SUPPLMENTARY INFORMATION

FOR

Heterocyclic Core Modifications in Trypanosomacidal 2-[(Phenylheteroaryl)ethyl]ureas

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Crystal Structure Determinations

Crystallographic data for the structures were collected at 100(2) K (180(2) K for **17**) on either an Oxford Diffraction Xcalibur or an Oxford Diffraction Gemini diffractometer using monochromated Mo Kα or CuKα radiation. Following multi-scan absorption corrections and solution by direct methods, the structures were refined against F^2 with full-matrix least-squares using the program SHELXL-2017. Except for the amide hydrogen atoms in **25a** and **27a**, all hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on those of the parent atom. Anisotropic displacement parameters were employed for all the non-hydrogen atoms.

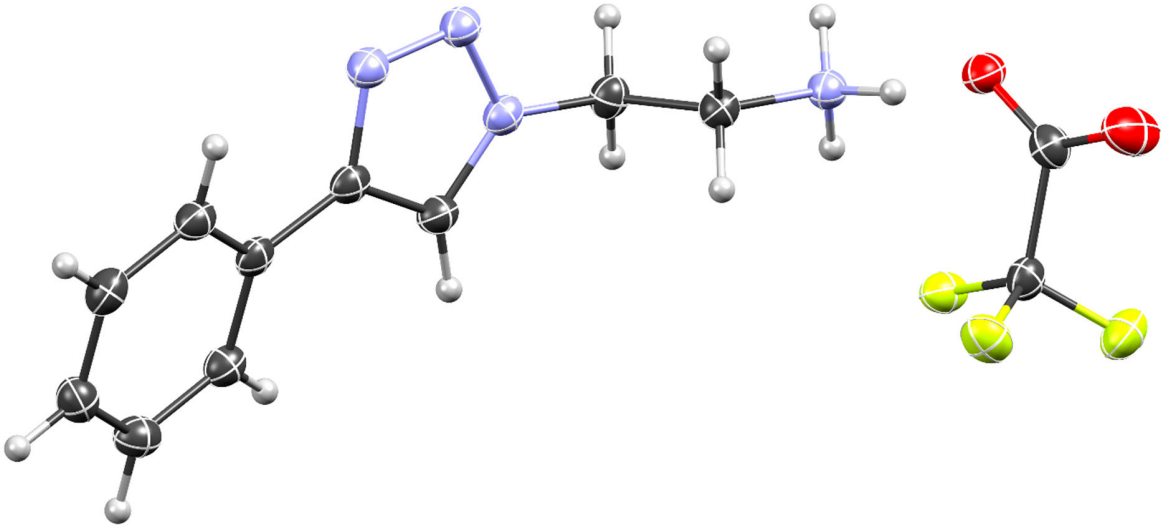


Figure S1. Representation of the crystal structure of **14**. Ellipsoids are shown at 50% probability amplitudes with hydrogen atoms assigned arbitrary radii.

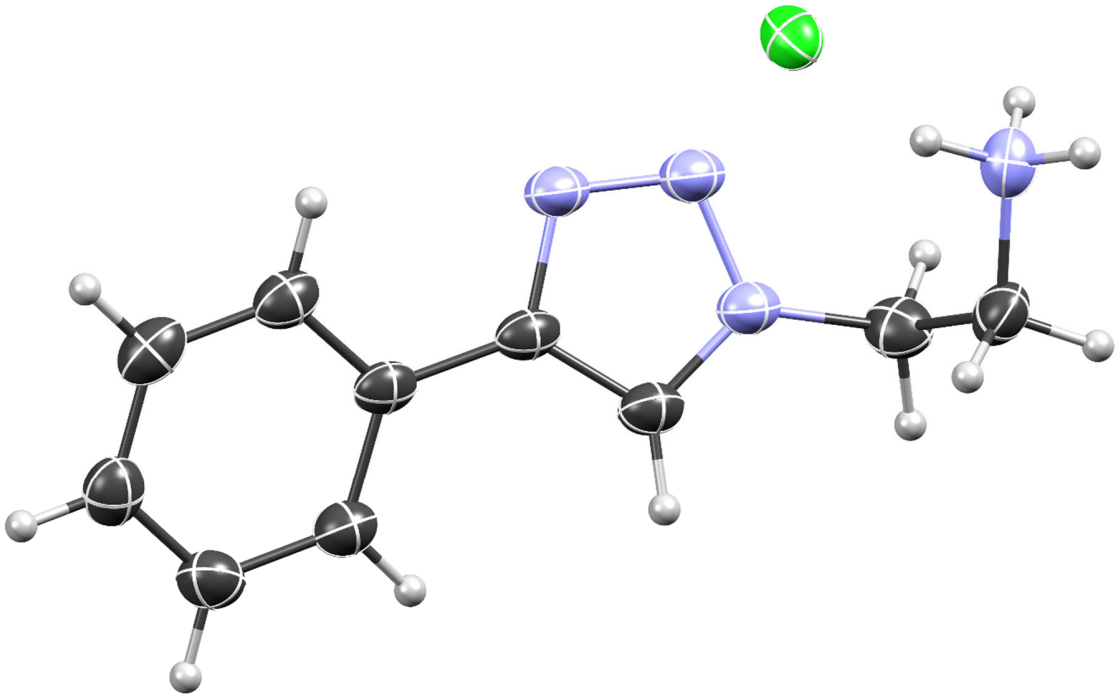


Figure S2. Representation of the crystal structure of **17**. Ellipsoids are shown at 50% probability amplitudes with hydrogen atoms assigned arbitrary radii.

