Crystal and molecular structure of 2-(4-methoxybenzyl)-6-phenyl-5-thiocyanatoimidazo[2,1-b][1,3,4]thiadiazole

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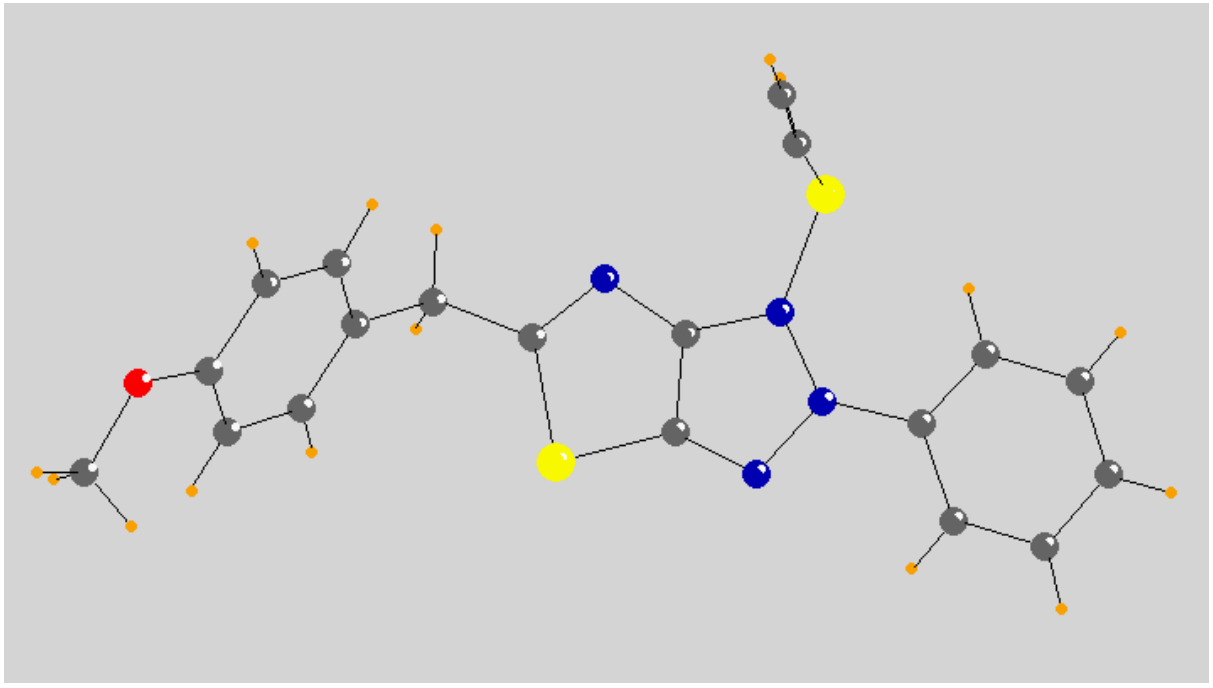
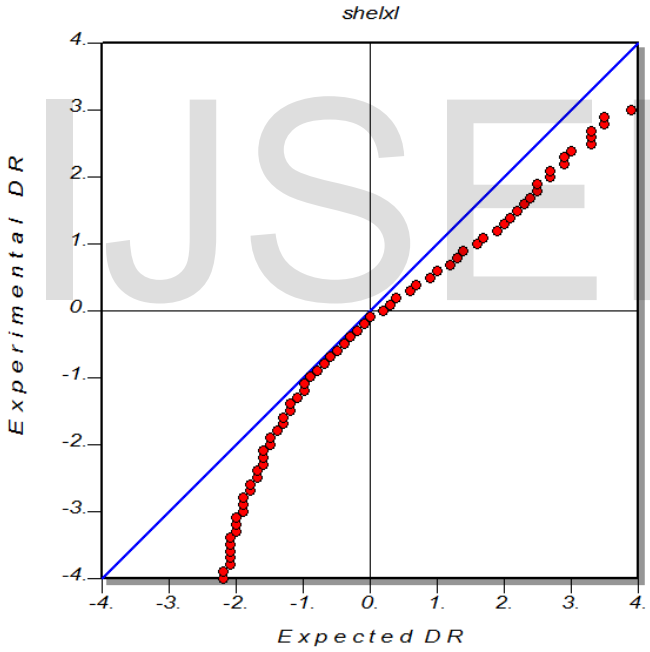
Abstract: Cancer is the second leading cause of death in the world. Despite advances in the diagnosis and treatment, overall survival of patients still remains poor. Hence, there is an urgent need for development of new anticancer agents. Considering promising biological activity of 1,3,4-thiadiazole derivatives, in the present study, synthesis and cytotoxicity assessment of new derivatives of this ring was done. All synthesized compounds were characterized by NMR, IR and spectroscopic method. Structure was determined by single crystal XRD.

