Synthesis of Pyrazolo[5,1-a]isoquinolines through Copper-Catalyzed Regioselective Bicyclization of N-Propargylic Sulfonylhydrazones

Hai-Tao Tang, Jia-Hao Zeng, Jun-Jia Chen, Yun-Bing Zhou, Ren-Hao Li, and Zhuang-Ping Zhan*

Department of Chemistry and Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, Fujian, P. R. China

zpzhan@xmu.edu.cn

Content

General Information......................................................................................................................S2
General procedure for synthesis of N-propargylic sulfonylhydrazones 1 and pyrazolo[5,1-a]isoquinolines 2......................................................................................................................................................S3
Single crystal X-ray structure for 2i ............................................................................................S4
The HRMS of 2n-18O..................................................................................................................S9
1H, 13C-NMR, IR, MP and MS Data of 2a-2g, 2i-2s, 2v, 4v, 12a .............................................S10
1H, 13C-NMR Spectra of products 2a-2g, 2i-2s, 2v, 4v, 12a......................................................S18
General Information

Unless otherwise noted, all reagents and solvents were obtained commercially and used without further purification. *N*-sulfonylhydrazones 1 were prepared according to our previous work. Column chromatography on silica gel (300-400 mesh) was carried out using technical grade 60-90 °C petroleum ether (distilled prior to use) and analytical grade EtOAc (without further purification). $^1$H and $^{13}$C spectra were recorded on a 500 MHz or 400 MHz spectrometer. Chemical shifts were reported in ppm. $^1$H NMR spectra were referenced to CDCl$_3$ (7.26 ppm), and $^{13}$C-NMR spectra were referenced to CDCl$_3$ (77.0 ppm). Peak multiplicities were designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; brs, broad singlet and J, coupling constant in Hz.$^1$ IR spectra were recorded on an FTIR spectrometer as thin film. Absorptions were given in wavenumbers (cm$^{-1}$). HRMS spectra were recorded with Micromass QTOF2 Quadrupole/Time-of-Flight Tandem mass spectrometer using electron spray ionization.
General procedure for synthesis of *N*-propargylic sulfonylhydrazones 1 and pyrazolo[5,1-\(a\)]isoquinolines 2

General procedure for synthesis of *N*-propargylic sulfonylhydrazones 1

![Chemical structure of 1](image)

To a solution of *N*-sulfonylhydrazone 5 (2 mmol) and propargyl bromide 6 (2.2 mmol) in DMF (10 mL), K₂CO₃ (2.2 mmol) were slowly added. The reaction mixture was stirred at room temperature, and the reaction progress monitored by TLC. Upon completion, the mixture was filtered off and water (20 mL) was added. The aqueous phase was extracted with CH₂Cl₂ (3×10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄. The solvent was removed under vacuum, and then the residue was further purified by silica gel column chromatography (petroleum ether and ethyl acetate) to afford propargylic hydrazone 1.

General procedure for synthesis pyrazolo[5,1-\(a\)]isoquinolines 2

![Chemical structure of 2](image)

To a solution of *N*-propargylic sulfonylhydrazone 1 (0.5 mmol) and Na₂CO₃ (0.5 mmol) in DMSO (5 mL), Cu(OTf)₂ (0.15 mmol) was added and the mixture was stirred at 150 °C in air. When the reaction was completed (30 min - 1 h, monitored by TLC), water was added to the mixture. The aqueous phase was extracted with CH₂Cl₂ (3×10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄. The solvent was removed under vacuum, and then the residue was further purified by silica gel column chromatography (petroleum ether and ethyl acetate) to afford product 2.
**Figure S1.** Single crystal X-ray structure for 2i (drawn with 30% probability).
checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: tht160623-1