Table S1. Crystal data and structure refinement for 14

Empirical formula	$C_{12}H_{13}F_3N_4O_2$
Formula weight	302.26
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.59850(10) Å
	b = 7.6657(2) Å
	c = 15.0325(4) Å
	β = 96.928(2)°
Volume	640.43(3) Å^3
Z	2
Density (calculated)	1.567 Mg/m^3
μ	1.212 mm^{-1}
Crystal size	0.25 × 0.09 × 0.02 mm^3
θ range for data collection	2.96 to 67.30°
Index ranges	–6<=h<=6, –5<=k<=9, –17<=l<=17
Reflections collected	4496
Independent reflections	1606 [R(int) = 0.0254]
Completeness to θ = 67.30°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00/0.93
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1606 / 1 / 191
Goodness-of-fit on F^2	1.035
Final R indices [I>2σ(I)]	R1 = 0.0258, wR2 = 0.0667
R indices (all data)	R1 = 0.0269, wR2 = 0.0677
Absolute structure parameter	–0.01(14)
Largest diff. peak and hole	0.140 and –0.177 e.Å^{-3}
CCDC No.	1846771

Table S2. Crystal data and structure refinement for 17

Empirical formula	$C_{10}H_{13}ClN_4$
Formula weight	224.69
Temperature	180(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.36630(10) Å
	b = 5.40550(10) Å
	c = 39.3933(9) Å
Volume	1142.70(4) Å^3
Z	4
Density (calculated)	1.306 Mg/m^3
μ	0.308 mm^{-1}
F(000)	472
Crystal size	0.20 × 0.18 × 0.02 mm^3
θ range for data collection	3.103 to 29.442°.
Index ranges	–7<=h<=6, –6<=k<=7, –54<=l<=53
Reflections collected	10374
Independent reflections	2977 [R(int) = 0.0353]
Completeness to θ = 28.500°	99.8 %
Absorption correction	Semi-empirical from equivalents
Max./min. transmission	1.00/0.991
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2977 / 0 / 138
Goodness-of-fit on F^2	1.073
Final R indices [I>2σ(I)]	R1 = 0.0433, wR2 = 0.0913
R indices (all data)	R1 = 0.0508, wR2 = 0.0943
Absolute structure parameter	0.25(10)
Largest diff. peak and hole	0.255 and –0.157 e.Å^{-3}
CCDC No.	1846844

Table S3. Crystal data and structure refinement for 25a

Empirical formula	$C_{15}H_{20}N_4O_2$
Formula weight	288.35
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 13.8888(13) Å
	b = 11.5000(7) Å
	c = 9.9679(7) Å
	β = 107.959(8)°
Volume	1514.5(2) $Å^3$
Z	4
Density (calculated)	1.265 Mg/m^3
μ	0.087 mm^{-1}
Crystal size	0.44 × 0.10 × 0.05 mm^3
θ range for data collection	3.63 to 27.50°.
Index ranges	–17<=h<=16, –14<=k<=14, –12<=l<=12
Reflections collected	11821
Independent reflections	3390 [R(int) = 0.0500]
Completeness to θ = 27.00°	98.9 %
Absorption correction	Semi-empirical from equivalents
Max./min. transmission	1.00/0.96
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3390 / 1 / 197
Goodness-of-fit on F^2	1.036
Final R indices [I>2σ(I)]	R1 = 0.0463, wR2 = 0.0930
R indices (all data)	R1 = 0.0768, wR2 = 0.1024
Largest diff. peak and hole	0.177 and –0.262 e.$Å^{-3}$
CCDC No.	1846871

Table S4. Crystal data and structure refinement for 27a

Empirical formula	$C_{14}H_{19}N_5O_2$
Formula weight	289.34
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 13.8479(6) Å
	b = 11.5901(4) Å
	c = 9.8993(4) Å
	β= 108.077(5)°
Volume	1510.40(10) $Å^3$
Z	4
Density (calculated)	1.272 Mg/m^3
μ	0.089 mm^{-1}
Crystal size	0.41 × 0.21 × 0.16 mm^3
θ range for data collection	2.79 to 32.26°.
Index ranges	–11<=h<=20, –14<=k<=17, –14<=l<=14
Reflections collected	16149
Independent reflections	4989 [R(int) = 0.0340]
Completeness to θ = 30.50°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.97156
Refinement method	Full-matrix least-squares on F^3
Data / restraints / parameters	4989 / 1 / 197
Goodness-of-fit on F^2	1.029
Final R indices [I>2σ(I)]	R1 = 0.0457, wR2 = 0.1035
R indices (all data)	R1 = 0.0601, wR2 = 0.1124
Largest diff. peak and hole	0.353 and –0.194 e.$Å^{-3}$
CCDC No.	1846727

