PERIÓDICO TCHÊ QUÍMICA
ARTIGO ORIGINAL

DADOS DE DIFRACÇÃO DE RAIOS-X PARA UM NOVO COMPOSTO DE PIRAZOLINE

X-RAY POWDER DIFFRACTION DATA FOR A NEW PIRAZOLINE COMPOUND

DELGADO, Gerzon E.[1*], DELGADO-NIÑO, Pilar[2], LOBATON, Robert[3], LIEW, Suk-Ming[4], JAMALIS, Joazaizulfazli[4]

[1] Laboratorio de Cristalografía, Departamento de Química, Facultad de Ciencias, Universidad de Los Andes, Mérida, Venezuela

[2] Facultad de Ingeniería, Universidad Libre, Bogotá, Colombia

[3] Laboratorio de Análisis Farmacéutico, Departamento de Análisis y Control, Facultad de Farmacia y Bioanálisis, Universidad de Los Andes, Mérida, Venezuela

[4] Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, Skudai Johor, Malaysia

** Correspondence author*
e-mail: gerzon@ula.ve

Received 03 October 2019; received in revised form 27 October 2019; accepted 27 October 2019

RESUMO

As pirazolinas são agentes importantes na química medicinal como um suporte promissor para estudos de modificação estrutural e desenvolvimento de medicamentos devido à sua ampla gama de atividades biológicas como, por exemplo, atividade anticâncer, antifúngica, antibacteriana, antidepressiva, anticonvulsivante, antitubercular, antioxidante, antileishmanial e anti-inflamatória. Estes compostos heterocíclicos podem ser preparados ao refluxo da chalcona com hidrato de hidrazina e acetato de sódio anidro na presença de ácido acético glacial. A caracterização estrutural, estrutura molecular e cristalina desses compostos orgânicos permite estudar suas propriedades biológicas para conhecer suas aplicações potenciais. Portanto, o uso do XRPD é muito importante, pois permite obter um registro para ser usado como método de identificação. O objetivo desta investigação foi obter e reportar dados de difração de pó de raios-X de boa qualidade do composto pirazolina 1- (3- (4-iodofenil) -5- (3-metil tiofen-2-il) -4,5 -di-hidro-1H-pirazol-1-il) etan-1-ona, que pode ser usado como potencial agente antimicrobiano e anticâncer. O padrão de pó foi indexado no grupo espacial monoclinico I2 / a com os parâmetros celulares unitários *a* = 25.440(5) Å, *b* = 5.124(2) Å, *c* = 26.261(6) Å, β = 105.75(2)° and figures of merit M_{20}= 38.2 and F_{20}= 66.6 (0.00573, 53). Todas as linhas medidas foram indexadas e são consistentes com o grupo espaço monoclínico. O padrão de pó será incluído no banco de dados do arquivo de difração de pó para ser usado como referência.

Palavras-chave: Difração de raios X, pirazolina, agente antimicrobiano e anticancerígeno.

ABSTRACT

Pyrazolines are important agents in medicinal chemistry as a promising scaffold for structural modification and drug development studies due to their wide range of biological activities such as anticancer, antifungal, antibacterial, antidepressant, anticonvulsant, antitubercular, antioxidant, antileishmanial and anti-inflammatory activity. These heterocyclic compounds can be prepared by refluxing chalcone with hydrazine hydrate and anhydrous sodium acetate in the presence of glacial acetic acid. The structural characterization, molecular and crystalline structure, of these organic compounds, allows studying their biological properties to know their potential applications. Hence the use of XRPD is very important because it allows obtaining a record to be used as a method of identification. The aim of this investigation was to obtain and reported good quality X-ray powder diffraction data the pyrazoline compound 1-(3-(4-iodophenyl)-5-(3-methyl thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one, which could be used as potential anti-microbial and anti-cancer agent. The powder pattern was indexed in the monoclinic space group *I*2/*a* with unit cell parameters *a* = 25.440(5) Å, *b* = 5.124(2) Å, *c* = 26.261(6) Å, β = 105.75(2)° and figures of merit M_{20}= 38.2 and F_{20}= 66.6 (0.00573, 53). All measured lines were indexed and are consistent with the monoclinic space group. The powder pattern will be included in the Powder Diffraction File database to be used as a reference.