<table>
<thead>
<tr>
<th>Bond precision: C-C = 0.0047 Å</th>
<th>Wavelength=0.71073</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell:</td>
<td></td>
</tr>
<tr>
<td>a=11.0348(7)</td>
<td>b=21.2718(12)</td>
</tr>
<tr>
<td>alpha=90</td>
<td>beta=90</td>
</tr>
<tr>
<td>c=7.2221(6)</td>
<td>gamma=90</td>
</tr>
<tr>
<td>Temperature:</td>
<td>184 K</td>
</tr>
<tr>
<td>Volume</td>
<td>1695.2(2)</td>
</tr>
<tr>
<td>Space group</td>
<td>P 2c a 2I</td>
</tr>
<tr>
<td>Hall group</td>
<td>P 2c -2ac</td>
</tr>
<tr>
<td>Moiety formula</td>
<td>C21 H17 N2 O3</td>
</tr>
<tr>
<td>Sum formula</td>
<td>C21 H17 N2 O3</td>
</tr>
<tr>
<td>Mr</td>
<td>345.37</td>
</tr>
<tr>
<td>Dx, g cm^-3</td>
<td>1.353</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Mu (mm-1)</td>
<td>0.092</td>
</tr>
<tr>
<td>F000</td>
<td>724.0</td>
</tr>
<tr>
<td>F000'</td>
<td>724.33</td>
</tr>
<tr>
<td>h,k,l max</td>
<td>13,25,8</td>
</tr>
<tr>
<td>Href</td>
<td>3013[ 1644]</td>
</tr>
<tr>
<td>Tmin,Tmax</td>
<td>0.982,0.991</td>
</tr>
<tr>
<td>Correction method= # Reported T Limits: Tmin=3.510 Tmax=*****</td>
<td></td>
</tr>
<tr>
<td>AbsCorr = MULTI-SCAN</td>
<td></td>
</tr>
<tr>
<td>Data completeness= 1.68/0.92</td>
<td>Theta(max)= 25.000</td>
</tr>
<tr>
<td>R(reflections)= 0.0634 (2472)</td>
<td>wR2(reflections)= 0.1335 (2770)</td>
</tr>
<tr>
<td>S = 1.200</td>
<td>Npar= 235</td>
</tr>
</tbody>
</table>

The following ALERTs were generated. Each ALERT has the format test-name ALERT alert-type alert-level.
Click on the hyperlink for more details of the test.
Alert level C

ABSTY02_ALERT_1_C  An _exptl_absorp_correction_type has been given without a literature citation. This should be contained in the _exptl_absorp_procedure_details field.

Absorption correction given as multi-scan

STEVA01_ALERT_2_C  Chirality of atom sites is inverted?

From the CIF: _reflns_is_abs_structure_Flack 2.000
From the CIF: _reflns_is_abs_structure_Flack(strcmp) 2.000
PLAT041_ALERT_1_C  Calc. and Reported SumFormula - String differ - Please Check
PLAT047_ALERT_1_C  Calculated and Reported Mol. Weight differ by 1.01 Check
PLAT065_ALERT_1_C  Reported F000 differs from Calc’d (or Missing) - Please Check
PLAT080_ALERT_2_C  Poor Data / Parameter Ratio (Smax < 18) - Please Check
PLAT210_ALERT_2_C  Non-Solvent Resid 1: C Ueq(max)/Ueq(min) Range 3.3 Ratio
PLAT242_ALERT_2_C  Low ‘MainMol’ Dq as Compared to Neighbors of C13 Check
PLAT250_ALERT_2_C  Large UI/UI Ratio for Average U(i,j) Tensor - Please Check
PLAT340_ALERT_2_C  Low Bond Precision on C-C Bonds - Please Check
PLAT420_ALERT_2_C  D-H Without Acceptor - Please Check
PLAT700_ALERT_2_C  Plack x > 0.5, Structure needs to be Inverted? - Please Check

Alert level G

FORM001_ALERT_2_D  There is a discrepancy between the atom counts in the chemical_formula_sum and the formula from the _atom_site data.

Atom count from chemical_formula_sum: C21 H16 N2 O3
Atom count from _atom_site data: C21 H17 N2 O3

CELLD01_ALERT_1_D  Difference between formula and _atom_site contents detected.

CELLD01_ALERT_1_D ALERT: Large difference may be due to a symmetry error - see SYMM test.

