Cite this: RSC Adv., 2021, 11, 9756

Received 13th January 2021
Accepted 23rd February 2021
DOI: 10.1039/d1ra00314c
rsc.li/rsc-advances

# Access and modulation of substituted 1-methyl-1,6-dihydropyrazolo[3,4-c] pyrazoles $\dagger$ 

Nicu-Cosmin Ostache, (D) ${ }^{\text {ab }}$ Marie-Aude Hiebel, (D) ${ }^{\text {a }}$ Adriana-Luminiţa Fînaru, (D) ${ }^{\text {b }}$ Hassan Allouchi, ${ }^{\text {c }}$ Gérald Guillaumet ${ }^{a}$ and Franck Suzenet (iD *a


#### Abstract

Despite the pharmacological potential of the pyrazolo[3,4-c]pyrazoles, only a few methods of preparation and direct functionalization of this moiety have been described. We report herein a convenient design of new pyrazolo[3,4-c]pyrazoles with a high therapeutic impact. The effective chosen strategy consists of hydrazine condensations and $\mathrm{C}-\mathrm{N}$ Ullmann-type cross-coupling reactions with microwave activation. Moreover, chemoselective bromination of the newly formed bipyrazoles followed by Suzuki-Miyaura cross-coupling reactions allowed the synthesis of a variety of modulated heterobicycles.


## Introduction

Fused bicyclic heterocycles are ubiquitous in nature. The most prominent include biological macromolecules (DNA and RNA with their purine bases), proteins and peptides, as well as physiologically important biomolecules (serotonin, melatonin etc.). ${ }^{1}$ In contrast, bicyclic heterocycles containing a nitrogennitrogen $(\mathrm{N}-\mathrm{N})$ bond are relatively rare in nature, but nonetheless prevalent in the pharmaceutical industry. ${ }^{2}$ Such a class is well represented by the ring-contracted [5:5] bicyclic aromatic rings. Among this group, the pyrazolo[3,4-c]pyrazole nucleus stands out from the little attention it was given, despite previous reports of interesting biologically activities. ${ }^{3-7}$ Differences in the distribution of ring electron densities and in spatial orientation between [5:5] bicyclic aromatic rings and their [6:5] and [6:6] analogs could explain these interesting therapeutic effects. ${ }^{8}$

The synthesis of this bicyclic scaffold are scarcely found in the literature and are almost exclusively based on an existing pyrazole motif. ${ }^{9-11}$ The desired bicyclic framework is afterward obtained either according to a mononuclear heterocyclic rearrangement ${ }^{1,8}$ (known as Boulton-Katritzky rearrangement Route A), an annulation strategy (Route B) ${ }^{12-17}$ or other miscellaneous methods (using isothiocyanates, ${ }^{\mathbf{1 8}}$ nitrilimines, ${ }^{9}$ arylsemicarbazides ${ }^{19}$ or 2-cyano- $N$-methyl-acrylamide ${ }^{20}$ ).

[^0]These methods, while apparently abundant, exhibit nonetheless several major limitations such as a narrow functional group tolerance, a lack of further modulation, a non-convergent strategy, multiple steps and complex starting materials (Scheme 1a). In order to overcome these difficulties, we hereby present an efficient one-pot approach and a robust process in the design of novel pyrazolo[3,4-c] pyrazoles, using the 5-bromo-1-methyl$1 H$-pyrazole- 4 -carbaldehyde ${ }^{21,22}$ (1) (Scheme 1b). The first modulation arises from the use of diverse aromatic hydrazines, followed by a C-N Ullmann-type cross-coupling reaction under microwave irradiation, leading to compound 2 . Chemoselective bromination of the formed bipyrazole ensures the formation of further functionalized scaffolds by a Suzuki-Miyaura crosscoupling. The main text of the article should appear here with headings as appropriate.

## Results and discussion

The one-pot sequence for the synthesis of the bipyrazole 2 a relies on previous studies on similar heterocycles. ${ }^{23-26}$ The


Scheme 1 State of the art and retrosynthetic approach.

Table 1 Optimization for the cyclization step


| Entry | DMEDA (mol\%) | CuI (mol\%) | $t$ <br> $(\mathrm{~min})$ | $T\left({ }^{\circ} \mathrm{C}\right)$ | Yield $^{a}(\%)$ |
| :--- | :---: | :---: | :--- | :--- | :--- |
| 1 | 10 | 5 | 30 | 120 | 36 |
| 2 | 10 | 5 | 30 | 150 | $64(30)^{b}(47)^{c}$ |
| 3 | 20 | 10 | 30 | 150 | 56 |
| 4 | 5 | 2.5 | 30 | 150 | $64^{d}$ |
| 5 | 5 | 2.5 | 60 | 150 | 73 |
| 6 | 10 | - | 30 | 150 | $28(0)^{c}$ |
| 7 | - | - | 30 | 150 | $13(0)^{c}$ |
| 8 | - | 2.5 | 60 | 150 | 76 |

${ }^{a}$ Isolated yield after silica gel chromatography purification. ${ }^{b}$ Yield obtained with conventional heating. ${ }^{c}$ Result obtained with 5-chloro-1-methyl- $1 H$-pyrazole-4-carbaldehyde as starting material. ${ }^{d}$ Traces of starting material present.
condensation step occurred quantitatively with a slight excess of phenylhydrazine. After a change of solvent and addition of the Ullmann-type catalysts, the expected fused heterocycle was obtained in an encouraging yield (Table 1, entry 1 ).

Increasing the reaction temperature to $150{ }^{\circ} \mathrm{C}$ allowed a significant yield improvement (Table 1, entries 2). The amount of catalyst and ligand was investigated and reducing to half the initial quantities lead to an identical yield, alongside traces of starting material (Table 1, entries 3-4). The chlorinated analogue was tried but gave lower yield. In order to increase the conversion to its fullest, the reaction time was doubled (Table 1, entry 5). Finally, the sole use of copper catalyst was proven to be

Table 2 Scope for the annulation step


| Entry | R-NH-NH2 | Product (yield\%) |
| :---: | :---: | :---: |
| 1 | Ph | 2a (76, $69^{b} \mathrm{~b}$ ) |
| 2 | $4-\mathrm{CH}_{3}-\mathrm{C}_{6} \mathrm{H}_{4}{ }^{a}$ | 2b (64) |
| 3 | $4-\mathrm{CH}_{3} \mathrm{O}-\mathrm{C}_{6} \mathrm{H}_{4}{ }^{a}$ | 2c ( $46,62^{\text {c }}$ ) |
| 4 | $4-\mathrm{CN}-\mathrm{C}_{6} \mathrm{H}_{4}{ }^{\text {a }}$ | 2d (76) |
| 5 | $4-\mathrm{CF}_{3}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 2e (54, $50{ }^{\text {d }}$ ) |
| 6 | $4-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}{ }^{a}$ | 2 f (62) |
| 7 | $3-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}{ }^{a}$ | 2g (85) |
| 8 | $2-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}{ }^{a}$ | 2h (46) |
| 9 | 4-Pyridine | 2 i (46) |

${ }^{a}$ Hydrazine used in a hydrochloride salt form. ${ }^{b}$ Reaction performed on 1.00 g of $1 .{ }^{c}$ Reaction performed on 2.40 g of $1 .{ }^{d}$ Reaction performed on 1.45 g of $\mathbf{1}$.
essential for the cyclization giving access to the optimized reaction conditions (Table 1, entries 6-8).

Next, the scope and generality of the cyclization step were examined (Table 2). Nonetheless, the condensation of various monosubstituted aromatic hydrazines requires two different reaction conditions, depending on the nature of the arylhydrazines. When salt free arylhydrazines are involved, a catalytic amount of acid is used (1) while under their hydrochloride salt form, a stoichiometric amount of sodium acetate is required (1*).

Hydrazines bearing electron-donating (Table 2, entries 1-3) or electron-withdrawing groups (Table 2, entries 4 and 5) were equally well tolerated since the corresponding pyrazolo[3,4-c] pyrazoles (2a-e) were isolated with good to excellent yields over the two steps. Regarding the fluoro substituent position (ortho, meta or para) on the aromatic ring, a slight effect was observed in favor of the meta position (Table 2, entries 6-8). Furthermore, heterocyclic hydrazines were found to be an accessible partner for the annulation step (Table 2, entry 9).

The scope of the reaction is unfortunately limited to aryl hydrazines since hydrazine lead to a bis-condensated compound, and alkylhydrazines to degradation or a lack of conversion.

We afterwards focused our attention on the insertion of a second point of diversity through a bromination step followed by a Suzuki-Miyaura cross-coupling reaction. The bromide was selectively introduced on C3. ${ }^{27}$ The ratio of the monobrominated (3a) and dibrominated (3a') compounds was optimized through diverse reaction conditions (Table 3).

A partial conversion was noticed, with the formation a mixture of a mono- and dibrominated analogue when using a slight excess of halogenation agent (Table 3, entry 1). Determined by this result, the amount of NBS was increased up to 1.5 equivalents, action that lead to a total conversion and an increased yield of the monobrominated bicycle of $69 \%$ (Table 3, entries 2 and 3). In order to render the reaction faster, conventional heating was replaced by microwave irradiation. Better results were attained after only 2 hours of reaction time (Table 3, entry 4).

After establishing the best reaction conditions which allow the major formation of the monobrominated bipyrazole, the

Table 3 Optimization for the bromination step


|  |  |  | $t$ |  |  |  |
| :--- | :--- | :--- | :--- | :--- | :--- | :--- |
| Entry | NBS (eq.) | Heating | (h) | $\mathbf{3 a}^{a}(\%)$ | $\mathbf{3 a}^{a}(\%)$ | $\mathbf{2 a} \mathbf{a}^{a}(\%)$ |
| 1 | 1.1 | Conventional | 24 | 27 | 10 | 40 |
| 2 | 1.3 | Conventional | 24 | 45 | 13 | 26 |
| 3 | 1.5 | Conventional | 24 | 69 | 19 | 0 |
| 4 | 1.5 | $\mu$ Wave | 2 | 77 | 17 | 0 |
| Isolated yield after silica gel chromatography purification. |  |  |  |  |  |  |

Table 4 Reactivity study of bipyrazoles towards the bromination step

Table 5 Generalization for the Suzuki-Miyaura cross-coupling reaction


| Entry | SM ( $\mathrm{R}^{1}$ ) | $\mathrm{R}^{2}$ | Yield (\%) |  |
| :---: | :---: | :---: | :---: | :---: |
| 1 | $3 \mathrm{a}\left(\mathrm{R}^{1}=\mathrm{H}\right)$ | 4-CH3-C6 $\mathrm{H}_{4}$ | 83 | 4 a |
| 2 |  | $3-\mathrm{CH}_{3}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 89 | 4b |
| 3 |  | $2-\mathrm{CH}_{3}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 86 | 4 c |
| 4 |  | Ph | 92 | 4d |
| 5 |  | $4-\mathrm{CH}_{3} \mathrm{O}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 90 | 4 e |
| 6 |  | $4-\mathrm{CF}_{3}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 86 | 4 f |
| 7 |  | $4-\mathrm{CN}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 72 | 4 g |
| 8 |  | $3-\mathrm{F}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 90 | 4h |
| 9 |  | 3-Thiophene | $85^{a} \mathrm{a}$ | 4 i |
| 10 |  | 4-Pyridine | 78 | 4j |
| 11 |  | Styril | 64 | 4k |
| 12 | 3b $\left(\mathrm{R}^{1}=\mathrm{OCH}_{3}\right)$ | $4-\mathrm{CN}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 75 | 41 |
| 13 |  | 4-Pyridine | 76 | 4 m |
| 14 |  | $4-\mathrm{CH}_{3} \mathrm{O}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 80 | 4n |
| 15 | $3 \mathrm{c}\left(\mathrm{R}^{1}=\mathrm{CF}_{3}\right)$ | $4-\mathrm{CN}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 68 | 40 |
| 16 |  | 4-Pyridine | 79 | 4p |
| 17 |  | $4-\mathrm{CH}_{3} \mathrm{O}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 94 | 4q |
| 18 |  | $4-\mathrm{CH}_{3}-\mathrm{C}_{6} \mathrm{H}_{4}$ | 86 | 4r |

${ }^{a} 2 \mathrm{~h}$ of $\mu$ Wave irradiation necessary for total conversion.

