Supporting Information

1-Aminomethylbenzocycloalkanes: conformationally-restricted hallucinogenic phenethylamine analogues as functionally-selective 5-HT_{2A} receptor agonists

Thomas H. McLean, Jason C. Parrish, Michael R. Braden, Danuta Marona-Lewicka, Alejandra Gallardo-Godoy, and David E. Nichols

Department of Medicinal Chemistry and Molecular Pharmacology,

School of Pharmacy and Pharmaceutical Sciences,

Purdue University, West Lafayette, IN 47907-1333, USA.

Contents

X-ray structure determination of (*S,S*)-12 ..... S2

2D-NOESY Spectrum of 4_{anti} S6

2D-COSY90 Spectrum of 4_{anti} S8

2D-HMBC Spectrum of 4_{anti} S9

Elemental Analysis Values S10

X-ray Crystallographic Structure Determination of (S)-3,6-dimethoxy-N-((S)-1-phenylethyl)-benzocyclobutene-1-carboxamide (S,S-12)

DATA COLLECTION

A colorless needle of $C_{19}H_{21}NO_3$ having approximate dimensions of 0.44 x 0.25 x 0.15 mm was mounted on a glass fiber in a random orientation. Preliminary examination and data collection were performed Mo K_α radiation (λ = 0.71073Å) on a Nonius KappaCCD equipped with a graphite crystal, incident beam monochromator.

Cell constants for data collection were obtained from least-squares refinement, using the setting angles of 20228 reflections in the range $2 < \theta < 27°$. The triclinic cell parameters and calculated volume are: a = 8.6164(4), b = 9.9039(3), c = 19.5662(8)Å, α = 103.8633(18), β = 92.5450(17), γ = 90.6137(17)°, V = 1619.07(11)Å^3. For Z = 4 and F.W. = 311.38 the calculated density is 1.28 g/cm^3. The refined mosaicity from DENZO/SCALEPACK was (ref 1) was 0.32° indicating good crystal quality. The space group was determined by the program XPREP(ref 2). There were no systematic absences; the space group was determined to be P1(# 1).

The data were collected at a temperature of 150(1)K. Data were collected to a maximum 2θ of 55.6°.

DATA REDUCTION

A total of 20228 reflections were collected, of which 12265 were unique. Frames were integrated with DENZO-SMN (ref 1).

Lorentz and polarization corrections were applied to the data. The linear absorption coefficient is 0.8 /cm for Mo K_α radiation. An empirical absorption correction using SCALEPACK (ref 1) was applied. Transmission coefficients ranged from 0.959 to 0.988. A secondary extinction correction was applied (ref 3). The final coefficient, refined in least-squares, was 0.0230000 (in absolute units). Intensities of equivalent reflections were averaged. The agreement factor for the averaging was 8.4% based on intensity.

STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by direct methods using SIR2002 (ref 4). The remaining atoms were located in succeeding difference Fourier syntheses. Hydrogen atoms were included in the refinement but restrained to ride on the atom to which they are bonded. The structure was refined in full-matrix least-squares where the function minimized was $\Sigma w(|Fo|^2-|Fc|^2)^2$ and the weight w is defined as $1/[\sigma^2(Fo^2)+(0.1609P)^2+0.0000P]$ where $P=(Fo^2+2Fc^2)/3$. Scattering factors were taken from the "International Tables for Crystallography" (ref 5). 12265 reflections were used in the refinements. However, only the 6773 reflections with $F_o^2>2\sigma(F_o^2)$ were used in calculating R1. The final cycle of refinement included 858 variable parameters and converged (largest parameter shift was <0.01 times its su) with unweighted and weighted agreement factors of:

$$R1 = \Sigma \, | Fo - Fc | \, / \, \Sigma \, Fo = 0.087$$

$$R2 = SQRT \, (\Sigma \, w \, (Fo^2 - Fc^2)^2 \, / \, \Sigma \, w \, (Fo^2)^2) = 0.222$$

The standard deviation of an observation of unit weight was 1.01. The highest peak in the final difference Fourier had a height of 0.50 e/A^3. The minimum negative peak had a height of -0.34 e/A^3. The factor for the determination of the absolute structure (ref 6) refined to -1.30.