Keywords: Powder X-ray diffraction, pyrazoline, anti-microbial agent, anti-cancer agent.

1. INTRODUCTION

The 5-membered heterocyclic compounds type pyrazolines are important agents in medicinal chemistry as a promising scaffold for structural modification and drug development studies due to their wide range of biological activities such as anticancer, antifungal, antibacterial, antidepressant, anticonvulsant, antitubercular, antioxidant, antileishmanial and anti-inflammatory activity (Kumar *et al*., 2013; Deng *et al*., 2012; Özdemir *et al*., 2007; Rani *et al*., 2011; Insuasty *et al*., 2012; 2013; 2015; Montoya *et al*., 2014; Moreno *et al*., 2018). Acetylated pyrazolines have been found to be more active than the non-acetylated pyrazolines (Khalil *et al*., 2012; Monga *et al*., (2014); Al-Maqtari *et al*., 2015). It has been reported that the introduction of the acetyl group at first position enhances the molluscicidal activity as well as increases the stability of pyrazolines (Mishriky et al., 1996). Moreover, pyrazolines are extensively useful synthons in organic chemistry and also, they have played a crucial role in the development of theory in heterocyclic chemistry (Ahmad *et al*., 2016; Shivalingegowda *et al*., 2017; Naveen *et al*., 2018; Sathish *et al*., 2018).

The method most used, by its simplicity, in the synthesis of pyrazolines is by refluxing chalcone with hydrazine hydrate and anhydrous sodium acetate in the presence of glacial acetic acid for 24 hours (Shaaban *et al*., 2012; Levai, 1997; 2002). An alternative route involves 1,3-dipolar cycloaddition of nitrile imines to carbon-carbon double bond of arylmethylene compounds (Farag *et al*., 1994; 1997).

An excellent method of crystalline solids characterization, of different chemical nature, is the Powder X-ray diffraction (PXPD). This method together with single-crystal X-ray diffraction are the more powerful techniques for crystal structure determination. X-ray diffraction patterns are very useful for the identification of new materials and hence the importance of reporting in the appropriate database: Powder Diffraction File of the International Centre for Diffraction Data (ICDD, 2017).

In this work, and as part of ongoing structural studies on active biologically molecules (Delgado *et al*., 2015; Delgado *et al*., 2016a; 2016b; Delgado *et al*., 2017; Delgado *et al*., 2018a; 2018b; Delgado *et al*., 2019a; 2019b; 2019c), a new *N*-acetylated pyrazoline was studied using PXRD technique. The X-ray powder diffraction data for 1-(3-(4-iodophenyl)-5-(3-methyl thio phen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one is reported. This compound was prepared among a series of chalcone and pyrazoline derivatives as potential anti-cancer and anti-microbial agents (Al-Maqtari *et al*., 2015).

The crystal structure of this compound was studied from single-crystal X-ray diffraction and crystallizes with monoclinic symmetry in the space group *I*2/*a* (Delgado *et al.*, 2019c). The objective of this investigation is to obtain a good quality X-ray powder pattern, reliable values of d-spacing and relative intensity of observed *hkl* reflections, of the mentioned pyrazoline.

2. MATERIALS AND METHODS

2.1. Synthesis and specimen preparation

A mixture of the iodinated chalcone (**1**) (0.8 mmol), hydrazine hydrate (2 mL) and sodium acetate (2.0 mmol) in glacial acetic acid (15 mL) was refluxed for 24 hours (Figure 1). Crushed ice was then added and the reaction mixture was stirred again for 30 minutes. The resulting solid (**2**) was filtered using a pump vacuum, washed with cold distilled water, dried and recrystallized from methanol.