Suitably, independent of the electronic nature of the functional group present on the aromatic moiety, the Suzuki-Miyaura cross-coupling reaction allowed very good to excellent yields (Table 5, entries 12-18).

Compound $4 \mathbf{n}$ was found appropriate for X-ray single crystallography, which confirmed that the bromination and


Fig. 1 ORTEP representation of pyrazolo[3,4-c]pyrazole 4n.
subsequent cross-coupling reaction take place at the C-3 position on the pyrazolo[3,4-c]pyrazoles (Fig. 1). ${ }^{29}$

## Conclusions

In summary, the quick access towards variously functionalized pyrazolo $[3,4-c]$ pyrazoles is herein described, starting from 5-bromo-1-methyl- 1 H -pyrazole-4-carbaldehyde (1). The approach relies on the use of substituted aromatic hydrazines engaged in efficient one-pot sequences. Thus the formed bipyrazoles were subsequently modulated by chemoselective bromination followed by high-yielding Suzuki-Miyaura crosscoupling reactions.

## Experimental section

## Materials and methods

All reagents and organic solvents were purchased from commercial suppliers and were used without further purification. Microwave assisted reactions were carried out in a Biotage Initiator microwave synthesis instrument and temperatures were measured by an IR sensor. Solvents mentioned as dry were purified with a dry station GT S100 immediately prior to use. The reactions were monitored by thin-layer chromatography (TLC) analysis using 0.2 mm precoated Kieselgel 60 F254 (Merck) silica gel plates visualized with a Macherey Nagel UV254 lamp. Column chromatography was performed on silica gel 60 (230-400 mesh, 40-63 $\mu \mathrm{m}$ ). Solvent ratios for chromatography and are reported as $\mathrm{v} / \mathrm{v}$ ratios and are indicated for each compound. Melting points ( $\mathrm{mp}\left[{ }^{\circ} \mathrm{C}\right]$ ) were taken on samples in open capillary tubes and are uncorrected on an IA9200 Thermo Scientific Electrothermal Melting Point apparatus/instrument. Infrared analyses were determined on a Thermo Scientific ATR Nicolet iS10 and interpreted using OMNIC software. ${ }^{1} \mathrm{H}$ NMR and ${ }^{13} \mathrm{C}$ NMR spectra were recorded either on a Bruker ULTRASHIELD® PLUS 400 MHz spectrometer $\left({ }^{13} \mathrm{C}, 100 \mathrm{MHz}\right)$ or on a Bruker AVANCE $250 \mathrm{MHz}\left({ }^{13} \mathrm{C}, 62.9 \mathrm{MHz}\right)$ spectrometer, as solutions in deuterated solvents. Unless otherwise indicated, chemical shifts ( $\delta$ ) are reported in parts per million (ppm) values, and coupling constants $(J)$ are reported in Hertz. Peak multiplicities are designated by the following abbreviations: $\mathrm{s}=$ singlet; $\mathrm{d}=$ doublet; $\mathrm{t}=$ triplet; $\mathrm{q}=$ quartet; $\mathrm{m}=$ multiplet; dd $=$ double doublet, $\mathrm{br}=$ broadened. High-resolution mass spectrometry analyses (HRMS) were performed on a Maxis Bruker 4G Spectrometer. X-ray diffraction data were collected on Xcalibur CCD area detector diffractometer equipped with monochromatized Mo-K $\alpha$ radiation $(0.71073 \AA$ ) at 296 K . The data collection, unit cell refinement, and data reduction were performed using the CrysAlis Pro, Oxford Diffraction Ltd. software package. Analytical numeric absorption correction using a multifaceted crystal model based on expressions derived was carried. The positions of non-H atoms were determined and refinement by SHELXS-2014 program. Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F2 using SHELXL-2014 program.

## Synthetic procedures

Synthesis of starting material compound 1. Copper(II) bromide ( $6.3 \mathrm{~g}, 0.0283 \mathrm{~mol}$ ) and tert-butyl nitrite ( $4.2 \mathrm{~mL}, 0.0354$ mol ) were combined in acetonitrile ( 50 mL ). Commercial ethyl 5-amino-1-methyl-1H-pyrazole-4-carboxylate ( $4.0 \mathrm{~g}, 0.0236 \mathrm{~mol}$ ) was slowly added portionwise, and the reaction was maintained left at room temperature for 30 minutes. The mixture was cooled to room temperature, poured into aqueous hydrochloric $\operatorname{acid}(6 \mathrm{~N}, 160 \mathrm{~mL})$, diluted with dichloromethane ( 150 mL ), and stirred for 10 min . The aqueous layer was extracted with dichloromethane ( $3 \times 100 \mathrm{~mL}$ ), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo. The crude obtained needed no further purification and was engaged in the next step. Yield: 96\% (5.33 g). Light yellow solid. Mp: $38-39{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}$, chlo-roform- $d$ ): $\delta 7.79(\mathrm{~s}, 1 \mathrm{H}), 4.19(\mathrm{q}, J=7.1 \mathrm{~Hz}, 2 \mathrm{H}), 3.78(\mathrm{~s}, 3 \mathrm{H})$, $1.23(\mathrm{t}, J=7.1 \mathrm{~Hz}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 161.4(\mathrm{C}=\mathrm{O}), 141.6(\mathrm{CH}), 117.7(\mathrm{C}), 113.6(\mathrm{C}), 60.1\left(\mathrm{CH}_{2}\right), 37.8$ $\left(\mathrm{N}-\mathrm{CH}_{3}\right), 14.1\left(\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 2995,2974,2931,2871,1709$, 1528, 1470, 1389, 1214, 1173, 1214, 1173, 1040, 770. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{7} \mathrm{H}_{10}{ }^{79} \mathrm{BrN}_{2} \mathrm{O}_{2}\right]^{+} 232.9920$; found 232.9917, calculated for $\left[\mathrm{C}_{7} \mathrm{H}_{10}{ }^{81} \mathrm{BrN}_{2} \mathrm{O}_{2}\right]^{+}$234.9900; found 234.9897. A solution of ethyl 5-bromo-1-methyl- $1 \mathrm{H}^{-}$ pyrazole-4-carboxylate ( $5.33 \mathrm{~g}, 0.0228 \mathrm{~mol}$ ) in anhydrous tetrahydrofuran ( 75 mL ) at $0{ }^{\circ} \mathrm{C}$ was treated with diisobutylaluminum hydride ( 1 M solution in tetrahydrofuran, $58 \mathrm{~mL}, 0.0571$ mol ), and the mixture was allowed to warm to room temperature and stir for 2 hours. A cold saturated aqueous sodium potassium tartrate solution was added, and stirring was continued for 4 hours. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulted crude mixture needed no further purification and was engaged in the next step. Yield: 94\% (4.14 g). Colorless solid. Mp: $55-56{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloro-form- $d$ ): $\delta 7.48(\mathrm{~s}, 1 \mathrm{H}), 4.46(\mathrm{~s}, 2 \mathrm{H}), 3.82(\mathrm{~s}, 3 \mathrm{H}), 2.53(\mathrm{~s}, 1 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform-d): $\delta 139.3$ (CH), 120.9 (C), 113.7 (C), $55.6\left(\mathrm{CH}_{2}\right), 37.6\left(\mathrm{~N}^{-} \mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 3255,2947,2896$, 2848, 2741, 1554, 1413, 1398, 1322, 1189, 1012, 995, 880. HRMS (ESI): $(m / z)[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{5} \mathrm{H}_{8}{ }^{79} \mathrm{BrN}_{2} \mathrm{O}\right]^{+}$190.9815; found 190.9815, calculated for $\left[\mathrm{C}_{5} \mathrm{H}_{8}{ }^{81} \mathrm{BrN}_{2} \mathrm{O}\right]^{+} 192.9794$, found 192.9796. A solution of 5-(bromo-1-methyl-1H-pyrazol-4-yl) methanol(iII) ( $4.14 \mathrm{~g}, 0.0216 \mathrm{~mol}$ ) in dichloromethane ( 25 mL ) was treated with activated manganese(iv) oxide ( $18.8 \mathrm{~g}, 0.216$ mol ) and the mixture was stirred at room temperature for 24 hours. Afterwards, the reaction mixture was filtered on Celite® and the filter pad washed with dichloromethane. The recovered filtrates were then concentrated under reduced pressure to yield the crude compound that required no further purification. Yield: $97 \%(4.01 \mathrm{~g})$. Light yellow solid. Mp: $75-76{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 9.78$ (s, 1H), $7.97(\mathrm{~s}, 1 \mathrm{H}), 3.94(\mathrm{~s}, 3 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 183.4(\mathrm{C}=\mathrm{O}), 141.0(\mathrm{CH})$, 121.7 (C), 119.7 (C), $37.6\left(\mathrm{~N}^{-} \mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 2953,2920,2852$, 1655, 1524, 1501, 1454, 1419, 1388, 1368, 1190, 1094, 763. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{5} \mathrm{H}_{6}{ }^{79} \mathrm{BrN}_{2} \mathrm{O}\right]^{+}$
188.9658; found 188.9653, calculated for $\left[\mathrm{C}_{5} \mathrm{H}_{6}{ }^{81} \mathrm{BrN}_{2} \mathrm{O}\right]^{+}$ 190.9638 , found 190.9634 .

## General procedures

Synthesis of 1-methyl-6-arylpyrazolo[3,4-c]pyrazoles 2a-i. To a stirred solution of 5-bromo-1-methyl-1H-pyrazole-4carbaldehyde 1 ( $100 \mathrm{mg}, 0.529 \mathrm{mmol}, 1.0 \mathrm{eq}$.) in ethanol ( 2 mL ) a few drops of glacial acetic acid and the desired hydrazine ( 1.1 eq., 0.58 mmol ) were added. If the hydrazine is found under its hydrochloric form salt, a stoichiometric amount of sodium acetate ( $1.1 \mathrm{eq} ., 0.58 \mathrm{mmol}$ ) is added to the mixture instead of the glacial acetic acid. This mixture was refluxed for 18 h and afterwards concentrated under reduced pressure. The crude was solubilized in DMF ( 3 mL ), transferred to a dry tube and then potassium carbonate ( $146 \mathrm{mg}, 1.06 \mathrm{mmol}, 2.0$ eq.) and copper iodide ( $2.5 \mathrm{mg}, 0.013 \mathrm{mmol}, 2.5 \mathrm{~mol} \%$ ) were added to the mixture. The tube was evacuated, backfilled with dry argon three times and then sealed. The reaction mixture was then heated at $150{ }^{\circ} \mathrm{C}$ for 1 hour under microwave irradiation. Solvent removal and purification by silica gel column chromatography using appropriate solvents afforded the expected bicyclic compound.