From the CIF: _cell_chemical_composition 4
From the CIF: _chemical_formula_sum C21 H17 N2 O3
TEST: Compare cell contents of formula and _atom_site data

atom Z(formula cif sites) diff
c 84.00 84.00 0.00
H 64.00 68.00 4.00
O 8.00 8.00 0.00
C 12.00 12.00 0.00

PLAT055_ALERT_2_C  No Embedded Refinement Details Found in the CIF - Please Do 1 Report
PLAT092_ALERT_2_C  Std. Uncertainty on Flack Parameter Value High - Please Do 1 Report
PLAT093_ALERT_2_C  No o.s.u.’s on H-positions, Refinement Reported as mixed - Please Do 1 Report
PLAT098_ALERT_3_C  Oriented isop222-Methyl Molecly - Please Do 1 Report
PLAT099_ALERT_4_C  SHELXL97 is Deprecated and Succeeded by SHELXL2014 - Please Do 1 Report
It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the
classifications point to easily fixed oversights, errors and omissions in your CIF or refinement
strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more
serious problems it may be necessary to carry out additional measurements or structure
refinements. However, the purpose of your study may justify the reported deviations and the more
serious of these should normally be commented upon in the discussion or experimental section of a
paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify
outliers and unusual parameters, but every test has its limitations and alerts that are not important
in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no
aspects of the results needing attention. It is up to the individual to critically assess their own
results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs
submitted for publication in IUCr journals (*Acta Crystallographica, Journal of Applied
Crystallography, Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta
Crystallographica Section C, E or IUCrData*, you should make sure that full publication checks
are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to
CIF submission.

PLATON version of 11/08/2016; check.def file version of 04/08/2016
The HRMS of 2n-^{18}O

**Figure S2.** 2n-^{18}O HRMS (ESI) \( m/z \) calcd for \( \text{C}_{24}\text{H}_{15}\text{ClN}_{2}{^{18}}\text{O} \) [M+Na]^+ 407.0808, found: 407.0816.
**1H, 13C-NMR, IR, MP and MS Data of 2a-2g, 2i-2s, 2v, 4v**

*Phenyl(5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)methanone (2a).* A white solid (mp: 182-183 °C, Rf = 0.6, petroleum ether/ethyl acetate = 6:1); 1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.32 (s, 1H), 7.50-7.58 (m, 5H), 7.59-7.64 (m, 1H), 7.65-7.72 (m, 2H), 7.81-7.88 (m, 3H), 7.96 (d, 2H, $J = 7.38$ Hz), 8.16 (s, 1H), 9.45 (d, 1H, $J = 7.74$ Hz); 13C NMR (100 MHz, CDCl$_3$) $\delta$ 115.8, 123.9, 126.9, 127.1, 127.7, 128.4, 128.4, 129.5, 129.7, 129.8, 130.9, 132.3, 133.4, 138.3, 139.8, 140.2, 146.2, 190.4; IR (film): 3056, 1645, 1519 cm$^{-1}$; HRMS (ESI) $m/z$ calcd for C$_{24}$H$_{16}$N$_2$O [M+Na]$^+$ 371.1155, found: 371.1149.

*(5-(4-Bromophenyl)pyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2b).* A yellow solid (mp: 212-213 °C, Rf = 0.4, petroleum ether/ethyl acetate = 6:1); 1H NMR (500 MHz, CDCl$_3$) $\delta$ 7.30 (s, 1H), 7.50-7.55 (m, 2H), 7.59-7.63 (m, 1H), 7.65-7.71 (m, 4H), 7.72-7.76 (m, 2H), 7.80-7.84 (m, 1H), 7.92-7.97 (m, 2H), 8.14 (s, 1H), 9.42 (d, 1H, $J = 7.97$ Hz); 13C NMR (125 MHz, CDCl$_3$) $\delta$ 115.8, 116.0, 123.9, 124.0, 126.9, 127.2, 127.9, 128.4, 129.7, 129.9, 130.7, 131.3, 131.7, 132.2, 132.4, 137.1, 139.8, 140.1, 146.1, 190.3; IR (film): 3058, 1639, 1520 cm$^{-1}$; HRMS (ESI) $m/z$ calcd for C$_{24}$H$_{15}$BrN$_2$O [M+Na]$^+$ 449.0260 and 451.0240, found: 449.0258 and 451.0238.