2.2. Fourier-transform infrared (FTIR) and nuclear magnetic resonance (NMR)

The chemical structure of pyrazoline (**2**) was elucidated using FTIR, ^{1}H NMR and ^{13}C NMR. Spectroscopic data were recorded using the FTIR Spectrometer Frontier (ATR-FTIR), Bruker Advancer 400 MHz and 300 MHz NMR spectrometer (^{1}H and ^{13}C NMR) in $CDCl_3$ or DMSO-d_6 using TMS as the internal standard. Brown solid (30.26% yield), m.p. 120-124ºC.

ATR-FTIR ν (cm^{-1}): 3109 (C-H sp^2), 2921 (C-H sp^3), 1656 (C=O), 1583 and 1406 (C=C aromatic), 1320 (C-N), 1006 (N-N), 717 (C-S), 659 (C-I)

^{1}H NMR 400 MHz, ($CDCl_3$) δ (ppm): 7.78 (dd, J = 8.4 Hz, 2H, H-3' and H-5'), 7.48 (d, J = 8.4 Hz, 2H, H-2' & H-6'), 7.06 (d, J = 4.8 Hz, 1H, H-5), 6.76 (d, J = 4.8 Hz, 1H, H-4), 5.86 (d, J_{xa} = 4.4 Hz, J_{xb} = 11.6 Hz, 1H, H_x), 3.68 (d, J_{bx} = 11.6 Hz, J_{ba} = 17.6 Hz, 1H, H_b), 3.20 (d, J_{ax} = 4.4 Hz, J_{ab} = 17.6 Hz, 1H, H_a), 2.41 (s, 3H, acetyl-CH_3), 2.34 (s, 3H, thiophene-CH_3)

^{13}C NMR 300 MHz, (DMSO-d_6) δ (ppm): 168.26 (C=O), 154.31 (C=N), 139.36 (C-2), 138.50 (C-3' and C-5'), 134.14 (C-3), 131.29 (C-1'), 130.90 (C-5), 129.28 (C-2' and C-6'), 123.50 (C-5), 54.71 (pyrazoline-CH), 42.45 (pyrazoline-

CH_2), 22.55 (acetyl-CH_3), 14.35 (thiophene-CH_3).

2.3. X-ray powder diffraction data

Powder diffraction data was collected at room temperature 298(1) K. A small quantity of the sample was ground mechanically in an agate mortar and pestle. The resulting fine powder, sieved to 106 μm, was mounted in a zero background holder covered with a thin layer of petroleum jelly (Buhrke *et al*., 1998). XRPD pattern was recorded with a Siemens D5005 diffractometer operating in Brag-Brentano geometry equipped with a Cu target X-ray tube (40 kV, 30 mA) and a diffracted beam graphite monochromator. The specimen was scanned from 5-65° 2θ, with a step size of 0.02° and counting time of 10 s. Quartz was used as an external standard. The software package Highscore Plus v3.0 was used to eliminate the $K\alpha_2$ component, establish the positions of the peaks and determine the peak intensities of the diffraction peaks.

3. RESULTS AND DISCUSSION:

The X-ray powder pattern of the pyrazoline (**2**) is shown in Figure 2. The 20 first peak positions were indexed using the program DICVOL04 (Boultif and Louër, 2004), which gave a unique solution in a monoclinic cell. This result confirms the crystal structure reported (Delgado *et al*., 2019a).

The complete powder diffraction dataset was reviewed in the monoclinic space group *I*2/a, using the software Highscore Plus v3.0. All measured lines were indexed and were consistent with the mentioned space group. From this analysis, the refined unit-cell parameters obtained were: *a* = 25.440(5) Å, *b* = 5.124(2) Å, *c* = 26.261(6) Å, β = 105.75(2)°, V = 3294.7(3) $Å^3$, Z = 8, with figures of merit M_{20}= 38.2 (de Wolff, 1968) and F_{20}= 66.6 (0.00573, 53) (Smith and Snyder, 1979). The calculated and observed values of XRD data are listed in Table 1. The unit cell parameters and space group assignment were validated by a Le-Bail fit (Le Bail, 2005) of PXRD data using a pseudo-Voigt peak profile function (Thompson *et al.,* 1987) with program Fullprof (Rodríguez-Carvajal, 2018) available in the software package WinPlotr (Roisnel and Rodríguez-Carvajal, 2001).