Synthesis of 3-bromo-1-methyl-6-arylpyrazolo[3,4-c]pyrazoles 3a, 3b and 3c. To a stirred solution of 1-methyl-6-aryl-pyrazolo [3,4-c]pyrazole ( $2 \mathrm{a}, 2 \mathrm{c}$ or 2 e ) ( 100 mg , 1.0 eq .) in acetonitrile ( 2 mL ) the correspondent amount of NBS is added. Depending on the nature of the substituent, the mixture is left under stirring at reflux or under microwave irradiation (sealed tube) for the given time. The reaction mixture is afterwards extracted with dichloromethane ( $3 \times 10 \mathrm{~mL}$ ) and water. The organic layers collected were washed with a saturated solution of $\mathrm{Na}_{2} \mathrm{~S}_{2} \mathrm{O}_{3}$, dried over $\mathrm{MgSO}_{4}$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using appropriate solvents.

Synthesis of 1-methyl-3-aryl-6-arylpyrazolo[3,4-c]pyrazoles 4a-r. To a stirred solution of 3-bromo-1-methyl-6-aryl-pyrazolo $[3,4-c]$ pyrazoles ( $\mathbf{3 a}, \mathbf{3 b}$ or $3 \mathbf{c}$ ) ( $100 \mathrm{mg}, 1.0 \mathrm{eq}$.) and corresponding boronic acid ( 1.5 eq .) in a mixture ( 3 mL ) of dioxane, ethanol and water ( $3: 1: 0.5$ ), a solution of cesium carbonate ( 1.3 eq.) in 0.5 mL of water was added. The tube was argon flushed three times and then $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}(1.25 \mathrm{~mol} \%)$ was added. The tube was again argon flushed, sealed and microwave irradiated at $140^{\circ} \mathrm{C}$ for 1 h . The reaction mixture was then filtrated on Celite ${ }^{\circledR}$, rinsed and extracted with EtOAc ( $3 \times 10 \mathrm{~mL}$ ). The organic layers collected were washed, dried on $\mathrm{MgSO}_{4}$, filtered and evaporated. The crude obtained was purified by silica gel column chromatography using appropriate solvents, affording the desired compound.

1-Methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole
(2a).
Prepared as described in the general procedure $\mathbf{A}$ (phenylhydrazine: $63 \mathrm{mg}, 57 \mu \mathrm{~L}, 0.58 \mathrm{mmol}$, CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol}$; $\mathrm{K}_{2} \mathrm{CO}_{3}: 146 \mathrm{mg}, 1.06 \mathrm{mmol}$ ). Yield: $76 \%$ ( 80 mg ). Orange oil. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=8 / 2 .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , acetone $-d_{6}$ ): $\delta 7.67(\mathrm{~d}, J=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.62(\mathrm{~s}, 1 \mathrm{H}), 7.58(\mathrm{t}, J$ $=7.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.45(\mathrm{~s}, 1 \mathrm{H}), 7.43(\mathrm{t}, J=7.9 \mathrm{~Hz}, 1 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H})$. ${ }^{13}$ C NMR ( 101 MHz , acetone- $d_{6}$ ): $\delta 149.1$ (C), 139.8 (C), 130.2 (2
$\times \mathrm{CH}), 130.0(\mathrm{CH}), 128.0(\mathrm{CH}), 127.6(\mathrm{CH}), 124.1(2 \times \mathrm{CH}), 121.0$ (C), $37.7\left(\mathrm{~N}-\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3056,2942,1682,1595,1508$, 1457, 1436, 1372, 1189, 1112, 1034, 1004, 990, 969, 844, 759, 715, 696. HRMS (ESI): $(m / z)[M+H]^{+}$calculated for $\left[\mathrm{C}_{11} \mathrm{H}_{11} \mathrm{~N}_{4}\right]^{+}$ 199.0978; found 199.0978.

1-Methyl-6-(p-tolyl)-1,6-dihydropyrazolo[3,4-c]pyrazole (2b). Prepared as described in the general procedure A (4-methylphenylhydrazine hydrochloride: $92 \mathrm{mg}, 0.58 \mathrm{mmol}$; NaOAc: $48 \mathrm{mg}, 0.58 \mathrm{mmol}$; CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol} ; \mathrm{K}_{2} \mathrm{CO}_{3}: 146 \mathrm{mg}$, 1.06 mmol ). Yield: $64 \%$ ( 72 mg ). Beige solid. Column chromatography eluents: PE/EtOAc $=8 / 2 . \mathrm{Mp}: 88-89{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR $(400$ MHz , acetone $\left.-d_{6}\right): \delta 7.59(\mathrm{~s}, 1 \mathrm{H}), 7.52(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.44(\mathrm{~s}$, $1 \mathrm{H}), 7.37(\mathrm{~d}, J=8.2 \mathrm{~Hz}, 2 \mathrm{H}), 3.81(\mathrm{~s}, 3 \mathrm{H}), 2.41(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , acetone- $d_{6}$ ): $\delta 149.1$ (C), 137.9 (C), 137.4 (C), 130.6 (2 $\times \mathrm{CH}), 129.6(\mathrm{CH}), 127.5(\mathrm{CH}), 124.2(2 \times \mathrm{CH}), 120.8(\mathrm{C}), 37.5$ $\left(\mathrm{N}^{-\mathrm{CH}_{3}}\right), 21.0\left(\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 3108,3041,2918,2854,1711$, 1604, 1583, 1515, 1436, 1416, 1376, 1365, 1216, 1198, 1108, 1036, 999, 977, 843, 819, 720. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$ calculated for $\left[\mathrm{C}_{12} \mathrm{H}_{13} \mathrm{~N}_{4}\right]^{+}$213.1134; found 213.1136.

1-(4-Methoxyphenyl)-6-methyl-1,6-dihydropyrazolo[3,4-c]pyrazole (2c). Prepared as described in the general procedure $\mathbf{A}$ (4methoxyphenylhydrazine hydrochloride: $102 \mathrm{mg}, 0.58 \mathrm{mmol}$; NaOAc: $48 \mathrm{mg}, 0.58 \mathrm{mmol}$; CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol} ; \mathrm{K}_{2} \mathrm{CO}_{3}$ : $146 \mathrm{mg}, 1.06 \mathrm{mmol}$ ). Yield: $46 \%$ ( 56 mg ). Light orange oil. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=8 / 2 .{ }^{1} \mathrm{H}$ NMR (400 MHz , chloroform- $d$ ): $\delta 7.57(\mathrm{~s}, 1 \mathrm{H}), 7.46(\mathrm{~s}, 1 \mathrm{H}), 7.44(\mathrm{~d}, J=$ $8.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.01(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}), 3.77(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 159.3$ (C), 148.7 (C), 131.6 (C), $129.1(\mathrm{CH}), 127.6(\mathrm{CH}), 125.7(2 \times \mathrm{CH}), 119.4(\mathrm{C}), 114.6(2 \times$ $\mathrm{CH}), 55.7\left(\mathrm{O}-\mathrm{CH}_{3}\right), 36.9\left(\mathrm{~N}-\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 3001,2935,2837$, 1600, 1585, 1514, 1444, 1421, 1370, 1299, 1246, 1182, 1137, 1109, 1035, 1013, 994, 969, 832, 718, 704. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+$ $\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{12} \mathrm{H}_{13} \mathrm{~N}_{4} \mathrm{O}\right]^{+} 229.1083$; found 229.1085.

4-(6-Methylpyrazolo[3,4-c]pyrazol-1(6H)-yl)benzonitrile (2d). Prepared as described in the general procedure A (4-cyanophenylhydrazine hydrochloride: $99 \mathrm{mg}, 0.58 \mathrm{mmol}$; NaOAc: 48 mg , 0.58 mmol ; CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol} ; \mathrm{K}_{2} \mathrm{CO}_{3}: 146 \mathrm{mg}, 1.06$ mmol ). Yield: $76 \%(90 \mathrm{mg})$. Light brown solid. Column chromatography eluents: PE/EtOAc $=7 / 3 . \mathrm{Mp}: 154-155{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 250 MHz , chloroform- $d$ ): $\delta 7.82$ (d, $J=8.9 \mathrm{~Hz}, 2 \mathrm{H}$ ), $7.72-7.67$ $(\mathrm{m}, 3 \mathrm{H}), 7.52(\mathrm{~s}, 1 \mathrm{H}), 3.94(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 63 MHz , chloro-form- $d$ ): $\delta 148.1(\mathrm{C}), 142.1(\mathrm{C}), 133.7(2 \times \mathrm{CH}), 131.6(\mathrm{CH}), 128.3$ (CH), $122.8(2 \times \mathrm{CH}), 121.0(\mathrm{C}), 118.2(\mathrm{CN}), 110.6(\mathrm{C}), 38.1(\mathrm{~N}-$ $\left.\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3133,3104,2924,2853,2224,1605,1591$, 1512, 1438, 1411, 1378, 1344, 1287, 1185, 1172, 1110, 1032, 996, 967, 837, 711, 704. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{12} \mathrm{H}_{10} \mathrm{~N}_{5}\right]^{+} 224.0930$; found 224.0930 .

1-Methyl-6-(4-(trifluoromethyl)phenyl)-1,6-dihydropyrazolo[3,4c]pyrazole (2e). Prepared as described in the general procedure A (4-(trifluoromethyl)-phenylhydrazine: $103 \mathrm{mg}, 0.58 \mathrm{mmol}$; CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol} ; \mathrm{K}_{2} \mathrm{CO}_{3}: 146 \mathrm{mg}, 1.06 \mathrm{mmol}$ ). Yield: 54\% (77 mg ). Light yellow solid. Column chromatography eluents: DCM/ EtOAc $=95 / 5 . \mathrm{Mp}: 89-90^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}$, chloroform- $d$ ): $\delta 7.78(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.68(\mathrm{~d}, J=8.5 \mathrm{~Hz}, 2 \mathrm{H}), 7.66(\mathrm{~s}, 1 \mathrm{H})$, $7.50(\mathrm{~s}, 1 \mathrm{H}), 3.90(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 148.2$ (C), 141.4 (C), $130.9(\mathrm{CH}), 129.2\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=33.0 \mathrm{~Hz}, \mathrm{C}\right)$,
$128.1(\mathrm{CH}), 126.8\left(\mathrm{q},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=3.8 \mathrm{~Hz}, 2 \times \mathrm{CH}\right), 123.8\left(\mathrm{q},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=\right.$ $\left.272.1 \mathrm{~Hz}, \mathrm{CF}_{3}\right), 122.9(2 \times \mathrm{CH}), 120.6(\mathrm{C}), 37.8\left(\mathrm{~N}-\mathrm{CH}_{3}\right) .{ }^{19} \mathrm{~F}$ NMR $\left(235 \mathrm{MHz}\right.$, chloroform- $d$ ): $\delta-62.4$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3106,2923,2854$, $1616,1597,1523,1507,1143,1318,1193,1180,1157,1118$, 1107, 1065, 1031, 999, 970, 872, 839, 823, 714, 690. HRMS (ESI): $(\mathrm{m} / z)[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{12} \mathrm{H}_{10} \mathrm{~F}_{3} \mathrm{~N}_{4}\right]^{+}$267.0852; found 267.0852.

