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ORIGINAL PAPER

Synthesis and crystal structure of bis-chalcone-derived fused-ring pyrazoline having an unusual substitution pattern

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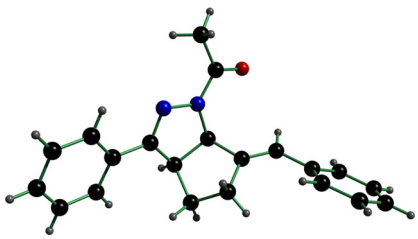
Abstract Pyrazolines are an important class of heterocyclic compounds with diverse applications. A novel bis-chalcone-derived fused ring pyrazoline has been obtained by the reaction of bis-chalcone with hydrazine hydrate in acetic acid solvent having a catalytic amount of HCl and characterized by IR, ^{1}H and ^{13}C NMR, GC–MS, and finally by X-ray single crystal analysis. Interestingly, the in situ post-cyclization substitution pattern on pyrazoline ring nitrogen is entirely different from the previously reported related pyrazoline derivatives. The new compound crystallizes out from its ethanolic solution, which has monoclinic crystal lattice with $P2_1/c$ space group, $a = 6.1001(4)$ Å, $b = 38.602(2)$ Å, $c = 7.7332(5)$ Å, $\alpha = 90°$, $\beta = 113.039(3)°$, $\gamma = 90°$, $V = 1675.73(19)$ Å^3, $Z = 4$, crystal size $= 0.38 \times 0.30 \times 0.18$ mm^3, and $R_{int} = 0.043$.

Graphical abstract



Keywords Heterocycles · Fused-ring pyrazoline · Structure elucidation · X-ray structure determination

Introduction

Pyrazoline derivatives have a unique place in realm of heterocyclic bioactive compounds [1–4]. They possess anti-fungal [5], anti-depressant [6], anticonvulsant [7], anti-inflammatory [8], anti-bacterial [9], anti-tumor [10], antiarrhythmic [11], antitubercular [12], antidiabetic [13], antipyretic [14], anticancer [15], antiviral [16], and so on [17] properties. In addition to their applications in medicinal chemistry, the pyrazoline derivatives carrying a phenyl substitution at 5-position have shown good film-forming properties and displayed excellent photophysical properties [18, 19]. The 2-pyrazolines (Fig. 1) can be synthesized from a number of different synthetic precursors such as Mannich bases [20], α,β-unsaturated esters [21], more commonly from α,β-unsaturated ketones known as "chalcones" [22–27] and more recently from bis-chalcones [28]. However, the 2-pyrazolines prepared from bis-chalcones are still limited in their number in comparison to the derivatives obtained from simple mono-chalcones despite of having an additional advantage of further functionalization through its double bond [29, 30]. Owing to this additional double bond, the properties and functions of the 2-pyrazoline derivatives can further be tuned by introducing desired functionalities. Therefore, this sub-class of 2-pyrazolines requires a lot of attention from synthetic and medicinal chemistry community.

In recent years, most of the derivatives of 2-pyrazoline have been obtained either by incorporating a substituent at N1 position or by introducing different substituents at 3-

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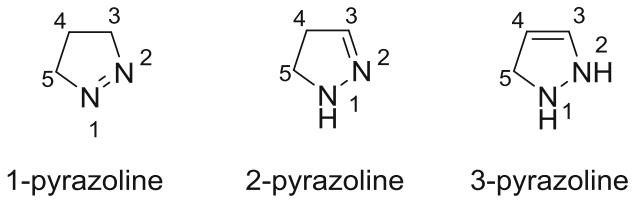


Fig. 1 Different isomeric forms of pyrazoline

and 5-positions. Considering the synthesis of 2-pyrazoline from chalcone, N1 position is always the nitrogen connected to the carbon coming from aldehyde component of the chalcone. In this context and to best of our knowledge, the substitution at N2 of 2-pyrazoline, whether it is prepared from simple chalcones or bis-chalcones, has not been reported so far. Herein, in this communication, as a result of our continuous interest in pyrazoline derivatives [22–27], we report the synthesis and crystal structure of a novel bis-chalcone derived fused ring pyrazoline **2** having an unusual substitution at N2 position.