Figure 2 shows the very good fit between the observed and calculated patterns.

4. CONCLUSIONS:

The new pyrazoline, 1-(3-(4-iodophenyl)-5-(3-methyl thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one, was prepared by refluxing an iodinated chalcone with hydrazine hydrate and anhydrous sodium acetate. Spectroscopic studies confirmed the molecular structure of the heterocyclic compound. This is a new pyrazoline derivative with potential anti-microbial and anti-cancer properties. The powder pattern was indexed in the monoclinic space group *I*2/*a* with unit cell parameters *a* = 25.440(5) Å, *b* = 5.124(2) Å, *c* = 26.261(6) Å, β = 105.75(2)° and figures of merit M_{20}= 38.2 and F_{20}= 66.6 (0.00573, 53). All lines of powder pattern data were indexed and are consistent with the *I*2/*a* monoclinic space group. The X-ray powder diffraction data for the title compound is reported and will be included in the PDF database to be used as a reference.

5. ACKNOWLEDGMENTS:

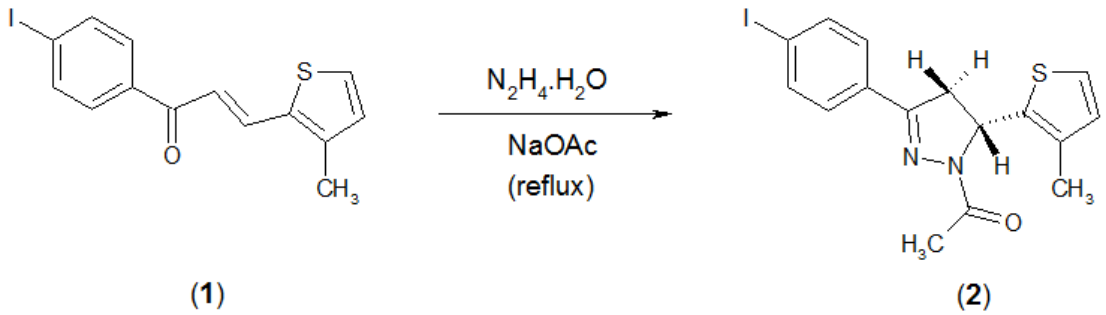
This work was supported by FONACIT (Grant LAB-97000821).

6. REFERENCES:

1. Kumar, H., Saini, D., Jain, S., Jain, N. Eur. *J. Med. Chem*. **2013**, 70, 248.
2. Deng, H., Yu, Z-Y., Chen, M-J., Tao, K., Hou, T-P. *Chem. Biol. Drug. Des*. **2012**, 79, 279.
3. Özdemir, Z., Kandilci, H.B., Gümüşel, B., Calis, Ü., Bilgin, A. *Eur. J. Med. Chem*. **2007**, 42, 373.
4. Rani, M., Yusuf, M., Khan, S.A., Sahota, P.P., Pandove, G. *Arab. J. Chem*. **2011**, 8, 174.
5. Insuasty, B., Chamizo, L., Muñoz, J., Tigreros, A., Quiroga, J., Abonía, R., Nogueras, M., Cobo, J. *Archiv. Pharm*. **2012**, 345, 275.
6. Insuasty, B., Montoya, A., Becerra, D., Quiroga, J., Abonia, R., Robledo, S., Vélez, I.D., Upegui, Y., Nogueras, M., , J. *Eur. J. Med. Chem*. **2013**, 67, 252.
7. Montoya, A., Quiroga, J., Abonia, R., Nogueras, M., Cobo, J., Insuasty, B. *Molecules*, **2014**, 19, 18656.
8. Insuasty, B., Ramírez, J., Becerra, D., Echeverry, C., Quiroga, J., Abonia, R.,

Robledo, S.M., Vélez, I.D., Upegui, Y., Muñoz, Ospina, V., Nogueras, M., Cobo, J. *Eur. J. Med. Chem*. **2015**, 93, 401.