1-(4-Fluorophenyl)-6-methyl-1,6-dihydropyrazolo[3,4-c]pyrazole (2f). Prepared as described in the general procedure $\mathbf{A}$ (4-fluorophenylhydrazine hydrochloride: $95 \mathrm{mg}, 0.58 \mathrm{mmol}$; NaOAc: $48 \mathrm{mg}, 0.58 \mathrm{mmol}$ CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol} ; \mathrm{K}_{2} \mathrm{CO}_{3}: 146 \mathrm{mg}$, $1.06 \mathrm{mmol})$. Yield: $62 \%(71 \mathrm{mg})$. Colorless oil. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=8 / 2 .{ }^{1} \mathrm{H} \mathrm{NMR}(400 \mathrm{MHz}$, chloroform-d): $\delta 7.60(\mathrm{~s}, 1 \mathrm{H}), 7.51(\mathrm{dd}, J=8.9,4.7 \mathrm{~Hz}, 2 \mathrm{H}), 7.48$ $(\mathrm{s}, 1 \mathrm{H}), 7.24-7.16(\mathrm{dd}, J=8.9,8.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.80(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}\right.$, chloroform- $d$ ): $\delta 161.9\left(\mathrm{~d},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=248.0 \mathrm{~Hz}, \mathrm{C}\right), 148.5$ (C), $134.7\left(\mathrm{~d},{ }^{4} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=3.1 \mathrm{~Hz}, \mathrm{C}\right), 129.8(\mathrm{CH}), 127.8(\mathrm{CH}), 125.7(\mathrm{~d}$, $\left.{ }^{3} J_{\mathrm{C}-\mathrm{F}}=8.6 \mathrm{~Hz}, 2 \times \mathrm{CH}\right), 119.8(\mathrm{C}), 116.5\left(\mathrm{~d},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=23.1 \mathrm{~Hz}, 2 \times\right.$ $\mathrm{CH}), 37.1\left(\mathrm{~N}-\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3111,3066,2943,1701,607$, 1594, 1513, 1443, 1417, 1371, 1218, 1190, 1218, 1190, 1152, 1033, 999, 969, 838, 815, 718, 701. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$ calculated for $\left[\mathrm{C}_{11} \mathrm{H}_{10} \mathrm{FN}_{4}\right]^{+}$217.0884; found 217.0884.

1-(3-Fluorophenyl)-6-methyl-1,6-dihydropyrazolo[3,4-c]pyrazole (2g). Prepared as described in the general procedure A (3-fluorophenylhydrazine hydrochloride: $95 \mathrm{mg}, 0.58 \mathrm{mmol}$; NaOAc: $48 \mathrm{mg}, 0.58 \mathrm{mmol}$; CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol} ; \mathrm{K}_{2} \mathrm{CO}_{3}: 146 \mathrm{mg}$, 1.06 mmol ). Yield: 85\% (98 mg). Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=8 / 2 . \mathrm{Mp}: 103-104{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR (400 MHz, chloroform- $d$ ): $\delta 7.62(\mathrm{~s}, 1 \mathrm{H}), 7.51-7.42(\mathrm{~m}, 2 \mathrm{H})$, $7.36-7.29(\mathrm{~m}, 2 \mathrm{H}), 7.09(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR $\left(101 \mathrm{MHz}\right.$, chloroform- $d$ ): $\delta 163.0\left(\mathrm{~d},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=248.4 \mathrm{~Hz}, \mathrm{C}\right), 148.2$ (C), $140.0\left(\mathrm{~d},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=10.2 \mathrm{~Hz}, \mathrm{CH}\right), 130.7\left(\mathrm{~d},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=9.2 \mathrm{~Hz}, \mathrm{C}\right)$, $130.2(\mathrm{CH}), 127.9(\mathrm{CH}), 120.2(\mathrm{C}), 118.6\left(\mathrm{~d},{ }^{4} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=3.2 \mathrm{~Hz}, \mathrm{CH}\right)$, $114.4\left(\mathrm{~d},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=21.1 \mathrm{~Hz}, \mathrm{CH}\right), 110.9\left(\mathrm{~d},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=24.7 \mathrm{~Hz}, \mathrm{CH}\right)$, $37.5\left(\mathrm{~N}-\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3091,2992,2934,2853,1161,1595$, 1509, 1464, 1429, 1414, 1379, 1199, 1171, 1148, 1113, 1081, 1030, 970, 869, 784, 712. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{11} \mathrm{H}_{10} \mathrm{FN}_{4}\right]^{+}$217.0884; found 217.0883.

1-(2-Fluorophenyl)-6-methyl-1,6-dihydropyrazolo[3,4-c]pyrazole (2h). Prepared as described in the general procedure $\mathbf{A}$ (2-fluorophenylhydrazine hydrochloride: $95 \mathrm{mg}, 0.58 \mathrm{mmol}$; NaOAc: $48 \mathrm{mg}, 0.58 \mathrm{mmol}$; CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol} ; \mathrm{K}_{2} \mathrm{CO}_{3}: 146 \mathrm{mg}$, 1.06 mmol ). Yield: $46 \%$ ( 53 mg ). Light brown solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=8 / 2 . \mathrm{Mp}: 57-58{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR (400 MHz, acetone- $d_{6}$ ): $\delta 7.72-7.67(\mathrm{~m}, 2 \mathrm{H}), 7.61-7.53$ (ddd, $J=8.2,8.1,4.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.48-7.40(\mathrm{~m}, 3 \mathrm{H}), 3.71(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR (101 MHz, acetone- $d_{6}$ ): $\delta 157.1\left(\mathrm{~d},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=248.7 \mathrm{~Hz}, \mathrm{C}\right)$, 150.1 (C), $131.0\left(\mathrm{~d},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=7.8 \mathrm{~Hz}, \mathrm{CH}\right), 130.8(\mathrm{CH}), 129.2$ (C), $127.6(\mathrm{CH}), 127.5(\mathrm{CH}), 126.1\left(\mathrm{~d},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=3.9 \mathrm{~Hz}, \mathrm{CH}\right), 120.1(\mathrm{C})$, $117.4\left(\mathrm{~d},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=19.5 \mathrm{~Hz}, \mathrm{CH}\right), 36.2\left(\mathrm{~s}, \mathrm{~N}-\mathrm{CH}_{3}\right) . \operatorname{IR} \nu\left(\mathrm{cm}^{-1}\right): 3113$, 3075, 2924, 2852, 1607, 1515, 1494, 1479, 1463, 1445, 1432, $1417,1370,1260,1216,1187,1103,1025,1000,972,846,836$, 755, 725, 717, 704. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{11} \mathrm{H}_{10} \mathrm{FN}_{4}\right]^{+}$217.0884; found 217.0882 .

1-Methyl-6-(pyridin-4-yl)-1,6-dihydropyrazolo[3,4-c]pyrazole (2i). Prepared as described in the general procedure $\mathbf{A}$ (4hydrazinopyridine: $64 \mathrm{mg}, 0.58 \mathrm{mmol}$; CuI: $2.5 \mathrm{mg}, 0.013 \mathrm{mmol}$;
$\mathrm{K}_{2} \mathrm{CO}_{3}: 146 \mathrm{mg}, 1.06 \mathrm{mmol}$ ). Yield: $46 \%$ ( 49 mg ). White yellow solid. Column chromatography eluents: $\mathrm{EtOAc} / \mathrm{MeOH}=95 / 5$. Mp: 105-106 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform-d): $\delta 8.75$ (br s, 2H), $7.68(\mathrm{~s}, 1 \mathrm{H}), 7.53(\mathrm{br} \mathrm{s}, 2 \mathrm{H}), 7.50(\mathrm{~s}, 1 \mathrm{H}), 4.00(\mathrm{~s}, 3 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform-d): $\delta 151.2(2 \times \mathrm{CH}), 147.9(\mathrm{C})$, $145.3(\mathrm{C}), 131.8(\mathrm{CH}), 128.3(\mathrm{CH}), 121.2(\mathrm{C}), 116.1(2 \times \mathrm{CH}), 38.5$ $\left(\mathrm{N}-\mathrm{CH}_{3}\right) . \operatorname{IR} \nu\left(\mathrm{cm}^{-1}\right): 3088,3036,2943,1682,1647,1587,1569$, 1508, 1440, 1417, 1381, 1191, 1115, 1030, 1009, 993, 696, 842, 820, 715. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{10} \mathrm{H}_{10} \mathrm{~N}_{5}\right]^{+}$ 200.0930; found 200.0930 .

3-Bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole (3a). Prepared as described in the general procedure $\mathbf{B}$ (1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole 2a: 100 mg , 0.5 mmol ; NBS: 1.5 eq., $135 \mathrm{mg}, 0.75 \mathrm{mmol}$; MeCN: 2 mL ; microwave irradiation at $100{ }^{\circ} \mathrm{C}$ for 2 h ). Yield: $77 \%(108 \mathrm{mg})$. Light orange oil. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=$ 95/5. ${ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform-d): $\delta 7.60(\mathrm{~s}, 1 \mathrm{H}), 7.55-7.50$ $(\mathrm{m}, 4 \mathrm{H}), 7.41(\mathrm{t}, J=8.6 \mathrm{~Hz}, 1 \mathrm{H}), 3.79(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR $(101 \mathrm{MHz}$, chloroform- $d$ ): $\delta 148.8(\mathrm{C}), 138.1(\mathrm{C}), 129.6(2 \times \mathrm{CH}), 129.1(\mathrm{CH})$, $128.1(\mathrm{CH}), 123.8(2 \times \mathrm{CH}), 119.9(\mathrm{C}), 113.1(\mathrm{C}-\mathrm{Br}), 37.6(\mathrm{~N}-$ $\left.\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3066,2928,1726,1594,1506,1457,1431$, $1367,1238,1148,1079,1038,1008,983,905,840,759,715,696$. HRMS (ESI): $(m / z)[M+H]^{+}$calculated for $\left[\mathrm{C}_{11} \mathrm{H}_{10}{ }^{79} \mathrm{BrN}_{4}\right]^{+}$ 277.0083; found 277.0084, calculated for $\left[\mathrm{C}_{11} \mathrm{H}_{10}{ }^{81} \mathrm{BrN}_{4}\right]^{+}$ 279.0064, found 279.0065 .

3-Bromo-6-(4-methoxyphenyl)-1-methyl-1,6-dihydropyrazolo [3,4-c]pyrazole (3b). Prepared as described in the general procedure B (1-(4-methoxyphenyl)-6-methyl-1,6-dihydropyr-azolo[3,4-c]pyrazole 2c: $100 \mathrm{mg}, 0.43 \mathrm{mmol}$; NBS: 78 mg , $0.43 \mathrm{mmol}, 1.0 \mathrm{eq} . ; \mathrm{MeCN}: 2 \mathrm{~mL}$; conventional heating at reflux for 4 h ). Yield: $55 \%(74 \mathrm{mg})$. Colorless oil. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=9 / 1 .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloro-form-d): $\delta 7.54(\mathrm{~s}, 1 \mathrm{H}), 7.41(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.00(\mathrm{~d}, J=$ $8.9 \mathrm{~Hz}, 2 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H}), 3.71(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR (101 MHz, chloroform- $d$ ): $\delta 159.5(\mathrm{C}), 149.0(\mathrm{C}), 131.0(\mathrm{C}), 128.5(\mathrm{CH}), 125.8$ $(2 \times \mathrm{CH}), 119.4(\mathrm{C}), 114.7(2 \times \mathrm{CH}), 112.8(\mathrm{C}-\mathrm{Br}), 55.7\left(\mathrm{O}-\mathrm{CH}_{3}\right)$, $37.2\left(\mathrm{~N}-\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right)$ : 3107, 2936, 2836, 1600, 1585, 1514, 1462, 1366, 1299, 1246, 1150, 1040, 904, 832, 716. HRMS (ESI): $(m / z)[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{12} \mathrm{H}_{12}{ }^{79} \mathrm{BrN}_{4} \mathrm{O}\right]^{+}$307.0189; found 307.0189, calculated for $\left[\mathrm{C}_{12} \mathrm{H}_{12}{ }^{81} \mathrm{BrN}_{4} \mathrm{O}\right]^{+}$309.0169, found 309.0168.