Refinement was performed on a LINUX PC using SHELX-97 (ref 3). Crystallographic drawings were done using programs ORTEP (ref 7), and PLUTON (ref 8).

References for X-ray crystallographic studies.

(1) Z. Otwinowski and W. Minor, Methods Enzymol., 276, 307 (1997).
(2) Bruker, XPREP in SHELXTL version 6.12, Bruker AXS Inc., Madison, Wisconson, USE, (2002)
(3) G. M. Sheldrick, SHELXL97. A Program for Crystal Structure Refinement. Univ. of Gottingen, Germany, (1997).
(4) M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori, and R. Spagna. , J. Appl. Cryst., 36, 1103 (2003)
(5) "International Tables for Crystallography", Vol. C, Kluwer Academic Publishers, Utrecht, The Netherlands, (1992), Tables 4.2.6.8 and 6.1.1.4
(6) H. D. Flack, Acta Cryst., A39, 876 (1983).
(7) C. K. Johnson, ORTEPII, Report ORNL-5138, Oak Ridge National Laboratory, Tennessee, USA (1976)
(8) A. L. Spek, PLUTON. Molecular Graphics Program. Univ. of Ultrecht, The Netherlands (1991)

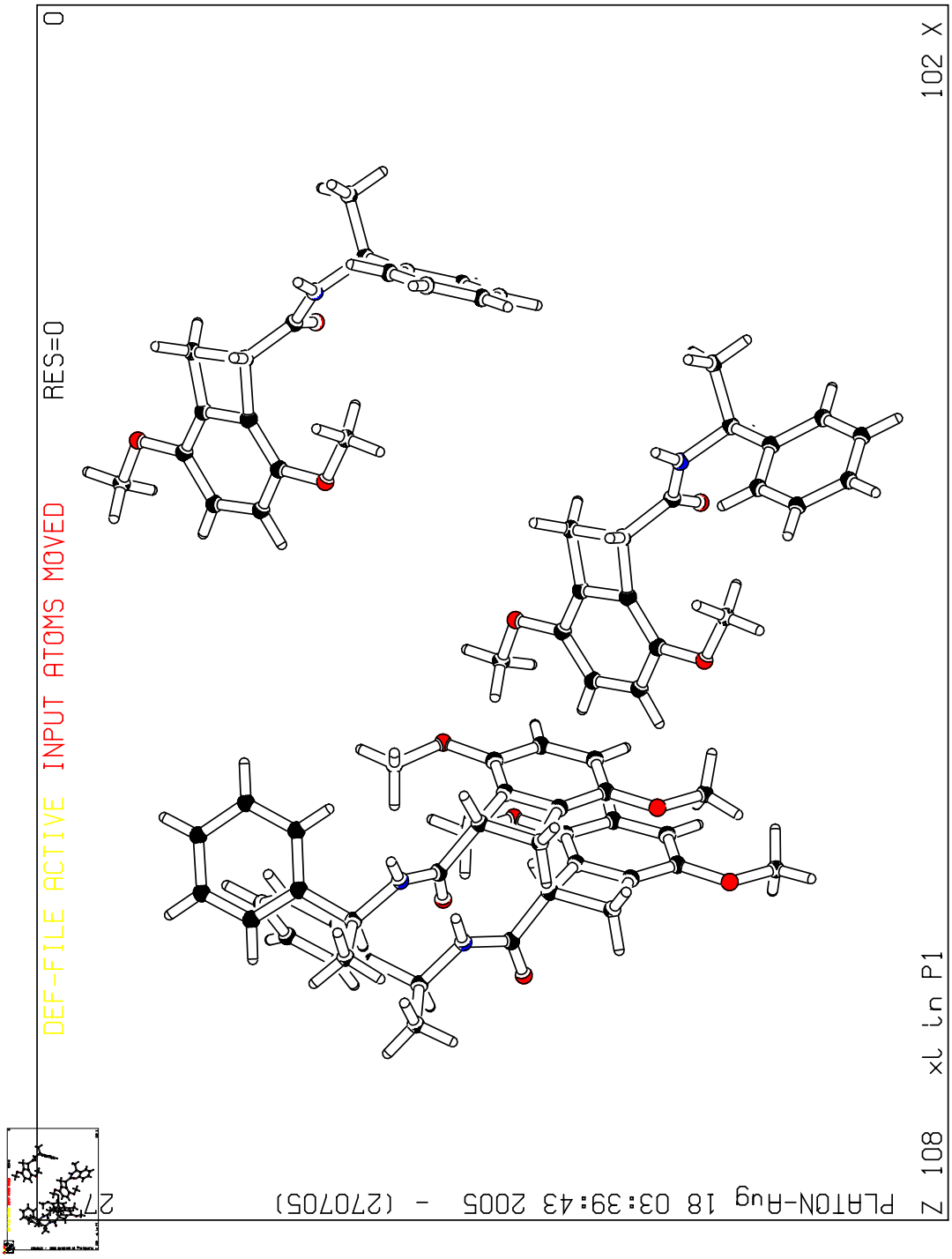

Figure 1. Unit cell representation of X-ray diffraction data for *S*,*S*-**12**.

