Concise approach toward tetrazolyl substituted benzoazocines via a novel isocyanide-based MCR.

Roman S. Borisov,Leonid G. Voskressensky, Anatoly I. Polyakov, Tatiana N. Borisova and Alexey V. Varlamov

SUPPORTING INFORMATION.

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>#</th>
<th>CONTENTS</th>
<th>PAGE #</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>General experiment</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>General experiment for Ugi-azido reaction (synthesis of compounds 4a-i)</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Initial optimization study for the synthesis of 5d</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>General experiment for the ring-expansion (synthesis of compounds 5a-d)</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>Multicomponent synthesis of 5d</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>Copies of 1H and 13C spectra</td>
<td>8</td>
</tr>
</tbody>
</table>
**General Experimental:**

Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F254 pre-coated plates. Visualization was accomplished with UV lamp or I2 stain. Silica gel 30-60 mesh size was used for flash chromatography using the combination of ethyl acetate and hexanes as an eluent on Buchi Separocpre apparatus. Methyl propiolate, acetyl acetelene and dimethyl acetelene dicarboxilate were purchased from Sigma-Aldrich and were used directly. All isonitriles and cotarnine chloride were commercial reagents and were used as received. Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded at 600 or 400 MHz. Chemical shifts were recorded in parts per million (ppm, \(\delta\)) relative to tetramethyl silane (\(\delta 0.00\)). \(^1\)H NMR splitting patterns are designated as singlet (s), doublet (d), double doublet (dd), triplet (t), double triplet(dt), quartet (q) or multiplet (m). Carbon nuclear magnetic resonance (\(^{13}\)C NMR) spectra were recorded at 150 or 100 MHz. MALDI mass spectra were measured on Bruker autoflex speed instrument in positive reflectron mode with DHB in THF (2 mg/ml) as matrix. High resolution mass spectrometry (HRMS) data was acquired on the same instrument (resolution 15000 FWHM) with internal calibration (PEG 400). Melting points were determined using an open capillary apparatus and are reported as uncorrected. Microwave activation was made using Anton Paar Monowave-300 reactor.
General experiment for Ugi-azido reaction (synthesis of compounds 4a-i)

Cotamine chloride 2 (1 mmol), isonitrile (1.2 mmol) and sodium azide (1.2 mmol) were dissolved in 5 ml of water-methanol (1:5) mixture and stirred at room temperature for 18-24 hours (TLC monitoring). Compounds 4a,b were isolated using flash chromatography (eluent - ethyl acetate-hexanes from 1:50 to 1:10). Compounds 4c-i precipitated from the reaction mixtures and were filtered off, washed with 15 ml of cold methanol and dried on air.

5-(1-cyclohexyl-1H-tetrazol-5-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (4a): Reaction time - 19 h. Yield 51%, colorless powder, mp 147-149 °C (ethyl acetate-hexanes). $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 1.18-1.33 (m, 2H), 1.37-1.47 (m, 1H), 1.60-1.71 (m, 2H), 1.72-1.79 (m, 2H), 1.79-1.87 (m, 2H), 1.91-1.97 (m, 1H), 2.21 (s, 3H), 2.56 (dt, 1H, $J$=4.8, 11.7 Hz), 2.64 (dt, 1H, $J$=4.8, 16.5 Hz), 2.79-2.86 (m, 1H), 2.90-2.96 (m, 1H), 3.50 (s, 3H), 4.51-4.59 (m, 1H), 5.18 (s, 1H), 5.90 (d, 2H, $J$=9.6 Hz), 6.50 (s, 1H). $^{13}$C NMR (DMSO-d$_6$, 150 MHz): $\delta$ = 25.1, 25.2, 25.3, 26.8, 33.1, 33.2, 42.2, 46.8, 52.7, 57.1, 59.3, 101.4, 103.3, 118.2, 129.5, 134.5, 139.9, 148.8, 154.6. HRMS (MALDI): calculated for C$_{19}$H$_{25}$N$_3$O$_3$Na [M+Na]$^+$ 394.1849, found 394.1861