3-Bromo-1-methyl-6-(4-(trifluoromethyl)-1,6-dihydrophenyl)pyr-azolo[3,4-c]pyrazole (3c). Prepared as described in the general procedure $\mathbf{B}$ (1-methyl-6-(4-(trifluoromethyl)phenyl)-1,6-dihy-dropyrazolo[3,4-c]pyrazole 2e: $100 \mathrm{mg}, 0.37 \mathrm{mmol}$; NBS: 101 mg , $0.56 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{MeCN}: 2 \mathrm{~mL}$; microwave irradiation at $100{ }^{\circ} \mathrm{C}$ for 4 h ). Yield: $92 \%(120 \mathrm{mg})$. Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=7 / 3 . \mathrm{Mp}: 132-133{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.79$ (d, $J=8.3 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.66 (d, $J=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.62(\mathrm{~s}, 1 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR (101 MHz, chloroform- $d$ ): $\delta 148.5(\mathrm{C}), 140.9(\mathrm{C}), 130.2(\mathrm{CH}), 129.7\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=\right.$ $33.2 \mathrm{~Hz}, \mathrm{C}), 126.9\left(\mathrm{q},{ }^{3} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=3.7 \mathrm{~Hz}, 2 \times \mathrm{CH}\right), 123.7\left(\mathrm{q},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=\right.$ $\left.272.2 \mathrm{~Hz}, \mathrm{CF}_{3}\right), 123.1(2 \times \mathrm{CH}), 120.6(\mathrm{C}), 113.4(\mathrm{C}-\mathrm{Br}), 38.1(\mathrm{~N}-$ $\mathrm{CH}_{3}$ ). ${ }^{19} \mathrm{~F}$ NMR ( 235 MHz , chloroform-d): -62.5 . IR $\nu\left(\mathrm{cm}^{-1}\right)$ : 3108, 2924, 2853, 1613, 1596, 1583, 1523, 1500, 1438, 1416, 1320, 1249, 1151, 1107, 1065, 1034, 1009, 904, 838. HRMS (ESI): $(m / z)[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{12} \mathrm{H}_{9}{ }^{79} \mathrm{BrF}_{3} \mathrm{~N}_{4}\right]^{+} 344.9957$; found
344.9958, calculated for $\left[\mathrm{C}_{12} \mathrm{H}_{9}{ }^{81} \mathrm{BrF}_{3} \mathrm{~N}_{4}\right]^{+}$346.9937, found 346.9938.

1-Methyl-6-phenyl-3-(p-tolyl)-1,6-dihydropyrazolo[3,4-c]pyrazole (4a). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole 3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol}$; 4-methylphenylboronic acid: 74 mg , $0.54 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ;$ $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $83 \%(87 \mathrm{mg})$. Light brown solid. Column chromatography eluents: PE/EtOAc $=9 / 1 . \mathrm{Mp}: 126-127^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , acetone- $d_{6}$ ): $\delta 7.98(\mathrm{~s}$, $1 \mathrm{H}), 7.87(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.70(\mathrm{~d}, J=7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.60(\mathrm{t}, J=$ $7.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.45(\mathrm{t}, J=7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.28(\mathrm{~d}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 3.88$ $(\mathrm{s}, 3 \mathrm{H}), 2.37(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , acetone- $d_{6}$ ): $\delta 150.1(\mathrm{C})$, 139.6 (C), 139.3 (C), 138.5 (C), 131.0 (C), 130.6 (CH), $130.3(2 \times$ $\mathrm{CH}), 130.2(2 \times \mathrm{CH}), 128.1(\mathrm{CH}), 126.6(2 \times \mathrm{CH}), 124.3(2 \times \mathrm{CH})$, $118.0(\mathrm{C}), 37.8\left(\mathrm{~N}-\mathrm{CH}_{3}\right), 21.3\left(\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 3013,2919$, 1854, 1596, 1510, 1496, 1459, 1416, 1310, 1295, 1278, 1206, 1087, 1040, 1017, 1002, 990, 909, 820, 766, 753, 724, 696. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{18} \mathrm{H}_{17} \mathrm{~N}_{4}\right]^{+}$289.1447; found 289.1446.

1-Methyl-6-phenyl-3-(m-tolyl)-1,6-dihydropyrazolo[3,4-c]pyrazole (4b). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole 3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol}$; 3-methylphenyl-boronic acid: 74 mg , $0.54 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ;$ $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $89 \%$ ( 93 mg ). White yellow solid. Column chromatography eluents: PE/EtOAc $=9 / 1 . \mathrm{Mp}: 137-138{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.85$ (s, 1H), 7.75 (s, 1H), $7.70(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.59(\mathrm{~d}, J=7.6 \mathrm{~Hz}$, $2 \mathrm{H}), 7.54(\mathrm{t}, J=7.6 \mathrm{~Hz}, 2 \mathrm{H}), 7.41(\mathrm{t}, J=7.6 \mathrm{~Hz}, 1 \mathrm{H}), 7.36(\mathrm{t}, J=$ $7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.19(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 2.44(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 149.4$ (C), 139.9 (C), 138.6 (C), 138.5 (C), 132.5 (C), $130.3(\mathrm{CH}), 129.6(2 \times \mathrm{CH}), 129.2(\mathrm{CH})$, $128.8(\mathrm{CH}), 127.8(\mathrm{CH}), 126.6(\mathrm{CH}), 123.8(2 \times \mathrm{CH}), 123.5(\mathrm{CH})$, $117.4(\mathrm{C}), 37.5\left(\mathrm{~N}-\mathrm{CH}_{3}\right), 21.6\left(\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 3059,2920$, 2851, 1596, 1579, 1505, 1456, 1417, 1315, 1196, 1172, 1081, 1039, 1025, 1014, 939, 825, 838, 796, 762. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+$ $\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{18} \mathrm{H}_{17} \mathrm{~N}_{4}\right]^{+}$289.1447; found 289.1447.

1-Methyl-6-phenyl-3-(o-tolyl)-1,6-dihydropyrazolo[3,4-c]pyrazole (4c). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole 3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol} ; 2$-methylphenyl-boronic acid: 74 mg , $0.54 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ;$ $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $86 \%(90 \mathrm{mg})$. Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=$ $8 / 2$. Mp: $134-135{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.71-$ $7.66(\mathrm{~m}, 2 \mathrm{H}), 7.59(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.53(\mathrm{t}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.40$ ( $\mathrm{t}, J=7.3 \mathrm{~Hz}, 1 \mathrm{H}$ ), $7.32-7.28(\mathrm{~m}, 3 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 2.61(\mathrm{~s}, 3 \mathrm{H})$. ${ }^{13} \mathrm{C}$ NMR (101 MHz, chloroform-d): $\delta 149.1$ (C), 140.6 (C), 138.9 (C), 136.7 (C), 132.2 (C), 131.5 (CH), 131.0 (CH), 129.9 (CH), $129.8(2 \times \mathrm{CH}), 128.5(\mathrm{CH}), 128.0(\mathrm{CH}), 126.3(\mathrm{CH}), 124.1(2 \times$ $\mathrm{CH}), 119.5(\mathrm{C}), 37.8\left(\mathrm{~N}-\mathrm{CH}_{3}\right), 21.7\left(\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 3059,3039$, 2953, 2923, 1597, 1526, 1507, 1457, 1414, 1379, 1302, 1270, 1206, 1074, 1041, 1010, 989, 908, 846, 760. HRMS (ESI): (m/z) [M $+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{18} \mathrm{H}_{17} \mathrm{~N}_{4}\right]^{+}$289.1447; found 289.1447.

1-Methyl-3,6-diphenyl-1,6-dihydropyrazolo[3,4-c]pyrazole (4d). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-
methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole 3a: 100 mg , 0.36 mmol ; phenylboronic acid: $66 \mathrm{mg}, 0.54 \mathrm{mmol}, 1.5 \mathrm{eq} . ;$ $\mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ; \operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}$, $0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%$ ). Yield: $92 \%$ ( 91 mg ). Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=9 / 1 . \mathrm{Mp}: 133-$ $135{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.92(\mathrm{~d}, J=8.3 \mathrm{~Hz}$, $2 \mathrm{H}), 7.85(\mathrm{~s}, 1 \mathrm{H}), 7.58(\mathrm{~d}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.52(\mathrm{t}, J=8.3 \mathrm{~Hz}, 2 \mathrm{H})$, $7.46(\mathrm{t}, J=7.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.43-7.33(\mathrm{~m}, 2 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 149.3$ (C), 139.6 (C), 138.4 (C), 132.5 (C), $130.1(\mathrm{CH}), 129.5(2 \times \mathrm{CH}), 128.8(2 \times \mathrm{CH}), 128.3(\mathrm{CH})$, $127.7(\mathrm{CH}), 126.1(2 \times \mathrm{CH}), 123.7(2 \times \mathrm{CH}), 117.3(\mathrm{C}), 37.4(\mathrm{~N}-$ $\mathrm{CH}_{3}$ ). IR $\nu\left(\mathrm{cm}^{-1}\right): 3089,3056,2923,2852,1595,1504,1455$, 1418, 1208, 1081, 1016, 988, 907, 758. 694. HRMS (ESI): ( $\mathrm{m} / \mathrm{z}$ ) [M $+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{17} \mathrm{H}_{15} \mathrm{~N}_{4}\right]^{+}$275.1291; found 275.1289.

3-(4-Methoxyphenyl)-1-methyl-6-phenyl-1,6-dihydropyrazolo [3,4-c]pyrazole (4e). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo [3,4-c]pyrazole 3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol}$; 4-methoxyphenylboronic acid: $83 \mathrm{mg}, 0.54 \mathrm{mmol}, 1.5$ eq.; $\mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}$, $0.47 \mathrm{mmol}, 1.3$ eq.; $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $90 \%(99 \mathrm{mg})$. Light brown solid. Column chromatography eluents: PE/EtOAc $=8 / 2 . \mathrm{Mp}: 108-109{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}$, chloroform- $d$ ): $\delta 7.84(\mathrm{~d}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H}), 7.82(\mathrm{~s}, 1 \mathrm{H}), 7.57(\mathrm{~d}, J=$ $8.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.54(\mathrm{t}, J=8.0 \mathrm{~Hz}, 2 \mathrm{H}), 7.40(\mathrm{t}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 6.99$ $(\mathrm{d}, J=8.8 \mathrm{~Hz}, 2 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 159.9$ (C), 149.4 (C), 139.6 (C), 138.5 (C), 130.2 (CH), $129.5(2 \times \mathrm{CH}), 127.7(\mathrm{CH}), 127.5(2 \times \mathrm{CH}), 125.4(\mathrm{C})$, $123.7(2 \times \mathrm{CH}), 117.1(\mathrm{C}), 114.3(2 \times \mathrm{CH}), 55.4\left(\mathrm{O}-\mathrm{CH}_{3}\right), 37.4(\mathrm{~N}-$ $\left.\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3052,2999,2941,2837,1596,1538,1506$, 1458, 1439, 1417, 1245, 1173, 1109, 1087, 1024, 1011, 989, 908, 827, 841, 792. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{18} \mathrm{H}_{17} \mathrm{~N}_{4} \mathrm{O}\right]^{+}$305.1396; found 305.1396.