Table S5. Hydrogen bonds for 14 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(11)-H(11A)...O(1)	0.91	1.95	2.810(3)	156.1
N(11)-H(11B)...O(1)[1]	0.91	1.92	2.785(2)	157.7
N(11)-H(11C)...N(2)[2]	0.91	2.34	3.054(2)	135.4

Symmetry transformations used to generate equivalent atoms: [1] 1–x,y+1/2,–z ; [2] x–1,y,z

Table S6. Hydrogen bonds for 17 [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(11)-H(11A)...Cl(1)	0.91	2.29	3.142(2)	155.1
N(11)-H(11B)...Cl(1)[1]	0.91	2.25	3.157(2)	171.6
N(11)-H(11C)...Cl(1)[2]	0.91	2.24	3.141(2)	170.3

Symmetry transformations used to generate equivalent atoms: [1] x–1,y,z ; [2] 1–x,y+1/2,3/2–z

Table S7. Hydrogen bonds for 25a [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(33)-H(33)...O(34)[1]	0.871(9)	2.114(10)	2.9460(14)	159.4(13)

Symmetry transformations used to generate equivalent atoms: [1] x,–y+1/2,z–1/2

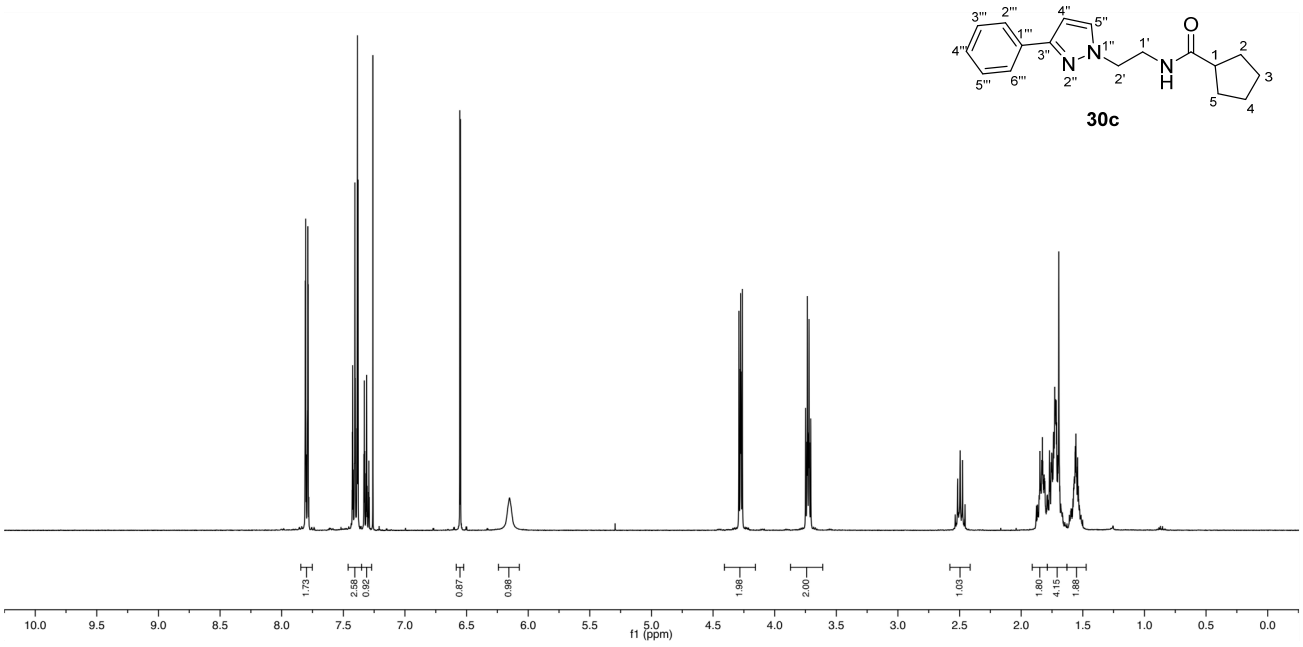
Table S8. Hydrogen bonds for 25a [Å and °]

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(33)-H(33)...O(34)[1]	0.879(8)	2.044(10)	2.8586(11)	153.5(13)

