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Facile, efficient and diastereoselective synthesis of α- hydrazine tetrazoles through a novel one-pot four-component reaction

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Abstract

A novel and efficient method for the diastereoselctive synthesis of α- hydrazine tetrazoles *via* an isocyanide-based multicomponent reaction is reported in good yields. The α- hydrazine tetrazoles were obtained by a facile azide Ugi four-component reaction (U-4CR) using cyclic ketones, trimethylsilyl azide, hydrazides, and corresponding isocyanide without any catalyst and with high bond forming efficiency at room temperature.

Keywords: α-hyrazino tetrazoles, α-hyrazino acids, One-pot four-component reaction, isocyanide-based multicomponent reaction, Azide Ugi reaction.

Dedicated to Prof. Thomas J. J. Mueller on the occasion of his birthday

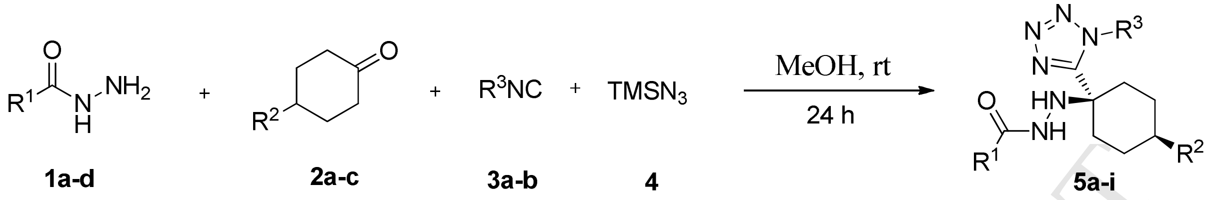
1. Introduction

Tetrazoles are useful heterocyclic skeletons because there are in many important biological compounds and drugs.[1-2] Among the pharmaceutically important tetrazoles losartan and valsartan, two widely used angiotensin receptor blockers, deserve a special mention. During the last decade considerable attention has been focused on the synthesis of 1,5-disubstituted tetrazoles due to their wide range of biological activities such as: NADPH oxidase inhibitors,[3a] glucokinase activators,[3b] hepatitis C virus (HCV) serine protease NS3 inhibitors,[3c] calcitonin gene-related peptide receptor antagonists, and antimigraine agents.[3d]

Prescribed agents featuring the 1,5-disubstituted tetrazole scaffold include the anti-inflammatory cilostazol and the since one of the most common strategy for *cis* amide bond peptide mimics[4] is the use of 1,5-disubstituted tetrazoles to constrain the amide bond in a *cis* conformation, they have also attracted a great deal of attention in the field of peptide chemistry. For example, analogues of somatostatine,[5] bradykinin,[6] and deaminooxytocin[7] containing the above core has been described. Furthermore, the potential utility of 1,5-disubstituted tetrazoles as synthetic intermediates are enormous;[8] they were used for the synthesis of energetic salts, 3,4-dihydropyrimidin-2(1H)-ones, piericidins, (+)-*trans*-5-allyl hexahydro-indolizidin-3-ones, acacetin, (+)-strictifolione, vinylsilianes, and leucascandrolide A.

Access to 1,5-disubstituted tetrazoles is of considerable interest, and numerous approaches to this scaffold have been disclosed in the literature. Major synthetic strategies utilized for the preparation of 1,5-disubstituted tetrazoles are *via* intermolecular cycloaddition reactions, and isocyanide-based reactions and conversion of substituted tetrazoles into 1,5-disubstituted tetrazoles. [9] Among the various pathways toward 1,5-disubstituted tetrazole derivatives, those based on the isocyanide multicomponent reactions are especially noteworthy. The first synthesis of these compounds via isocyanide-based reactions was undertaken by Ugi and Meyr, in which they reported the synthesis of 1,5-disubstituted tetrazoles using a Passerini three-component reaction (P-3CR) of isocyanides, highly reactive carbonyl compounds, and hydrazoic acid (HN_3).[10] Nixey and Hulme developed a $TMSN_3$-modified P-3CR for the synthesis of these compounds.[11] Also, the Ugi four-component reaction (U-4CR) of isocyanides with amines, aldehydes or ketones, and $TMSN_3$ affords 1,5-disubstituted tetrazoles.[12]

As part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds by means of isocyanide-based multicomponent reactions,[13] herein, we describe a novel diastereoselective synthesis of α-hydrazino tetrazoles *via* a facile azide Ugi four-component reaction using various cyclic ketones, hydrazides, isocyanides and trimethylsilylazide as Ugi acidic partner (Scheme **1**).

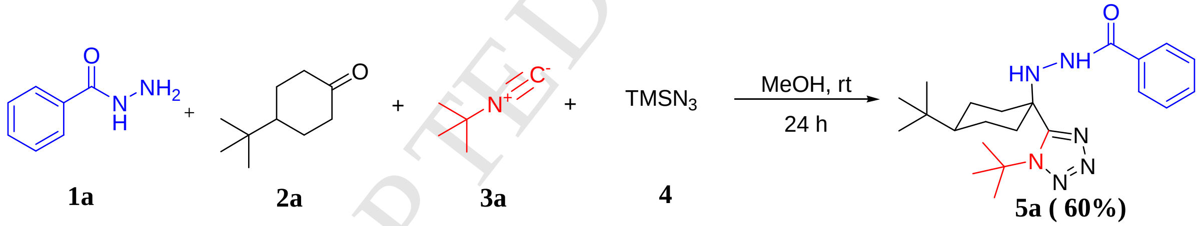


R^1 = Boc-phe-$NHNH_2$, phenyl, *p*-toluenesulfyl, thienyl
R^2 = *t*-butyl, ethyl, methyl
R^3 = *t*-butyl, cyclohexyl

Scheme 1.Diastereoselective synthesis of α- hydrazine tetrazoles via a facile azide Ugi four-component reaction.