Cancer is a disease in which cells can be aggressive, invasive and/or metastatic. These are three malignant properties of cancer cells that differentiate them from benign tumors which are self-limited in their growth and do not invade or metastasize (1-4). Cancer is the second leading cause of death in the world. Despite advances in the diagnosis and treatment, overall survival of patients still remains poor. Until recently, surgery, chemotherapy, radiotherapy and endocrine therapyhave been the standard treatment options available for cancer patients. This has improved survival in several types of solid tumors; however, drug toxicity and emergence of drug resistance have been the major causes of failure in treatment. Hence, there is an urgent need for discovery of new anticancer agents to overcome the disadvantages of the currently available anticancer drugs (3, 5-7).Diverse chemical structure containing 1,3,4-Thiadiazole have been reported with potential anticancer activity . Recently Maurizio Botta and coworkers reported the discovery of new derivatives of N-(5- (benzylthio)-1,3,4-thiadiazol-2-yl) benzamide as potent inhibitors of abl and src tyrosine kinases (14, 15) . In the present study, we synthesized a new derivatives .The chemistry and pharmacology of [1,3,4] thiadiazole derivatives has been of great interest to medicinal chemists. Thiazoles containing N=C-S moiety has been employed as antipsychotic and antibacterial. Thiadiazole derivative particularly**2-(4-methoxybenzyl)-6-phenyl-5-thiocyanatoimidazo[2,1-b][1,3,4]thiadiazole** play *vital* role in pharmaceutical practice owing to their wide biological activities like fungicidal, antimicrobial, anti TB, anti cancer and anti-inflammatory. The title compound $C_{19}H_{14}N_4OS_2$was synthesized and structure was solved by X-ray crystallography. The final R-factor is 0.048 for unique 3069 reflections with I >2σ(I). The cell parameters a = 6.117(2) Å, b= 7.47(4) Å, c = 18.25(3)Å, β =97.97(2)^o. The molecular conformation is planar. Crystal packing is stabilized by weak C-H…O interactions. The molecular geometry, mode of packing and the nature of he bonding will be discussed.

Structure of 2-(4-methoxybenzyl)-6-phenyl-5-thiocyanatoimidazo[2,1-b][1,3,4]thiadiazole





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References:

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Spek, A. L. (2009). Acta Cryst. D65, 148–155.

Supplementary Material:

Phy_359_0m in P-1
P

Crystal data
a = 7.9672(0.0002) alpha= 81.30(0.00)
b = 8.5515(0.0002) beta = 79.22(0.00)
c = 13.8882(0.0003) gamma= 75.03(0.00)
V = 892.67(0.04) cubic-Angstrom

Niggli reduced cell: 7.967 8.552 13.888 81.30 79.22 75.03
Niggli matrix: 63.4763 73.1282 192.8821
17.9645 20.7015 17.5993
Transformation matrix: 1.00 0.00 0.00
0.00 1.00 0.00
0.00 0.00 1.00

C 19. H 17. N 4. O 1. S 2.
M = 381.489 (Atomic weights 1977)
Z = 2.00
D(calc.)= 1.4193 Mg/m3**
F(000) = 398.0
mu = 3.146 cm-1 (Int.Tab. Vol.C, Table 4.2.4.2, p.193)**
Lambda = 0.7107300 Angstrom