*Phenyl(5-(p-tolyl)pyrazolo[5,1-a]isoquinolin-1-yl)methanone (2c).* A white solid (mp: 184-185 °C, Rf = 0.7, petroleum ether/ethyl acetate = 6:1); 1H NMR (400 MHz, CDCl$_3$) $\delta$ 2.46 (s, 3H), $\delta$ 7.30 (s, 1H), 7.36 (d, 2H, $J = 7.92$ Hz), 7.49-7.56 (m, 2H), 7.58-7.70 (m, 3H), 7.72-7.76 (m, 2H), 7.79-7.85 (m, 1H), 7.91-8.00 (m, 2H), 8.15 (s, 1H), 9.44 (d, 1H, $J = 7.90$ Hz); 13C NMR (100 MHz, CDCl$_3$) $\delta$ 21.4, 115.5, 115.8,
123.8, 126.9, 127.0, 127.5, 128.4, 129.1, 129.6, 129.8, 130.5, 131.0, 132.3, 138.4,
139.6, 139.8, 140.2, 146.2, 190.4; IR (film): 3061, 1642, 1508 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd for \(\text{C}_{25}\text{H}_{18}\text{N}_2\text{O} [\text{M+Na}]^+\) 385.1311, found: 385.1308.

\((5-(4\text{-Methoxyphenyl})\text{pyrazolo[5,1-a]isoquinolin-1-yl})(\text{phenyl})\text{methanone (2d).}\) A white solid (mp: 195-196 °C, Rf = 0.5, petroleum ether/ethyl acetate = 5:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.90 (s, 3H), \(\delta\) 7.05-7.09 (m, 2H), 7.28 (s, 1H), 7.50-7.54 (m, 2H), 7.59-7.70 (m, 3H), 7.78-7.84 (m, 3H), 7.93-7.97 (m, 2H), 8.15 (s, 1H), 9.43 (d, 1H, \(J = 8.15\) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 55.4, 113.9, 115.3, 115.8, 123.8, 125.8, 126.9, 127.0, 127.5, 128.4, 129.8, 131.1, 132.3, 138.2, 139.8, 140.3, 146.2, 160.6, 190.4; IR (film): 3058, 1640, 1511 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd for \(\text{C}_{26}\text{H}_{20}\text{N}_2\text{O} [\text{M+Na}]^+\) 401.1260, found: 401.1256.

\((5-(4\text{-Ethylphenyl})\text{pyrazolo[5,1-a]isoquinolin-1-yl})(\text{phenyl})\text{methanone (2e).}\) A white solid (mp: 179-180 °C, Rf = 0.7, petroleum ether/ethyl acetate = 6:1); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.32 (t, 3H, \(J = 7.62\) Hz), \(\delta\) 2.77 (q, 2H, \(J = 7.60\) Hz), 7.31 (s, 1H), 7.38-7.41 (m, 2H), 7.50-7.54 (m, 2H), 7.59-7.70 (m, 3H), 7.75-7.79 (m, 2H), 7.80-7.84 (m, 1H), 7.93-7.98 (m, 2H), 8.16 (s, 1H), 9.44 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 15.3, 28.8, 115.6, 115.8, 123.8, 126.9, 127.0, 127.5, 128.0, 128.4, 129.6, 129.8, 130.7, 131.0, 132.3, 138.4, 139.8, 140.2, 145.9, 146.2, 190.4; IR (film): 3055, 1642, 1508 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd for \(\text{C}_{26}\text{H}_{20}\text{N}_2\text{O} [\text{M+Na}]^+\) 399.1468, found: 399.1465.

\(\text{Phenyl}(5-(m\text{-tolyl})\text{pyrazolo[5,1-a]isoquinolin-1-yl})\text{methanone (2f).}\) A white solid (mp: 185-186 °C, Rf = 0.6, petroleum ether/ethyl acetate = 6:1); \(^1\)H NMR (400 MHz,
CDCl$_3$) δ 2.47 (s, 3H), 7.30 (s, 1H), 7.32-7.36 (m, 1H), 7.42-7.48 (m, 1H), 7.50-7.55 (m, 2H), 7.58-7.71 (m, 5H), 7.80-7.85 (m, 1H), 7.93-7.98 (m, 2H), 8.15 (s, 1H), 9.45 (d, 1H, $J = 7.86$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 21.5, 115.8, 115.8, 123.9, 126.8, 126.9, 127.1, 127.6, 128.3, 128.4, 129.8, 130.2, 130.3, 131.0, 132.3, 133.4, 138.2, 138.5, 139.8, 140.2, 146.3, 190.4; IR (film): 3055, 1643, 1518 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{25}$H$_{18}$N$_2$O [M+Na]$^+$ 385.1311, found: 385.1308.