2. Results and discussion

The synthesis of (**5a**) was selected as model reaction. Thus, a mixture of benzhydrazide (**1a**), 4-*tert* butyl cyclohexanone (**2a**), *tert*-butyl isocyanide(**3a**) and trimethylsilyl azide (**4**) was stirred at room temperature in methanol to produce the corresponding diastereomericα-hydrazinotetrazole (**5a**) in 60% yield (Table (**2**)).



Scheme 2. The model reaction for the synthesis of product **5a**.

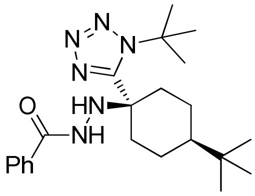
Our synthetic challenge involved determining the best reaction conditions for the synthesis of **5a** in high yield. Consequently, the model reaction between 4-*tert* butyl cyclohexanone (**2a**), benzhydrazide (**1a**), *tert*-butyl isocyanide (**3a**) and trimethylsilyl azide (**4**) was used to survey various solvents (Scheme 2). Different solvents were used as reaction media for the model reaction; such as methanol, ethanol, dichloromethane and acetonitrile. Since the yields were marginally better with methanol (Table 1), this solvent was then utilized in the synthesis of a focused library of α-hydrazino tetrazoles (Table 1).

Table 1. Optimization of the solvent for the synthesis of **5a**

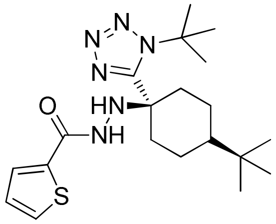
Solvent	**yields**
CH_2Cl_2	20
CH_3CN	27
MeOH	60
EtOH	52

In initial studies, diastereomeric ratios were determined by ^{1}H NMR spectral data on the crude reaction products (Table **2**). For instance, determinations of diastereomer ratios of product **5a** (68:32) were based on the NMR integration of the areas under the –NH-N<u>H</u>-CO peak, resonated at δ 7.83 in the axial position and 8.30 ppm in the equatorial position two configurational diastereomers, respectively. In the next step, the crude product was separated by crystallization procedures into its two diastereomers due to their major difference of solubility in ethanol. The single diastereomer was obtained in 60% yield. The separated single crystal contained the major diastereomer, confirmed by its ^{1}H NMR spectra. After finding suitable conditions, the scope and limitations of this reaction were explored by using different hydrazides **1a–d**, cyclic ketones **2a-c** and isocyanides **3a–b**. The results are summarized in Table 2. The yields of reactions are reported on the basis of the yield of crystalline formed as single diastereomer (Table 2). In Table 2 the structure of products, the yield of single diastereomer and also the ratio of two diastereomers were shown.

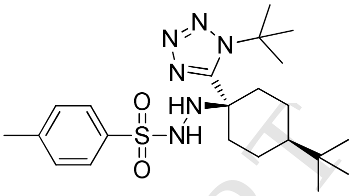
Table 2. One-pot four-component reaction for the diastereoselcetive synthesis of hydrazine tetrazoles **5a-i** *via* reaction of hydrazides **1a-d**, cyclic ketones **2a-c**, isocyanides **3a-b** and trimethylsilyl azide at room temperature.



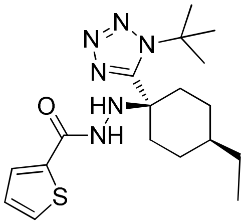
5a (60%)
dr (68:32)



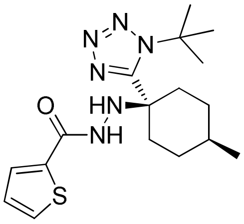
5b (55%)
dr (79:21)



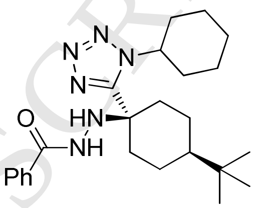
5c (67%)
dr (80:20)



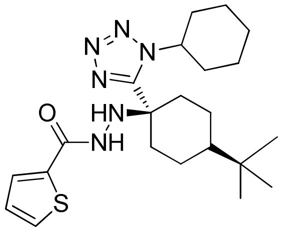
5d (54%)
dr (75: 25)



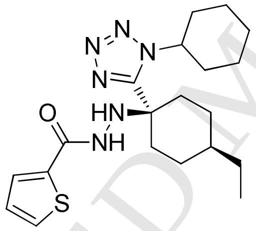
5e (70%)
dr (74:26)



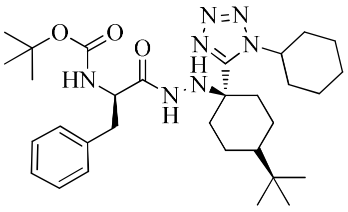
5f (65%)
dr (77:23)