Number of atoms: 41

Atomic coordinates

Atom	X/a	Y/b	Z/c
S1	0.70450(11)	0.31020(9)	0.35526(6)
S2	0.51004(14)	0.93607(9)	0.37807(7)
O1	0.80936(35)	1.41553(32)	-0.00037(19)
N1	0.56264(33)	0.69238(29)	0.27588(18)
N2	0.69897(37)	0.48454(32)	0.40659(20)
N3	0.73192(34)	0.51359(32)	0.49659(19)
N4	0.67004(36)	0.67629(30)	0.51007(18)
C1	0.76917(54)	1.57427(44)	0.03012(30)
H1A	0.64797(0)	1.62587(0)	0.02635(0)
H1B	0.84271(0)	1.63764(0)	-0.01223(0)
H1C	0.78969(0)	1.56643(0)	0.09682(0)

C2	0.71471(40)	1.30845(38)	0.04888(22)
C3	0.57029(44)	1.34762(39)	0.12178(24)
H3	0.53431(0)	1.45194(0)	0.14144(0)
C4	0.48106(44)	1.23058(41)	0.16457(25)
H4	0.38408(0)	1.25804(0)	0.21305(0)
C5	0.52987(41)	1.07388(36)	0.13834(22)
C6	0.42813(46)	0.94884(39)	0.18601(25)
H6A	0.30696(0)	1.00397(0)	0.20708(0)
H6B	0.42856(0)	0.87800(0)	0.13757(0)
C7	0.50211(40)	0.84695(35)	0.27330(22)
C8	0.61887(31)	0.63734(27)	0.36454(16)
C9	0.81913(36)	0.39971(35)	0.57255(20)
C10	0.91138(60)	0.24393(48)	0.55765(30)
H10	0.91930(0)	0.20612(0)	0.49721(0)
C11	0.99349(72)	0.14142(56)	0.63193(38)
H11	1.05537(0)	0.03604(0)	0.62050(0)
C12	0.98408(53)	0.19399(54)	0.72129(30)
H12	1.03593(0)	0.12427(0)	0.77138(0)
C13	0.89268(54)	0.29444(45)	0.27913(32)
C14	1.02276(53)	0.26806(56)	0.22021(33)
H14	1.12456(0)	0.24742(0)	0.17410(0)
C15	0.60600(39)	0.74431(33)	0.42876(21)
C16	0.89854(65)	0.34839(64)	0.73568(30)
H16	0.89642(0)	0.38695(0)	0.79513(0)
C17	0.81363(60)	0.45065(51)	0.66321(27)
H17	0.75175(0)	0.55556(0)	0.67576(0)
C18	0.67493(50)	1.03680(41)	0.06534(27)
H18	0.71118(0)	0.93238(0)	0.04583(0)
C19	0.76582(49)	1.15288(45)	0.02147(27)
H19	0.86265(0)	1.12574(0)	-0.02714(0)

Orthogonal coordinates (Angstrom)
Orthogonalization matrix:

a	b cosgamma	c cosbeta	7.96720	2.20897	2.59834
0	b singamma	-c sinbeta cosalpha*	0.00000	8.26127	1.47978
0	0	c sinbeta sinalpha*	0.00000	0.00000	13.56248

Atom	X	Y	Z
S1	7.2212(0.0009)	3.0884(0.0007)	4.8182(0.0008)
S2	7.1137(0.0011)	8.2926(0.0008)	5.1276(0.0009)
O1	9.5742(0.0029)	11.6935(0.0027)	-0.0050(0.0026)
N1	6.7289(0.0027)	6.1282(0.0024)	3.7416(0.0024)
N2	7.6956(0.0031)	4.6046(0.0027)	5.5144(0.0027)
N3	8.2562(0.0028)	4.9777(0.0027)	6.7350(0.0026)
N4	8.1576(0.0030)	6.3418(0.0025)	6.9178(0.0024)
C1	9.6839(0.0045)	13.0500(0.0037)	0.4085(0.0041)
H1A	8.8225(0.0000)	13.4707(0.0000)	0.3574(0.0000)
H1B	10.2998(0.0000)	13.5109(0.0000)	-0.1659(0.0000)
H1C	10.0034(0.0000)	13.0840(0.0000)	1.3131(0.0000)
C2	8.7116(0.0033)	10.8818(0.0032)	0.6629(0.0030)
C3	7.8369(0.0037)	11.3133(0.0032)	1.6516(0.0033)
H3	7.8317(0.0000)	12.2042(0.0000)	1.9183(0.0000)
C4	6.9786(0.0037)	10.4097(0.0034)	2.2320(0.0034)

