs, 1H, CH), 6.71 (bs, 1H, CH), 5.99 (bs, 1H, CH), 3.89-3.52 (m, 2H, CH\(_2\)), 2.53-2.38 (m, 4H, CH\(_2\)), 1.97-1.34 (m, 12H, 4 CH\(_3\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 152.7 (C), 150.3 (C), 148.8 (CH), 139.0 (C), 136.5 (CH), 122.1 (CH), 120.0 (CH), 103.5 (CH), 80.4 (CH), 69.6 (C), 46.8 (CH\(_3\)), 34.2 (CH), 32.9 (CH\(_2\)), 28.2 (2CH\(_3\)), 23.7 (CH\(_2\)), 22.3 (CH\(_2\)), 11.3 (CH\(_3\)). Some signals are splitted due to rotamers.


**tert-Butyl** \((S)-2-(3-(6-ethynylpyridin-2-yl)-5-methyl-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate\) (mixture of rotamers, 1:1.5) \(3l\)

![3l]

Following **Method 1** (slow addition), from 2,6-diethynylpyridine (0.34 mmol, 43 mg) and \(\text{tert-butyl-2-(1-(2-tosylhydrazineylidene)ethyl)pyrrolidine-1-carboxylate}\) (0.34 mmol, 130 mg), were obtained 37 mg of \(3l\) (53% isolated yield) as a yellowish oil. \(\text{Rf} = 0.34\) (Hexane/EtOAc, 2:1).
$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.99 (d, $J = 8.0$ Hz, 1H, CH), 7.65 (t, $J = 7.8$ Hz, 1H, CH), 7.37 (d, $J = 7.5$ Hz, 1H, CH), 6.71 (d, $J = 13.4$ Hz, 1H, CH), 5.66 (bs, 1H, CH), 3.92 – 3.44 (m, 2H, CH$_2$), 3.15 (s, 1H, CH), 2.52 (m, 2H, CH$_2$), 2.38 (s, 3H, CH$_3$), 1.99 (m, 4H, CH$_2$), 1.36 (m, 9H, Boc).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 153.6 (C), 149.9 (C), 141.5 (C), 140.7 (C), 138.9 (C), 136.4 (CH), 125.9 (CH), 119.8 (CH), 104.0 (CH), 83.3 (C), 80.4 (C), 79.9 (CH), 69.5 (CH), 46.8 (CH$_2$), 28.2 (CH$_3$), 23.7 (CH$_2$), 22.2 (CH$_2$), 11.3 (3 CH$_3$). Some signals are splitted due to rotamers.


(S)-2-(5-Methyl-1-(3-methyl-1-(1H-pyrrol-1-yl)butyl)-1H-pyrazol-3-yl)pyridine (3m)

Following Method 1, from 2-ethynlypyridine (0.20 mmol, 20 µl) and (S,E)-4-methyl-N’-(5-methyl-3-(1H-pyrrol-1-yl)hexan-2-ylidene)benzenesulfonohydrazide (0.24 mmol, 83 mg), were obtained 36 mg of 3m (51% isolated yield) as a colorless oil. Rf = 0.21 (Hexane/EtOAc, 2:1).

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 8.62 (ddd, $J = 4.9$ Hz, 1H), 8.06 (dt, $J = 8.0$, 1.1 Hz, 1H), 7.75 (td, $J = 7.7$, 1.8 Hz, 1H), 7.22 (ddd, $J = 7.5$, 4.9, 1.2 Hz, 1H), 6.93 (t, $J = 2.2$ Hz, 2H), 6.69 (s, 1H), 6.16 (t, $J = 2.2$ Hz, 2H), 6.11 (t, $J = 7.5$ Hz 1H), 2.63 – 2.39 (m, 2H), 2.37 (s, 3H), 1.55 – 1.30 (m, 1H), 0.99 (d, $J = 6.7$ Hz, 3H), 0.97 (d, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 152.5 (C) 150.9 (C), 149.2 (CH), 139.8 (C), 136.4 (CH), 122.3 (CH), 120.2 (CH), 118.9 (CH), 108.8 (CH), 104.9 (CH), 69.10 (CH), 43.5 (CH), 24.4 (CH), 22.4 (CH$_3$), 22.3 (CH$_3$), 11.2 (CH$_3$).

2-(1-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-5-ethynylpyridine (3n)

Following **Method 3**, from 2,5-diethynylpyridine (0.31 mmol, 40 mg), 2-bromo-1-phenylethan-1-one (0.68 mmol, 0.13 g), 3,5-dimethyl-1H-pyrazole (0.68 mmol, 65 mg) and 4-methylbenzenesulfonohydrazide (0.69 mmol, 0.128 g) were obtained 51.5 mg of 3n (47% isolated yield) as an orange solid. m.p. = 172 – 174 °C. Rf = 0.20 (Hexane/AcOEt, 3:1).

\[ ^1 \text{H} \text{NMR (300 MHz, CDCl}_3 \text{)} \delta (\text{ppm}) = 8.73 (\text{dd, } J = 2.1, 0.8 \text{ Hz, } 1\text{H, CH}), 7.99 (\text{dd, } J = 8.2, 0.9 \text{ Hz, } 1\text{H, CH}), 7.82 (\text{m, } 3\text{H, CH}), 7.52 (\text{m, } 3\text{H, CH}), 6.99 (\text{s, } 1\text{H, CH}), 6.19 (\text{s, } 2\text{H, CH}_2), 5.84 (\text{s, } 1\text{H, CH}), 3.27 (\text{s, } 1\text{H, CH}), 2.47 (\text{s, } 3\text{H, CH}_3), 2.20 (\text{s, } 3\text{H, CH}_3). \]

\[ ^{13} \text{C} \text{NMR (75 MHz, CDCl}_3 \text{)} \delta (\text{ppm}) = 152.4 (\text{CH}), 151.5 (\text{C}), 151.3 (\text{C}), 148.9 (\text{C}), 146.3 (\text{C}), 140.9 (\text{C}), 139.5 (\text{CH}), 129.7 (\text{2CH}), 129.6 (\text{C}), 129.0 (\text{CH}), 128.8 (\text{2CH}), 119.4 (\text{CH}), 117.8 (\text{C}), 106.4 (\text{CH}), 105.7 (\text{CH}), 80.7 (\text{CH}), 76.9 (\text{C}), 60.3 (\text{CH}_2), 13.6 (\text{CH}_3), 11.3 (\text{CH}_3). \]


1-((5-Phenyl-3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)-1H-benzo[d][1,2,3]triazole (3o)

Following **Method 2**, from 2-ethynylpyridine (0.16 mmol, 16.2 µl), (E)-N’-(2-bromo-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.16 mmol, 60.2 mg) and 1H-
benzo[d][1,2,3]triazole (0.082 mmol, 9.8 mg) were obtained 9.0 mg of 3o (31% isolated yield).