5g (60%)
dr (72:28)



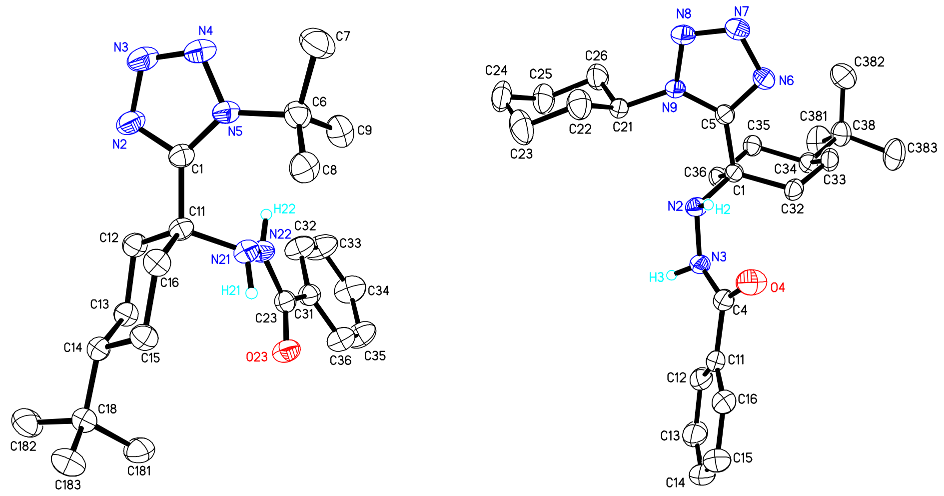
5h (63%)
dr (78:22)



5i (65%)
dr (68:32)

The structures of the products **5a-i** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR and ESI-HRMS spectra. For example, the ^{1}H NMR spectrum of **5a** consisted of multiplet signals for the methylene groups of cyclohexyl ring at δ 1.05-2.49, a doublet for NH at δ 6.17 and a multiplet was observed at δ 7.41-7.68 for aromatic protons and –NH (*t*-butyl) of amide and a doublet for amide proton of NH-N<u>H</u>-COPh at δ 9.93. The proton decoupled ^{13}C NMR spectrum of **5a** showed 14 distinct resonances in agreement with the proposed structure. Data arising from a combined analysis of 2D H-H COSY allowed us to assign signals of the ^{1}H NMR spectrum of compound **5a**. 2D H-H-COSY spectrum was used to determine the relationship between –NH-N<u>H</u>-CO and the other –NH amide proton. According to this result, it is clear that two –NH protons have correlation at δ 6.17 and 9.93 ppm which could confirm the relation between –NH of amide and amine (–NH-NH-CO).

Meanwhile, for two samples **5a** and **5f** the single crystals were obtained and the ORTEP structure could confirm their structure (Figure 1).The X-ray data for two single crystals **5a** and **5f** showed clearly the orientation of the substituent and this was evidence to confirming getting the single diastereomer.

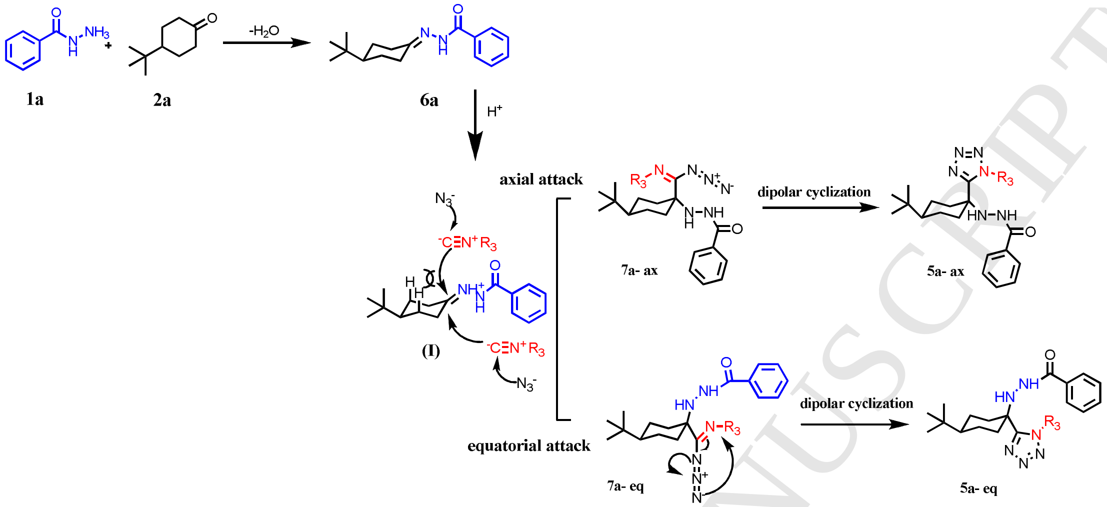


5a **5f**

5a

Fig. 1. ORTEP structure of compounds **5a** and **5f**.