**(Phenyl(5-(thiophen-3-yl)pyrazolo[5,1-a]isoquinolin-1-yl)methanone (2g).** A white solid (mp: 167-168 °C, Rf = 0.6, petroleum ether/ethyl acetate = 5:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48-7.56 (m, 4H), 7.60-7.67 (m, 2H), 7.67-7.71 (m, 1H), 7.72-7.76 (m, 1H), 7.81-7.85 (m, 1H), 7.94-7.97 (m, 2H), 8.20 (s, 1H), 8.26-8.30 (m, 1H), 9.41 (d, 1H, $J = 8.05$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 114.9, 115.8, 123.6, 125.5, 126.8, 127.0, 127.3, 127.7, 128.2, 128.4, 129.8, 130.8, 132.4, 133.3, 133.4, 139.9, 140.2, 146.1, 190.5; IR (film): 3051, 1638, 1507 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{22}$H$_{14}$N$_2$OS [M+Na]$^+$ 377.0719, found: 377.0716.

**(1-Benzoylpyrazolo[5,1-a]isoquinolin-5-yl)methyl acetate (2i).** A white solid (mp: 138-139 °C, Rf = 0.5, petroleum ether/ethyl acetate = 5:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 2.21 (s, 3H), 5.70 (s, 2H), 7.38 (s, 1H), 7.51-7.55 (m, 2H), 7.60-7.72 (m, 3H), 7.81-7.85 (m, 1H), 7.91-7.95 (m, 2H), 8.19 (s, 1H), 8.42 (d, 1H, $J = 7.81$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 20.9, 60.8, 114.8, 116.0, 124.2, 127.0, 127.2, 128.1, 128.4, 129.7, 129.8, 130.2, 132.3, 132.7, 139.3, 140.1, 146.4, 170.4, 190.3; IR (film): 3061, 1745, 1642, 1520 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{21}$H$_{16}$N$_2$O$_3$ [M+Na]$^+$ 367.1053, found: 367.1050.
(5-Cyclopropylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2j). A white solid (mp: 112-115 °C, Rf = 0.6, petroleum ether/ethyl acetate = 6:1); $^1$H NMR (500 MHz, CDCl$_3$) δ 0.94-0.98 (m, 2H), 1.21-1.26 (m, 2H), 2.71-2.79 (m, 1H), 6.93 (s, 1H), 7.50-7.54 (m, 2H), 7.56-7.65 (m, 3H), 7.69-7.73 (m, 1H), 7.92-8.00 (m, 2H), 8.21 (s, 1H), 9.40 (d, 1H, $J$ = 8.26 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 7.3, 11.7, 110.3, 115.9, 123.2, 126.4, 126.8, 126.9, 128.3, 129.5, 129.7, 131.0, 132.2, 139.4, 140.3, 140.6, 146.2, 190.4; IR (film): 3058, 2917, 1645, 1514 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{21}$H$_{16}$N$_2$O [M+Na]$^+$ 335.1155, found: 335.1151.

(5-Pentylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2k). A yellow solid (mp: 59-60 °C, Rf = 0.7, petroleum ether/ethyl acetate = 6:1); $^1$H NMR (500 MHz, CDCl$_3$) δ 0.94 (t, 3H, $J$ = 7.14 Hz), 1.40-1.50 (m, 4H), 1.88-1.94 (m, 2H), 3.22 (t, 2H, $J$ = 7.68 Hz), 7.09 (s, 1H), 7.50-7.54 (m, 2H), 7.57-7.65 (m, 3H), 7.72-7.75 (m, 1H), 7.92-7.96 (m, 2H), 8.16 (s, 1H), 9.42 (d, 1H, $J$ = 8.17 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 14.0, 22.4, 26.7, 31.2, 31.5, 113.0, 115.7, 123.3, 126.3, 126.8, 126.8, 128.3, 129.5, 129.7, 130.9, 132.1, 139.3, 139.4, 140.3, 146.1, 190.3; IR (film): 3056, 2955, 1648, 1517 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{23}$H$_{22}$N$_2$O [M+Na]$^+$ 365.1624, found: 365.1621.