H4	6.3926(0.0000)	10.7083(0.0000)	2.8895(0.0000)
C5	6.9532(0.0034)	9.0763(0.0030)	1.8762(0.0030)
C6	5.9903(0.0038)	8.1139(0.0032)	2.5228(0.0034)
H6A	5.2014(0.0000)	8.6005(0.0000)	2.8085(0.0000)
H6B	5.7113(0.0000)	7.4570(0.0000)	1.8658(0.0000)
C7	6.5814(0.0033)	7.4013(0.0029)	3.7066(0.0030)
C8	7.2857(0.0026)	5.8047(0.0022)	4.9441(0.0022)
C9	8.8968(0.0030)	4.1494(0.0029)	7.7652(0.0027)
C10	9.2489(0.0050)	2.8404(0.0040)	7.5631(0.0041)
H10	9.0715(0.0000)	2.4386(0.0000)	6.7434(0.0000)
C11	9.8697(0.0060)	2.1034(0.0047)	8.5705(0.0052)
H11	10.1002(0.0000)	1.2159(0.0000)	8.4155(0.0000)
C12	10.1430(0.0045)	2.6700(0.0045)	9.7825(0.0041)
H12	10.5323(0.0000)	2.1681(0.0000)	10.4618(0.0000)
C13	8.4878(0.0045)	2.8455(0.0037)	3.7857(0.0043)
C14	9.3128(0.0045)	2.5404(0.0047)	2.9866(0.0045)
H14	9.9585(0.0000)	2.3016(0.0000)	2.3612(0.0000)
C15	7.5863(0.0032)	6.7834(0.0027)	5.8151(0.0028)
C16	9.8400(0.0054)	3.9668(0.0053)	9.9776(0.0041)
H16	10.0627(0.0000)	4.3733(0.0000)	10.7839(0.0000)
C17	9.2011(0.0050)	4.7043(0.0042)	8.9948(0.0037)
H17	8.9724(0.0000)	5.5896(0.0000)	9.1650(0.0000)
C18	7.8373(0.0041)	8.6620(0.0034)	0.8862(0.0037)
H18	7.8448(0.0000)	7.7705(0.0000)	0.6216(0.0000)
C19	8.7039(0.0041)	9.5560(0.0037)	0.2912(0.0037)
H19	9.2891(0.0000)	9.2599(0.0000)	-0.3681(0.0000)

Displacement parameters, U(I,J)x104**
exp(-2*pi2(U11*h**2*(a*)**2+...+2*U12*h*k*(a*)*(b*)+...)**

Atom	U11	U22	U33	U23	U13	U12
S1	637(5)	414(4)	528(4)	-90(3)	-65(3)	-159(3)
S2	901(7)	372(4)	623(5)	-49(3)	-217(4)	-108(4)
O1	729(15)	657(15)	642(14)	-61(11)	38(12)	-310(12)
N1	554(13)	445(12)	450(12)	-4(9)	-89(10)	-174(10)
N2	612(15)	466(13)	526(13)	-57(10)	-56(11)	-144(11)
N3	558(14)	496(13)	518(14)	-45(10)	-28(11)	-196(11)
N4	660(15)	425(12)	438(12)	-56(9)	-94(11)	-167(10)
C1	754(22)	572(19)	729(22)	-9(16)	-120(18)	-288(17)
H1A	1000(0)					
H1B	1000(0)					
H1C	1000(0)					
C2	555(16)	518(15)	448(14)	-22(11)	-96(12)	-175(12)