Results and discussion

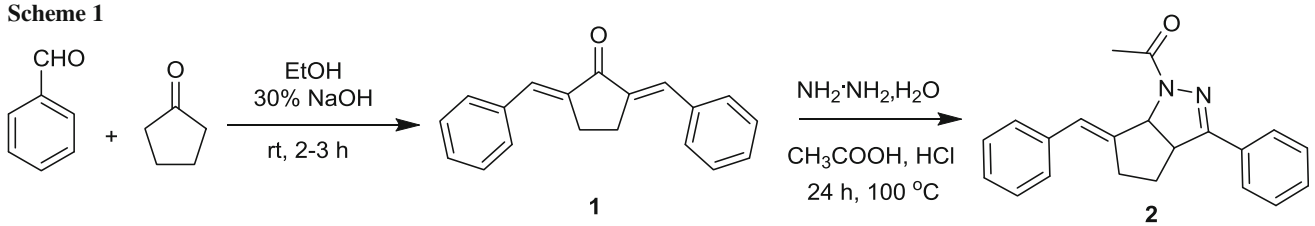
The N2-substituted pyrazoline derivative **2** was obtained in good yield by the reaction of bis-chalcone intermediate **1** with hydrazine hydrate in acetic acid solvent containing catalytic amount of hydrochloric acid in reflux conditions (Schemes 1, 2). The bis-chalcone intermediate **1** in turn was obtained by Claisen–Schmidt condensation reaction of two equivalents of benzaldehydes with one equivalent of cyclopentanone in ethanol solvent and in the presence of 30% NaOH. It is worth addressing here that we [22–27] and various others previously prepared pyrazoline derivatives from simple or mono-chalcones under similar conditions where the acyl substituent always goes to N1 position. Similarly, Azam et al. [31] and Song et al. [28] reported some bis-chalcone derived pyrazoline derivatives that also have substitution at N1 position. The structure of this somewhat usual that bis-chalcone-derived pyrazoline **2** was deduced on the basis of its FT-IR, ^{1}H and ^{13}C NMR, GCMS data, and finally by X-ray single crystal diffraction analysis.

In FT-IR spectroscopy, two characteristic absorption bands appeared at 1600 and 1176 cm^{-1} were assigned to the carbon nitrogen double bond (C=N) and carbon nitrogen single bond (C–N), respectively. Both of these indicated the formation of pyrazoline ring. Another stretching band at 1688 cm^{-1} showed the presence of carbonyl moiety of *N*-acetyl group [32, 33]. The formation of five membered pyrazoline ring was further confirmed by the ^{1}H NMR spectroscopy. All protons were found at their expected regions and the chemical shift values for these protons are provided in the experimental section. The ^{13}C NMR spectrum complimented the results further with the observation of all the carbon signals. Finally, a molecular ion peak ($M^{+\cdot}$) observed at $m/z = 316$ in its GC–MS spectrum confirmed the formation of pyrazoline derivative **2**.