Following Method 3, from 2-ethynylpyridine (0.16 mmol, 16.6 µl), 2-bromo-1-phenylethan-1-one (0.16 mmol, 32.6 mg), 1H-benzo[d][1,2,3]triazole (0.082 mmol, 9.8 mg) and 4-methylbenzenesulfonohydrazide (0.18 mmol, 33.5 mg) were obtained 9.8 mg of 3n (35% isolated yield).

Compound 3n is obtained as a yellow solid. m.p. = 137 – 138 °C. Rf = 0.19 (Hexane/EtOAc, 2:1).

1H NMR (300 MHz, CDCl3) δ (ppm) = 8.65 (d, J = 4.2 Hz, 1H, CH), 8.06 (t, J = 7.9 Hz, 2H, CH), 8.00 (d, J = 8.4 Hz, 1H, CH), 7.78 (td, J = 7.7, 1.8 Hz, 1H, CH), 7.63 (m, 2H, CH), 7.56 (m, 4H, CH), 7.41 (m, 1H, CH), 7.24 (m, 1H, CH), 7.02 (s, 1H, CH), 6.92 (s, 2H, CH2).

13C NMR (75 MHz, CDCl3) δ (ppm) = 152.5 (C), 151.6 (C), 149.3 (CH), 146.7 (C), 146.2 (C), 137.0 (CH), 133.2 (C), 133.0 (C), 129.6 (CH), 129.4 (2CH), 129.2 (2CH), 128.0 (CH), 124.6 (CH), 123.2 (CH), 120.5 (CH), 120.0 (CH), 111.0 (CH), 106.2 (CH), 60.3 (CH2).


1-((3-(6-Methoxypyridin-2-yl)-5-phenyl-1H-pyrazol-1-yl)methyl)-1H-benzo[d][1,2,3]triazole (3p)

Following Method 2, from 2-ethynyl-6-methoxypyridine (0.16 mmol, 62.7 mg), (E)-N-(2-bromo-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.16 mmol, 60.2 mg) and 1H-benzo[d][1,2,3]triazole (0.082 mmol, 9.8 mg) were obtained 14.4 mg of 3p (46% isolated yield) as a yellow solid. m.p. = 180 – 182 °C. Rf = 0.39 (Hexane/EtOAc, 8:1).
\[^1\]H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 8.06 (dd, \(J = 8.3, 5.4\) Hz, 2H, CH), 7.60 (m, 4H, CH), 7.53 (m, 4H, CH), 7.42 (m, 1H, CH), 6.90 (s, 1H, CH), 6.72 (s, 2H, \(\text{CH}_2\)), 6.71 (dd, \(J = 6.2, 2.8\) Hz, 1H, CH), 4.00 (s, 3H, OCH\(_3\)).

\[^{13}\]C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 163.8 (C), 152.8 (C), 149.0 (C), 146.2 (C), 146.0 (C), 139.1 (CH), 133.1 (C), 129.5 (3CH), 129.2 (C), 129.1 (2CH), 128.0 (CH), 124.4 (CH), 119.9 (CH), 112.6 (CH), 111.2 (CH), 110.0 (CH), 106.3 (CH), 60.2 (CH\(_2\)), 53.2 (OCH\(_3\)).


2-(1-((4,5-Diphenyl-1H-imidazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (3q)

![Diagram of 3q]

Following **General Method 2**, from 2-ethynylpyridine (0.16 mmol, 16.2 µl), \((E)-N'-(2-bromo-1-phenylethylidene)-4-methylbenzenesulfonylhydrazide\) (0.16 mmol, 60.2 mg) and 4,5-diphenyl-1H-imidazole (0.082 mmol, 18 mg) were obtained 10.5 mg of 3q (42\% isolated yield) as a yellow oil. Rf = 0.29 (Hexane/EtOAc, 1:3).

\[^1\]H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 8.64 (d, \(J = 4.8\) Hz, 1H, CH), 8.01 (dt, \(J = 7.9, 1.1\) Hz, 1H), 7.76 (dt, \(J = 7.9, 1.8\) Hz, 1H, CH), 7.67 (s, 1H, CH), 7.28 (m, 7H, CH), 7.22 (m, 2H, CH), 7.16 (m, 7H, CH), 6.99 (s, 1H, CH), 6.09 (s, 2H, CH\(_2\)).

\[^{13}\]C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 152.6 (C), 151.6 (C), 149.4 (CH), 145.8 (C), 138.2 (C), 136.9 (CH), 136.6 (CH), 134.1 (C), 130.9 (2CH), 129.5 (C), 129.2 (2CH), 129.1 (3CH), 129.0 (2CH), 128.9 (C), 128.7 (2CH), 128.1 (2CH), 126.6 (2CH), 126.5 (C), 123.0 (CH), 120.3 (CH), 106.22 (CH), 57.3 (CH\(_2\)).

EI HRMS: calcd. for C\(_{30}\)H\(_{24}\)N\(_5\) [M+1]+: 454.2026, found: 454.2026.
2-(1-((4,5-Diphenyl-1H-imidazol-1-yl)methyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pyridine (3r)

Following **Method 2**, from 2-ethynylpyridine (0.16 mmol, 16.2 µl), (E)-N’-(2-bromo-1-(4-methoxyphenyl)ethylidene)-4-methylbenzenesulfonohydrazide (0.16 mmol, 62.9 mg) and 4,5-diphenyl-1H-imidazole (0.082 mmol, 18.1 mg) were obtained 18.2 mg of **3r** (46% isolated yield) as a yellow oil. Rf = 0.22 (Hexane/EtOAc, 1:3).

**1H NMR (300 MHz, CDCl3):** δ (ppm) = 8.65 (d, J = 4.8 Hz, 1H, CH), 8.00 (d, J = 7.9 Hz, 1H, CH), 7.77 (td, J = 7.8, 1.8 Hz, 1H, CH), 7.69 (s, 1H, CH), 7.35 (m, 6H, CH), 7.17 (m, 4H), 7.12 (d, J = 8.7 Hz, 2H, CH), 6.90 (m, 3H, CH), 6.08 (s, 2H, CH2), 5.32 (s, 1H, CH), 3.88 (s, 3H, OCH3).

**13C NMR (75 MHz, CDCl3) δ (ppm) =** 160.2 (C), 152.5 (C), 151.7 (C), 149.4 (CH), 145.7 (C), 138.2 (C), 136.9 (CH), 136.6 (CH), 134.1 (C), 131.0 (2CH), 130.0 (2CH), 129.5 (C), 129.0 (2CH), 128.8 (CH), 128.1 (2CH), 127.6 (C), 126.6 (2CH), 126.5 (CH), 122.9 (CH), 121.4 (C), 120.3 (CH), 114.5 (2CH), 105.9 (CH), 57.2 (CH2), 55.4 (OCH3).