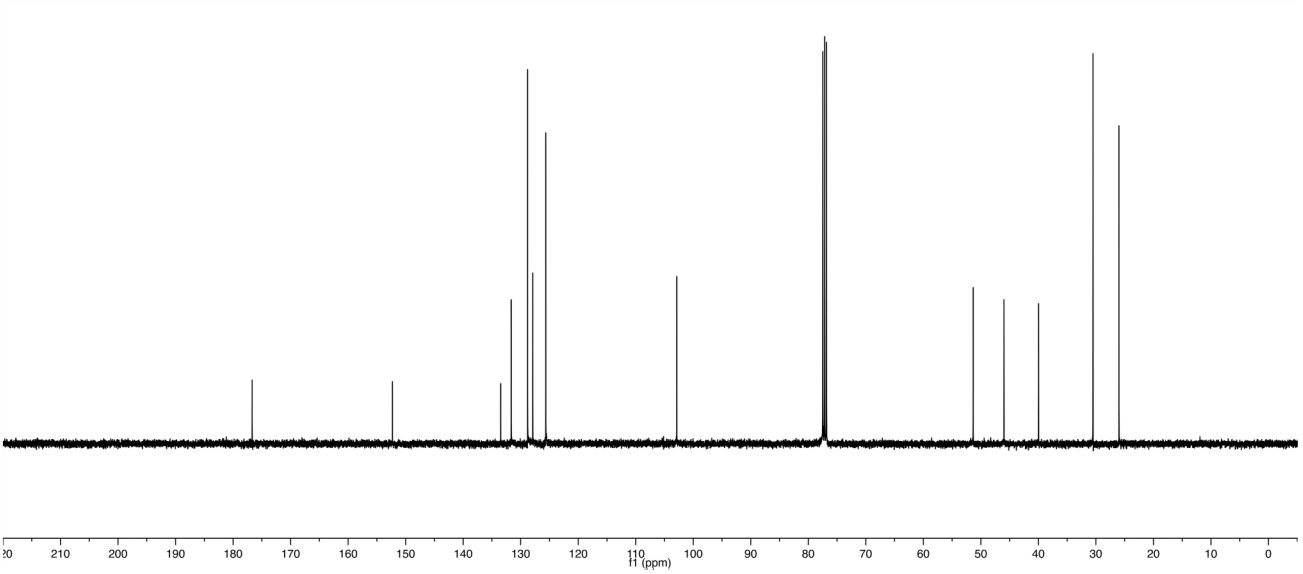
Symmetry transformations used to generate equivalent atoms: [1] x,1/2–y,z–1/2

Representative NMR spectra of target compounds

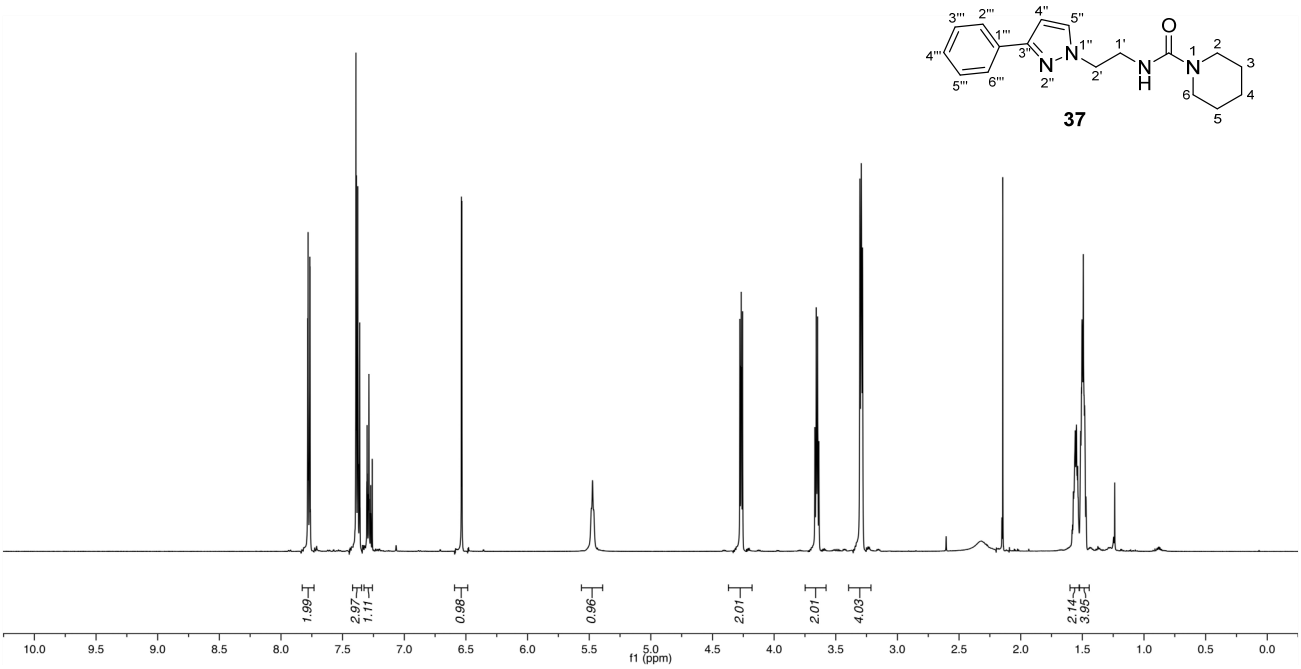
400 MHz ^{1}H NMR spectrum of **30c** in $CDCl_3$