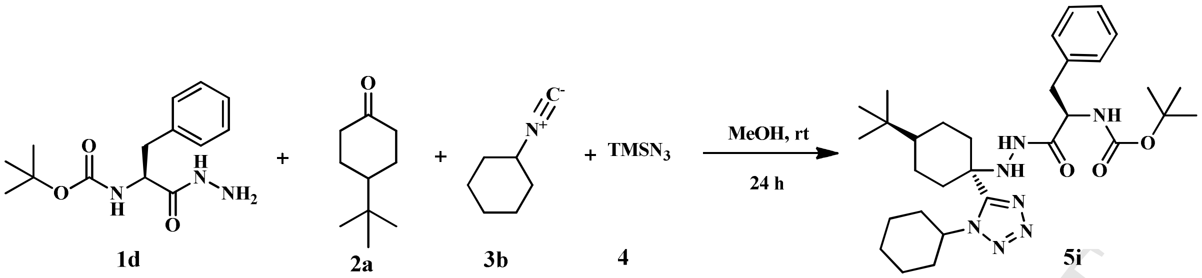
A mechanism rationalization for this reaction is provided in (Scheme 3). The first step is the formation of the hydrazone intermediate (**6a**). Hydrazone formation is resulted from the reaction of the ketone with the hydrazide. Then, it could form the hydrazonium form (**I**) in the presence of acid. Based on the the chemistry of isocyanides, it iss reasonable to assume that the nucleophilic attack of isocyanide on the hydrazonium ion followed by nucleophilic attack of the azide leads to the formation of intermediate **7a** which undergoes intramolecular cyclization to afford the corresponding product **5a**. The ratio of major diastereomers was in 68-80%. There are two possibilities for the nucleophilic addition of isocyanide and trimethylsilyl azide to the hydrazonium intermediate through axial or equatorial approach. The transition state for axial attack suffers from steric clashes between the 1, 3 axial hydrogens and the incoming isocyanide reagent. But addition of isocyanide through equatorial attack is more suitable with less steric effect to provide **5a-i** and it causes the regio-and diastereoselectivity of the reaction. (Scheme 3)



Scheme 3. Proposed mechanism for the concerted nucleophilic addition of azide-isocyanide for the synthesis of hydrazine tetrazoles **5a-I** *via* azide Ugi reaction.

It seems that the nucleophilic addition of isocyanide and azide could proceed through simultaneous nucleophilic attack of the azide on the isocyanide, followed by nucleophilic attack of the isocyanide on the hydrazonium ion. (Scheme 3)

To extend the synthetic approach for the preparation of aza-peptides containing a tetrazole ring, amino acid hydrazides were also used which produced high yields of the desired products. (Scheme 4) One of the advantages of this approach is that after the Boc-deprotection step, the resulting compounds can be used as the precursors for the synthesis of aza-peptides containing a tetrazole ring. (Scheme 4)



Scheme 4. Synthesis of α-hydrazino tetrazole **5i** which contained protected phenylalanine.

Formation of the aggregated forms of molecules could affect their physical and chemical properties and it has also been proven to play an efficient role in different biological process. The molecular aggregation is usually mediated through low energy interactions. The main forces included in construction and controlling the size and shape of these supramolecular structures are the electrostatic interactions, van der Waals bonds, hydrogen bonding, and π-stacking forces.[14-16]

As shown in Fig 2, the rod-shaped structures (size = 218 nm) are produced which confirms the linear and highly-ordered self-aggregation of compound **5c** in the three-component solvent mixture [(hexafluoro isopropanol, methanol, water (100 µl: 400 µl: 500 µl)]. A stacking interaction between the aromatic moieties and few hydrogen bonds are proposed for the initial fabrication which is further stabilized and extended to rod-like contributions by numerous hydrogen and π interactions in adjacent positions.

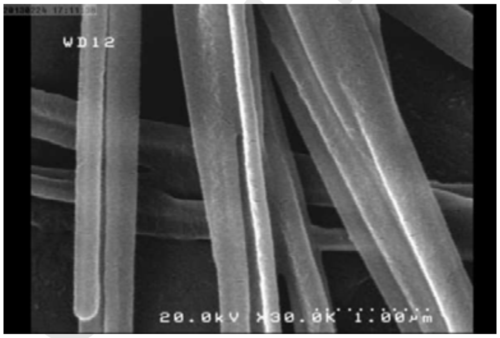


Fig 2. SEM image of compound **5c**

These data could confirm that hydrogen bonding mediated self-assembly. In all synthesized compounds, the molecules have more sites for forming hydrogen bonding, and ability to construct hydrogen bonding has direct influence on the stability of the self-assembled structures. According to our finding, since **5c** was used as a single diastereomer, it is clear that chirality has essential role in self-assembly and aggregation to afforded rod structures.

In conclusion , we have reported a convenient, simple and efficient synthesis of diastereomeric α-hydrazino tetrazoles of potential synthetic and pharmacological interest via a facile azide Ugi four-component reaction. The present methodology offers several advantages, such as simple procedure with an easy work-up, high yields, the absence of any catalysts, high bond forming efficiency and carrying out the reaction in one-pot reaction conditions at room temperature.

Experimental Section:

Commercially available materials were used without further purification. Melting points were determined on an Electrothermal 9100 apparatus and were uncorrected. IR spectra were obtained on an ABB FT-IR FTLA 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on Bruker DRX-300 AVANCE spectrometers at 300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR. DMSO-d_6 and $CDCl_3$ was used as solvent. High resolution mass spectra were recorded on Mass-ESI-POS (Apex Qe-FT- ICR instrument) spectrometer. The scanning electron microscope (Hitachi 4160, Japan) was used for getting the scanning electron micrographs.