**HRMS:** calcd. For [M+H] C31H26N5O: 484.2131, found: 484.2132.

2-(1-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-6-ethynylpyridine (3s)
Following **Method 3**, from 2,6-diethynylpyridine (0.16 mmol, 20 mg), 2-bromo-1-phenylethanol (0.31 mmol, 31.7 mg), 3,5-dimethyl-1H-pyrazole (0.35 mmol, 33.2 mg) and 4-methylbenzenesulfonylhydrazide (0.35 mmol, 64.2 mg) were obtained 23.8 mg of **3s** (42% isolated yield) as a white solid. Rf = 0.18 (Hexane/EtOAc, 4:1).

\[ \text{1H NMR (300 MHz, CDCl}_3\text{)} \delta (ppm) = 8.00 (d, J = 8.1 Hz, 1H, CH), 7.80 (m, 2H, CH), 7.68 (t, J = 7.8 Hz, 1H, CH), 7.48 (m, 3H, CH), 7.40 (d, J = 7.7 Hz, 1H, CH), 7.08 (s, 1H, CH), 6.18 (s, 2H, CH\textsubscript{2}), 5.84 (s, 1H, CH), 3.17 (s, 1H, CH), 2.47 (s, 3H, CH\textsubscript{3}), 2.18 (s, 3H, CH\textsubscript{3}). \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{)} \delta (ppm) = 152.6 (C), 151.3 (C), 148.8 (C), 146.1 (C), 141.7 (C), 140.9 (C), 136.6 (CH), 130.0 (C), 129.6 (2CH), 128.9 (CH), 128.7 (3CH), 126.4 (CH), 120.0 (CH), 106.4 (CH), 105.9 (CH), 83.1 (C), 60.2 (CH\textsubscript{2}), 13.6 (CH\textsubscript{3}), 11.3 (CH\textsubscript{3}). \]

EI HRMS: calcd. for C\textsubscript{22}H\textsubscript{20}N\textsubscript{5}[M+1]\textsuperscript{+} : 354.1716, found : 354.1713.

**2-(1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pyridine (3t)**

Following **Method 3**, from 2-ethylpyridine (0.16 mmol, 17 µl), 2-bromo-1-(4-methoxyphenyl)ethanol (0.16 mmol, 37.6 mg), 3,5-dimethyl-1H-pyrazole (0.082 mmol, 8 mg) and 4-methylbenzenesulfonylhydrazide (0.12 mmol, 33.6 mg) were obtained 13.9 mg of **3t** as a yellowish oil (47% isolated yield). Rf = 0.61 (Hexane/EtOAc, 2:1).

\[ \text{1H NMR (300 MHz, CDCl}_3\text{)} \delta (ppm) = 8.64 (d, J = 4.9 Hz, 1H, CH), 8.00 (d, J = 7.9 Hz, 1H, CH), 7.77 (m, 3H, CH), 7.25 (m, 1H, CH), 7.06 (d, J = 8.8 Hz, 2H, CH), 7.01 (s, 1H, CH), 6.18 (s, 2H, CH\textsubscript{2}), 5.84 (s, 1H, CH), 3.90 (s, 3H, OCH\textsubscript{3}), 2.50 (s, 3H, CH\textsubscript{3}), 2.19 (s, 3H, CH\textsubscript{3}). \]
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 160.1 (C), 151.9 (C), 151.4 (C), 148.9 (CH), 148.8 (C), 146.1 (C), 140.9 (C), 136.8 (CH), 131.0 (2CH), 122.6 (CH), 122.0 (C), 120.3 (CH), 114.2 (2CH), 106.4 (CH), 105.1 (CH), 60.2 (CH$_2$), 55.4 (CH$_3$), 13.6 (CH$_3$), 11.37 (CH$_3$).

EI HRMS: calcd. for C$_{21}$H$_{22}$N$_5$O$^+$: 360.1818, found: 360.1819.

2-(1-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)-6-methoxypyridine (3u)

Following **Method 3**, from 2-ethynyl-6-methoxypyridine (0.1 mmol, 38.2 mg), 2-bromo-1-(4-methoxyphenyl)ethan-1-one (0.1 mmol, 22.9 mg), 3,5-dimethyl-1H-pyrazole (0.05 mmol, 4.81 mg) and 4-methylbenzenesulfonohydrazide (0.15 mmol, 27.9 mg) were obtained 18.1 mg of 3u (31% isolated yield) as a yellowish oil. Rf = 0.26 (Hexane/DCM, 1:2).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.77 (d, $J = 8.8$ Hz, 2H, CH), 7.58 (m, 2H, CH), 7.06 (d, $J = 8.8$ Hz, 2H, CH), 6.90 (s, 1H, CH), 6.68 (dd, $J = 7.0$, 2.0 Hz, 1H, CH), 6.15 (s, 2H, CH$_2$), 5.83 (s, 1H, CH), 4.00 (s, 3H, OCH$_3$), 3.90 (s, 3H, OCH$_3$), 2.53 (s, 3H, CH$_3$), 2.20 (s, 3H, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 163.6 (C), 160.1 (C), 151.9 (C), 149.5 (C), 148.7 (C), 145.7 (C), 143.0 (C), 142.9 (C), 141.0 (C), 138.9 (CH), 131.1 (2 x CH), 114.1 (2 x CH), 112.5 (CH), 109.4 (CH), 106.3 (CH), 105.2 (CH), 60.1 (CH$_2$), 55.4 (CH$_3$), 53.2 (CH$_3$), 13.6 (CH$_3$), 11.4 (CH$_3$).

EI HRMS: calcd. for C$_{22}$H$_{24}$N$_5$O$^+$: 390.1923, found: 390.1925.
2-(1-((4,5-diphenyl-1H-imidazol-1-yl)methyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)-6-methoxypyridine (3v)

Following Method 3, from 2-ethynyl-6-methoxypyridine (0.1 mmol, 38.2 mg), 2-bromo-1-(4-methoxyphenyl)ethan-1-one (0.1 mmol, 22.9 mg), 4,5-diphenyl-1H-imidazole (0.05 mmol, 11 mg) and 4-methylbenzenesulfonylhydrazide (0.15 mmol, 27.9 mg) were obtained 11 mg of 3v (43% isolated yield) as a yellow oil. Rf = 0.32 (Hexane/EtOAc, 1:1).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 7.65 (m, 2H, CH), 7.59 (m, 1H, CH), 7.39 (m, 5H, CH), 7.17 (m, 7H, CH), 6.87 (m, 3H, CH), 6.71 (d, \(J = 8.0 \text{ Hz}\), 1H, CH), 6.06 (s, 2H, CH\(_2\)), 4.01 (s, 3H, OCH\(_3\)), 3.88 (s, 3H, OCH\(_3\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 163.7 (C), 160.2 (C), 152.7 (C), 149.1 (C), 145.3 (C), 139.1 (CH), 138.1 (C), 136.9 (CH), 134.2 (C), 131.0 (2CH), 130.1 (2CH), 129.6 (C), 129.0 (2CH), 128.8 (CH), 128.1 (2CH), 127.6 (C), 126.6 (2CH), 126.5 (CH), 121.6 (C), 114.5 (2CH), 112.7 (CH), 109.8 (CH), 106.4 (CH), 57.1 (CH\(_2\)), 55.4 (CH\(_3\)), 53.2 (CH\(_3\)).