9. Moreno, L.M., Quiroga, J., Abonia, R., Ramírez-Prada, J., Insuasty, B. *Molecules*, **2018**, 23, 1956.
10. Khalil, N.A., Ahmend, E.M., El-Nassan, H.B., Ahmed, O.K., Al-Abd, A.M. *Arch. Pharm. Res*. 2012, 35, 995.
11. Monga, V., Goyal, K., Steindel, M., Malhotra, M., Rajani, D.P., Rajani, S.D. *Med. Chem. Res*. 2014, 23, 2019.
12. Al-Maqtari, H.M., Jamalis, J., Sirat, H.M. *Jurnal Teknologi*, 2015, 77, 55.
13. Mishriky, N., Asaad, F.M., Ibrahim, Y.A, Girgis, A.S. *Indian J. Chem*. **1996**, 35B, 935.
14. Ahmad, N.A., Naveen, S., Kumara, K.K., Jamalis, J., Lokanath, N.K. *Der Phar. Chem*. **2016**, 8, 49.
15. Shivalingegowda, N., Ming, L.S., Jamalis, J., Kumar, C.S.A., Lokanath, N.K. *Chem. Data Coll*. **2017**, 7-8, 58.
16. Naveen, S., Ahmad, N.S., Deepa Urs, M.V., Lingegowda, N.S., Jamalis, J., Reddy, K.R., Lokanath, N.K. *Chem. Data Coll*. **2018**, 17-18, 132.
17. Sathish, M., Meenakshi, G., Xavier, S., Sebastian, S., Periandy, S., Ahmad, N.A., Jamalis, J., Rosli, M., Fun, H.K. J. Mol. Struct. **2018**, 1164, 420.
18. Shaaban, M.R., Mayhoub, A.S, Farag, A.M. *Expert Opin. Ther. Patents*, **2012**, 22, 253.
19. Levai, A. *Chem. Heterocycl. Compd*. **1997**, 33, 647.
20. Levai, A. *J. Heterocyclic. Chem*. **2002**, 39, 1.
21. Farag, A.M., Abbas, I.M., Abdallah, M.A. *J. Chem. Res. S*, **1994**, 286, 7.
22. Farag, A.M., Kheder, N.A., Budesinsky, M. *Tetrahedron*, **1997**, 53, 9293.
23. ICDD-PDF-2 (Database), International Centre for Diffraction Data, Newtown Square, PA, USA, **2017**.
24. Delgado, G.E., Mora, A.J., Contreras, J.E., Chacón, C. *Powder Diffr*. **2015**, 30, 178.
25. Delgado, G.E., Mora, A.J., González, T., Uzcátegui, J., Lobaton, R., Marroquín, G. *Mol. Cryst. Liq. Cryst*. **2016**a, 625, 225.
26. Delgado, G.E., Rodríguez, J.A., Mora, A.J., Bruno-Colmenárez, J., Uzcátegui, J., Chacón, C. *Mol. Cryst. Liq. Cryst*. **2016**b, 629, 96.
27. Delgado, G.E., Belandria, L.M., Mora, A.J., Bruno, J., Marroquín, G. *J. Tchê Quím*. **2017**, 14, 66.
28. Delgado, G.E., Osal, E., Mora, A.J., González, T., Palma, A., Bahsas, A. *J. Struct. Chem*. **2018**a, 59, 1248.
29. Delgado, G.E., Henao, J.A., Quintana, J.A., Al-Maqtari, H.M., Jamalis, J., Sirat, H.M. *J. Struc. Chem*. **2018**b, 59, 1493.
30. Delgado, G.E. Mora, A.J. González, T., Santos, I., Rivas, P., Seijas, L.E. *J. Tchê Quím*. **2019**a, 16, 347.
31. Delgado, G.E., Delgado-Niño, P., Jamalis, J. *J. Tchê Quím*. **2019**b, 16, 878.
32. Delgado, G.E., Liew, S.M., Jamalis, J., Cisterna, J., Cárdenas, A., Brito, I. *J. Chi. Chem. Soc*. **2019**c, In press.
33. Boultif, A., Louër, D. *J. Appl. Cryst.* **2004**, 37, 724.
34. Buhrke, V., Jenkins, R., Smith, D. *Preparation of specimens for X-ray fluorescence and X-ray diffraction analysis* (Wiley, New York), pp. 141-142. **1998**.
35. de Wolff, P.M. *J. Appl. Crystallogr*. **1968**, 1, 108
36. Smith, G.S., Snyder, R.L. *J. Appl. Crystallogr*. **1979**, 12, 60.
37. Le Bail, A. *Powder Diffr*. **2005**, 20, 316.
38. Thompson, P., Cox, D.E., Hastings, J.B. *J. Appl. Cryst*. **1987**, 20, 79.
39. Rodriguez-Carvajal J Fullprof, version 6.0, LLB, CEA-CNRS, France, **2018**.
40. Roisnel, T., Rodríquez-Carvajal, J. *Mater. Sci. Forum*, **2001**, 378-381, 118.