General procedure for the synthesis of α-hydrazino-tetrazoles:

To a solution of hydrazide **1** (1 mmol), ketone **2** (1 mmol), isocyanide **3** (1.2 mmol) and trimethylsilylazide **4** (1 mmol) in 8 mL MeOH was added. The mixture was stirred for 24 h at ambient temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/n-hexane, 1:3), the solvent was removed under vacuum, and the residue was precipitated by addition of 3 mL of EtOH and 1 mL of H_2O. The precipitate was filtered off and then crystallized from ethanol.

5a:N'-((1*SR*,4*SR*)-4-*tert*-butyl-1-(1-*tert*-butyl-1H-tetrazol-5-yl)cyclohexyl)benzohydrazide(238 mg, 60%) as a white solid; mp 247-248˚C; R_f (33% EtOAc/ Hexane) 0.33; υ_{max} (KBr) 3300, 3278, 3066, 2956, 1647, 1461 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 0.85 (*s*, 9H, $H_{t\text{-Bu}}$), 1.05-1.92 (*m*, 8H, $H_{\text{Cyclohexyl}}$), 1.79 (*s*, 9H, $H_{t\text{-Bu}}$), 2.45-2.49 (*m*, 1H, $H_{\text{eqCyclohexyl}}$), 6.17 (*d*, 1H, *J* 8.4 Hz, NH), 7.41-7.49 (*m*, 3H, H_{Ar}), 7.68 (*d*, 2H, *J* 7.0 Hz, H_{Ar}), 9.93 (*d*, 1H, *J* 8.4 Hz, NH); δ_C (75 MHz, DMSO-d_6) 21.3, 27.3, 30.7, 32.0, 33.9, 46.0, 58.3, 63.9, 127.2, 128.2, 131.2, 132.8, 159.6, 163.8. HRMS (ESI): [M+H]$^+$ found 399.28743 $C_{22}H_{35}N_6O$ requires 399.28762. [M+Na]$^+$ found 421.26938 $C_{22}H_{34}N_6NaO$ requires 421.26956.

colourless crystal (polyhedron), dimensions 0.35 x 0.26 x 0.14 mm^3, crystal system triclinic, space group P$\bar{1}$, Z = 4, a = 12.4093(7) Å, b = 12.7843(7) Å, c = 16.2326(9) Å, alpha = 89.082(1) deg, beta = 77.274(1) deg, gamma = 62.717(1) deg, V = 2221.8(2) Å^3, rho = 1.192 g/cm^3, T = 199(2)

K, Theta$_{max}$ = 26.37 deg, radiation Mo Kalpha, lambda = 0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 4.37 and a completeness of 99.9% to a resolution of 0.80Å, 39749 reflections measured, 9089 unique (R(int)=0.0330), 6706 observed (I >2δ(I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[17a] based on the Laue symmetry of the reciprocal space, mu=0.08mm^{-1}, T$_{min}$=0.97, T$_{max}$=0.99, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package [17b], 539 parameters refined, hydrogen atoms were treated using appropriate riding models, except thos at the hydrazinic nitrogen atoms N21 and N22, which were refined isotropically, goodness of fit 1.03 for observed reflections, final residual values R1(F)=0.046, wR(F^2)=0.100 for observed reflections, residual electron density 0.21 to 0.20 eÅ^{-3}. CCDC 950021contains the supplementary crystallographic data for this paper.

5b: N'-((1*RS*, 4*RS*)-4-*tert*-butyl-1-(1-*tert*-butyl-1H –tetrazol-5-yl)cyclohexyl)thiophene-2-carbohydrazide

(222 mg, 55%) as a white solid; mp 242-244˚C; R$_f$ (33% EtOAc/ Hexane) 0.25; υ$_{max}$(KBr) 3283, 3116, 2954, 1634, 1473 cm^{-1}; δ$_H$ (300 MHz, CDCl$_3$) 0.91 (*s*, 9H, H $_{t\text{-Bu}}$), 1.08-1.72 (*m*, 5H, H$_{Cyclohexyl}$), 1.89 (*s*, 9H, H $_{t\text{-Bu}}$),1.99-2.10 (*m*, 2H, H$_{Cyclohexyl}$), 2.46-2.50 (*m*, 2H, H$_{Cyclohexyl}$), 5.95 (*brs*, 1H, NH), 6.99 (*brs*, 1H,H$_{Thienyl}$), 7.45 (*d*, 1H, *J*4.5 Hz, H$_{Thienyl}$), 7.66 (*brs*, 1H, H$_{Thienyl}$),8.82 (*brs*, 1H, NH); δ$_C$ (75 MHz, CDCl$_3$) 21.9, 27.5, 31.1, 32.4, 33.9, 46.9, 59.8, 65.1, 127.6, 128.1, 129.9, 137.1, 160.0, 160.2. HRMS (ESI): [M+H]$^+$ found 405.24318 $C_{20}H_{33}N_6OS$ requires 405.24320, [M+Na]$^+$ found 427.22514 $C_{20}H_{32}N_6NaOS$ requires 427.22516.