C1	-H1C	C1	...N1	(1)	H1C	...N1
0.960(.004)		3.669(.005)		2.956(.002)		132.06(0.25)
1.080			2.877		130.28	(**)

C16	-H16	C16	...O1	(2)	H16	...O1
0.930(.005)		3.705(.005)		2.827(.003)		157.73(0.26)
1.080			2.689		156.52	(**)

C1	-H1C	C1	...N1	(1)	H1C	...N1
0.960(.004)		3.669(.005)		2.956(.002)		132.06(0.25)
1.080			2.877		130.28	(**)

Number of possible hydrogen bonds 5

(**) Values normalized following G.A.Jeffrey & L.Lewis, Carbohydr.Res. (1978).60,179; R.Taylor, O.Kennard, Acta Cryst.(1983).B39,133.

Equivalent positions:
(0) x,y,z
(1) x,+y+1,+z
(2) x,+y-1,+z+1

I hope that you succeeded in using this program and that the results of the calculations are useful to have a better understanding of your structure. Best wishes!

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Phy__359_0m in P-1

Sunday, 9 February 2014 at 12:04:34 SIR92 runs on: jt-vs

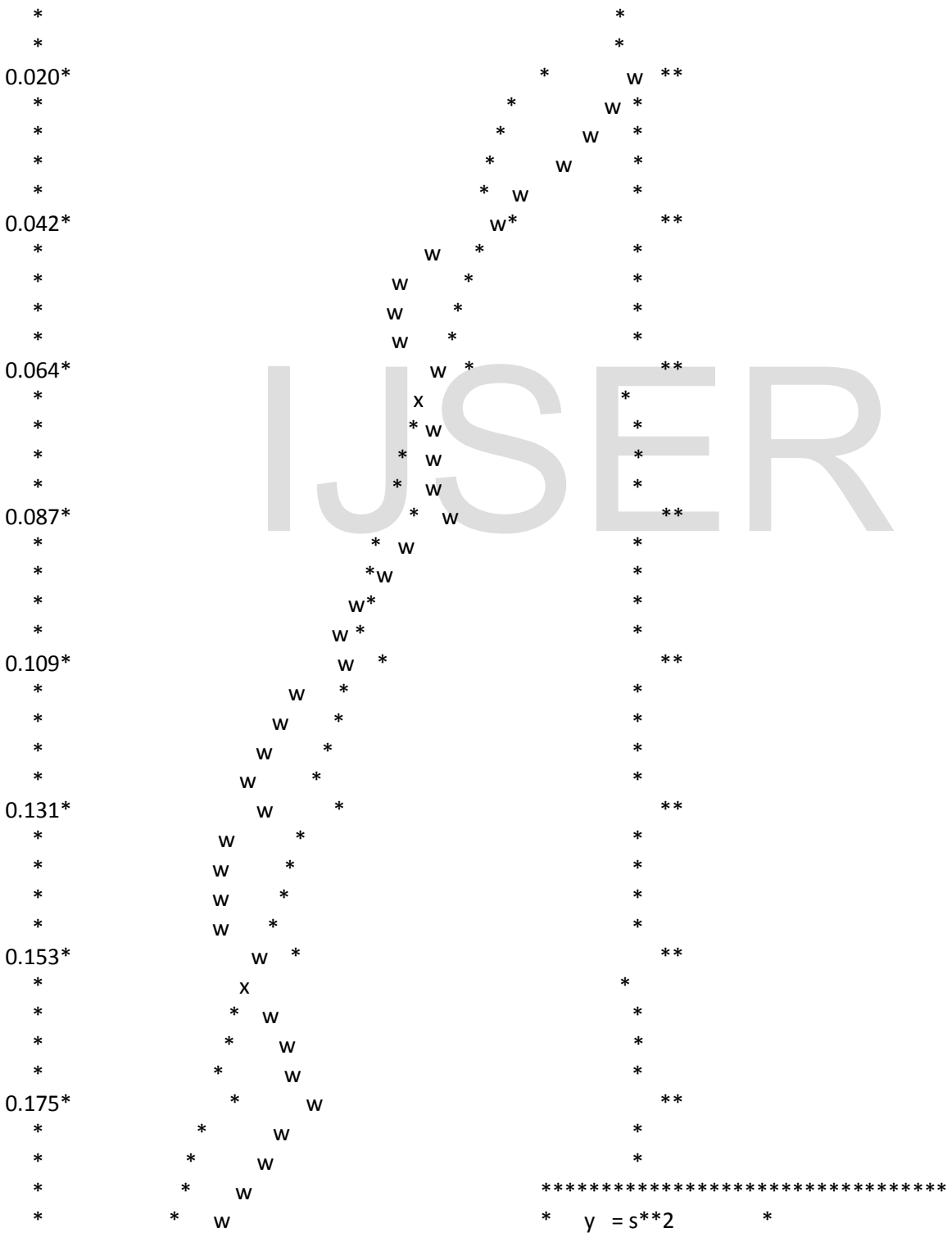
Used commands & directives:


```
%data       Cell    7.967  8.552 13.888 81.300 79.217 75.030
            Space   P -1
            Content C 38 H 34 N 8 O 2 S 4
            Rhomax  0.250
            Reflections jt-vs.hkl
            Format  (3i4,2f8.0)
            Fosquare

%normal     default

%invariants default

%phase      default

%fourier    default

%export     shelx  jt-vs.res

%end
```