EI HRMS: calcd. for C\(_{32}\)H\(_{28}\)N\(_5\)O\(_2\) [M+1]\(^+\) : 514.2237, found : 514.2238.

2-(1-((4,5-Diphenyl-1H-imidazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-6-ethynylpyridine (3w)
Following **Method 3**, from 2,6-diethynylpyridine (0.16 mmol, 20 mg), 2-bromo-1-phenylethan-1-one (0.63 mmol, 0.125 g), 4,5-diphenyl-1H-imidazole (0.69 mmol, 0.15 g) and 4-methylbenzenesulfonohydrazide (0.69 mmol, 0.128 g) were obtained 33.7 mg of 3w (45% isolated yield) as a yellow oil. Rf = 0.4 (Hexane/EtOAc, 1:2).

\[ ^{1}H \text{ NMR (300 MHz, CDCl}_3 \delta (ppm) = 7.98 (dd, J = 8.0, 0.8 Hz, 1H, CH), 7.74 (t, J = 7.8 Hz, 1H, CH), 7.65 (s, 1H, CH), 7.40 (m, 10H, CH), 7.18 (ddd, J = 6.3, 4.4, 1.7 Hz, 6H, CH), 7.08 (s, 1H, CH), 6.07 (s, 2H, CH\textsubscript{2}), 3.18 (s, 1H, CH). \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \delta (ppm) = 152.1 (C), 151.9 (C), 145.7 (C), 141.8 (C), 138.2 (C), 137.0 (CH), 136.7 (CH), 134.1 (C), 130.9 (2CH), 129.5 (C), 129.2 (CH), 129.1 (C), 129.0 (5CH), 128.9 (CH), 128.7 (2CH), 128.1 (2CH), 127.6 (C), 126.7 (CH), 126.6 (2CH), 126.5 (CH), 120.1 (CH), 106.7 (CH), 83.0 (C), 57.2 (CH\textsubscript{2}). \]

EI HRMS: calcd. for C\textsubscript{32}H\textsubscript{24}N\textsubscript{5} [M+1]\textsuperscript{+} : 478.2021, found : 478.2026.

**8-Methoxy-1-(pyridin-2-yl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-c]pyrazole (4a)**

[Image of 4a]

Following **Method 1**, from 2-ethynylpyridine (0.1 mmol, 10\textmu l) and N’-(6-methoxy-3,4-dihydronaphthalen-1(2\textit{H})-ylidene)-4-methylbenzenesulfonohydrazide (0.12 mmol, 41.3 mg), were obtained 14.4 mg of 4a (50% isolated yield) as a colorless oil. Rf = 0.52 (Hexane/EtOAc, 3:1). In this case the slow addition was not possible as the tosylhydrazone employed was not soluble enough.

\[ ^{1}H \text{ NMR (300 MHz, CDCl}_3 \delta (ppm) = 8.65 (s, 1H, CH), 7.70 (d, J = 8.0 Hz, 1H, CH), 7.61 (t, J = 7.7 Hz, 1H, CH), 7.32-7.18 (m, 3H, CH), 6.93 (d, J = 2.6 Hz, 1H, CH), 6.81 (dd, J = 8.4, 2.7 Hz, 1H, CH), 3.88 (s, 3H, CH\textsubscript{3}), 2.69 (td, J = 7.2, 2.9 Hz, 4H, CH\textsubscript{2}), 2.24 (m, 2H, CH\textsubscript{2}). \]
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 158.5 (C), 152.7 (C), 149.5 (CH), 148.7 (C), 142.4 (C), 136.9 (C), 136.6 (CH), 129.7 (CH), 125.6 (C), 122.7 (CH), 120.7 (CH), 117.3 (C), 115.1 (CH), 111.6 (CH), 55.3 (CH$_3$), 32.6 (CH$_2$), 30.7 (CH$_2$), 23.4 (CH$_2$).

El HRMS: calcd. for C$_{18}$H$_{16}$N$_3$O [M+1]$^+$: 292.1444; found 292.1444.

8-Methoxy-1-(6-methylpyridin-2-yl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-c]pyrazole (4b)

Following Method 1, from 2-ethynyl-6-methylpyridine (0.17 mmol, 23.3 mg) and N^-(6-methoxy-3,4-dihydronaphthalen-1(2H)-ylidene)-4-methylbenzenesulfonohydrazide (0.20 mmol, 68.9 mg), were obtained 36.8 mg of 4b (71% isolated yield) as a colorless oil. Rf = 0.18 (Hexane/EtOAc, 1:3).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.48 (m, 2H, CH), 7.33 (m, 2H, CH), 7.06 (dd, $J$ = 6.0, 2.6 Hz, 1H, CH), 6.92 (d, $J$ = 2.6 Hz, 1H, CH), 6.80 (dd, $J$ = 8.4, 2.7 Hz, 1H, CH), 3.87 (s, 3H, OCH$_3$), 2.68 (td, $J$ = 7.2, 3.2 Hz, 4H, CH$_2$), 2.60 (s, 3H, CH$_3$), 2.24 (q, $J$ = 7.1 Hz, 2H, CH$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 158.5 (C), 158.4 (C), 152.7 (C), 147.9 (C), 142.4 (C), 137.0 (C), 136.8 (CH), 129.8 (CH), 125.8 (C), 122.3 (CH), 117.6 (CH), 117.0 (C), 115.0 (CH), 111.5 (CH), 55.2 (CH$_3$), 32.6 (CH$_2$), 30.7 (CH$_2$), 24.5 (CH$_3$), 23.5 (CH$_2$).