1-Methyl-6-phenyl-3-(4-(trifluoromethyl)phenyl)-1,6-dihydropyr-azolo[3,4-c]pyrazole (4f). Prepared as described in the general procedure C (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo [3,4-c]pyrazole 3a: $100 \mathrm{mg}, \quad 0.36 \mathrm{mmol}$; 4-trifluoromethylphenylboronic acid: $103 \mathrm{mg}, 0.54 \mathrm{mmol}, 1.5 \mathrm{eq}$.; $\mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ; \operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}$, $0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%)$. Yield: $86 \%$ ( 107 mg ). Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=8 / 2 . \mathrm{Mp}: 136-$ $137{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 8.01(\mathrm{~d}, J=8.1 \mathrm{~Hz}$, $2 \mathrm{H}), 7.85(\mathrm{~s}, 1 \mathrm{H}), 7.71(\mathrm{~d}, J=8.1 \mathrm{~Hz}, 2 \mathrm{H}), 7.61-7.51(\mathrm{~m}, 4 \mathrm{H}), 7.43$ $(\mathrm{t}, J=8.1 \mathrm{~Hz}, 1 \mathrm{H}), 3.89(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR $(101 \mathrm{MHz}$, chloroformd): $\delta 149.4$ (C), 138.3 (C), 138.0 (C), 136.0 (C), $130.3\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=\right.$ $32.5 \mathrm{~Hz}, \mathrm{C}), 129.8(\mathrm{CH}), 129.6(2 \times \mathrm{CH}), 128.0(\mathrm{CH}), 126.2(2 \times$ CH), $125.9\left(\mathrm{q},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=3.8 \mathrm{~Hz}, 2 \times \mathrm{CH}\right), 124.3\left(\mathrm{q},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=272.0 \mathrm{~Hz}\right.$, $\mathrm{CF}_{3}$ ), $123.9(2 \times \mathrm{CH}), 117.4(\mathrm{C}), 37.6\left(\mathrm{~N}-\mathrm{CH}_{3}\right) .{ }^{19} \mathrm{~F}$ NMR (235 MHz , chloroform- $d$ ): $\delta-62.5$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3113$, 3063, 2950, 1616, 1590, 1590, 1575, 1540, 1495, 1169, 1110, 1082, 1041, 1010, 990, 955, 854, 845. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{18} \mathrm{H}_{14} \mathrm{~F}_{3} \mathrm{~N}_{4}\right]^{+} 343.1165$; found 343.1166.

4-(1-Methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazol-3-yl) benzonitrile ( $\mathbf{4 g}$ ). Prepared as described in the general procedure C (3-bromo-1-methyl-6-phenyl1,6-dihydro-pyrazolo[3,4-c] pyrazole 3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol}$; 4-cyanophenyl- boronic acid: $80 \mathrm{mg}, 0.54 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ;$ $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $72 \%(78 \mathrm{mg})$.

Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=$ 7/3. Mp: 203-204 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 8.00$ (d, $J=8.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), $7.85(\mathrm{~s}, 1 \mathrm{H}), 7.74(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.61-$ $7.52(\mathrm{~m}, 4 \mathrm{H}), 7.44(\mathrm{t}, J=8.0 \mathrm{~Hz}, 1 \mathrm{H}), 3.90(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR (101 MHz, chloroform- d): $\delta 149.5$ (C), 138.2 (C), 137.4 (C), 137.0 (C), $132.8(2 \times \mathrm{CH}), 129.7(2 \times \mathrm{CH}), 129.7(\mathrm{CH}), 128.1(\mathrm{CH}), 126.5(2$ $\times \mathrm{CH}), 124.0(2 \times \mathrm{CH}), 119.0(\mathrm{CN}), 117.4(\mathrm{C}), 111.5(\mathrm{C}), 37.7(\mathrm{~N}-$ $\left.\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3056,2943,2226,1592,1581,1502,1435$, 1417, 1296, 1281, 1206, 1081, 1041, 1019, 990, 908, 844. HRMS (ESI): $(m / z)[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{18} \mathrm{H}_{14} \mathrm{~N}_{5}\right]^{+} 300.1243$; found 300.1244.

3-(3-Fluorophenyl)-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4c]pyrazole (4h). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole
3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol}$; 3-fluorophenyl-boronic acid: 76 mg , $0.54 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ;$ $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $90 \%(95 \mathrm{mg})$. Beige solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=8 / 2$. Mp: 97-98 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.83(\mathrm{~s}, 1 \mathrm{H})$, $7.67(\mathrm{~d}, J=7.7 \mathrm{~Hz}, 1 \mathrm{H}), 7.62(\mathrm{~d}, J=9.8 \mathrm{~Hz}, 1 \mathrm{H}), 7.59-7.50(\mathrm{~m}, 4 \mathrm{H})$, $7.45-7.39(\mathrm{~m}, 2 \mathrm{H}), 7.04(\mathrm{dd}, J=8.5,8.2 \mathrm{~Hz}, 1 \mathrm{H}), 3.87(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 163.3$ (d, $\left.{ }^{1} J_{\mathrm{C}-\mathrm{F}}=245.5 \mathrm{~Hz}, \mathrm{C}\right)$, 149.4 (C), 138.4 (C), 138.3 (C), 134.8 (d, ${ }^{3} J_{\mathrm{C}-\mathrm{F}}=8.3 \mathrm{~Hz}, \mathrm{C}$ ), 130.4 (d, $\left.{ }^{3} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=8.4 \mathrm{~Hz}, \mathrm{CH}\right), 129.9(\mathrm{CH}), 129.6(2 \times \mathrm{CH}), 127.9(\mathrm{CH}), 123.8$ $(2 \times \mathrm{CH}), 121.9\left(\mathrm{~d},{ }^{4} J_{\mathrm{C}-\mathrm{F}}=2.8 \mathrm{~Hz}, \mathrm{CH}\right), 117.3(\mathrm{C}), 115.1\left(\mathrm{~d},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=\right.$ $21.3 \mathrm{~Hz}, \mathrm{CH}), 112.8\left(\mathrm{~d},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=22.8 \mathrm{~Hz}, \mathrm{CH}\right), 37.5\left(\mathrm{~N}-\mathrm{CH}_{3}\right) .{ }^{19} \mathrm{~F}$ NMR ( 235 MHz , chloroform- $d$ ): $\delta-112.9$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3054,2931$, 2850, 1595, 1580, 1507, 1481, 1449, 1411, 1297, 1183, 1082, 1018, 990, 881, 831. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{17} \mathrm{H}_{14} \mathrm{FN}_{4}\right]^{+}$293.1197; found 293.1197.

1-Methyl-6-phenyl-3-(thiophen-3-yl)-1,6-dihydropyrazolo[3,4-c] pyrazole (4i). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole 3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol}$; 3-thienylboronic acid: 70 mg , $0.54 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ;$ $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $85 \%$ ( 86 mg ). Light brown solid. Column chromatography eluents: PE/EtOAc $=8 / 2 . \mathrm{Mp}: 100-101{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.78$ $(\mathrm{s}, 1 \mathrm{H}), 7.68(\mathrm{~s}, 1 \mathrm{H}), 7.61-7.50(\mathrm{~m}, 5 \mathrm{H}), 7.43-7.38(\mathrm{~m}, 2 \mathrm{H}), 3.84$ (s, 3H). ${ }^{13}$ C NMR ( 101 MHz , chloroform- $d$ ): $\delta 149.1$ (C), 138.5 (C), 136.0 (C), 134.2 (C), 129.8 (CH), $129.5(2 \times \mathrm{CH}), 127.7$ (CH), $126.4(\mathrm{CH}), 125.9(\mathrm{CH}), 123.7(2 \times \mathrm{CH}), 122.0(\mathrm{CH}), 117.4(\mathrm{C})$, $37.3\left(\mathrm{~N}^{\left.-\mathrm{CH}_{3}\right) . ~ I R ~} \nu\left(\mathrm{~cm}^{-1}\right): 3095,3061,2947,1596,1510,1460\right.$, 1413, 1282, 1211, 1188, 1038, 1013, 1001, 951, 870, 793, 779. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{15} \mathrm{H}_{13} \mathrm{~N}_{4} \mathrm{~S}\right]^{+} 281.0855$; found 281.0858 .

1-Methyl-6-phenyl-3-(pyridin-4-yl)-1,6-dihydropyrazolo[3,4-c] pyrazole (4j). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole 3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol}$; 4-pyridinylboronic acid: 67 mg , $0.54 \mathrm{mmol} 1.5 \mathrm{eq}$. ; $\mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ;$ $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $78 \%(78 \mathrm{mg})$. Beige solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=1 / 9$. $\mathrm{Mp}: 158-159{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 8.68$ (br s, 2H), 7.84 (s, 1H), 7.75 (br s, 2H), 7.58-7.47 (m, 4H), 7.41 (t, $J=6.8 \mathrm{~Hz}, 1 \mathrm{H}), 3.86(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 150.3(2 \times \mathrm{CH}), 149.3$ (C), 139.8 (C), 138.1 (C), 136.7 (C), 129.6
$(2 \times \mathrm{CH}), 129.5(\mathrm{CH}), 128.0(\mathrm{CH}), 123.8(2 \times \mathrm{CH}), 120.3(2 \times$ $\mathrm{CH}), 117.5(\mathrm{C}), 37.7\left(\mathrm{~N}-\mathrm{CH}_{3}\right)$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3034,2925,1609$, 1594, 1556, 1506, 1432, 1407, 1388, 1323, 1291, 1204, 1094, 1019, 1002, 992, 917, 826. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{~N}_{5}\right]^{+}$276.1243; found 276.1244.
(E)-1-Methyl-6-phenyl-3-styryl-1,6-dihydropyrazolo[3,4-c]pyrazole (4k). Prepared as described in the general procedure C (3-bromo-1-methyl-6-phenyl-1,6-dihydropyrazolo[3,4-c]pyrazole 3a: $100 \mathrm{mg}, 0.36 \mathrm{mmol}$; trans-2-phenylvinylboronic acid: 81 mg , $0.54 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 153 \mathrm{mg}, 0.47 \mathrm{mmol}, 1.3 \mathrm{eq} . ;$ $\left.\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5.5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $64 \%(70 \mathrm{mg})$. Light brown solid. Column chromatography eluents: PE/EtOAc $=8 / 2 . \mathrm{Mp}: 140-141{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.84$ (s, 1H), 7.60-7.47 (m, 6H), $7.37(\mathrm{q}, J=7.8 \mathrm{~Hz}, 3 \mathrm{H}), 7.27(\mathrm{t}, J=$ $7.4 \mathrm{~Hz}, 1 \mathrm{H}), 7.18(\mathrm{~d}, J=18.5 \mathrm{~Hz}, 1 \mathrm{H}), 7.14(\mathrm{~d}, J=18.5 \mathrm{~Hz}, 1 \mathrm{H})$, 3.79 ( $\mathrm{s}, 3 \mathrm{H}$ ). ${ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 149.0$ (C), 139.9 (C), 138.3 (C), 136.7 (C), 132.8 (CH), 130.0 (CH), 129.5 ( $2 \times$ $\mathrm{CH}), 128.8(2 \times \mathrm{CH}), 128.1(\mathrm{CH}), 127.7(\mathrm{CH}), 126.6(2 \times \mathrm{CH})$, $123.7(2 \times \mathrm{CH}), 120.2(\mathrm{CH}), 116.6(\mathrm{C}), 37.3\left(\mathrm{~N}-\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right)$ : 3100, 3061, 3030, 2946, 1591, 1580, 1505, 1494, 1429, 1304, 1261, 1201, 1046, 1013, 1001, 989, 961, 906, 874, 852, 744. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{19} \mathrm{H}_{17} \mathrm{~N}_{4}\right]^{+} 301.1447$; found 301.1449.