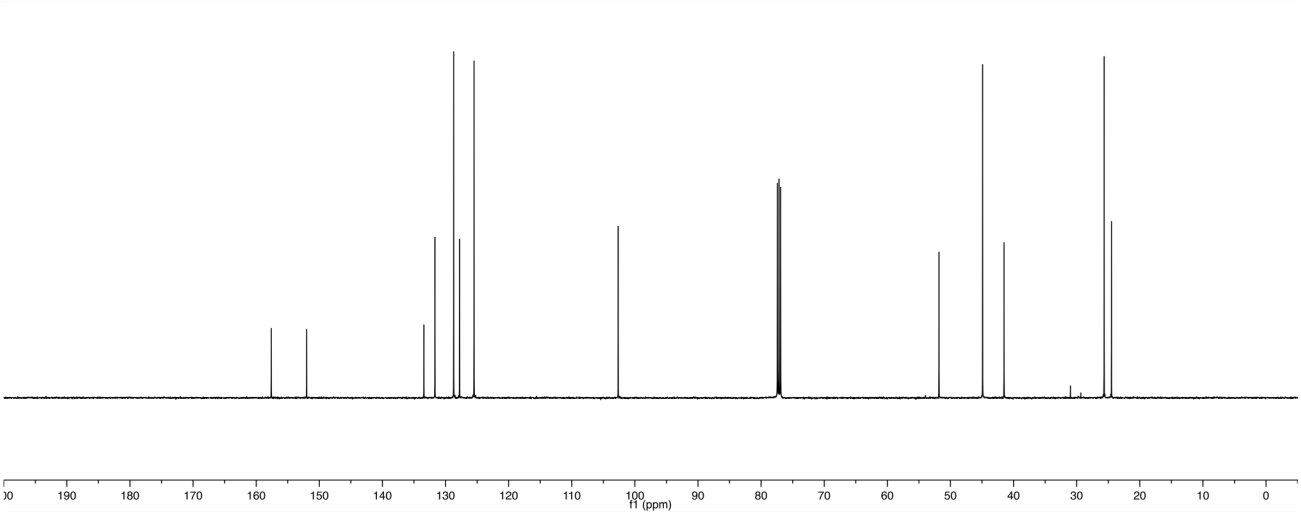
100 MHz ^{1}H NMR spectrum of **30c** in $CDCl_3$



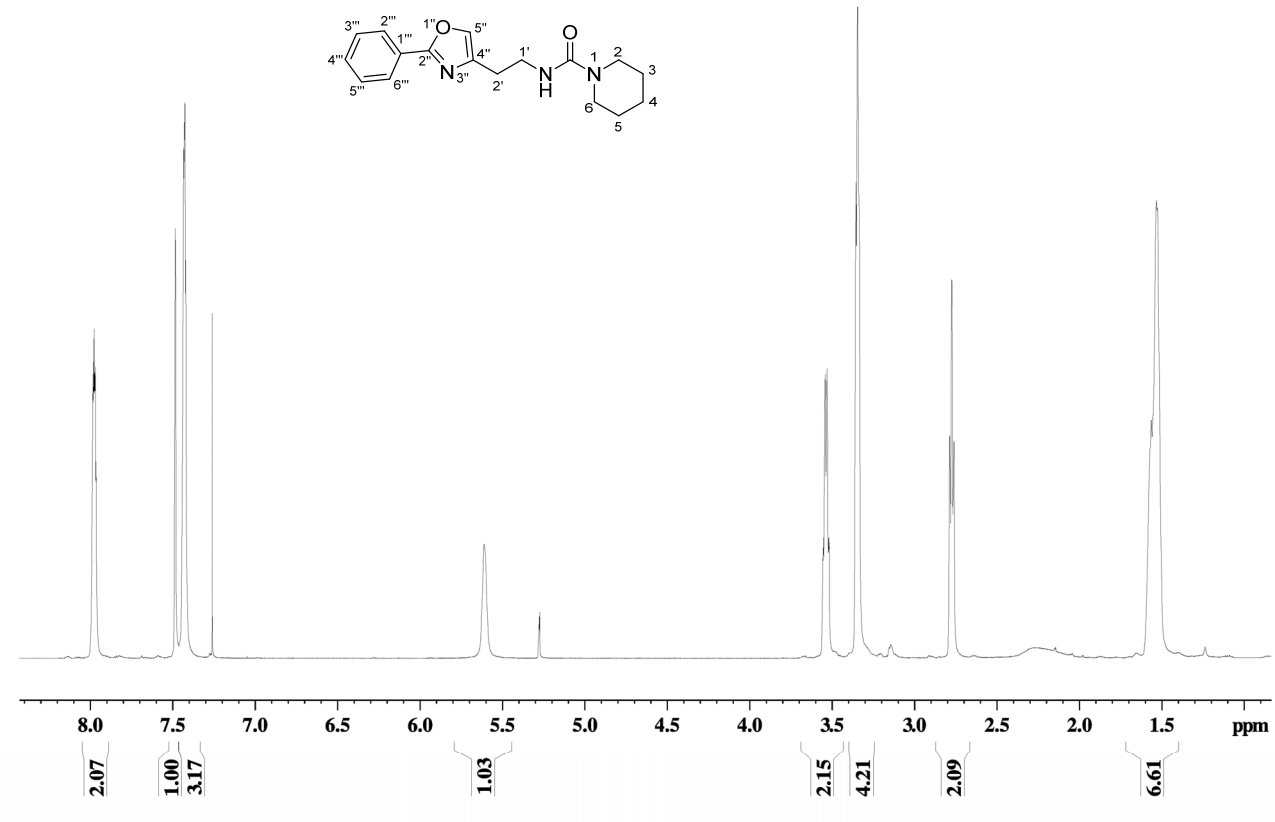
500 MHz ^{1}H NMR spectrum of **37** in $CDCl_3$