Files used in sir:

Channel	Name
1	card reader
2	line printer
30	direct access structure file jt-vs.bin
31	direct access scratch file

32 sequential scratch file
34 reflection input file jt-vs.hkl
41 scattering factors file c:\wingx\files\form.dat
(Release : 92.11)
35 fourier peaks file jt-vs.ins
36 peaks file to be plotted jt-vs.plt
33 sequential scratch file



```
0.198*             *   w                    *     x   = ln <i> / sigfsq    *
   *             * w                     *   ( w ) = wilson           *
   *            *w                       *   ( * ) = calc             *
   *          w*                         **********************************
   *         w*                          *      intercept =   -3.04428 *
0.220*        w*                           *         slope =   -7.45342 *
   *       w *                           *        b(iso) =    3.72671 *
   *      w *                            *        u(iso) =    0.04720 *
   *     w *                             *         scale =   20.99497 *
   *   w   *                             * scale*f(obs.)**2 =  f(abs.)**2 *
0.242*  w  *                               **********************************
   *                                           *
   *                                           *
```

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*** pseudotranslation section ***

Phy_359_0m in P-1

*** program searched for pseudo-translational symmetry ***

*** no pseudo-translational symmetry has been found ***

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*** final statistics section ***

distribution of <E**2> with sin(theta)/lambda

sinth/lam	0.0500	0.1000	0.1500	0.2000	0.2500	0.3000	0.3500	0.4000	0.4500	0.5000
<E**2>	0.5163	0.8893	1.6355	1.1156	0.7742	1.1490	0.8568	0.8308	1.1815	0.9692
number	1	14	34	66	116	170	234	315	416	489

average values

average	numeric			graphic
	all data	acentric	centric	hypercentric	a. c. h.
mod(E)	0.793	0.886	0.798	0.718	*
E**2	1.000	1.000	1.000	1.000	
E**3	1.639	1.329	1.596	1.916	*
E**4	3.226	2.000	3.000	4.500	*
E**5	7.279	3.323	6.383	12.260	*
E**6	18.248	6.000	15.000	37.500	*
mod(E**2-1)	0.981	0.736	0.968	1.145	*
(E**2-1)**2	2.226	1.000	2.000	3.500	*
(E**2-1)**3	10.571	2.000	8.000	26.000	*
(mod(E**2-1))**3	11.273	2.415	8.691	26.903	*