5-(1-cyclopentyl-1H-tetrazol-5-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (4b): Reaction time - 22 h. Yield 53%, colorless powder, mp 150-152 °C (ethyl acetate-hexanes). $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 1.62-1.73 (m, 2H), 1.77-1.85 (m, 1H), 1.85-1.97 (m, 3H), 1.98-2.06 (m, 1H), 2.18-2.24 (m, 1H), 2.19 (s, 3H), 2.54-2.59 (m, 1H), 2.62 (dt, 1H, $J$=4.1, 16.5 Hz), 2.78-2.87 (m, 1H), 2.94 (qd, 1H, $J$=4.8, 12.4 Hz), 3.52 (s, 3H), 5.15-5.24 (m, 1H), 5.19 (s, 1H), 5.90 (d, 2H, $J$=6.9 Hz), 6.50 (s, 1H). $^{13}$C NMR (DMSO-d$_6$, 150 MHz): $\delta$ = 24.9, 24.9, 26.7, 33.6, 33.7, 42.1, 46.3, 52.1, 58.4, 59.3, 101.4, 103.3, 118.4, 129.3, 134.3, 139.9, 148.8, 154.9. HRMS (MALDI): calculated for C$_{18}$H$_{23}$N$_3$O$_3$Na [M+Na]$^+$ 380.1693, found 380.1685

5-(1-Benzyl-1H-tetrazol-5-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (4c): Reaction time - 18 h. Yield 63%, pale-yellow solid, mp 115-117°C. $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 2.16 (s, 3H), 2.56 (dt, 1H, $J$=4.1, 12.4 Hz), 2.62 (dt, 1H, $J$=4.1, 16.5 Hz), 2.77-2.85 (m, 1H), 2.87-2.95 (m, 1H), 3.38 (s, 3H), 5.15 (s, 1H), 5.68 (s, 2H), 5.83 (s, 1H), 5.89 (s, 1H), 6.46 (s, 1H), 7.23 (d, 2H, $J$=7.2 Hz), 7.27-7.32 (m, 1H), 7.32-7.37 (m, 2H). $^{13}$C NMR (DMSO-d$_6$, 150 MHz): $\delta$ = 25.8, 39.6, 39.7, 41.9, 46.6, 50.4, 52.8, 59.0, 101.3, 103.3, 117.5, 128.4, 128.6, 129.1, 129.3, 134.3, 135.2, 140.0, 148.9, 155.9. HRMS (MALDI): calculated for C$_{20}$H$_{21}$N$_3$O$_3$Na [M+Na]$^+$ 402.1536, found 402.1525
$^{5}$-(1-(2-Ethyl-6-methylphenyl)-1H-tetrazol-5-yl)-4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (4d): Reaction time - 21 h. Yield 57%, colorless solid, mp 166-168°C. $^1$H NMR (DMSO-d$_6$, 600 MHz): Mixture of 2 rotamers A:B=1.2:1;

for A: $\delta$ = 0.98 (t, 3H, $J$=7.6 Hz), 1.80-1.91 (m, 1H), 1.95 (s, 3H), 1.97 (s, 3H), 2.01-2.12 (m, 1H), 2.09-2.22 (m, 1H), 2.54 (dt, 1H, $J$=4.1, 12.4 Hz), 2.57-2.64 (m, 1H), 2.64-2.71 (m, 1H), 3.66 (s, 3H), 4.56 (s, 1H), 5.91 (s, 2H), 6.40 (s, 1H), 7.27 (t, 1H, $J$=8.2 Hz), 7.31 (d, 1H, $J$=7.6 Hz), 7.47 (td, 1H, $J$=2.8, 7.6 Hz).

for B: $\delta$ = 1.04 (t, 3H, $J$=7.6 Hz), 1.76 (s, 3H), 1.95 (s, 3H), 2.09-2.22 (m, 2H), 2.35-2.43 (m, 1H), 2.57-2.64 (m, 1H), 2.64-2.71 (m, 2H), 3.67 (s, 3H), 4.55 (s, 1H), 5.95 (d, 2H, $J$=4.8 Hz), 6.42 (s, 1H), 7.27 (t, 1H, $J$=8.2 Hz), 7.35 (d, 1H, $J$=7.6 Hz), 7.47 (td, 1H, $J$=2.8, 7.6 Hz).