125 MHz ^{1}H NMR spectrum of **37** in $CDCl_3$



500 MHz ^{1}H NMR spectrum of **52** in $CDCl_3$



Representative HPLC traces of target compounds

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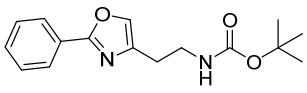

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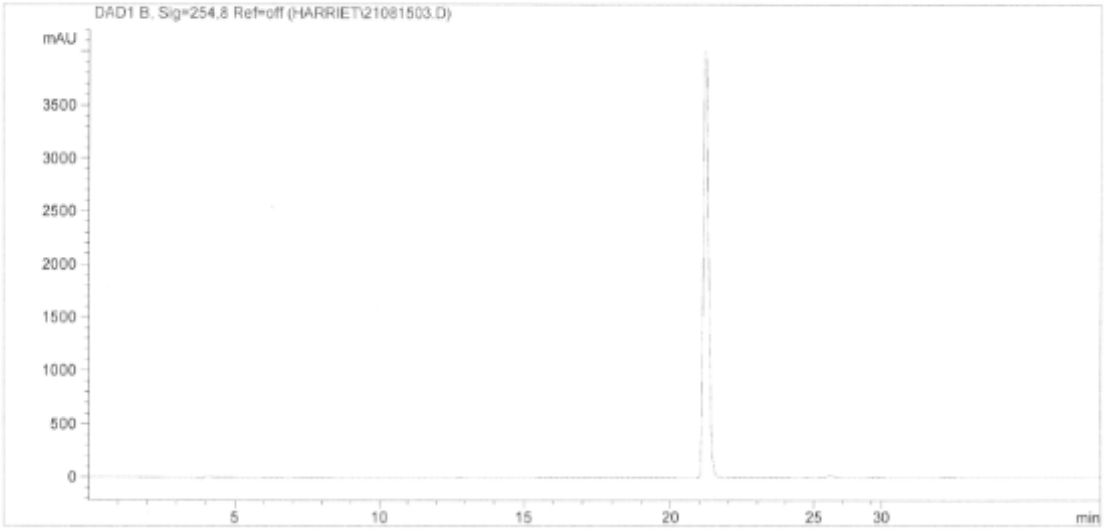

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Area Percent Report

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Results obtained with enhanced integrator!

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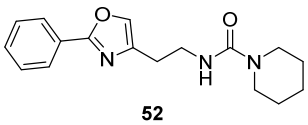

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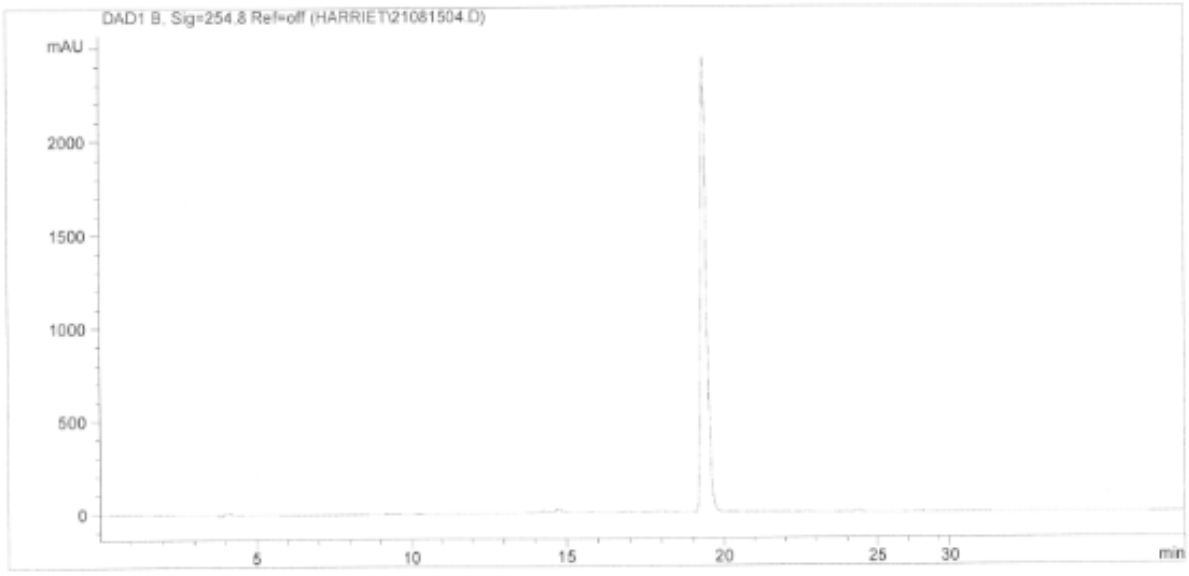