n(z) cumulative probability distribution

z	all data	acentric	centric	hypercentric	a. c. h.
0.1	0.251	0.095	0.248	0.368	*
0.2	0.350	0.181	0.345	0.463	*
0.3	0.424	0.259	0.416	0.526	*
0.4	0.483	0.330	0.473	0.574	*
0.5	0.531	0.393	0.520	0.612	*
0.6	0.569	0.451	0.561	0.643	*
0.7	0.605	0.503	0.597	0.670	*
0.8	0.637	0.551	0.629	0.694	*
0.9	0.659	0.593	0.657	0.715	*
1.0	0.686	0.632	0.683	0.733	*
1.2	0.733	0.699	0.727	0.765	*
1.4	0.767	0.753	0.763	0.791	*
1.6	0.808	0.798	0.794	0.813	*
1.8	0.831	0.835	0.820	0.832	*
2.0	0.852	0.865	0.843	0.848	*
2.2	0.865	0.889	0.862	0.863	*
2.4	0.882	0.909	0.879	0.875	*
2.6	0.898	0.926	0.893	0.886	*
2.8	0.911	0.939	0.906	0.896	*
3.0	0.921	0.950	0.917	0.905	*
3.2	0.930	0.959	0.926	0.913	*
3.4	0.937	0.967	0.935	0.920	*
3.6	0.942	0.973	0.942	0.926	*
3.8	0.948	0.978	0.949	0.932	*
4.0	0.953	0.982	0.954	0.938	*

distribution of E - number of E's .gt. limit

E	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	2.0	2.1	2.2	2.3	2.4	2.5
no.	872	770	668	582	494	415	331	288	238	196	159	125	107	87	72	60	49	34	29

number and percentage of F's > param * sigma(F)

number	1811	1811	1811	1801	1790	1774	1749	1726	1710	1691
percentage	98%	98%	98%	97%	96%	96%	94%	93%	92%	91%
param	0.50	1.00	1.50	2.00	2.50	3.00	3.50	4.00	4.50	5.00

number and percentage of F's > limit

number	185	370	555	740	925	1110	1295	1480	1665	1850
percentage	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
limit	5.53	3.90	3.00	2.31	1.81	1.40	1.01	0.69	0.37	0.00

354 largest E-values to phase

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SIR92 : Invariants routine Release 93.02

Phy_359_0m in P-1

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Psi-zero relationships estimated among the 354 strongest and the 118 weakest reflections

Negative quartets relationships estimated using 3002 psi-zero relationships

Negative quartet's statistic
Distribution of g - number of g's .gt. limit

g	0.0	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6	2.0	2.5	3.0	3.5	4.0	5.0	6.0	8.0	10.0	15.0
no.	750	750	750	743	331	163	80	45	30	11	2	0	0	0	0	0	0	0	0

Sigma2 relationships estimated among the 354 strongest reflections - (Emin = 1.27)

Triplet's statistic
Distribution of g - number of g's .gt. limit

g	0.0	0.2	0.4	0.6	0.8	1.0	1.2	1.4	1.6	2.0	2.5	3.0	3.5	4.0	5.0	6.0	8.0	10.0	15.0
no.	3963	3825	3739	3673	3084	2497	1922	1452	1078	565	212	81	29	8	2	0	0	0	0

4915 triplets have been strengthened by 45 free vectors using p-10 formula

Psi-e relationships among the 354 strongest and the 177 following reflections

centrosymmetric, g(min) for psi-e = 0.600

Insufficient psi-e found - lower g value and try again

Psi-e relationships among the 354 strongest and the 177 following reflections

	Number of relationships Calculated	stored
Positive estimated triplets	3476	3476
Negative estimated triplets	487	487
enantiomorph sensitive triplets	-	-
psi-zero triplets	3002	3002

psi-e triplets	4453	4453
Negative estimated quartets	2750	750
enantiomorph sensitive quartets	-	-

++

SIR92: Phase routine Release 93.02

Phy__359_0m in P-1

++

*** converge / diverge section ***

Origin fixing reflexion(s)

code	h	k	l	E	phase restriction	assigned phase
58	4	4	3	2.22	0,180	360
9	2	-1	4	2.95	0,180	360
13	1	0	4	2.83	0,180	360

Selected symbols

code	h	k	l	E	phase restriction
97	3	2	8	1.95	0,180
83	0	3	10	2.03	0,180
113	3	3	-10	1.87	0,180
8	1	-6	3	2.95	0,180
25	2	-3	10	2.59	0,180