El HRMS: calcd. for C$_{19}$H$_{20}$N$_3$O [M+1]$^+$: 306.1604; found 306.1601.
 Following Method 1, from 2,6-diethynylpyridine (0.034 mmol, 4.3 mg) and (E)-N’-(2-((1H-indol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (5a), were obtained 7 mg of 5a (35% isolated yield) as a white solid. m.p. = 185 - 187 °C. Rf = 0.39 (Hexane/EtOAc, 3:1). In this case the slow addition of the tosylhydrazone was not possible owing to the lack of solubility of the hydrazone as starting material.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta \) (ppm) = 8.01 (d, \(J = 7.7\) Hz, 2H, CH), 7.81 (dd, \(J = 8.3, 7.3\) Hz, 1H, CH), 7.48 (m, 8H, CH), 7.34 (m, 4H, CH), 7.19 (m, 2H, CH), 7.09 (m, 4H, CH), 7.00 (s, 2H, CH), 6.90 (d, \(J = 3.3\) Hz, 2H, CH), 6.38 (dd, \(J = 3.3, 0.7\) Hz, 2H, CH), 6.35 (s, 4H, CH\(_2\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta \) (ppm) = 152.0 (C), 151.4 (C), 145.3 (C), 137.2 (CH), 135.6 (C), 130.1 (C), 129.4 (2CH), 129.2 (CH), 128.9 (2CH), 128.7 (C), 127.4 (CH), 122.0 (CH), 120.7 (CH), 120.1 (CH), 119.1 (CH), 110.0 (CH), 106.6 (CH), 103.0 (CH), 59.0 (CH\(_2\)).

HRMS: calcd. For [M+H] C\(_{41}\)H\(_{32}\)N\(_7\): 622.2641, found: 622.2642.
2,6-bis(1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (5b)

Following Method 1 (slow addition), from 2,6-diethynylpyridine (0.053 mmol, 6.8 mg) and (E)-N°-(2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-phenylethylidene)-4-methylbenzenesulfonylhydrazide (0.18 mmol, 70.5 mg), were obtained 11.7 mg of 5b as a white solid (44% isolated yield). m.p. = 192 - 197 °C. Rf = 0.27 (Hexane/EtOAc, 2:1).

\[^1\text{H} \text{NMR (300 MHz, CDCl}_3\] \delta (ppm) = 7.94 (d, J = 7.7 Hz, 2H, CH), 7.82 (m, 4H, CH), 7.74 (dd, J = 8.2, 7.4 Hz, 1H, CH), 7.49 (m, 6H, CH), 7.35 (m, 1H, CH), 7.10 (s, 2H, CH), 6.19 (s, 4H, CH\(_2\)), 5.83 (s, 2H, CH), 2.49 (s, 6H, CH\(_3\)), 2.19 (s, 6H, CH\(_3\)).

\[^{13}\text{C} \text{NMR (75 MHz, CDCl}_3\] \delta (ppm) = 152.2 (C), 151.5 (C), 148.7 (C), 145.9 (C), 140.9 (CH), 136.9 (C), 129.9 (C), 129.7 (2CH), 128.9 (CH), 128.7 (2CH), 118.9 (CH), 106.3 (CH), 105.7 (CH), 60.3 (CH\(_2\)), 13.6 (CH\(_3\)), 11.3 (CH\(_3\)).


tert-Butyl (S)-2-(3-((6-(1-((R)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-5-methyl-1H-pyrazol-3-yl)pyridin-2-yl)-5-methyl-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (mixture of rotamers: 1:1.1) (5c)

Following Method 1, from 2,6-diethynylpyridine (0.17 mmol, 22 mg) and 3 equivalents of tert-butyl-2-(1-(2-tosylhydrazineylidene)ethyl)pyrrolidine-1-carboxylate (0.52
mmol, 199 mg), were obtained 29 mg of 5c (30% isolated yield). In this case, the product was obtained carrying out the reaction at 90 ºC, as we observed similar yield at 110 ºC. Compound 5c is obtained as a yellow-lish oil. Rf = 0.69 (Hexane/EtOAc, 2:1).

1H NMR (300 MHz, CDCl₃) δ (ppm) = 7.85 (m, 2H, CH), 7.67 (d, J = 7.1 Hz, 1H, CH), 6.61 (m, 2H, rotamers), 5.96 (m, 2H, rotamers), 3.81 (m, 2H, rotamers), 3.48 (m, 2H, rotamers), 2.78 (m, 2H, rotamers), 2.54 (s, 3H), 2.41 (s, 3H), 1.87 (m, 6H), 1.41 (s, 9H, rotamers), 1.30 (s, 9H, rotamers).

13C NMR (75 MHz, CDCl₃) δ (ppm) = 153.6 (C), 152.2 (C), 151.1 (2C), 140.4 (2C), 138.5 (CH), 136.5 (2C), 118.1 (2CH), 103.6 (2CH), 80.3 (CH), 79.8 (CH), 69.5 (C), 68.9 (C), 46.8 (2CH₂), 34.2 (CH₂), 32.9 (CH₂), 28.4 (3CH₃), 28.3 (CH₂), 23.8 (CH₂), 22.2 (CH₂), 11.3 (2CH₃).


2,6-Bis(8-methoxy-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepin-2-yl)pyridine (5d)

Following Method 1 with slow addition, from 2,6-diethylpyridine (0.17 mmol, 22 mg) and 4 equivalents of N-(2-methoxycyclohexylidene)-4-methylbenzenesulfonylhydrazide (0.68 mmol, 201 mg), we obtained 45 mg of 5d (65% isolated yield). In this case, the product was obtained carrying out the reaction at 90 ºC, as we observed similar yield at 110 ºC. Compound 5d is obtained as a yellow-lish oil. Rf = 0.56 (Hexane/EtOAc, 2:1).

1H NMR (300 MHz, CDCl₃) δ (ppm) = 7.84 (dd, J = 8.2, 1.0 Hz, 2H, CH), 7.74 (dd, J = 8.7, 6.9 Hz, 1H, CH), 6.81 (s, 2H, 2CH), 5.59 (d, J = 3.5 Hz, 2H, 2CH), 3.25 (s, 6H, 2OCH₃), 2.96 (dd, J = 13.0, 5.7 Hz, 1H, CH₂), 2.79 (t, J = 13.4 Hz, 2H, CH₂), 2.31 (m, 3H, CH₂, CH₂), 2.09 (m, 3H, OCH₃), 1.83 (m, 4H, 2CH₂), 1.45 (q, J = 12.9 Hz, 2H, CH₂).

13C NMR (75 MHz, CDCl₃) δ (ppm) = 151.8 (2C), 149.8 (2C), 145.5 (CH), 137.1 (2C), 118.5 (2CH), 105.6 (2CH), 91.9 (2CH), 55.8 (2OCH₃), 32.6 (CH₂), 27.4 (CH₂), 25.9 (CH₂), 23.2 (CH₂).
HRMS: calcd. For [M+H] C_{23}H_{30}N_{5}O_{2}: 408.2321, found: 408.2458.