(2-Methyl-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2l). A yellow solid (mp: 55-56 °C, Rf = 0.7, petroleum ether/ethyl acetate = 7:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 2.28 (s, 3H), 7.16 (s, 1H), 7.36-7.41 (m, 1H), 7.45-7.62 (m, 7H), 7.72-7.77 (m, 1H), 7.90-7.96 (m, 4H), 8.22 (d, 1H, $J$ = 8.24 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.2, 114.0, 123.0, 125.3, 127.2, 127.2, 128.3, 128.7, 129.4, 129.7, 129.7,
IR (film): 3058, 1642, 1526 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{25}$H$_{18}$N$_2$O [M+Na]$^+$ 385.1311, found: 385.1307.

(2-Ethyl-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2m). A white solid (mp: 51-52 °C, Rf = 0.7, petroleum ether/ethyl acetate = 7:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 1.18 (t, 3H, J = 7.55 Hz), 2.68 (q, 2H, J = 7.54 Hz), 7.15 (s, 1H), 7.32-7.38 (m, 1H), 7.44-7.56 (m, 6H), 7.57-7.62 (m, 1H), 7.71-7.75 (m, 1H), 7.93-7.98 (m, 4H), 8.08 (d, 1H, J = 8.30 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.0, 21.5, 113.1, 113.8, 123.1, 125.2, 127.2, 127.2, 128.3, 128.6, 128.7, 129.4, 129.7, 129.8, 130.5, 133.2, 133.6, 138.0, 138.6, 139.3, 156.2, 193.9; IR (film): 3061, 2965, 1649, 1530 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{26}$H$_{20}$N$_2$O [M+Na]$^+$ 399.1468, found: 399.1465.

(9-Chloro-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2n). A white solid (mp: 199-200 °C, Rf = 0.6, petroleum ether/ethyl acetate = 5:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.27 (s, 1H), 7.50-7.56 (m, 5H), 7.59-7.65 (m, 2H), 7.73-7.77 (m, 1H), 7.82-7.86 (m, 2H), 7.91-7.95 (m, 2H), 8.17 (s, 1H), 9.56 (d, 1H, J = 1.66 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 115.1, 116.1, 124.8, 126.3, 128.4, 128.4, 129.2, 129.6, 130.4, 132.4, 133.0, 130.4, 133.6, 138.6, 138.8, 140.0, 146.4, 190.2; IR (film): 3064, 1642, 1517 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{24}$H$_{15}$ClN$_2$O [M+Na]$^+$ 405.0765, found: 405.0761.

(9-Methoxy-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2o). A white solid (mp: 192-193 °C, Rf = 0.5, petroleum ether/ethyl acetate = 5:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 4.02 (s, 3H), 7.28 (s, 1H), 7.29-7.34 (m, 1H), 7.48-7.63 (m, 6H),
7.70-7.75 (m, 1H), 7.81-7.95 (m, 4H), 8.15 (s, 1H), 9.14 (d, 1H, $J = 2.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 55.8, 107.4, 115.6, 115.7, 121.1, 125.3, 125.3, 128.3, 128.4, 128.4, 129.3, 129.6, 129.7, 132.0, 133.6, 136.1, 139.5, 140.7, 146.8, 159.0, 190.6; IR (film): 3098, 1639, 1520 cm$^{-1}$; HRMS (ESI) $m/z$ calcd for C$_{25}$H$_{18}$N$_2$O$_2$ [M+Na]$^+$ 401.1260, found: 401.1256.