CRYSTAL DATA AND DATA COLLECTION PARAMETERS FOR $C_{19}H_{21}NO_3$

formula weight	311.38
space group	P1 (No. 1)
a, Å	8.6164(4)
b, Å	9.9039(3)
c, Å	19.5662(8)
a, deg	103.8633(18)
b, deg	92.5450(17)
g, deg	90.6137(17)
V, $Å^3$	1619.07(11)
Z	4
d_{calc}, g cm^{-3}	1.277
crystal dimensions, mm	0.44x0.25x0.15
temperature, K	150.
radiation (wavelength, Å)	Mo K_a (0.71073)
monochromator	graphite
linear abs coef, mm^{-1}	0.080
absorption correction applied	empirical[a]
transmission factors: min, max	0.96, 0.99
diffractometer	Nonius KappaCCD
h, k, l range	-11 to 10 -12 to 12 -25 to 25
2q range, deg	4.24-55.64
mosaicity, deg	0.32
programs used	SHELXTL
F_{000}	664.0
Weighting	$1/[s^2(Fo^2)+(0.1609P)^2+0.0000P]$ where $P=(Fo^2+2Fc^2)/3$
data collected	20228
unique data	12265
R_{int}	0.084
data used in refinement	9988
cutoff used in R-factor calculations	$F_o^2>2.0s(F_o^2)$
data with I>2.0s(I)	6773
refined extinction coef	0.0230
number of variables	858
largest shift/esd in final cycle	0.00
$R(F_o)$	0.087
$R_w(F_o^2)$	0.222
goodness of fit	1.012
absolute structure determination	Flack parameter[b] (-1(2))