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Area Percent Report

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4	19.355	1	BP	3.27438e4	2447.27124	97.9843
5	24.361	1	VB	127.56327	10.36617	0.3817
Totals :				3.34174e4	2495.29073	

Results obtained with enhanced integrator!

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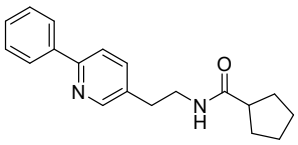

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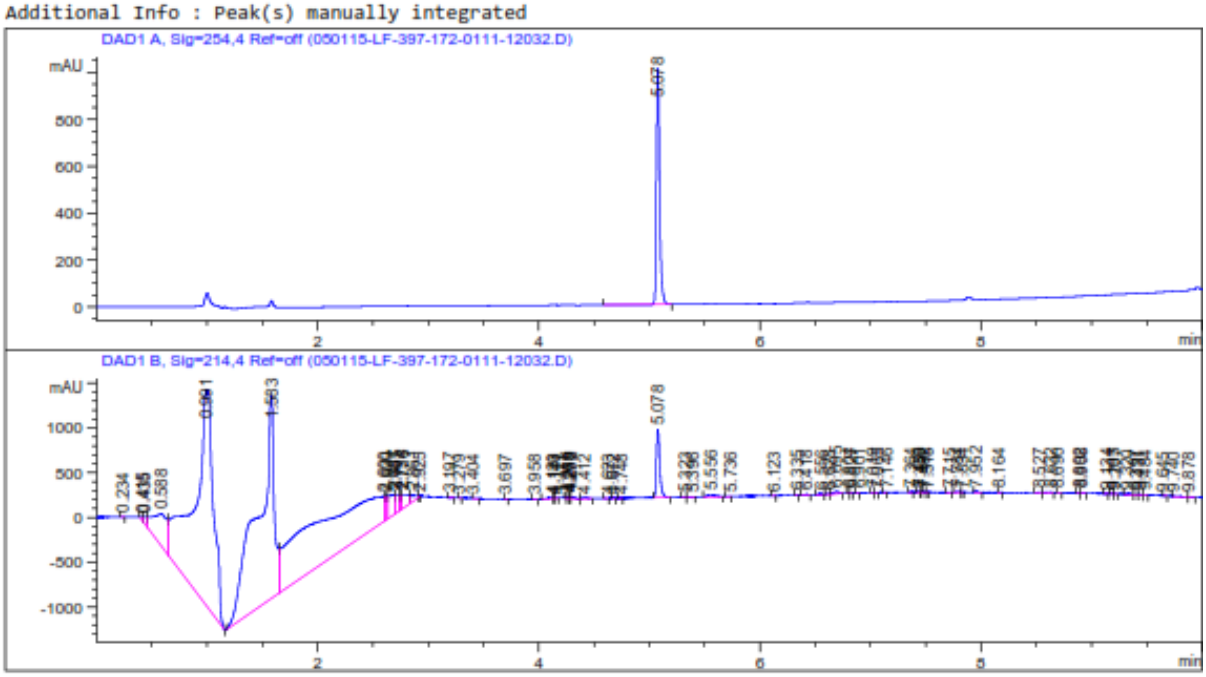


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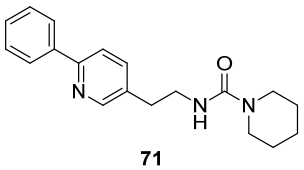