**(8-Methyl-5-phenylpyrazolo[5,1-a][isoquinolin-1-yl](phenyl)methanone (2p).** A white solid (mp: 142-143 °C, Rf = 0.7, petroleum ether/ethyl acetate = 6:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.56 (s, 3H), 7.25 (s, 1H), 7.47-7.56 (m, 6H), 7.58-7.63 (m, 2H), 7.81-7.86 (m, 2H), 8.14 (s, 1H), 9.37 (d, 1H, $J = 8.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.7, 115.4, 115.6, 121.8, 126.7, 126.9, 128.3, 128.4, 129.4, 129.5, 129.7, 131.2, 132.2, 133.5, 138.2, 139.9, 140.2, 146.3, 190.3; IR (film): 3058, 1645, 1517 cm$^{-1}$; HRMS (ESI) $m/z$ calcd for C$_{25}$H$_{18}$N$_2$O [M+Na]$^+$ 385.1311, found: 385.1308.

*Naphthalen-1-yl(5-phenylpyrazolo[5,1-a][isoquinolin-1-yl)methanone (2q).** A white solid (mp: 85-86 °C, Rf = 0.5, petroleum ether/ethyl acetate = 5:1); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37 (s, 1H), 7.51-7.56 (m, 6H), 7.74-7.78 (m, 3H), 7.83-7.88 (m, 3H), 7.94-7.97 (m, 2H), 8.00-8.04 (m, 1H), 8.32-8.38 (m, 1H), 9.98-10.02 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 116.2, 118.0, 124.1, 124.4, 125.7, 126.4, 127.0, 127.2, 127.5, 127.8, 128.3, 129.5, 129.7, 130.1, 130.9, 131.1, 131.2, 133.3, 133.8, 138.3, 138.8, 139.9, 147.6, 191.2; IR (film): 3055, 1642, 1514 cm$^{-1}$; HRMS (ESI) $m/z$ calcd for C$_{28}$H$_{18}$N$_2$O [M+Na]$^+$ 421.1311, found: 421.1307.

**(4-Chlorophenyl)(5-phenylpyrazolo[5,1-a][isoquinolin-1-yl)methanone (2r).** A
white solid (mp: 166-167 °C, Rf = 0.4, petroleum ether/ethyl acetate = 5:1); ¹H NMR (400 MHz, CDCl₃) δ 7.32 (s, 1H), 7.47-7.51 (m, 2H), 7.52-7.58 (m, 3H), 7.63-7.72 (m, 2H), 7.80-7.90 (m, 5H), 8.12 (s, 1H), 9.40 (d, 1H, J = 7.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 115.5, 116.0, 123.8, 126.8, 127.1, 127.7, 128.4, 128.7, 129.6, 129.7, 129.9, 131.0, 131.1, 133.3, 138.3, 138.5, 138.6, 139.8, 145.9, 188.9; IR (film): 3058, 1642, 1517 cm⁻¹; HRMS (ESI) m/z calcd for C₂₄H₁₅ClN₂O [M+Na]⁺ 405.0765, found: 405.0761.

(5-Phenylpyrazolo[5,1-a]isoquinolin-1-yl)(p-tolyl)methanone (2s). A white solid (mp:142-143 °C, Rf = 0.6, petroleum ether/ethyl acetate = 6:1); ¹H NMR (400 MHz, CDCl₃) δ 2.44 (s, 3H), 7.31 (s, 1H), 7.38-7.44 (m, 2H), 7.52-7.59 (m, 3H), 7.63-7.71 (m, 2H), 7.72-7.79 (m, 2H), 7.81-7.88 (m, 3H), 8.17 (s, 1H), 9.44(d, 1H, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.3, 115.8, 115.9, 123.9, 126.9, 127.1, 127.7, 128.2, 128.4, 129.5, 129.7, 129.8, 130.3, 130.9, 133.1, 138.2, 138.3, 139.7, 140.1, 146.2, 190.6; IR (film): 3055, 1642, 1517 cm⁻¹; HRMS (ESI) m/z calcd for C₂₅H₁₈N₂O [M+Na]⁺ 385.1311, found: 385.1308.