$^{13}$C NMR (DMSO-d$_6$, 150 MHz): $\delta$ = 14.7, 15.1, 16.9, 17.3, 21.9, 22.4, 23.4, 23.6, 41.2, 41.3, 45.1, 45.4, 52.9, 53.1, 59.1, 101.3, 103.1, 103.2, 115.4, 126.9, 127.1, 128.7, 128.8, 129.7, 129.8, 131.3, 131.4, 131.7, 134.1, 135.5, 137.2, 140.7, 141.1, 142.8, 148.9, 157.4, 157.5.

HRMS (MALDI): calculated for C$_{22}$H$_{25}$N$_5$O$_3$Na [M+Na]$^+$ 430.1850, found 430.1837

N-(4-Isopropylphenyl)-3-(5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1H-tetrazol-1-yl)benzamide (4e): Reaction time - 24 h. Yield 69%, colorless solid, mp 124-126°C. $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 1.17 (d, 6H, $J$=6.9 Hz), 2.15 (s, 3H), 2.50 (dt, 1H, $J$=4.1, 16.5 Hz), 2.61 (dt, 1H, $J$=4.8, 12.4 Hz), 2.69-2.78 (m, 1H), 2.95-3.03 (m, 1H), 3.58 (s, 3H), 5.00 (s, 1H), 5.82 (s, 1H), 5.88 (s, 1H), 6.38 (s, 1H), 7.21 (d, 2H, $J$=8.9 Hz), 7.65 (d, 2H, $J$=8.9 Hz), 7.75-7.85 (m, 2H), 8.13 (s, 1H), 8.19 (d, 1H, $J$=7.6 Hz), 10.38 (s, 1H).$^{13}$C NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 24.4, 25.6, 25.9, 33.4, 42.1, 46.4, 52.8, 59.3, 67.5, 101.4, 103.1, 117.2, 121.1, 125.1, 126.9 (2C), 128.9, 129.6, 129.9, 130.5, 134.1, 134.3, 136.9, 137.0, 139.8, 144.6, 148.9, 155.9. HRMS (MALDI): calculated for C$_{29}$H$_{30}$N$_6$O$_4$Na [M+Na]$^+$ 549.2220, found 549.2241

Ethyl 3-(5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1H-tetrazol-1-yl)benzoate (4f): Reaction time - 19 h. Yield 58%, pale-brown solid, mp 139-141°C. $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 1.30 (t, 3H, $J$=7.2 Hz), 2.16 (s, 3H), 2.45-2.52 (m, 1H), 2.60 (dt, 1H, $J$=4.8, 11.7 Hz), 2.68-2.77 (m, 1H), 2.95-3.04 (m, 1H), 3.56 (s, 3H), 4.33 (q, 2H, $J$=7.2 Hz), 4.94 (s, 1H), 5.87 (d, 2H, $J$=17.9 Hz), 6.37 (s, 1H), 7.78 (t, 1H, $J$=7.6 Hz), 7.90 (d, 1H, $J$=8.2 Hz), 8.11 (s, 1H), 8.16 (d, 1H, $J$=7.6 Hz).$^{13}$C NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 14.5, 25.5, 42.0, 46.5, 46.5, 52.9, 59.3, 61.9, 101.4, 103.1, 117.0, 126.1, 129.7, 130.6, 131.4, 131.9, 134.1, 134.5, 139.7, 148.9, 155.9, 164.9. HRMS (MALDI): calculated for C$_{22}$H$_{23}$N$_5$O$_5$Na [M+Na]$^+$ 460.1591, found 460.1593