2D-NMR Spectra for Compound 4_{anti}

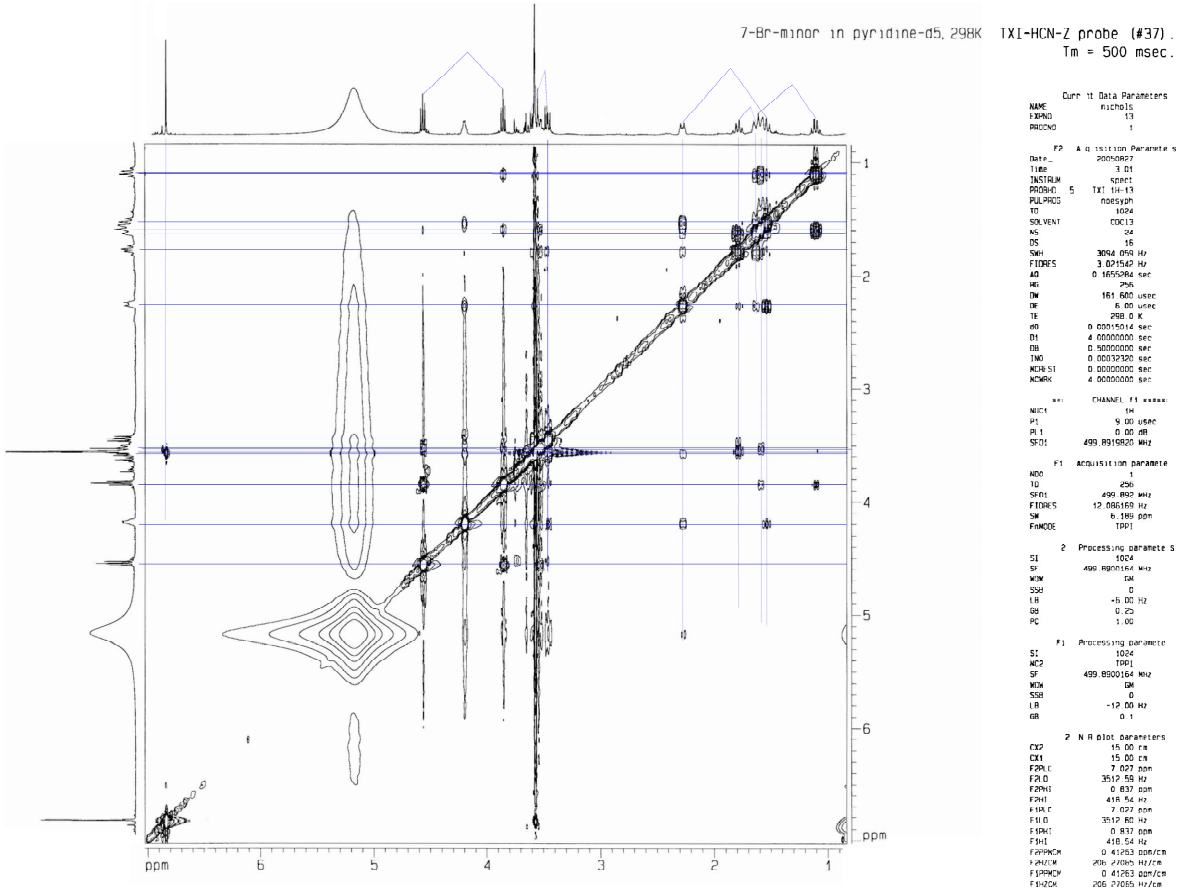

Figure 2. 2D-NOESY Spectrum of $\mathbf{4}_{anti}$ in pyridine-*d*5, 298 K, T_m = 500 ms.