++

*** Fourier recycling section ***

Phy__359_0m in P-1

1298 (70% of total) reflections used with Fo > 1.01

Step	cycle	residual
A	1	30.03%
A	2	22.47%

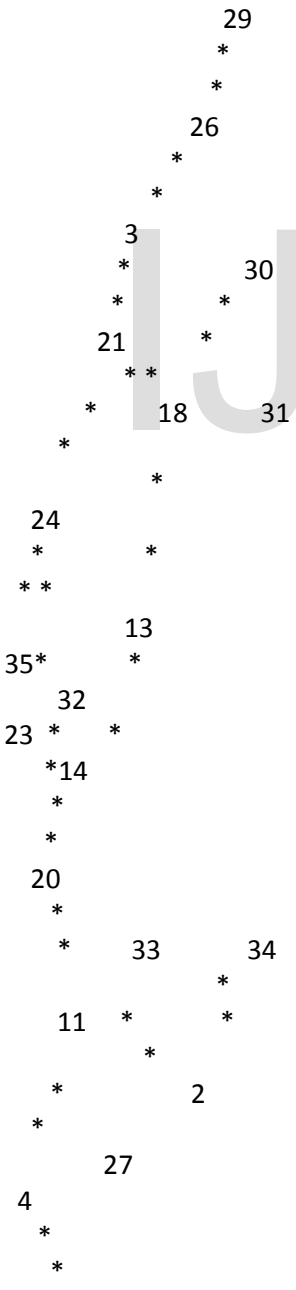
A 3 23.38%

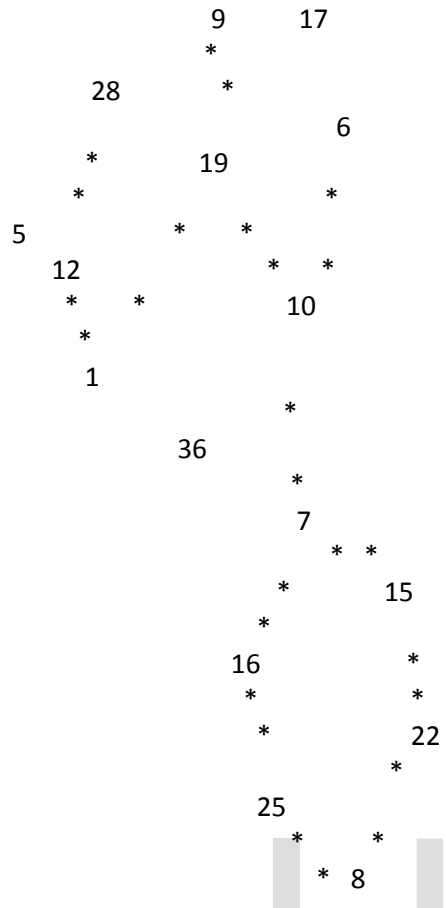
++

*** Intermediate interpretation ***

Fragment n. 1 ,fused rings could be found around peaks
7 14

---------- Overall plot of the structure ----------
---------- Projection on l.s.q. plane ---- scale: 2.50 cms/a ----------





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*** Fourier recycling restarted ***

In step B scale factor, atomic coordinates and isotropic
Thermal factors are refined via diagonal matrix.

Step	cycle	residual
B	4	11.90%
B	5	11.02%
B	6	10.27%
B	7	10.27%

++

*** Final interpretation ***

Phy__359_0m in P-1

Assumed atomic parameters and limits for interatomic bonds and angles
(Interspecies and intraspecies)

	Distances		angles		atomic	user
Type	radius	minimum	maximum	minimum	maximum	number	conditions
S	1.020	1.21	2.45	85.00	145.00	16.000	
O	0.730	0.92	2.16	85.00	145.00	8.000	
N	0.750	0.94	2.18	85.00	145.00	7.000	
C	0.770	0.96	2.20	85.00	145.00	6.000	

Tentative of peak labelling in terms of atomic species

Group	peaks	possible	species	range of
Number	included	chemical species	assigned	bond angles