1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrazole (8a)

Following **Method 2**, from 1-ethynyl-4-(trifluoromethyl)benzene (0.15 mmol, 25.6 mg), (E)-N'-((2-bromo-1-phenylethylidene)-4-methylbenzenesulfonylhydrazide (0.15 mmol, 55.1 mg) and 3,5-dimethyl-1H-pyrazole (0.075 mmol, 7.21 mg) were obtained 10.8 mg of 8a (41% isolated yield) as a white solid. m.p. = 104 – 107 °C. Rf = 0.69 (Hexane/DCM, 1:2).

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 7.92 (d, \(J = 8.1\) Hz, 2H, CH), 7.81 (dd, \(J = 7.9, 1.5\) Hz, 2H, CH), 7.64 (d, \(J = 8.2\) Hz, 2H, CH), 7.51 (m, 3H, CH), 6.67 (s, 1H, CH), 6.17 (s, 2H, CH\(_2\)), 5.85 (s, 1H, CH), 2.52 (s, 3H, CH\(_3\)), 2.21 (s, 3H, CH\(_3\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) (ppm) = 150.1 (C), 149.0 (C), 146.3 (C), 141.0 (C), 136.6 (C), 129.7 (2CH), 129.6 (q, \(J_{CF} = 9.0\) Hz, C), 129.1 (CH), 128.8 (2CH), 126.1 (C), 125.8 (2CH), 125.6 (CH), 125.5 (q, \(J_{CF} = 4.3\) Hz, 2CH), 106.4 (CH), 104.3 (CH), 60.1 (CH\(_2\)), 13.6 (CH\(_3\)), 11.4 (CH\(_3\)).

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) (ppm) = -62.5

HRMS: calcd. For [M+H] C_{22}H_{20}F_{3}N_{4}: 397.1629, found: 397.1635.

1-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-3-(4-fluorophenyl)-5-phenyl-1H-pyrazole (8b)
Following **General Method 2**, from 1-ethynyl-4-fluorobenzene (0.16 mmol, 18.7 µl), (E)-N’-(2-bromo-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.16 mmol, 58.8 mg) and 3,5-dimethyl-1H-pyrazole (0.082 mmol, 7.9 mg) were obtained 8.6 mg of **8b** (40% isolated yield) as a yellow solid. m.p. = 123 – 125 ºC. Rf = 0.55 (Hexane/DCM, 1:2).

\[ 1^\text{H} \text{NMR (300 MHz, CDCl}_3 \delta (ppm) = 7.80 (m, 4H, CH), 7.52 (m, 3H, CH), 7.10 (t, J = 8.7 Hz, 2H, CH), 6.57 (s, 1H, CH), 6.15 (s, 2H, CH\textsubscript{2}), 5.84 (s, 1H, CH), 2.50 (s, 3H, CH\textsubscript{3}), 2.20 (s, 3H, CH\textsubscript{3}). \]

\[ 1^\text{C} \text{NMR (75 MHz, CDCl}_3 \delta (ppm) = 162.6 (d, J\textsubscript{CF} = 251.2 Hz, C), 150.6 (C), 148.8 (C) 146.1 (C), 141.0 (C), 129.8 (C), 129.7 (2CH), 129.3 (d, J\textsubscript{CF} = 4.6 Hz, C), 129.0 (CH), 128.7 (2CH), 127.4 (d, J\textsubscript{CF} = 7.6 Hz, 2CH), 125.6 (CH), 115.6 (CH), 115.4 (d, J\textsubscript{CF} = 22.4 Hz, 2CH), 106.3 (CH), 103.7 (CH), 60.0 (CH\textsubscript{2}), 13.6 (CH\textsubscript{3}), 11.4 (CH\textsubscript{3}). \]

\[ 1^\text{F} \text{NMR (282 MHz, CDCl}_3 \delta (ppm) = -114.24. \]

HRMS: calcd. For [M+H] C\textsubscript{21}H\textsubscript{20}FN\textsubscript{4}: 347.1668, found: 347.1667.

**1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-3,5-diphenyl-1H-pyrazole (8c)**

Following **Method 3**, from ethynylbenzene (0.16 mmol, 18 µl), 2-bromo-1-phenylethan-1-one (0.16 mmol, 32.6 mg), 3,5-dimethyl-1H-pyrazole (0.082 mmol, 7.9 mg) and 4-methylbenzenesulfonohydrazide (0.16 mmol, 33.5 mg) were obtained 11 mg of **8c** (41% isolated yield) as a colorless oil. Rf = 0.24 (DCM).

\[ 1^\text{H} \text{NMR (300 MHz, CDCl}_3 \delta (ppm) = 7.82 (m, 4H, CH), 7.49 (m, 3H, CH), 7.39 (t, J = 7.3 Hz, 2H, CH), 7.32 (d, J = 7.3 Hz, 1H, CH), 6.63 (s, 1H, CH), 6.16 (s, 2H, CH\textsubscript{2}), 5.83 (s, 1H, CH), 2.53 (s, 3H, CH\textsubscript{3}), 2.20 (s, 3H, CH\textsubscript{3}). \]

\[ 1^\text{C} \text{NMR (75 MHz, CDCl}_3 \delta (ppm) = 151.5 (C), 148.7 (C), 145.9 (C), 141.0 (C), 133.1 (C), 129.9 (C), 129.6 (2CH), 128.9 (CH), 128.7 (2CH), 128.5 (2CH), 127.9 (CH), 125.6 (2CH), 106.3 (CH), 103.9 (CH), 60.1 (CH\textsubscript{2}), 13.6 (CH\textsubscript{3}), 11.4 (CH\textsubscript{3}). \]

HRMS: calcd. For [M+H] C\textsubscript{21}H\textsubscript{21}N\textsubscript{4}: 329.1762, found: 329.1761.
1-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-3-(4-methoxyphenyl)-5-phenyl-1H-pyrazole (8d)

Following General Method 2, from 1-ethynyl-4-methoxybenzene (0.32 mmol, 41.5 µl), N'-{(2-bromo-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.32 mmol, 0.12 g) and 3,5-dimethyl-1H-pyrazole (0.16 mmol, 0.16 g) were obtained 33.3 mg of 8d (58% isolated yield) as a yellow solid. m.p. = 130 – 134 °C. Rf = 0.36 (Hexane/EtOAc, 1:1).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.79 (ddd, $J = 8.9, 7.5, 1.9$ Hz, 4H, CH), 7.51 (ddd, $J = 8.6, 7.6, 6.1$ Hz, 3H, CH), 6.95 (d, $J = 8.9$ Hz, 2H, CH), 6.55 (s, 1H, CH), 6.14 (s, 2H, CH$_2$), 5.83 (s, 1H, CH), 3.86 (s, 3H, OCH$_3$), 2.51 (s, 3H, CH$_3$), 2.19 (s, 3H, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 159.5 (C), 151.3 (C), 148.6 (C), 145.9 (C), 141.0 (C), 130.0 (C), 129.6 (2CH), 128.8 (CH), 128.7 (2CH), 128.4 (C), 126.9 (2CH), 113.9 (2CH), 106.3 (CH), 103.5 (CH), 60.1 (CH$_2$), 55.3 (OCH$_3$), 13.6 (CH$_3$), 11.4 (CH$_3$).