3-(5-(4-Methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1H-tetrazol-1-yl)benzohydrazide (4g): Reaction time - 23 h. Yield 63%, colorless solid, mp 115-117°C. $^1$H NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 2.12 (s, 3H), 2.50 (dt, 1H, $J$=3.4, 16.5 Hz), 2.60 (dt, 1H, $J$=4.1, 12.4 Hz), 2.69-2.77 (m, 1H), 2.94-3.01 (m, 1H), 3.32 (s, 3H), 4.57 (br.s, 2H), 4.98 (s, 1H), 5.88 (d, 2H, $J$=18.6 Hz), 6.39 (s, 1H), 7.68-7.79 (m, 2H), 8.01 (s, 1H), 8.03 (t, 1H, $J$=7.6 Hz), 10.01(s, 1H).$^{13}$C NMR (DMSO-d$_6$, 600 MHz): $\delta$ = 25.6, 42.1, 46.3, 52.7, 59.3, 101.4, 103.1, 117.2, 124.5, 128.5, 129.1, 129.6, 130.5, 134.1, 134.4, 135.3, 139.8, 148.9, 155.9, 164.7. HRMS (MALDI): calculated for C$_{20}$H$_{21}$N$_7$O$_4$Na [M+Na]$^+$ 446.1547, found 446.1561
4\textsuperscript{5}(5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1H-tetrazol-1-yl)benzohydrazide (4h): Reaction time - 19 h. Yield 55%, colorless solid. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 600 MHz): δ =2.12 (s, 3H), 2.50 (dt, 1H, J=3.4, 16.5 Hz), 2.61 (dt, 1H, J=4.8, 12.4 Hz), 2.72-2.80 (m, 1H), 2.94-3.04 (m, 1H), 3.52 (s, 3H), 4.58 (br.s, 2H), 4.95 (s, 1H), 5.89 (d, 2H, J=2.8 Hz), 6.42 (s, 1H), 7.70 (d, 2H, J=8.2 Hz), 8.05 (d, 2H, J=8.2 Hz), 9.09 (s, 1H).

\textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 600 MHz): δ = 25.3, 42.0, 46.1, 52.6, 59.2, 101.2, 103.2, 117.2, 125.8 (2C), 129.0(2C), 129.4, 134.3, 135.5, 136.1, 139.8, 148.9, 156.0, 165.0 HRMS (MALDI): calculated for C\textsubscript{20}H\textsubscript{21}N\textsubscript{7}O\textsubscript{4}Na [M+Na]\textsuperscript{+} 446.1547, found 446.1558

Methyl 2-(5-(4-methoxy-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinolin-5-yl)-1H-tetrazol-1-yl)benzoate (4i): Reaction time - 24 h. Yield 55%, colorless solid. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}, 600 MHz): δ = 2.06 (s, 3H), 2.10 (dt, 1H, J=4.8, 15.8 Hz), 2.36-2.45 (m, 2H), 2.66-2.77 (m, 1H), 3.56 (s, 3H), 3.57 (s, 3H), 4.69 (s, 1H), 5.89 (s, 2H), 6.20 (s, 1H), 7.23 (d, 1H, J=5.5 Hz), 7.63-7.74 (m, 2H), 7.93-8.03 (m, 1H).

\textsuperscript{13}C NMR (DMSO-d\textsubscript{6}, 600 MHz): δ = 25.5, 42.3, 47.8, 52.8, 54.4, 59.2, 101.3, 102.9, 116.5, 128.7,128.8, 129.9, 131.3, 131.6, 132.9, 133.6, 134.4, 140.2, 148.9, 156.7, 164.4. HRMS (MALDI): calculated for C\textsubscript{21}H\textsubscript{21}N\textsubscript{5}O\textsubscript{5}Na [M+Na]\textsuperscript{+} 446.1434, found 446.1442

Initial optimization study for the synthesis of 5d

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp °C (reaction time hrs)\textsuperscript{1}</th>
<th>Yield of 5d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH</td>
<td>20 (18)</td>
<td>22</td>
</tr>
<tr>
<td>MeOH</td>
<td>45 (10)\textsuperscript{2}</td>
<td>45</td>
</tr>
<tr>
<td>EtOH</td>
<td>45 (15)\textsuperscript{2}</td>
<td>25</td>
</tr>
<tr>
<td>MeCN</td>
<td>45 (15)</td>
<td>0</td>
</tr>
<tr>
<td>CF\textsubscript{3}CH\textsubscript{2}OH</td>
<td>35 (5)</td>
<td>85</td>
</tr>
<tr>
<td>CF\textsubscript{3}CH\textsubscript{2}OH</td>
<td>Reflux (3)\textsuperscript{2}</td>
<td>37</td>
</tr>
<tr>
<td>DCM</td>
<td>rt (15)\textsuperscript{2}</td>
<td>12</td>
</tr>
<tr>
<td>THF</td>
<td>rt (15)</td>
<td>0</td>
</tr>
<tr>
<td>THF</td>
<td>100 (1)\textsuperscript{3}</td>
<td>13</td>
</tr>
</tbody>
</table>