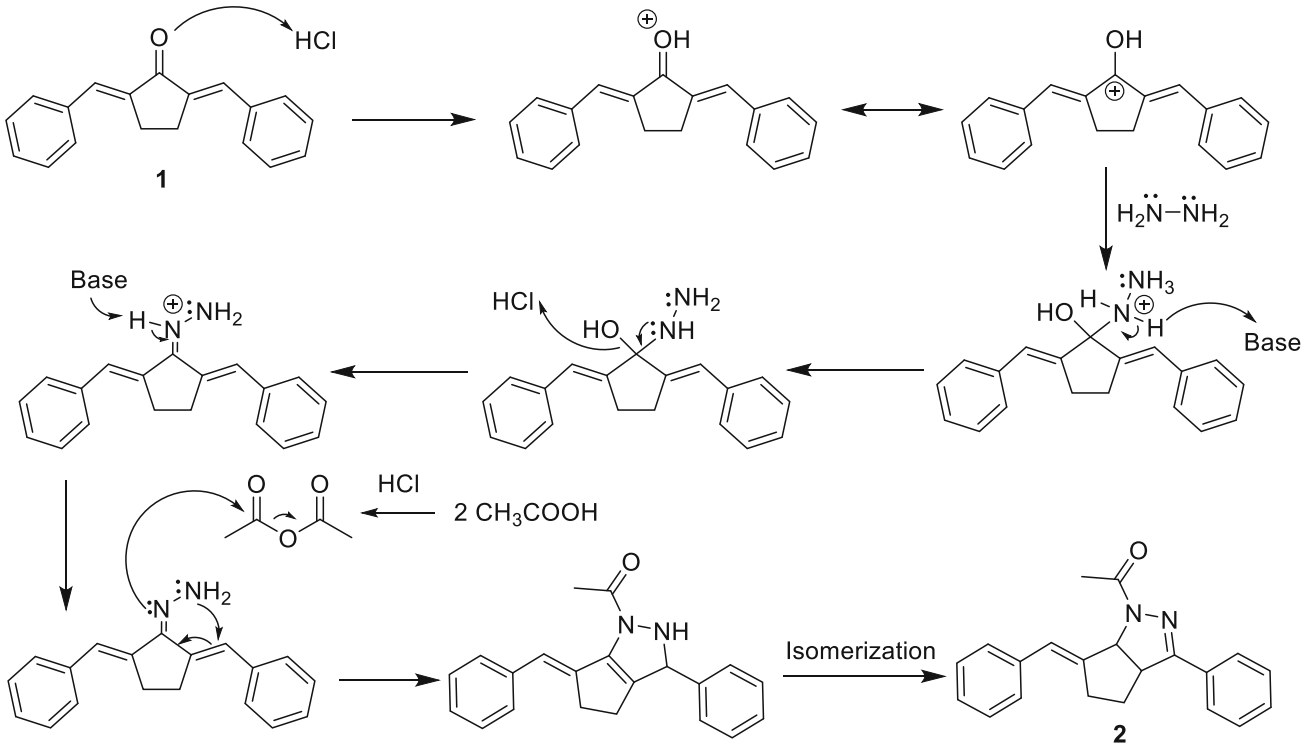
The structure of compound **2** was further characterized unambiguously by growing the single crystals suitable for X-ray diffraction analysis from its ethanolic solution. The ORTEP diagram of **2** with the numbering scheme is shown in Fig. 2. The phenyl ring [C(1)–C(6)] directly attached to the pyrazoline ring is nearly in the same plane as pyrazoline ring, making a dihedral angle of 8.47° [C(1)–C(6)–C(7)–N(1)]. The other phenyl ring [C(16)–C(21)] that is directly attached to the cyclopentane ring through a double bond is tilted, making a dihedral angle of 34.87° [C(14)–C(15)–C(16)–C(17)] with the double bond. All of the bond lengths and bond angles related to the phenyl rings are in the normal range. Selected bond lengths and bond angles are provided in Table 1. In the cyclopentananopyrazolinyl ring, the N(1)=C(7) bond length [1.284(2) Å] is slightly shorter than those found in a similar fused cyclohexananopyrazoline derivative [1.287(3) Å] [28] and the related simple pyrazoline derivatives [1.290(2) Å, 1.293(3) Å] [25], while the bond lengths of N(1)–N(2) [1.389(2) Å] and N(2)–N(10) [1.471(2) Å] are comparable to those with pyrazolines prepared from both mono- and bis-chalcones.

The compound **2** packs in 1D-supramolecular chains in the solid state driven mainly by CH···O [C(13)–H(13A)···O(1) 2.590 Å] and π···π [34, 35] [C(1)···O(8) 3.326 Å] stacking interactions (Fig. 3a). These chains are further connected to the neighboring chains by means of