HRMS: calcd. For [M+H] C$_{22}$H$_{23}$N$_4$O: 359.1865, found: 359.1866.

1-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-3-(thiophen-3-yl)-1H-pyrazole (8e)

Following General Method 2, from 3-ethynlythiophene (0.32 mmol, 31.5 µl), N’-(2-bromo-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.32 mmol, 0.12 g) and 3,5-dimethyl-1H-pyrazole (0.16 mmol, 0.16 g) were obtained 25.1 mg of 8e (47% isolated yield) as a yellow oil. Rf = 0.62 (Hexane/EtOAc, 3:1).
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.80 (dd, $J = 8.0$, 1.5 Hz, 2H, CH), 7.59 (dd, $J = 3.0$, 1.2 Hz, 1H, CH), 7.51 (m, 4H, CH), 7.35 (dd, $J = 5.0$, 3.0 Hz, 1H, CH), 6.51 (s, 1H, CH), 6.14 (s, 2H, CH$_2$), 5.82 (s, 1H, CH), 2.49 (d, $J = 0.5$ Hz, 3H, CH$_3$), 2.19 (s, 3H, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 148.7 (C), 147.9 (C), 145.7 (C), 141.0 (C), 135.0 (C), 129.8 (C), 129.7 (2CH), 128.9 (CH), 128.7 (2CH), 126.0 (CH), 125.8 (CH), 120.8 (CH), 106.3 (CH), 104.3 (CH), 60.1 (CH$_2$), 13.6 (CH$_3$), 11.3 (CH$_3$).

HRMS: calcd. For [M+H] C$_{19}$H$_{19}$N$_4$S: 335.1319, found: 335.1325.

2-((5-(4-Methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)-2H-benzo[d][1,2,3]triazole (8f)

Following General Method 2, from 1-ethynyl-4-methoxybenzene (0.32 mmol, 41.2 µl), N’-(2-bromo-1-phenylethylidene)benzenesulfonohydrazide (0.32 mmol, 0.12 g) and 2H-benzo[d][1,2,3]triazole (0.16 mmol, 19 mg) were obtained 31.7 mg of 8f (52% isolated yield) as a yellow oil. Rf = 0.64 (Hexane/EtOAc, 1:1).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 8.07 (d, $J = 9.3$ Hz, 2H, CH), 7.84 (dd, $J = 11.8$, 4.8 Hz, 4H, CH), 7.58 (m, 4H, CH), 6.98 (d, $J = 8.8$ Hz, 2H, CH), 6.86 (s, 2H, CH$_2$), 6.59 (s, 1H, CH), 3.87 (s, 3H, OCH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 159.8 (C), 152.1 (C), 146.3 (C), 146.2 (C), 133.1 (C), 129.9 (C), 129.4 (2CH), 129.3 (C), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.0 (2CH), 126.1 (CH), 124.4 (CH), 119.8 (CH), 114.1 (CH), 111.3 (CH), 104.3 (CH), 60.1 (CH$_2$), 55.3 (OCH$_3$).

HRMS: calcd. For [M+H] C$_{23}$H$_{20}$N$_5$O: 382.1655, found: 382.1656.
1-((4,5-Diphenyl-1H-imidazol-1-yl)methyl)-3,5-diphenyl-1H-pyrazole (8g)

Following Method 2, from phenylacetylene (0.32 mmol, 36 µl), N′-(2-bromo-1-phenylethylidene)benzenesulfonohydrazide (0.32 mmol, 0.12 g) and 4,5-diphenyl-1H-imidazole (0.16 mmol, 35 mg) were obtained 48.5 mg of 8g (67% isolated yield) as a yellow oil. Rf = 0.10 (Hexane/EtOAc, 3:1).

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 7.85 (m, 2H, CH), 7.65 (s, 1H, CH), 7.41 (m, 14H, CH), 7.19 (m, 4H, CH), 6.64 (s, 1H, CH), 6.06 (s, 2H, CH$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 152.3 (C), 145.7 (C), 138.1 (C), 136.9 (CH), 134.1 (C), 132.6 (C), 131.0 (2CH), 129.5 (C), 129.4 (C), 129.2 (CH), 129.1 (2CH), 129.0 (2CH), 128.9 (CH), 128.7 (2CH), 128.7 (2CH), 128.4 (CH), 128.3 (2CH), 126.6 (2CH), 126.5 (CH), 125.8 (2CH), 125.1 (C), 105.0 (CH), 57.1 (CH$_2$).

HRMS: calcd. For [M+H] C$_{31}$H$_{25}$N$_4$: 453.2061, found: 453.2074.

1-((4,5-Diphenyl-1H-imidazol-1-yl)methyl)-3-(4-methoxyphenyl)-5-phenyl-1H-pyrazole (8h)

Following Method 2, from phenylacetylene (0.32 mmol, 36 µl), N′-(2-bromo-1-phenylethylidene)-4-methylbenzenesulfonohydrazide (0.32 mmol, 0.12 g) and 4,5-diphenyl-1H-imidazole (0.16 mmol, 35 mg) were obtained 34.7 mg of 8h (45% isolated yield) as a yellow oil. Rf = 0.25 (Hexane/diethyl ether, 1:30).
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ (ppm) = 7.84 (m, 3H, CH), 7.67 (s, 1H, CH), 7.56 (d, $J$ = 7.8 Hz, 1H, CH), 7.42 (m, 6H, CH), 7.17 (m, 7H, CH), 6.89 (d, $J$ = 8.8 Hz, 3H, CH), 6.58 (s, 1H, CH), 6.05 (s, 2H, CH$_2$), 3.88 (s, 3H, OCH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ (ppm) = 160.2 (C), 152.2 (C), 145.5 (C), 136.9 (CH), 134.2 (C), 132.7 (C), 131.0 (2CH), 130.0 (2CH), 129.0 (2CH), 128.8 (CH), 128.7 (2CH), 128.5 (CH), 128.2 (CH), 128.1 (2CH), 126.6 (2CH), 126.5 (C), 125.7 (2CH), 121.6 (C), 114.5 (2CH), 114.0 (C), 113.7 (C), 104.7 (CH), 57.0 (CH$_2$), 55.4 (OCH$_3$).

HRMS: calcd. For [M+H] C$_{32}$H$_{27}$N$_4$O: 483.2165, found: 483.2179.