(9-Chloro-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(p-tolyl)methanone (2v). A white solid (mp: 135-136 °C, Rf = 0.5, petroleum ether/ethyl acetate = 5:1); ¹H NMR (400 MHz, CDCl₃) δ 2.47 (s, 3H), 7.27 (s, 1H), 7.30-7.35 (m, 2H), 7.50-7.59 (m, 3H), 7.61-7.66 (m, 1H), 7.72-7.78 (m, 1H), 7.80-7.88 (m, 4H), 8.17 (s, 1H), 9.48 (d, 1H, J = 1.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 21.6, 115.0, 116.3, 124.9, 126.3, 128.4, 128.5, 129.1, 129.6, 129.7, 130.0, 130.3, 133.1, 133.6, 137.3, 138.6, 138.7, 143.3, 146.2, 190.0; IR (film): 3052, 1642, 1524 cm⁻¹; HRMS (ESI) m/z calcd for
C_{25}H_{17}ClN_{2}O [M+Na]^+ \text{419.0922, found: 419.0920.}

9-Chloro-1-(methoxy(p-tolyl)methyl)-5-phenylpyrazolo[5,1-a]isoquinoline (4v) A colourless liquid (Rf = 0.4, petroleum ether/ethyl acetate = 5:1); ^1H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.39 (s, 3H), 3.54 (s, 3H), 5.85 (s, 1H), 7.02 (s, 1H), 7.20-7.26 (m, 2H), 7.40-7.44 (m, 2H), 7.46-7.55 (m, 4H), 7.63-7.68 (m, 2H), 7.79-7.88 (m, 2H), 8.30-8.38 (m, 1H); ^13C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 21.1, 56.5, 78.3, 112.4, 116.8, 124.7, 125.3, 127.4, 128.0, 128.1, 128.3, 129.2, 129.4, 133.0, 133.5, 134.9, 136.6, 137.7, 138.8, 141.7; IR (film): 3055, 2923, 1598 cm\textsuperscript{-1}; HRMS (ESI) m/z calcd for C_{26}H_{21}ClN_{2}O [M+Na]^+ 435.1235, found: 435.1233.

3-phenylisoquinoline (12a) This compound is known (CAS: 37993-76-3). ^1H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.43-7.48 (m, 1H), 7.51-7.61 (m, 3H), 7.66-7.74 (m, 1H), 7.85-7.90 (m, 1H), 7.97-8.02 (m, 1H), 8.08 (s, 1H), 8.14-8.20 (m, 2H) 9.37 (s, 1H); ^13C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 116.4, 126.8, 126.9, 127.0, 127.5, 128.7, 130.4, 136.6, 139.5, 151.2, 152.3.
$^1$H, $^{13}$C-NMR Spectra of products 2a-2g, 2i-2s, 2v, 4v

Phenyl(5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)methanone (2a)
(5-(4-Bromophenyl)pyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2b)
Phenyl(5-(p-tolyl)pyrazolo[5,1-a]isoquinolin-1-yl)methanone (2c)
(5-(4-Methoxyphenyl)pyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2d)
(5-(4-Ethylphenyl)pyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2e)
Phenyl(5-(m-tolyl)pyrazolo[5,1-a]isoquinolin-1-yl)methanone (2f)
Phenyl(5-(thiophen-3-yl)pyrazolo[5,1-a]isoquinolin-1-yl)methanone (2g)
(1-Benzoylpyrazolo[5,1-a]isoquinolin-5-yl)methyl acetate (2i)
(5-Cyclopropylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2j)
(5-Pentylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2k)
(2-Methyl-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2I)
(2-Ethyl-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2m)
(9-Chloro-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2n)
(9-Methoxy-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2o)
(8-Methyl-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(phenyl)methanone (2p)
Naphthalen-1-yl(5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)methanone (2q)
(4-Chlorophenyl)(5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)methanone (2r)
(5-Phenylpyrazolo[5,1-a]isoquinolin-1-yl)(p-tolyl)methanone (2s)
(9-Chloro-5-phenylpyrazolo[5,1-a]isoquinolin-1-yl)(p-tolyl)methanone (2v)
9-Chloro-1-(methoxy(p-tolyl)methyl)-5-phenylpyrazolo[5,1-a]isoquinoline (4v)
3-phenylisoquinoline (12a)