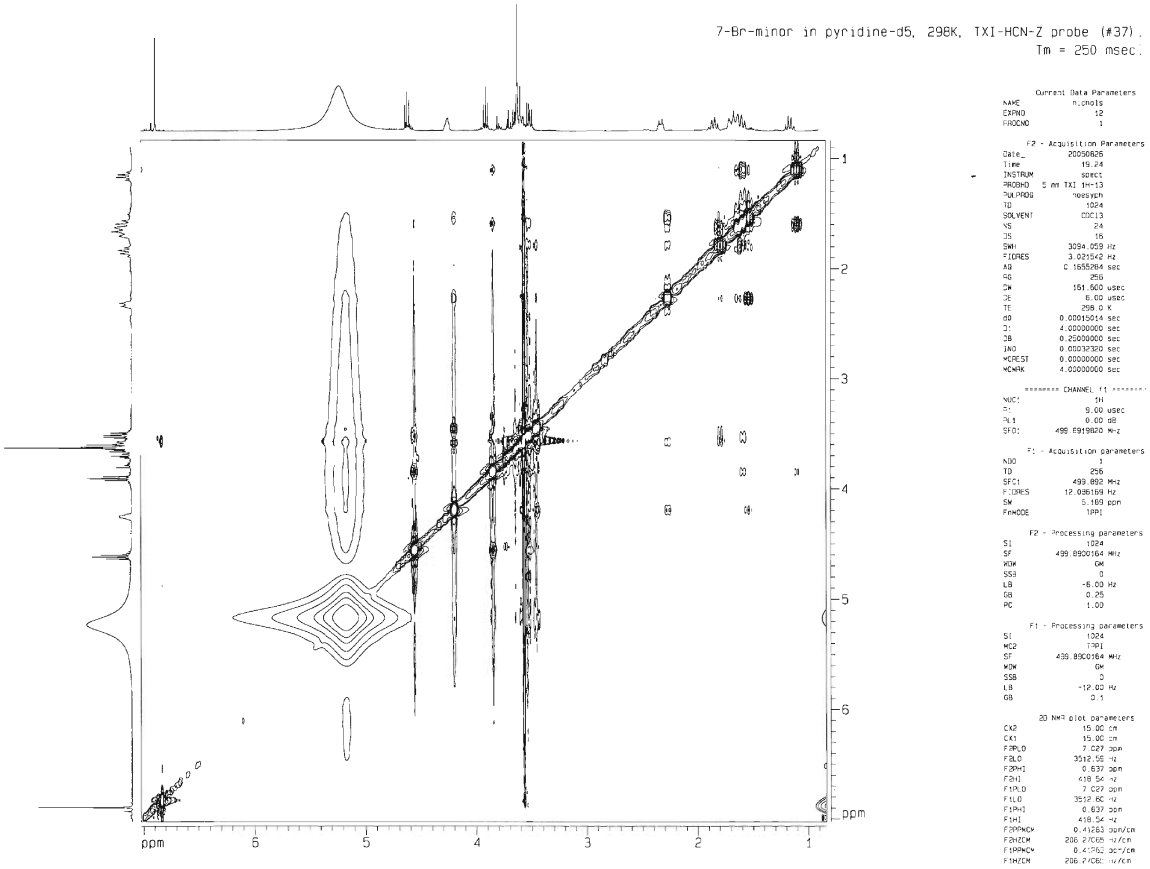

Figure 3. 2D-NOESY Spectrum of **4**$_{\mathbf{anti}}$ in pyridine-*d*5, 298 K, T_m = 250 ms.