**4. Synthesis of polyheterocycle 10 by click reaction starting from 3s.**

A reaction tube was charged with 1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-6-ethynlypyridine (3s) (0.07 mmol, 25 mg), 2-bromo-1-phenylethan-1-one 10 (0.07 mmol, 14 mg), sodium azide (0.074 mmol, 5 mg), CuSO$_4$·5H$_2$O (5 mol%), sodium ascorbate (10 mol%) and a 1:1 mixture of $^1$BuOH/H$_2$O (4 ml). After 2 h at 60 °C, the reaction was stirred at room temperature during 20 min and 5 ml of 10% NH$_3$ solution were added to the reaction mixture. The yellow precipitate formed was filtered and dried under vacuum. The crude was purified by flash chromatography (silica gel, a mixture of Hexane/AcOEt 1:1 as eluent) and 9.4 mg of the pure product 10 as a yellowish solid were obtained.
2-(5-(6-(1-((3,5-Dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridin-2-yl)-1H-1,2,3-triazol-1-yl)-1-phenylethan-1-one (10)

m. p. = 230 – 232 °C
Rf = 0.43 (Hexane/AcOEt, 1:1)

$^1$H NMR (300 MHz, CDCl$_3$) δ (ppm) = 8.43 (s, 1H, CH), 8.13 (d, $J$ = 7.6 Hz, 1H, CH), 8.04 (d, $J$ = 7.4 Hz, 2H, CH), 7.95 (d, $J$ = 7.5 Hz, 1H, CH), 7.82 (t, $J$ = 7.6 Hz, 3H, CH), 7.67 (t, $J$ = 7.4 Hz, 1H, CH), 7.51 (m, 5H, CH), 7.04 (s, 1H, CH), 6.19 (s, 2H, CH$_2$), 5.93 (s, 2H, CH$_2$), 5.83 (s, 1H, CH), 2.48 (s, 3H, CH$_3$), 2.17 (s, 3H, CH$_3$).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ (ppm) = 190.0 (C), 151.9 (C), 151.6 (C), 149.6 (C), 149.0 (C), 148.8 (C), 146.0 (C), 141.0 (C), 137.3 (CH), 134.6 (CH), 134.0 (C), 129.8 (C), 129.7 (2CH), 129.2 (2CH), 128.9 (CH), 128.7 (2CH), 128.2 (2CH), 124.2 (CH), 119.2 (CH), 119.1 (CH), 106.4 (CH), 105.7 (CH), 60.2 (CH$_2$), 55.6 (CH$_2$), 13.6 (CH$_3$), 11.3 (CH$_3$).

HRMS: calcd. For [M+H] C$_{30}$H$_{27}$N$_8$O: 515.5930, found: 515.5932.
5. Copies of the $^1$H and $^{13}$C NMR spectra.

2-(1-Benzyl-5-phenyl-$^{1}H$-pyrazol-3-yl)pyridine (3a)
2-(1-benzyl-5-phenyl-1H-pyrazol-3-yl)-6-bromopyridine (3b)
2-(1-(Methoxymethyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (3c)
8-Methoxy-2-(pyridin-2-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine (3d)
(R)-8-methoxy-2-(6-methylpyridin-2-yl)-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine (3e)
(R)-2-(6-bromopyridin-2-yl)-8-methoxy-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepine (3f)
2-[(3,5-dimethyl-1H-pyrazol-1-yl)methyl]-5-phenyl-1H-pyrazol-3-yl]pyridine (3g)
2-(1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-6-methoxypyridine (3h)
1-[(5-Phenyl-3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl]-1H-indole (3i)
2-(1-((4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (3j)
tert-Butyl (S)-2-(5-methyl-3-(pyridin-2-yl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (3k)
**tert-Butyl (S)-2-(3-(6-ethynylpyridin-2-yl)-5-methyl-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (3l)**
(S)-2-(5-methyl-1-(3-methyl-1-(1H-pyrrolo-1-yl)butyl)-1H-pyrazol-3-yl)pyridine
(3m)
2-(1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-5-ethynylpyridine (3n)
1-((5-phenyl-3-(pyridin-2-yl)-1H-pyrazol-1-yl)methyl)-1H-benzo[d][1,2,3]triazole (3a)
1-((3-(6-methoxypyridin-2-yl)-5-phenyl-1H-pyrazol-1-yl)methyl)-1H-benzo[d][1,2,3]triazole (3p)
2-(1-((4,5-diphenyl-1H-imidazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (3q)
2-(1-((4,5-diphenyl-1H-imidazol-1-yl)methyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pyridine (3r)
2-(1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-6-ethynylpyridine (3s)
2-(1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)pyridine (3t)
2-(1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)-6-methoxypyridine (3u)
2-(1-((4,5-diphenyl-1H-imidazol-1-yl)methyl)-5-(4-methoxyphenyl)-1H-pyrazol-3-yl)-6-methoxypyridine (3v)
2-(1-((4,5-diphenyl-1H-imidazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)-6-ethynylpyridine (3w)
8-methoxy-1-(pyridin-2-yl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-c]pyrazole (4a)
8-methoxy-1-(6-methylpyridin-2-yl)-3,4,5,6-tetrahydrobenzo[3,4]cyclohepta[1,2-c]pyrazole (4b)
2,6-bis(1-((1H-indol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (5a)
2,6-bis(1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridine (5b)
tert-butyl \((S)-2-(3-(6-(1-(R)-1-(tert-butoxycarbonyl)pyrrolidin-2-yl)-5-methyl-1H-pyrazol-3-yl)pyridin-2-yl)-5-methyl-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (5c)\)
2,6-bis(8-methoxy-5,6,7,8-tetrahydro-4H-pyrazolo[1,5-a]azepin-2-yl)pyridine (5d)
1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-3-(4-(trifluoromethyl)phenyl)-1H-pyrazole (8a)
1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-3-(4-fluorophenyl)-5-phenyl-1H-pyrazole

(8b)
1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-3,5-diphenyl-1H-pyrazole (8c)
1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-3-(4-methoxyphenyl)-5-phenyl-1H-pyrazole (8d)
1-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-3-(thiophen-3-yl)-1H-pyrazole (8e)
2-\(((5\-(4\-methoxyphenyl)-3\-phenyl-1H\-pyrazol-1\-yl)methyl)-2H\-benzo[d][1,2,3]triazole (8f)
1-((4,5-diphenyl-1H-imidazol-1-yl)methyl)-3,5-diphenyl-1H-pyrazole (8g)
1-((4,5-diphenyl-1H-imidazol-1-yl)methyl)-3-(4-methoxyphenyl)-5-phenyl-1H-pyrazole (8h)
2-(5-(6-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-5-phenyl-1H-pyrazol-3-yl)pyridin-2-yl)-1H-1,2,3-triazol-1-yl)-1-phenylethan-1-one (10)