\textsuperscript{1} TLC monitoring

\textsuperscript{2} Isolation - column chromatography

\textsuperscript{3} Microwave activation - 500W, 100° C
General experiment for the ring-expansion (synthesis of compounds 5a-d)

![Chemical structure](image)

DMAD, methyl propionate or acetylacrylene (1.2 mmol) was added to a solution of the derivative 4a,c (1 mmol) in TFE (10 ml). The reaction mixture was stirred for 4-8 hours at 35 °C (TLC monitoring). The solvent was evaporated under reduced pressure and the residue was recrystallized from ethyl acetate-hexane to give the corresponding benzoazocine-tetrazoles 5a-d.

**Methyl 10-(1-benzyl-1H-tetrazol-5-yl)-11-methoxy-7-methyl-5,6,7,10-tetrahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-d]azocine-9-carboxylate (5a)** Reaction time - 8 h. Yield 75%, pale-brown solid, m.p. 116-118°C.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 2.74$ (dt, 1H, $J=5.5$, 16.5 Hz), 2.80 (s, 3H), 2.80-2.88 (m, 1H), 2.49 (dt, 1H, $J=5.5$, 15.1 Hz), 3.68 (s, 3H), 3.78 (s, 3H), 3.96-4.08 (m, 1H), 5.42 (AB, 2H, $J=15.6$ Hz), 5.90 (s, 2H), 6.25 (s, 1H), 6.86 (s, 1H), 7.00-7.44 (m, 2H), 7.21-7.29 (m, 3H), 7.33 (s, 1H).

$^{13}$C NMR (DMSO-d6, 100 MHz): $\delta = 29.9$, 35.2, 45.3, 50.6, 51.6, 52.4, 60.2, 92.9, 101.3, 105.8, 121.8, 127.2 (2C), 128.1, 128.6 (2C), 132.9, 134.3, 136.2, 141.3, 148.1, 154.2, 159.3, 169.7.

HRMS (MALDI): calculated for C$_{24}$H$_{25}$N$_3$O$_5$Na [M+Na]$^+$ 486.1747, found 486.1758

(1-(10-(1-Benzy1-1H-tetrazol-5-yl)-11-methoxy-7-methyl-5,6,7,10-tetrahydro-[1,3]dioxolo[4',5':4,5]benzo[1,2-d]azocin-9-yl)ethanone (5b) Reaction time - 6 h. Yield 64%, pale-yellow solid, m.p. 168-170°C.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 2.08$ (s, 3H), 2.65 (dt, 1H, $J=4.4$, 16.8 Hz), 2.69-2.79 (m, 1H), 2.81 (s, 3H), 2.93 (dt, 1H, $J=4.9$, 15.6 Hz), 3.73 (s, 3H), 4.08-4.20 (m, 1H), 5.31 (AB, 2H, $J=15.8$ Hz), 5.83 (d, 2H, $J=1.3$ Hz), 6.16 (s, 1H), 6.89-7.99 (m, 2H), 7.08 (s, 1H), 7.15-7.21 (m, 4H).

$^{13}$C NMR (CDCl$_3$, 400 MHz): $\delta = 25.3$, 27.6, 35.0, 45.3, 50.3, 52.3, 60.2, 101.3, 105.7 (2C), 107.8 121.9, 127.0 (2C), 128.0, 128.5 (2C), 132.7, 134.4, 136.3, 141.5, 148.1, 156.0, 159.3. HRMS (MALDI): calculated for C$_{24}$H$_{26}$N$_3$O$_4$ [M+H]$^+$ 446.1979, found 446.1982