(**1**) (**2**)

Figure 1. *Chemical synthesis of the title pirazoline (**2**) from an iodinated chalcone.*

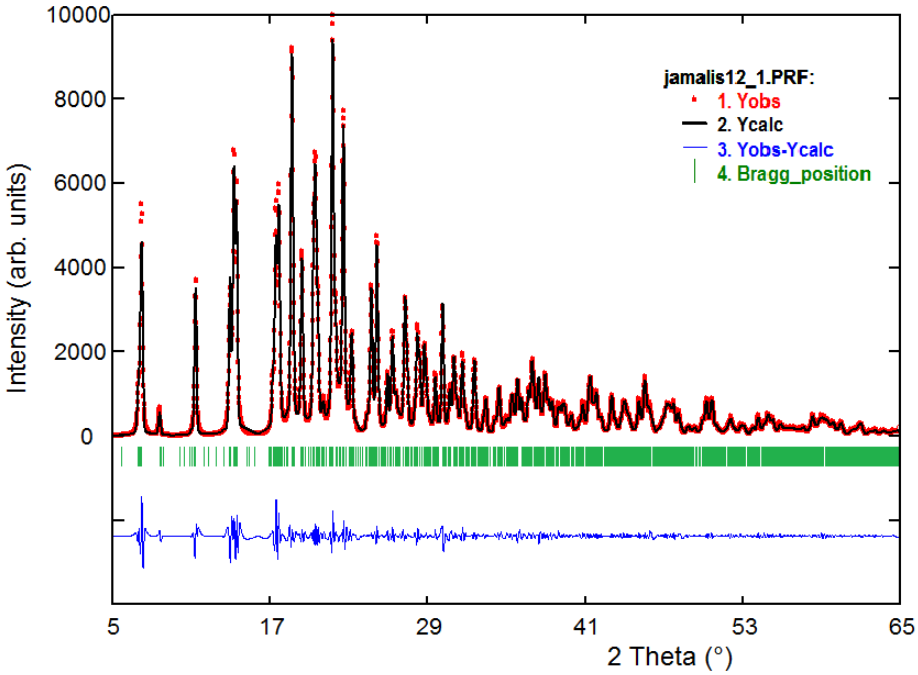


Figure 2. *Observed (red) and calculated (black) XRD patterns of the pirazoline (**2**) from the Le Bail refinement. Vertical bars (green) indicate the positions of the Bragg peaks. The lower trace depicts the difference between the experimental and calculated intensity values.*

Table 1. *X-ray powder diffraction data of 1-(3-(4-iodophenyl)-5-(3-methylthiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)ethan-1-one.*