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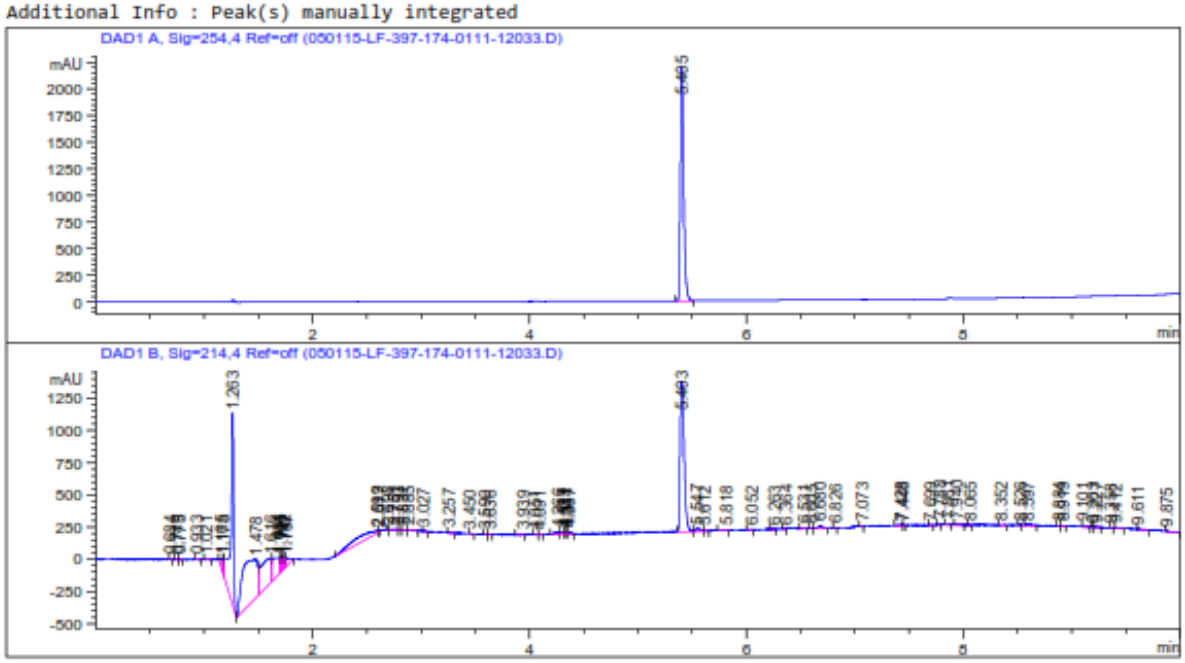


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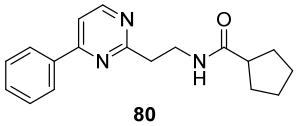

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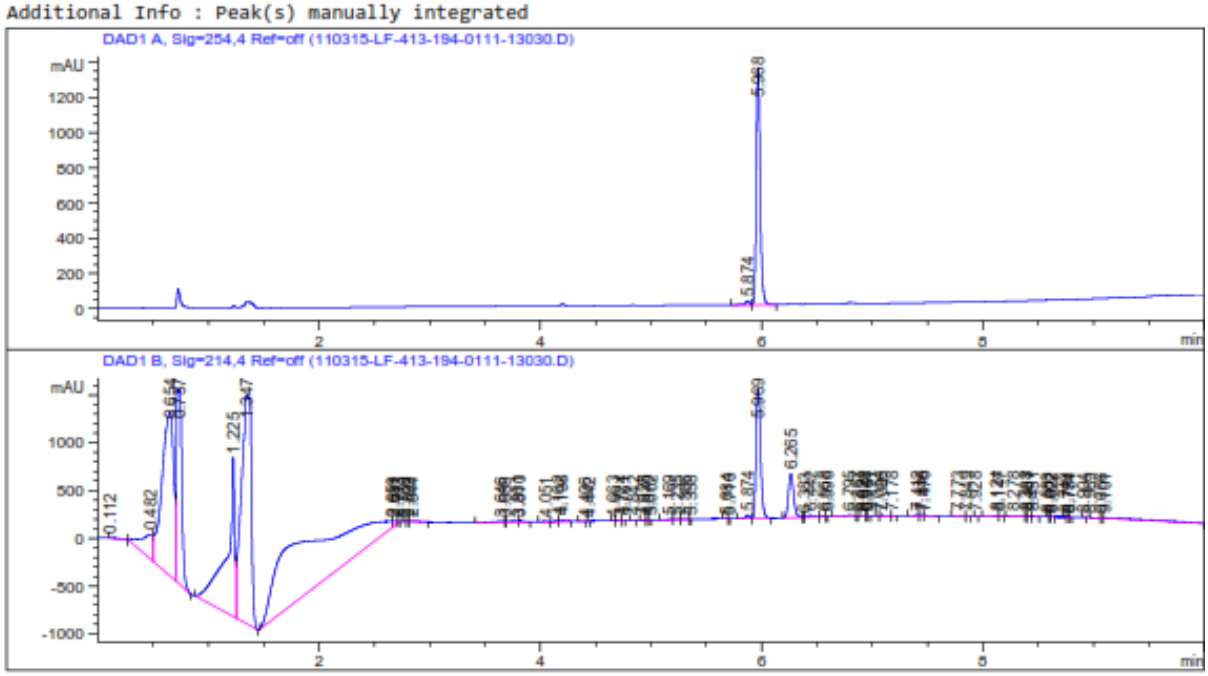


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