Scheme 1



Scheme 2



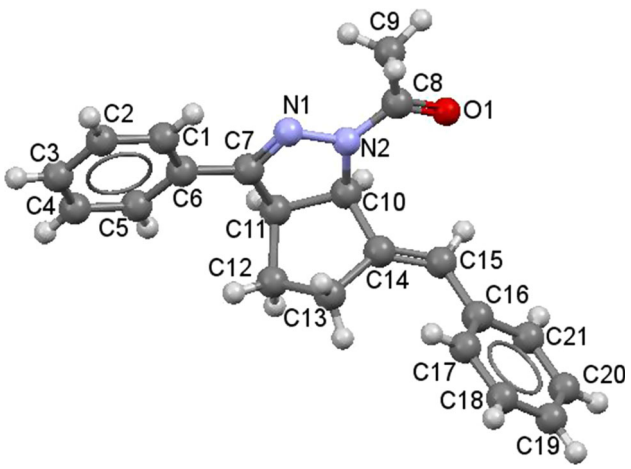


Fig. 2 Molecular structure (ORTEP diagram) of **2**

CH···π [27] [C(9)–H(9A)···C(3) 2.874 Å, C(9)–H(9A)···C(4) 2.788 Å] interactions forming an overall 2D network structure (Fig. 3b).

Conclusion

In conclusion, we have reported the synthesis and crystal structure of a novel fused-ring pyrazoline **2** having an unusual post-cyclization substitution pattern on pyrazoline nucleus. It undergoes substitution at the nitrogen which is directly attached to the ketone component of the bis-chalcone which has not been previously reported. It packs in 1D-supramolecular chains in the solid state driven mainly by CH···O and π···π stacking interactions. We are currently investigating this reaction that provided an unusual product, in more detail, and the results regarding the reason of its formation, substrate scope, etc. will be subject of our future paper.

Experimental

All the reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as required. Thin layer chromatography (TLC) was performed using aluminium sheets coated with silica gel 60 F254 (Merck). Melting point was determined in open capillary tube using Gallenkamp apparatus (MP-D) and was uncorrected. IR spectrum in the range of 4000–400 cm^{-1} was obtained on a Thermo Nicolet-6700 FT-IR Spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 300 and 75 MHz in $CDCl_3$, respectively, using residual solvent signals as a reference. The GC–MS spectrum was recorded on Agilent 5973 inert mass selective detector in combination with Agilent 6890 N gas chromatograph.

Table 1 Selected geometric parameters; bond lengths/Å, bond angles/°, and torsion angles/° for fused-ring pyrazoline **2**

Compound	**2**
O(1)–C(8)	1.220(2)
N(1)–C(7)	1.284(2)
N(1)–N(2)	1.389(2)
N(2)–C(8)	1.361(2)
N(2)–C(10)	1.471(2)
C(6)–C(7)	1.471(2)
C(10)–C(14)	1.512(3)
C(14)–C(15)	1.329(3)
C(15)–C(16)	1.466(3)
C(7)–N(1)–N(2)	108.18(15)
C(8)–N(2)–N(1)	122.79(16)
C(8)–N(2)–C(10)	124.23(16)
N(1)–N(2)–C(10)	112.79(15)
N(1)–C(7)–C(6)	120.86(17)
N(1)–C(7)–C(11)	114.61(16)
N(2)–C(8)–C(9)	117.25(18)
N(2)–C(10)–C(14)	112.10(16)
N(2)–C(10)–C(11)	102.21(14)
C(7)/N(1)/N(2)/C(8)	170.81(18)
C(7)/N(1)/N(2)/C(10)	−4.4(2)
N(2)/N(1)/C(7)/C(6)	179.37(15)
N(2)/N(1)/C(7)/C(11)	−0.4(2)
C(1)/C(6)/C(7)/N(1)	−8.4(3)
C(14)/C(15)/C(16)/C(17)	−34.8(3)

(E)-1-(6-Benzylidene-3-phenyl-4,5,6,6a-tetrahydrocyclopenta[c]pyrazol-1(3aH)-yl)ethanone (**2**, $C_{21}H_{20}N_2O$) A round bottom flask containing 15 cm^3 ethanol and benzaldehyde (0.02 mol) was added 30% NaOH solution at room temperature with stirring. After about 30 min of continuous stirring, cyclopentanone (0.01 mol) was then added and stirring was continued at room temperature for another 3–4 h. The precipitates thus appeared after cooling the reaction mixture with ice were filtered and washed thoroughly with distilled water to obtain 2,5-dibenzylidenecyclopentanone (**1**).