$2\theta_{obs}$ (°)	d_{obs} (Å)	$(I/I_o)_{obs}$	*h*	*k*	*l*	$2\theta_{cal}$ (°)	d_{cal} (Å)	$\Delta 2\theta$ (°)
6.995	12.62597	9.7	1	0	-1	6.988	12.63999	0.008
7.218	12.23747	46.1	2	0	0	7.218	12.23746	0.000
8.578	10.30047	5.6	1	0	1	8.577	10.30063	0.000
11.341	7.79618	31.3	3	0	-1	11.340	7.79700	0.001
13.997	6.32213	23.9	2	0	-2	14.002	6.31982	-0.005
14.255	6.20840	53.9	3	0	1	14.255	6.20810	-0.001
14.464	6.11893	50.5	4	0	-1	14.422	6.13683	0.042
17.211	5.14798	9.6	2	0	2	17.205	5.14981	0.006
17.444	5.07965	46.9	4	0	-2	17.439	5.08137	0.006
17.670	5.01543	107	1	1	0	17.679	5.01287	-0.009
18.675	4.74765	75.8	0	1	1	18.661	4.75123	0.014
19.427	4.56558	39.1	2	1	-1	19.393	4.57354	0.034
20.310	4.36897	39.5	1	0	-3	20.327	4.36544	-0.017
20.457	4.33788	56.9	3	1	0	20.458	4.33761	-0.001
20.634	4.30100	26.3	2	1	1	20.651	4.29759	-0.017
21.071	4.21294	6.4	3	0	-3	21.067	4.21360	0.003
21.770	4.07906	100.0	6	0	0	21.770	4.07918	0.001
21.988	4.03925	22.8	1	1	-2	21.993	4.03837	-0.005
22.592	3.93262	73.0	4	1	-1	22.594	3.93228	-0.002
23.234	3.82530	22.3	3	1	-2	23.234	3.82539	0.001
24.716	3.59925	32.1	4	1	1	24.740	3.59573	-0.025
25.146	3.53856	51.0	5	1	0	25.146	3.53866	0.001
25.930	3.43344	14.3	3	0	3	25.931	3.43325	-0.001
26.317	3.38381	25.6	3	1	2	26.318	3.38361	-0.002
26.851	3.31765	4.1	1	1	-3	26.813	3.32232	0.038
27.278	3.26675	32.2	0	1	3	27.274	3.26720	0.004
27.426	3.24941	18.1	3	0	-4	27.437	3.24818	-0.011
28.224	3.15931	25.2	1	1	3	28.212	3.16067	0.012
28.395	3.14068	18.7	4	0	3	28.380	3.14231	0.015
28.761	3.10149	19.9	6	0	2	28.739	3.10389	0.023
29.583	3.01719	15.3	2	1	3	29.585	3.01700	-0.002
30.135	2.96316	4.9	6	1	1	30.136	2.96307	-0.001
30.703	2.90967	11.1	2	0	4	30.703	2.90968	0.000
31.010	2.88153	16.4	5	1	2	31.004	2.88207	0.006
31.275	2.85773	8.2	7	1	-2	31.273	2.85790	0.002
31.648	2.82486	20.7	6	1	-3	31.641	2.82547	0.007
31.881	2.80479	5.9	9	0	-1	31.883	2.80461	-0.002
32.554	2.74831	17.2	1	1	-4	32.532	2.75009	0.022
33.263	2.69136	4.2	4	1	-4	33.287	2.68945	-0.024
33.440	2.67746	10.2	4	1	3	33.429	2.67837	0.012
34.104	2.62688	3.8	1	1	4	34.101	2.62708	0.003
34.481	2.59897	8.3	1	0	-5	34.484	2.59877	-0.003
35.013	2.56070	5.2	0	2	0	35.012	2.56077	0.001
35.422	2.53206	6.2	2	1	4	35.453	2.52991	-0.031
35.885	2.50044	11.3	10	0	-2	35.885	2.50045	0.000
36.170	2.48141	8.0	2	2	-1	36.144	2.48316	0.026
36.681	2.44802	12.1	6	0	-5	36.684	2.44783	-0.003