5c: N'-((1*SR*, 4*SR*)-4-*tert*-butyl-1-(1-*tert*-butyl-1H-tetrazol-5-yl)cyclohexyl)-4-methyl benzene sulfonohydrazide (300 mg, 67%) as a white solid; mp 197-198˚C; R$_f$ (33% EtOAc/ Hexane) 0.24; υ$_{max}$ (KBr) 3479, 3272, 3117, 2938, 2864, 1655, 1600, 1462, 1320, 1156 cm^{-1}; δ$_H$ (300 MHz, CDCl$_3$) 0.73 (*s*, 9H, H $_{t\text{-Bu}}$), 0.92-1.90 (*m*, 7H, H$_{Cyclohexyl}$), 1.70 (*s*, 9H, H $_{t\text{-Bu}}$), 2.35 (*s*, 3H, Me), 2.36-2.44 (*m*, 2H, H$_{Cyclohexyl}$), 3.80 (*d*, 1H, *J* 4.5 Hz, NH), 7.01 (*d*, 1H, *J* 4.5 Hz, NH), 7.22 (*d*, 2H, *J* 8.0 Hz, H$_{Ar}$), 7.68 (*d*, 2H, *J* 8.0 Hz, H$_{Ar}$); δ$_C$ (75 MHz, CDCl$_3$) 18.4, 21.5, 24.0, 27.4, 31.1, 32.1, 33.9, 46.9, 58.4, 60.9, 64.9, 128.0, 129.5, 135.2, 143.7, 155.6. HRMS (ESI): [M+H]$^+$found 449.26984 $C_{22}H_{37}N_6O_2S$ requires 449.26996, [M+Na]$^+$found 471.25176 $C_{22}H_{36}N_6NaO_2S$ requires 471.25186.

5d: N'-((1*SR*, 4*SR*)-1-(1-*tert*-butyl-1H-tetrazol-5-yl)-4-ethylcyclohexyl)thiophene-2-carbohydrazide

(263 mg, 70%) as a white solid; mp 243-246˚C; Rf (33% EtOAc/ Hexane) 0.31; υ_{max} (KBr) 3293, 3255, 3118, 2930, 1642, 1448 cm^{-1}; δH (300 MHz, $CDCl_3$) 0.85 (*t*, 3H, *J* 7.0 Hz, CH_3), 1.22-1.62(*m*, 7H, $H_{Cyclohexyl}$), 1.79 (*s*, 9H, $H_{t\text{-}Bu}$), 1.83-1.94 (*m*, 2H, $H_{Cyclohexyl}$), 2.37 (*m*, 2H, $H_{Cyclohexyl}$), 5.99 (*d*, 1H, *J* 5.7 Hz, NH), 7.09 (*t*, 1H, *J* 4.0 Hz, $H_{Thionyl}$), 7.63 (*d*, 1H, *J* 4.0 Hz, $H_{Thienyl}$), 7.74 (*d*, 1H, *J* 4.8 Hz, $H_{Thienyl}$),9.86 (*d*, 1H, *J* 7.2 Hz, NH); δC (75 MHz, $CDCl_3$) 11.3, 26.6, 28.7, 30.7, 33.1, 37.0, 58.8, 64.1, 127.7, 128.1, 130.7, 137.1, 158.7, 159.4. HRMS (ESI): $[M+H]^+$found 377.21185 $C_{18}H_{29}N_6OS$ requires 377.21186, $[M+Na]^+$found 399.19379 $C_{18}H_{28}N_6NaOS$ requires 399.19380.

5e: *N*'-((1*SR*, 4*SR*)-1-(1-*tert*-butyl-1H-tetrazol-5-yl)-4-methylcyclohexyl)thiophene-2-carbohydrazide

(253 mg, 70%) as a white solid; mp 262-265˚C; R_f (33% EtOAc/ Hexane) 0.28; υ_{max} (KBr) 3265, 3118, 2954, 2864, 1631, 1443 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.98 (*d*, *J* 4.5 Hz, 3H, CH_3), 1.50-1.77 (*m*, 5H, $H_{Cyclohexyl}$), 1.89 (*s*, 9H, H $_{t\text{-}Bu}$), 2.04- 2.11 (*m*, 2H, $H_{Cyclohexyl}$), 2.33-2.38 (*m*, 2H, $H_{Cyclohexyl}$), 5.81 (*brs*, 1H, NH), 7.01 (*d*, 1H, *J* 4.0 Hz , $H_{Thienyl}$), 7.46 (*d*, 1H, *J* 4.0 Hz, $H_{Thienyl}$), 7.60 (*brs*, 1H, $H_{Thienyl}$), 8.57(*brs*, 1H, NH); δ_C (75 MHz, $CDCl_3$) 22.1, 29.4, 31.2, 31.4, 33.3, 46.9, 59.8, 65.1, 127.6, 128.1, 130.1, 136.8, 149.9, 160.1. HRMS (ESI): $[M+H]^+$ found 363.19632 $C_{17}H_{27}N_6OS$ requires 363.19637, $[M+Na]^+$found 385.17824 $C_{17}H_{26}N_6NaOS$ requires 385.17828.