**Dimethyl 10-(1-benzyl-1H-tetrazol-5-yl)-11-methoxy-7-methyl-5,6,7,10-tetrahydro-[1,3]dioxolo [4',5':4,5]benzo[1,2-d]azocine-8,9-dicarboxylate (5c)** Reaction time - 4 h. Yield 94%, colorless powder, m.p. 157-159°C $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 2.41-2.49$ (m, 1H), 2.49 (s, 3H), 2.87-2.98 (m, 1H), 3.28 (dt, 1H, $J=5.6$, 14.9 Hz), 3.59 (s, 3H), 3.71 (s, 3H),
1H NMR (DMSO-d₆, 600 MHz): for A: δ = 0.98 (t, 3H, J=7.6 Hz ), 1.85-1.91 (m, 1H), 1.95 (s, 3H), 1.98-2.11 (m, 1H), 2.88-2.95 (m, 1H), 2.95 (s, 3H), 2.95-3.06 (m, 1H), 3.17-3.28 (m, 1H), 3.38 (s, 3H), 3.60 (s, 3H), 4.05-4.19 (m, 1H), 5.91 (s, 2H), 6.46 (s, 1H), 6.62 (s, 1H), 7.10-7.19 (m, 1H), 7.21-7.31 (m, 1H), 7.40 (t, 1H, J=7.6 Hz), 7.46 (s, 1H).

for B: δ = 1.11 (t, 3H, J=7.6 Hz), 1.73 (s, 3H), 1.98-2.11 (m, 1H), 2.31-2.36 (m, 1H, J=7.6 Hz), 2.88-2.95 (m, 1H), 2.95 (s, 3H), 2.95-3.06 (m, 1H), 3.17-3.28 (m, 1H), 3.37 (s, 3H), 3.61 (s, 3H), 4.05-4.19 (m, 1H), 5.90 (s, 2H), 6.47 (s, 1H), 6.61 (s, 1H), 7.10-7.19 (m, 1H), 7.21-7.31 (m, 1H), 7.40 (t, 1H, J=7.6 Hz), 7.44 (s, 1H).

13C NMR (DMSO-d₆, 150 MHz): δ = 13.4, 13.6, 15.8, 16.3, 22.4, 22.8, 29.2, 33.9, 44.1, 50.0, 51.3, 58.9, 91.8, 100.5, 104.5, 120.7, 125.7, 125.9, 127.6, 127.8, 129.9, 130.8, 132.8, 132.9, 134.5, 135.0, 140.5, 140.8, 147.1, 152.5, 152.7, 160.1, 160.2, 167.7.

HRMS (MALDI): calculated for C₂₆H₂₇N₅O₇Na [M+Na]^⁺ 544.1802, found 544.1787

**Methyl 10-(1-(2-Ethyl-6-methylphenyl)-1H-tetrazol-5-yl)-11-methoxy-7-methyl-5,6,7,10-tetrahydro-[1,3]dioxol[4',5':4,5]benzo[1,2-d]azocine-9-carboxylate (5d)** Mixture of 2 rotameres A:B=1.5:1 Reaction time 4 hours, yield 85%. Pale-yellow solid mp 201-203°C.

Multicomponent synthesis of 5d

![Chemical structure](attachment:image.png)

Cotamine chloride 2 (200 mg, 0.78 mmol), sodium azide (52 mg, 0.8 mmol), isocyanide 3d (116 mg, 0.8 mmol) and methylpropiolate (0.067 g, 0.8 mmol) were dissolved in 10 ml of MeOH/H₂O (5:1) and the reaction mixture was intensively stirred for 24 hours at room temperature (TLC monitoring). The solvent was evaporated under reduced pressure, the oily residue was purified using flash chromatography to yield 5d (0.13 g, 35%).
Chemical Shift (ppm)

Normalized Intensity

0.98 3.99 0.95 2.05 1.01 1.93 3.00 4.43 3.07

0.99 8.06 8.04 6.42 5.9.9 5.89 4.95 5.89 6.42 7.71 7.69 8.06 8.04

4h
The diagram shows a structural formula of compound 5a with chemical shifts listed on the y-axis and normalized intensity on the x-axis. The chemical shifts are indicated at various ppm values, and the normalized intensity ranges from 0 to 1.00.