4-(6-(4-Methoxyphenyl)-1-methyl-1,6-dihydropyrazolo[3,4-c] pyrazol-3-yl)benzonitrile (4l). Prepared as described in the general procedure C (3-bromo-6-(4-methoxyphenyl)-1-methyl-1,6-dihydropyrazolo[3,4-c]pyrazole 3c: $100 \mathrm{mg}, 0.32 \mathrm{mmol}$; 4 cyanophenylboronic acid: $72 \mathrm{mg}, 0.48 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}$ : $138 \mathrm{mg}, 0.42 \mathrm{mmol}, 1.3 \mathrm{eq} . ; \operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5 \mathrm{mg}, 0.004 \mathrm{mmol}$, $1.25 \mathrm{~mol} \%$ ). Yield: $75 \%$ ( 81 mg ). Colorless solid. Column chromatography eluents: PE/EtOAc $=7 / 3 . \mathrm{Mp}$ : 186-187 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.99$ (d, $J=8.3 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.81 (s, $1 \mathrm{H}), 7.73(\mathrm{~d}, J=8.3 \mathrm{~Hz}, 2 \mathrm{H}), 7.47(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.04(\mathrm{~d}, J=$ $8.9 \mathrm{~Hz}, 2 \mathrm{H}), 3.88(\mathrm{~s}, 3 \mathrm{H}), 3.83(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 159.6$ (C), 149.7 (C), 137.3 (C), 137.1 (C), 132.7 $(2 \times \mathrm{CH}), 131.1(\mathrm{C}), 129.1(\mathrm{CH}), 126.4(2 \times \mathrm{CH}), 126.0(2 \times \mathrm{CH})$, $119.0(\mathrm{CN}), 116.9(\mathrm{C}), 114.7(2 \times \mathrm{CH}), 111.3(\mathrm{C}), 55.7\left(\mathrm{O}-\mathrm{CH}_{3}\right)$, $37.3\left(\mathrm{~N}-\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 3105,3082,3012,2942,2842,2221$, 1610, 1593, 1580, 1517, 1439, 1299, 1253, 1203, 1110, 1086, 1045, 1017, 989, 910, 841, 826. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$ calculated for $\left[\mathrm{C}_{19} \mathrm{H}_{16} \mathrm{~N}_{5} \mathrm{O}\right]^{+} 330.1349$; found 330.1353.

6-(4-Methoxyphenyl)-1-methyl-3-(pyridin-4-yl)-1,6-dihydropyr-azolo[3,4-c]pyrazole (4m). Prepared as described in the general procedure C (3-bromo-6-(4-methoxyphenyl)-1-methyl-1,6-dihy-dropyrazolo[3,4-c]pyrazole 3c: $100 \mathrm{mg}, 0.32 \mathrm{mmol}$; 4-pyridinylboronic acid: $61 \mathrm{mg}, 0.48 \mathrm{mmol}, 1.5 \mathrm{eq}$.; $\mathrm{Cs}_{2} \mathrm{CO}_{3}: 138 \mathrm{mg}$, $\left.0.42 \mathrm{mmol}, 1.3 \mathrm{eq} . ; \operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%\right)$. Yield: $76 \%$ ( 76 mg ). Colorless solid. Column chromatography eluents: DCM/EtOAc $=5 / 5 . \mathrm{Mp}: 198-199^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR $(400 \mathrm{MHz}$, chloroform- $d$ ): $\delta 8.68(\mathrm{~d}, J=6.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.83(\mathrm{~s}, 1 \mathrm{H}), 7.76(\mathrm{~d}, J=$ $6.2 \mathrm{~Hz}, 2 \mathrm{H}), 7.47(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 7.04(\mathrm{~d}, J=8.9 \mathrm{~Hz}, 2 \mathrm{H}), 3.88$ $(\mathrm{s}, 3 \mathrm{H}), 3.83(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 159.6$ (C), $150.5(2 \times \mathrm{CH}), 149.7$ (C), 140.0 (C), 136.7 (C), 131.1 (C), $129.1(\mathrm{CH}), 126.0(2 \times \mathrm{CH}), 120.3(2 \times \mathrm{CH}), 117.0(\mathrm{C}), 114.7(2 \times$ $\mathrm{CH}), 55.7\left(\mathrm{O}-\mathrm{CH}_{3}\right), 37.3\left(\mathrm{~N}-\mathrm{CH}_{3}\right) . \mathrm{IR} \nu\left(\mathrm{cm}^{-1}\right): 3067,2951,2847$, 1593, 1556, 1518, 1455, 1438, 1409, 1298, 1255, 1208, 1166,

1108, 1094, 1017, 991, 917, 821. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$ calculated for $\left[\mathrm{C}_{17} \mathrm{H}_{16} \mathrm{~N}_{5} \mathrm{O}\right]^{+} 306.1349$; found 306.1349.

3,6-Bis(4-methoxyphenyl)-1-methyl-1,6-dihydropyrazolo[3,4-c] pyrazole (4n). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-6-(4-methoxyphenyl)-1-methyl-1,6-dihydropyrazolo [3,4-c]pyrazole 3c: $100 \mathrm{mg}, 0.32 \mathrm{mmol}$; 4-methoxyphenylboronic acid: $75 \mathrm{mg}, 0.48 \mathrm{mmol}, 1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 138 \mathrm{mg}, 0.42 \mathrm{mmol}, 1.3$ eq.; $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 5 \mathrm{mg}, 0.004 \mathrm{mmol}, 1.25 \mathrm{~mol} \%$ ). Yield: $80 \%$ ( 88 mg ). Colorless solid. Column chromatography eluent: DCM. Mp: 212-213 ${ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.84(\mathrm{~d}, J=$ $8.7 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.78 (s, 1H), 7.47 (d, $J=8.9 \mathrm{~Hz}, 2 \mathrm{H}$ ), 7.02 (d, $J=$ $8.9 \mathrm{~Hz}, 2 \mathrm{H}), 6.99(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 3.87(\mathrm{~s}, 3 \mathrm{H}), 3.85(\mathrm{~s}, 3 \mathrm{H})$, $3.78(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 160.1$ (C), 159.6 (C), 150.0 (C), 139.8 (C), 131.8 (C), 129.9 (CH), 127.7 ( $2 \times$ $\mathrm{CH}), 126.1(2 \times \mathrm{CH}), 125.8(\mathrm{C}), 116.9(\mathrm{C}), 114.9(2 \times \mathrm{CH}), 114.6$ $(2 \times \mathrm{CH}), 56.0\left(\mathrm{O}-\mathrm{CH}_{3}\right), 55.7\left(\mathrm{O}-\mathrm{CH}_{3}\right), 37.2\left(\mathrm{~N}-\mathrm{CH}_{3}\right)$. IR $\nu$ $\left(\mathrm{cm}^{-1}\right): 3105,3002,2974,2941,1840,1596,1537,1513,1500$, 1452, 1438, 1302, 1244, 1168, 1106, 1043, 1024, 1013, 907, 839, 824. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{19} \mathrm{H}_{19} \mathrm{~N}_{4} \mathrm{O}_{2}\right]^{+}$ 335.1502; found 335.1505.

4-(1-Methyl-6-(4-(trifluoromethyl)phenyl)-1,6-dihydropyrazolo [3,4-c]pyrazol-3-yl)benzonitrile (4o). Prepared as described in the general procedure C (3-bromo-1-methyl-6-(4-(trifluoromethyl) phenyl)-1,6-dihydro pyrazolo[3,4-c]pyrazole $3 \mathbf{e}: 100 \mathrm{mg}$, 0.28 mmol ; 4 -cyanophenylboronic acid: $64 \mathrm{mg}, 0.43 \mathrm{mmol}$, 1.5 eq.; $\mathrm{Cs}_{2} \mathrm{CO}_{3}: 123 \mathrm{mg}, 0.37 \mathrm{mmol}, 1.3$ eq.; $\operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}$ : $4.5 \mathrm{mg}, 0.003 \mathrm{mmol}, 1.25 \mathrm{~mol} \%$ ). Yield: $68 \%$ ( 73 mg ). Colorless solid. Column chromatography eluents: PE/EtOAc $=9 / 1 . \mathrm{Mp}: 226-227{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.98(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.88(\mathrm{~s}, 1 \mathrm{H}), 7.82(\mathrm{~d}, J=8.6 \mathrm{~Hz}, 2 \mathrm{H})$, 7.76-7.69 (m, 4H), $3.96(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloro-form- $d$ ): $\delta 149.2$ (C), 141.0 (C), 137.7 (C), 136.6 (C), $132.7(2 \times$ $\mathrm{CH}), 130.7(\mathrm{CH}), 129.7\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=33.1 \mathrm{~Hz}, \mathrm{C}\right), 126.9\left(\mathrm{q},{ }^{3} J_{\mathrm{C}-\mathrm{F}}=\right.$ $3.7 \mathrm{~Hz}, 2 \times \mathrm{CH}), 126.5(2 \times \mathrm{CH}), 123.8\left(\mathrm{~d},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=272.2 \mathrm{~Hz}\right.$, $\mathrm{CF}_{3}$ ), $123.3(2 \times \mathrm{CH}), 118.9(\mathrm{CN}), 118.0(\mathrm{C}), 111.7(\mathrm{C}), 38.2(\mathrm{~N}-$ $\mathrm{CH}_{3}$ ). ${ }^{19}$ F NMR ( 235 MHz , chloroform- $d$ ): $\delta-62.5$. IR $\nu\left(\mathrm{cm}^{-1}\right)$ : 3343, 2923, 1852, 2225, 1616, 1579, 1522, 1541, 1421, 1384, 1315, 1168, 1103, 1038, 1013, 989, 955, 909, 839. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{19} \mathrm{H}_{13} \mathrm{~F}_{3} \mathrm{~N}_{5}\right]^{+}$368.1117; found 368.1116.

1-Methyl-3-(pyridin-4-yl)-6-(4-(trifluoromethyl)phenyl)-1,6dihydro pyrazolo[3,4-c]pyrazole (4p). Prepared as described in the general procedure $\mathbf{C}$ (3-bromo-1-methyl-6-(4-(trifluoromethyl) phenyl)-1,6-dihydro pyrazolo[3,4-c]pyrazole $3 \mathrm{e}: 100 \mathrm{mg}$, 0.28 mmol ; 4-pyridinylboronic acid: $54 \mathrm{mg}, 0.43 \mathrm{mmol}, 1.5 \mathrm{eq} . ;$ $\mathrm{Cs}_{2} \mathrm{CO}_{3}: 123 \mathrm{mg}, 0.37 \mathrm{mmol}, 1.3$ eq.; $\mathrm{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 4.5 \mathrm{mg}$, $0.003 \mathrm{mmol}, 1.25 \mathrm{~mol} \%$ ). Yield: $79 \%$ ( 79 mg ). Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=5 / 5 . \mathrm{Mp}$ : 196$197{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 8.69(\mathrm{~d}, J=5.4 \mathrm{~Hz}$, $2 \mathrm{H}), 7.90(\mathrm{~s}, 1 \mathrm{H}), 7.82(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.76(\mathrm{~d}, J=5.4 \mathrm{~Hz}, 2 \mathrm{H})$, 7.71 (d, $J=8.4 \mathrm{~Hz}, 2 \mathrm{H}$ ), $3.96(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 150.5(2 \times \mathrm{CH}), 149.2(\mathrm{C}), 141.0(\mathrm{C}), 139.5(\mathrm{C})$, 137.2 (C), $130.7(\mathrm{CH}), 129.7\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=33.1 \mathrm{~Hz}, \mathrm{C}\right), 127.0\left(\mathrm{q},{ }^{3} J_{\mathrm{C}-\mathrm{F}}\right.$ $=3.7 \mathrm{~Hz}, 2 \times \mathrm{CH}), 123.8\left(\mathrm{q},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=272.2 \mathrm{~Hz}, \mathrm{CF}_{3}\right), 123.3(2 \times$ $\mathrm{CH}), 120.3(2 \times \mathrm{CH}), 118.2(\mathrm{C}), 38.2\left(\mathrm{~N}-\mathrm{CH}_{3}\right) .{ }^{19} \mathrm{~F}$ NMR (235 MHz , chloroform- $d$ ): $\delta-62.5$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3067,2952,1614$, 1581, 1556, 1526, 1420, 1324, 1219, 1184, 1113, 1094, 1016, 992,

917, 846, 739. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{17} \mathrm{H}_{13} \mathrm{~F}_{3} \mathrm{~N}_{5}\right]^{+}$344.1117; found 344.1118.