Compound **1** (0.01 mol, 0.5 g) was dissolved in 15 cm^3 glacial acetic acid containing few drops of concentrated hydrochloric acid and heated to 60–65 °C for 30 min. Hydrazine hydrate (0.03 mol) was then added and heated the reaction mixture to reflux for 24 h. The reaction mixture was then cooled to room temperature and poured into crushed ice. The precipitates so obtained were filtered off, washed with distilled water, and dried in desiccator to get crude **2** which was further purified by column chromatography using *n*-hexane/ethylacetate (4:1) as eluent.

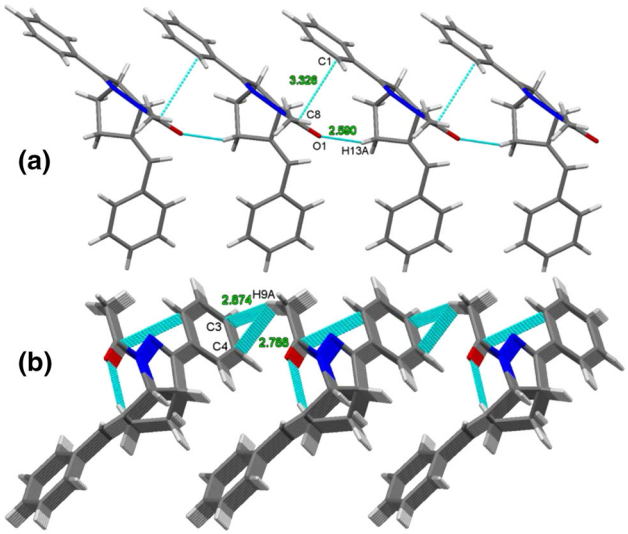


Fig. 3 Molecular packing of **2** in the solid state; **a** 1D supramolecular chain, **b** 2D structure

Yield 70%; light yellow crystals; m.p.: 118–120 °C; $R_f = 0.52$ (*n*-hexane:ethyl acetate, 4:1); IR: $\bar{\nu} = 1176$ (C–N), 1600 (C=N), 1688 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.99$–1.2 (1H, m), 1.33–1.39 (1H, m), 1.69–1.74 (2H, m), 1.85 (3H, s, CH_3), 2.06 (1H, m), 5.9 (1H, m), 7.11 (1H, s), 7.30 (2H, dd, Ph), 7.46 (1H, t, Ph), 7.78 (2H, d, Ph), 7.79 (2H, dd, Ph), 7.80 (1H, t, Ph), 8.02 (2H, d, Ph) ppm;^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.7$, 29.60, 29.65, 31.93, 53.19, 115.87, 119.99, 127.03, 128.55, 128.79, 128.88, 137.45, 141.89, 157.73, 164.89 ppm; EI-MS: $m/z = 316$ (M^+ base peak).

Crystallographic data collection and structural refinement

Single crystals of **2** were mounted on a thin glass fiber at room temperature and the reflection data were collected on a Bruker kappa APE XII CCD diffractometer equipped with graphite mono-chromated MoKα radiation ($\lambda = 0.71073$ Å). The data were also corrected to Lorentz and polarization effect. The structure was solved using SHELXS-97. Final refinement on F2 was carried out by full-matrix least-squares techniques using SHELXL-97 [36].

Crystal data (CCDC 1529599): $C_{21}H_{20}N_2O$, $M = 316.39$, crystal size 0.38 × 0.30 × 0.18 mm^3, crystal system: monoclinic, space group: $P2_1/c$, $a = 6.1001(4)$ Å, $b = 38.602(2)$ Å, $c = 7.7332(5)$ Å, $\alpha = 90°$, $\beta = 113.039(3)°$, $\gamma = 90°$, $V = 1675.73(19)$ Å^3, $Z = 4$, $\rho = 1.254$ g cm^{-3}, $T = 296(2)$ K, R_1, wR_2[$I > 2\sigma(I)$] = 0.0556, 0.1172, R_1, wR_2 (all data) = 0.0891, 0.1321, quality of fit = 1.037.