5f: *N*'-((1*SR*, 4*SR*)-4-*tert*-butyl-1-(1-cyclohexyl-1H-tetrazol-5-yl) cyclohexyl)benzohydrazide

(275 mg, 65%) as a white solid; mp 273-275˚C; R_f (33% EtOAc/ Hexane) 0.30; υ_{max} (KBr) 3338, 3250, 2941, 2858, 1667, 1532, 1453 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.81 (*s*, 9H, H $_{t\text{-}Bu}$), 1.12-2.08 (*m*, 17H, $H_{Cyclohexyl}$), 2.65 (*d*, 2H, *J* 12.5 Hz, $H_{eqCyclohexyl}$), 4.98-5.05 (*m*, 1H, CHN), 5.34 (*brs*, 1H, NH), 7.33 (*t*, 2H, *J* 7.5 Hz, H_{Ar}), 7.47 (*t*, 1H, *J* 7.5 Hz, H_{Ar}), 7.52 (*brs*, 1H, NH), 7.68 (*d*, 2H, *J* 8.1 Hz, H_{Ar}); δ_C (75 MHz, $CDCl_3$) 23.9, 24.9, 25.5, 27.5, 32.2, 33.4, 34.9,47.6, 59.3, 60.0, 127.1, 128.6, 132.0, 132.2, 154.4, 167.8. HRMS (ESI): $[M+H]^+$found 425.30296 $C_{24}H_{37}N_6O$ requires 425.30311, $[M+Na]^+$ found 447.28485 $C_{24}H_{36}N_6NaO$ requires 447.28498.

colourless crystal (polyhedron), dimensions 0.62 x 0.29 x 0.21 mm^3, crystal system orthorhombic, space group Pbca, Z = 8, a = 12.1572(8) Å, b = 11.6707(8) Å, c = 33.725(2) Å, alpha = 90 deg, beta = 90 deg, gamma = 90 deg, V = 4784.9(6) Å^3, rho = 1.179 g/cm^3, T = 200(2) K, $Theta_{max}$ = 28.95 deg, radiation Mo Kalpha, lambda=0.71073 Å, 0.5 deg omega-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 7.29 and a completeness of 98.7% to a resolution of 0.84Å, 47926 reflections measured, 6241 unique

(R(int)=0.0367), 4739 observed (I >2σ(I)), intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[17a] based on the Laue symmetry of the reciprocal space, mu = 0.08mm^{-1}, T_{min} = 0.95, T_{max} = 0.98, structure solved by direct methods and refined against F^2 with a Full-matrix least-squares algorithm using the SHELXTL (Version 2008/4) software package[17b], 291 parameters refined, hydrogen atoms were treated using appropriate riding models, except H2 and H3 of the hydrazine-unit, which were refined isotropically, goodness of fit 1.04 for observed reflections, final residual values R1(F) = 0.048, wR(F^2) = 0.103 for observed reflections, residual electron density 0.16 to 0.24 eÅ^{-3}. CCDC 950022 contains the supplementary crystallographic data for this paper.

5g: N'- ((1*SR*, 4*SR*)- 4- *tert*- butyl- 1- (1- cyclohexyl- 1H- tetrazol- 5- yl) cyclohexyl) thiophene-2-carbohydrazide

(258 mg, 60%) as a white solid; mp 243-246˚C; R_f (33% EtOAc/ Hexane) 0.35; υ_{max} (KBr) 3296, 3222, 3092, 2937,1620, 1446 cm^{-1}; δ_H (300 MHz, DMSO-*d*$_6$) 0.84 (*s*, 9H, H $_{t\text{-Bu}}$), 0.90-1. 78 (*m*, 19H, $H_{\text{Cyclohexyl}}$), 3.38-3.41 (*m*, 1H, -CHN), 5.29 (*d*, 1H, *J* 2.5 Hz, NH), 7.13 (*t*, 1H, *J* 4.8 Hz, H_{Thienyl}), 7.75 (*d*, 1H, *J* 4.2 Hz, H_{Thienyl}), 7.80 (*d*, 1H, *J* 3.6 Hz, NH), 8.15 (*d*, 1H, *J* 8.0 Hz, H_{Thienyl}), 9.32 (*d*, 1H, *J* 2.5 Hz, NH); δ_C (75 MHz, DMSO-*d*$_6$) 21.6, 24.5, 25.2, 27.5, 30.9, 32.1, 32.2, 47.1, 47.4, 63.2, 127.8, 128.6, 131.0, 137.8, 161.9, 174.0. HRMS (ESI): $[M+H]^+$ found 431.25973 $C_{22}H_{35}N_6OS$ requires 431.25996, $[M+Na]^+$found 453.24171 $C_{22}H_{34}N_6NaOS$ requires 453.24193.

5h: N'-((1*SR*, 4*SR*)-1-(1-cyclohexyl-1H-tetrazol-5-yl)-4-ethylcyclohexyl)thiophene-2-carbohydrazide

(253 mg, 63%) as a white solid; mp 243-246˚C; R_f (33% EtOAc/ Hexane) 0.25; υ_{max} (KBr) 3301, 3248, 1629, 1444 cm^{-1}; δ_H (300 MHz, DMSO-*d*$_6$) 0.86 (*t*, 3H, *J* 7.0 Hz, CH_3), 0.75-2.48 (*m*, 21H, $H_{\text{Cyclohexyl}}$), 5.07 (*m*, 1H, CHN), 5.83 (*s*, 1H, HN), 7.07-7.10 (*m*, 1H, H_{Thionyl}), 7.65 (*d*, 1H, *J* 2.0 Hz,H_{Thionyl}), 7.73 (t, 1H, *J* 4.0Hz,H_{Thionyl}), 9.66 (*s*, 1H,NH); δ_C (75 MHz, DMSO-*d*$_6$) 11.3, 24.9, 26.6, 28.5, 31.4, 32.9, 33.1, 33.3, 37.1, 57.4, 58.2, 127.6, 128.4, 130.8, 137.2, 157.0, 164.4. HRMS (ESI): $[M+H]^+$ found 403.22755 $C_{20}H_{31}N_6OS$ requires 403.22757, $[M+Na]^+$ found 425.20946 $C_{20}H_{30}N_6NaOS$ requires 425.20947.