3-(4-Methoxyphenyl)-1-methyl-6-(4-(trifluoromethyl)phenyl)-1,6dihydro pyrazolo[3,4-c]pyrazole (4q). Prepared as described in the general procedure C (3-bromo-1-methyl-6-(4-(trifluoromethyl) phenyl)-1,6-dihydro pyrazolo[3,4-c]pyrazole 3e: 100 mg , 0.28 mmol ; 4-methoxyphenylboronic acid: $67 \mathrm{mg}, 0.43 \mathrm{mmol}$, 1.5 eq .; $\mathrm{Cs}_{2} \mathrm{CO}_{3}: 123 \mathrm{mg}, 0.37 \mathrm{mmol}, 1.3 \mathrm{eq} . ; \operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 4.5 \mathrm{mg}$, $0.003 \mathrm{mmol}, 1.25 \mathrm{~mol} \%)$. Yield: $94 \%(102 \mathrm{mg})$. Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=9 / 1 . \mathrm{Mp}: 205-$ $206{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.88-7.77(\mathrm{~m}, 5 \mathrm{H})$, $7.71(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.00(\mathrm{~d}, J=8.7 \mathrm{~Hz}, 2 \mathrm{H}), 3.91(\mathrm{~s}, 3 \mathrm{H}), 3.86$ ( $\mathrm{s}, 3 \mathrm{H}$ ). ${ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroform- $d$ ): $\delta 160.0$ (C), 149.2 (C), $141.4(\mathrm{C}), 140.0(\mathrm{C}), 131.4(\mathrm{CH}), 129.3\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=33.1 \mathrm{~Hz}, \mathrm{C}\right)$, $127.5(2 \times \mathrm{CH}), 126.8\left(\mathrm{q},{ }^{3} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=3.7 \mathrm{~Hz}, 2 \times \mathrm{CH}\right), 125.0(\mathrm{C}), 123.0$ $(2 \times \mathrm{CH}), 121.2\left(\mathrm{~d},{ }^{1} \mathrm{~J}_{\mathrm{C}-\mathrm{F}}=272.1 \mathrm{~Hz}, \mathrm{CF}_{3}\right), 117.8(\mathrm{C}), 114.4(2 \times$ $\mathrm{CH}), 55.4\left(\mathrm{O}-\mathrm{CH}_{3}\right), 37.8\left(\mathrm{~N}-\mathrm{CH}_{3}\right) .{ }^{19} \mathrm{~F}$ NMR $(235 \mathrm{MHz}$, chloro-form- $d$ ): $\delta-62.4$. IR $\nu\left(\mathrm{cm}^{-1}\right): 3338,3057,2937,2845,1596$, 1614, 1540, 1425, 1323, 1251, 1107, 1088, 1031, 1007, 858, 832, 721, 715. HRMS (ESI): $(\mathrm{m} / \mathrm{z})[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{19} \mathrm{H}_{16} \mathrm{~F}_{3} \mathrm{~N}_{4} \mathrm{O}\right]^{+}$373.1270; found 373.1268.

1-Methyl-3-(p-tolyl)-6-(4-(trifluoromethyl)phenyl)-1,6-dihydro pyrazolo[3,4-c]pyrazole (4r). Prepared as described in the general procedure C (3-bromo-1-methyl-6-(4-(trifluoromethyl) phenyl)-1,6-dihydro pyrazolo[3,4-c]pyrazole 3e: 100 mg , 0.28 mmol ; 4-methylphenylboronic acid: $60 \mathrm{mg}, 0.43 \mathrm{mmol}$, $1.5 \mathrm{eq} . ; \mathrm{Cs}_{2} \mathrm{CO}_{3}: 123 \mathrm{mg}, 0.37 \mathrm{mmol}, 1.3 \mathrm{eq} . ; \operatorname{Pd}\left(\mathrm{PPh}_{3}\right)_{4}: 4.5 \mathrm{mg}$, $0.003 \mathrm{mmol}, 1.25 \mathrm{~mol} \%$ ). Yield: $86 \%$ ( 89 mg ). Colorless solid. Column chromatography eluents: $\mathrm{PE} / \mathrm{EtOAc}=9 / 1 . \mathrm{Mp}: 204-$ $205{ }^{\circ} \mathrm{C} .{ }^{1} \mathrm{H}$ NMR ( 400 MHz , chloroform- $d$ ): $\delta 7.87$ (s, 1H), 7.79 $(\mathrm{d}, J=7.8 \mathrm{~Hz}, 4 \mathrm{H}), 7.70(\mathrm{~d}, J=8.4 \mathrm{~Hz}, 2 \mathrm{H}), 7.27(\mathrm{~d}, J=7.8 \mathrm{~Hz}$, $2 \mathrm{H}), 3.92(\mathrm{~s}, 3 \mathrm{H}), 2.40(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{C}$ NMR ( 101 MHz , chloroformd): $\delta 149.2$ (C), 141.4 (C), 140.2 (C), 138.6 (C), 131.4 (CH), 129.6 $(2 \times \mathrm{CH}), 129.5(\mathrm{C}), 129.3\left(\mathrm{q},{ }^{2} J_{\mathrm{C}-\mathrm{F}}=33.0 \mathrm{~Hz}, \mathrm{C}\right), 126.9\left(\mathrm{q},{ }^{3} J_{\mathrm{C}-\mathrm{F}}\right.$ $=3.7 \mathrm{~Hz}, 2 \times \mathrm{CH}), 126.1(2 \times \mathrm{CH}), 123.9\left(\mathrm{q},{ }^{1} J_{\mathrm{C}-\mathrm{F}}=272.1 \mathrm{~Hz}\right.$, $\left.\mathrm{CF}_{3}\right), 123.1(2 \times \mathrm{CH}), 118.0(\mathrm{C}), 37.9\left(\mathrm{~N}-\mathrm{CH}_{3}\right), 21.5\left(\mathrm{CH}_{3}\right) .{ }^{19} \mathrm{~F}$ NMR ( 235 MHz , chloroform- $d$ ): $\delta-62.4$. IR $\nu\left(\mathrm{cm}^{-1}\right): 2926$, 1614, 1594, 1582, 1522, 1504, 1424, 1317, 1162, 1110, 1085, 1066, 1039, 1014, 990, 965, 952, 909, 842, 825, 737. HRMS (ESI): $(m / z)[\mathrm{M}+\mathrm{H}]^{+}$calculated for $\left[\mathrm{C}_{19} \mathrm{H}_{16} \mathrm{~F}_{3} \mathrm{~N}_{4}\right]^{+}$357.1249; found 357.1247.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by "Vasile Alecsandri" University of Bacau (ERASMUS grants and CNFIS-FDI-0151/2017), Francophone University Agency in Central and Eastern Europe (CE_124_FF_2016), Campus France (N 857352 B, N 902192 B) and the Eiffel Scholarship Program of Excellence (N 870738 C) as well as partially supported by Orléans University, CNRS, Labex SynOrg (ANR-11-LABX-0029), Labex IRON (ANR-11-LABX-0018-01), région Centre-Val de Loire.

## Notes and references

1 K. W. Knouse, L. E. Ator, L. E. Beausoleil, Z. J. Hauseman, R. L. Casaubon and G. R. Ott, Tetrahedron Lett., 2017, 58, 202.

2 L. M. Blair and J. Sperry, J. Nat. Prod., 2013, 76, 794.
3 S. A. Bahashwan, A. A. Fayed, M. A. Ramadan, A. E.-G. E. Amr and N. O. Al-Harbi, Int. J. Mol. Sci., 2014, 15, 21587.
4 G. H. Sayed, M. E. Azab, N. A. Negm and K. E. Anwer, J. Heterocycl. Chem., 2018, 55, 1615.
5 S. M. Gomha, H. M. Abdel-aziz and A. A. M. El-Reedy, J. Heterocycl. Chem., 2018, 55, 1960.
6 S. Ojha, A. Bapna and G. L. Talesara, Arkivoc, 2008, 112.
7 R. Mallikarjuna Rao, J. Sreeramulu, L. K. Ravindranath, G. Nagaraja Reddy, K. Hanumanthurayudu, G. Nageswara Reddy, A. Jayaraju and P. Madhusudhan, J. Chem. Pharm. Res., 2012, 4, 272.
8 D. A. Berry, T.-C. Chien and L. B. Townsend, Heterocycles, 2004, 63, 2475.
9 A. S. Shawali, Chem. Rev., 1993, 93, 2731.
10 T. K. Shkineva, I. L. Dalinger and S. A. Shevelev, Chem. Heterocycl. Compd., 1995, 31, 509.
11 R. E. Khidre, H. A. Mohamed and B. F. Abdel-Wahab, Turk. J. Chem., 2013, 37, 1.
12 I. M. A. Awad, Monatsh. Chem., 1990, 121, 1023.
13 S. Paul, M. Gupta, R. Gupta and A. Loupy, Tetrahedron Lett., 2001, 42, 3827.
14 E.-S. A. Aly, M. A. Abdo and A. A. El-Gharably, J. Chin. Chem. Soc., 2004, 51, 983.
15 F. M. Abd El Latif, M. A. Barsy, E. A. Elrady and M. Hassan, J. Chem. Res., Synop., 1999, 696.

16 R. A. Pawar and A. A. Patil, Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem., 1994, 33, 156.
17 F. M. Abd El Latif, J. Indian Chem. Soc., 1994, 71, 631.
18 R. M. Mohareb, A. Habashi, N. S. Ibrahim and S. M. Sherif, Synthesis, 1987, 228.
19 G. H. Elgemeie, H. A. Ali, A. H. Elghandour and A. M. Hussein, Heterocycl. Commun., 2002, 8, 443.

20 S. Asadi, F. Alizadeh-Bami and H. Mehrabi, Arkivoc, 2020, 238.

21 P. Gillespie, R. A. Goodnow and Q. Zhang, US Pat., 20060223852A1, 2006Chem. Abstr., 2006, 145, 397512.
22 C. J. Helal, T. A. Chappie and J. M. Humphrey, WO2012168817A1, 2012Chem. Abstr., 2012, 158, 56278.
23 N.-C. Ostache, M.-A. Hiebel, A.-L. Fînaru, G. Guillaumet and F. Suzenet, ChemCatChem, 2019, 11, 3530.

24 K. Liubchak, A. Tolmachev and K. Nazarenko, J. Org. Chem., 2012, 77, 3365.
25 X. Xiong, Y. Jiang and D. Ma, Org. Lett., 2012, 14, 2552.
26 L. Xu, Y. Peng, Q. Pan, Y. Jiang and D. Ma, J. Org. Chem., 2013, 78, 3400.
27 M. Naas, PhD dissertation, Université d'Orléans, Orléans, 2016.

28 S. Grosse, C. Pillard, F. Himbert, S. Massip, J. M. Léger, C. Jarry, P. Bernard and G. Guillaumet, Eur. J. Org. Chem., 2013, 4146.
29 Crystallographic data for the structure $4 n$ have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1994906. $\dagger$


[^0]:    ${ }^{a}$ Institut de Chimie Organique et Analytique (ICOA), Université d'Orléans, UMR CNRS 7311, BP 6759, 45067 Orléans Cedex 2, France. E-mail: franck.suzenet@univ-orleans. fr
    ${ }^{b}$ Center of Applied Chemistry and Process Engineering (CAIP), University "Vasile Alecsandri" of Bacau, Calea Mărășesști, Bacău, 600115, Romania
    ${ }^{\text {'S Synthèse e }}$ Isolement de Molécules BioActives (SIMBA), EA 7502, Laboratoire de Chimie Physique, Université de Tours, 31, Avenue Monge, 37200 Tours, France
    $\dagger$ Electronic supplementary information (ESI) available. CCDC 1994906. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra00314c