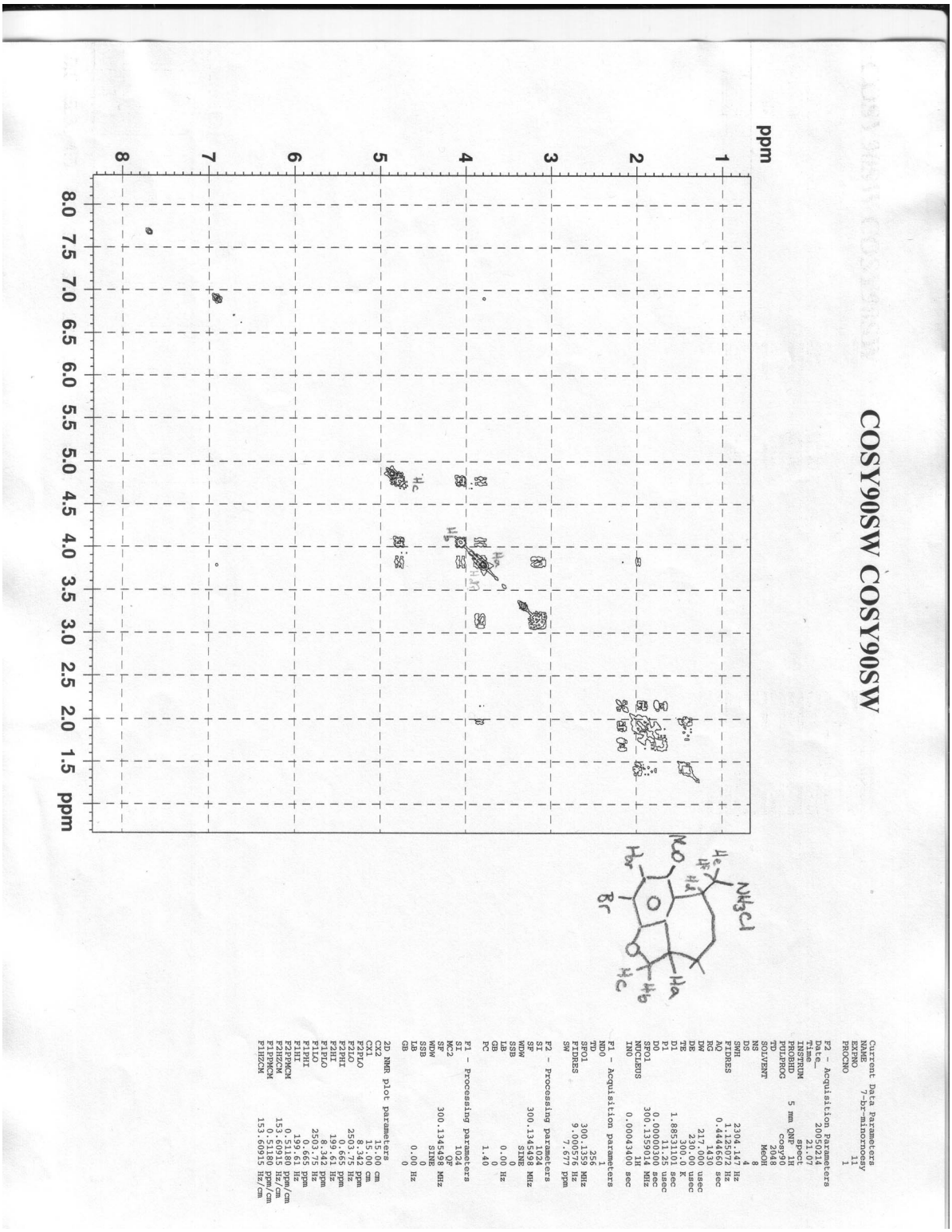

Figure 4. 2D-COSY-90 Spectrum of **4**$_{\mathbf{anti}}$.