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References

1. Elinson MN, Nasybullin RF, Ryzhkov FV, Zaimovskaya TA, Nikishin GI (2015) Monatsh Chem 146:631
2. Albuquerque HMT, Santos CMM, Cavaleiro JAS, Silva AMS (2014) Curr Org Chem 18:2750
3. Seebacher W, Michl G, Belaj F, Brun R, Saf R, Weis R (2003) Tetrahedron 59:2811
4. Tong X, Chen R, Zhang TT, Han Y, Tang WJ, Liu XH (2015) Bioorg Med Chem 23:515
5. Montoya A, Quiroga J, Abonia R, Derita M, Sortino M, Ornelas A, Zacchino S, Insuasty B (2016) Molecules 21:969
6. Kaplancikli ZA, Ozdemir A, Turan-Zitouni G, Altintop MD, Can OD (2010) Eur J Med Chem 45:4383
7. Bhandari S, Tripathi AC, Saraf SK (2013) Med Chem Res 22:5290
8. Jadhav SY, Shirame SP, Kulkarni SD, Patil SB, Pasale SK, Bhosale RB (2013) Bioorg Med Chem Lett 23:2575
9. Evranos-Aksoz B, Onurdag FK, Ozgacar SO (2015) Z Naturforsch C 70:183
10. Elmeligie S, Khalil NA, Ahmed EM, Emam SH, Zaitone SAB (2016) Biol Pharm Bull 39:1611
11. Bruno O, Bondavalli F, Ranise A, Schenone P, Losasso C, Cilenti L, Matera C, Marmo E (1990) Farmaco 45:147
12. Harikrishna N, Isloor AM, Ananda K, Obaid A, Fun HK (2016) New J Chem 40:73
13. Ahn JH, Kim HM, Jung SH, Kang SK, Kim KR, Rhee SD, Yang SD, Cheon HG, Kim SS (2004) Bioorg Med Chem Lett 14:4461
14. Amr AE, AL-Omar MA, Abdalla MM (2016) Lat Am J Pharm 35:950
15. Lee Y, Kim BS, Ahn S, Koh D, Lee YH, Shin SY, Lim Y (2016) Bioorg Chem 68:166
16. Havrylyuk D, Zimenkovsky B, Vasylenko O, Lesyk R (2013) J Heterocycl Chem 50:E55
17. Mete E, Comez B, Gul HI, Gulcin I, Supuran CT (2016) J Enz Inhib Med Chem 31:1
18. Szukalski A, Haupa K, Miniewicz A, Mysliwiec J (2015) J Phys Chem C 119:10007
19. Szukalski A, Miniewicz A, Haupa K, Przybyl B, Janczak J, Sobolewski AL, Mysliwiec J (2016) J Phys Chem C 120:14813
20. Afsah EM, Kandeel EEDM, Khalifa MM, Hammouda WM (2007) Z Naturforsch B 62:540
21. Levai A (2002) J Heterocycl Chem 39:1
22. Abbas A, Flores-Holguin N, Naseer MM (2015) New J Chem 39:4359
23. Abbas A, Hussain S, Hafeez N, Naseer MM (2014) Spectrochim Acta A 133:182
24. Abbas A, Hussain S, Hafeez N, Hasan A, Naseer MM (2014) Spectrochim Acta A 127:32
25. Abbas A, Nazir H, Naseer MM, Bolte M, Hussain S, Hafeez N, Hasan A (2014) Spectrochim Acta A 120:176
26. Abbas A, Naseer MM (2014) Acta Chim Slov 61:792
27. Anam F, Abbas A, Lo KM, Zia-ur-Rehman, Hameed S, Naseer MM (2014) New J Chem 38:5617
28. Song J, Zhao PS, Zhang WG (2010) Bull Korean Chem Soc 31:1875
29. Asiri AM, Khan SA (2012) J Heterocycl Chem 49:1434
30. Asiri AM, Khan SA (2011) Molecules 16:523
31. Azam MA, Gomathy S, Alam F, Suresh B (2008) Indian J Heterocycl Chem 18:157
32. Hadi S, Rilyanti M (2010) Orient J Chem 26:775
33. Hadi S, Afriyani H, Anggraini WD, Qudus HI, Suhartati T (2015) Asian J Chem 27:1509
34. Naseer MM, Hameed S (2012) Cryst Eng Comm 14:4247
35. Ahmad M, Pervez H, Hadda TB, Toupet L, Naseer MM (2014) Tetrahedron Lett 55:5400
36. Sheldrick GM (2008) Acta Crystallogr A 64:112