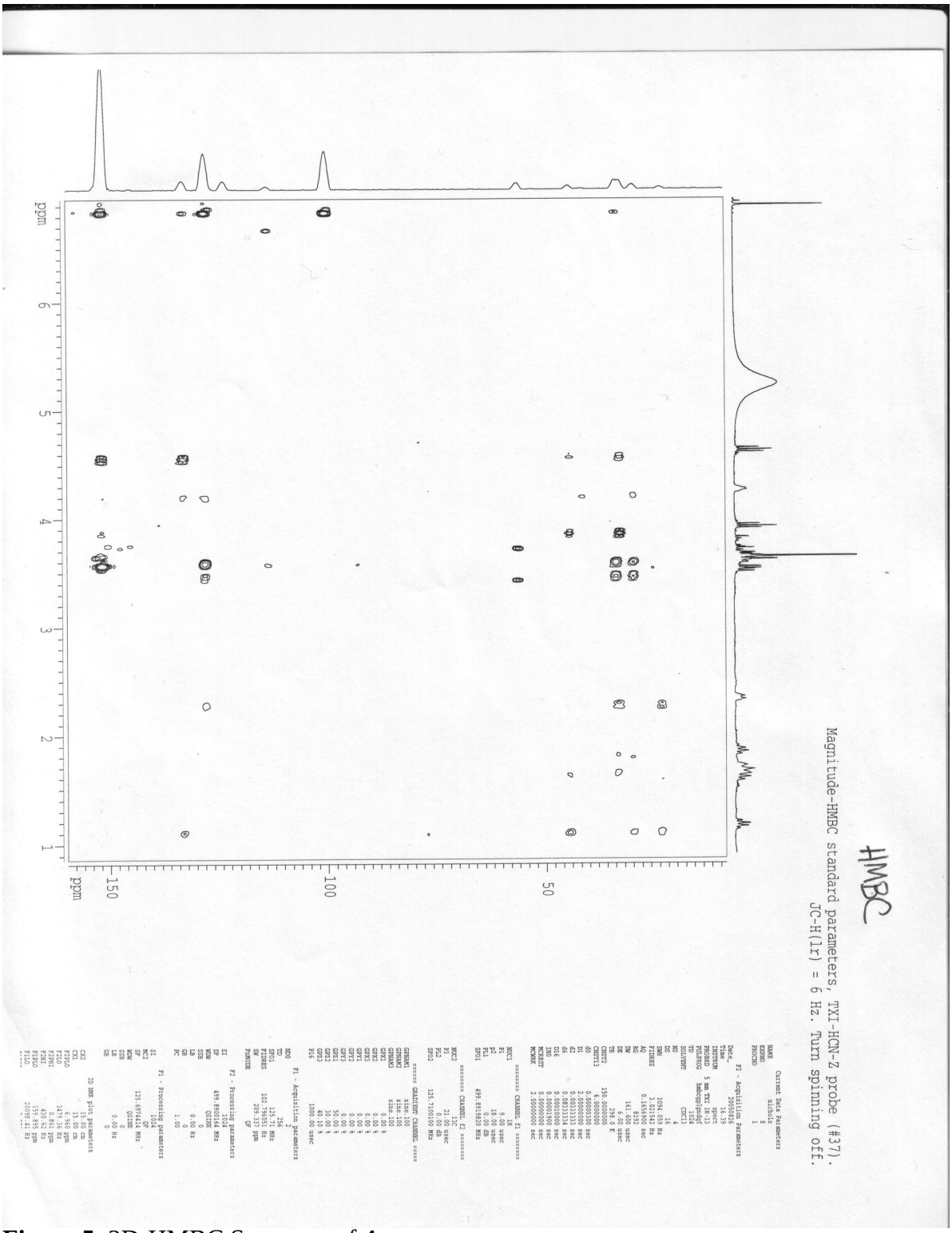

Figure 5. 2D-HMBC Spectrum of **4**$_{\mathbf{anti}}$.

Appendix – Elemental Analysis Values

Compound No	Formula	Calculated			Found		
		C	**H**	**N**	**C**	**H**	**N**
***R*-2**	$C_{11}H_{15}Br_2NO_2$	37.42	4.28	3.97	37.80	4.32	3.74
***S*-2**	$C_{11}H_{15}Br_2NO_2$	37.42	4.28	3.97	37.77	4.43	3.94
(±)-3	$C_{12}H_{17}BrClNO_2$	44.67	5.31	4.34	45.06	4.42	4.00
(±)-4_{anti}	$C_{14}H_{19}BrClNO_2$ + 0.3 eq. Benzene	45.56	4.98	3.43	45.44	5.03	3.36
(±)-4_{syn}	$C_{14}H_{19}Br_2NO_2$ + 0.2 eq. Benzene	44.67	4.98	3.43	44.82	5.06	3.70
(±)-7	$C_{11}H_{11}NO_2$	69.83	5.86	7.40	69.46	5.93	7.09
(±)-8	$C_{11}H_{16}ClNO_2$	57.52	7.02	6.10	57.44	6.81	5.85
(±)-11	$C_{11}H_{12}O_4$	63.45	5.81	--	63.30	5.86	--
(±)-12	$C_{19}H_{21}NO_3$	73.29	6.80	4.50	72.96	7.08	4.23
(*S*,*R*)-13	$C_{19}H_{23}NO_2$	76.73	7.80	4.71	76.49	7.81	4.83
(*S*,*S*)-13	$C_{19}H_{23}NO_2$	76.73	7.80	4.71	76.38	7.52	4.98
15	$C_{12}H_{11}NO_2$	71.63	5.51	6.96	71.68	5.63	6.72

(±)-16	$C_{12}H_{18}ClNO_2$ + 1/3 H_2O	57.71	7.53	5.61	57.94	7.30	5.42
(±)-20	$C_{13}H_{16}O_4$	66.09	6.83	--	65.75	6.95	--
(±)-21	$C_{13}H_{14}O_3$	71.54	6.47	--	71.51	6.21	--
(±)-22	$C_{14}H_{13}NO_2$	73.99	5.77	6.16	73.80	5.89	6.03
(±)-23	$C_{14}H_{20}ClNO_2$	62.33	7.47	5.19	62.40	7.40	5.15