5i: *tert*-butyl 1-(2-((1*SR*, 4*SR*)-4-*tert*-butyl-1-(1-cyclohexyl-1H-tetrazol-5-yl)cyclohexyl)hydrazinyl)-1-oxo-3-phenylpropan-2-ylcarbamate

(369mg, 65%) as a white solid; mp 188-189˚C; R_f (33% EtOAc/ Hexane) 0.36; υ_{max}(KBr) , 3350, 3293, 3096, 2965, 1719, 1680, 1504 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 0.91 (S, 9H, $H_{t\text{-Bu}}$),1.00-2.09 (*m*, 19H, $H_{\text{cyclohexyl}}$), 1.32 (*s*, 9H, $H_{t\text{-Bu}}$), 3.00 (*m*, 2H, CH_2), 4.16-4.24 (*m*, 1H, CHN), 4.88-4.90 (*m*, 1H, CH), 5.28(*d*, 1H, *J* 7.0 Hz, NH), 7.10- 7.30 (*m*, 6H, H_{Ar}, NH), 7.53 (br*s*, 1H, NH); δ_C (75 MHz, $CDCl_3$) 21.6, 21.8, 24.9, 25.6, 27.4, 28.1, 31.7, 32.4, 32.6, 33.4, 33.5, 46.9, 58.1, 59.3, 80.4, 127.0, 128.6, 129.1, 136.2, 157.0, 170.0; HRMS (ESI): $[M+H]^+$ found 568.39664 $C_{31}H_{50}N_7O_3$ requires 568.39658; $[M+Na]^+$found 590.37859 $C_{31}H_{49}N_7NaO_3$ requires 590.37854.

Scanning Electron Microscopy

The self-aggregation of compound (**5c**) was studied by dissolving 2 mg of the sample in 1 ml of the solvent system containing 1,1,1,3,3,3 Hexafluoroisopropanol, methanol, and mili Q water (1:4:5). The scanning electron micrographs (SEM, Hitachi 4160, Japan) of the assembled constructions were obtained after 4 hrs.

Acknowledgements

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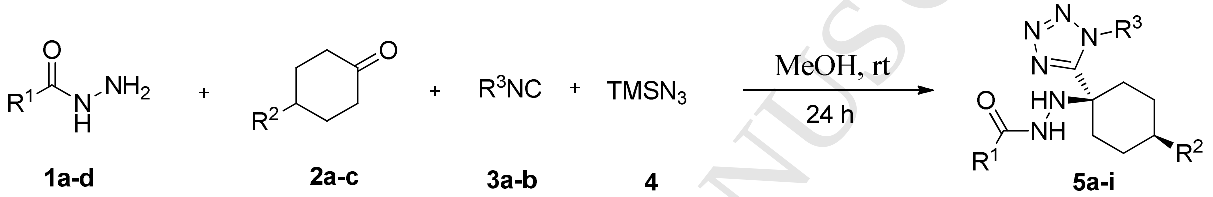
Graphical Abstract

Facile, efficient and diastereoselective synthesis of α- hydrazine tetrazoles *via* a novel one-pot four-component reaction

Sorour Ramezanpour[a], Saeed Balalaie[a*], Frank Rominger[b], Nahid S. Alavijeh[a], Hamid Reza Bijanzadeh[a]



R^1 = Boc-phe-$NHNH_2$, phenyl, *p*-toluenesulfyl, thienyl

R^2 = *t*-butyl, ethyl, methyl

R^3 = *t*-butyl, cyclohexyl

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

No syntax errors found.   CIF dictionary   Interpreting this report

Datablock: sba97

```
Bond precision:  C-C = 0.0028 A          Wavelength=0.71073

Cell:          a=12.4093(7)      b=12.7843(7)     c=16.2326(9)
               alpha=89.082(1)   beta=77.274(1)   gamma=62.717(1)
Temperature:   199 K

                Calculated                 Reported
Volume          2221.8(2)                  2221.8(2)
Space group     P -1                       P-1
Hall group      -P 1                       ?
Moiety formula  C22 H34 N6 O               ?
Sum formula     C22 H34 N6 O               C22 H34 N6 O
Mr              398.55                     398.55
Dx,g cm-3       1.191                      1.192
Z               4                          4
Mu (mm-1)       0.076                      0.076
F000            864.0                      864.0
F000’           864.27
h,k,lmax        15,15,20                   15,15,20
Nref            9099                       9089
Tmin,Tmax       0.977,0.989                0.974,0.989
Tmin’           0.974

Correction method= MULTI-SCAN

Data completeness= 0.999         Theta(max)= 26.370

R(reflections)= 0.0463( 6706)     wR2(reflections)= 0.1158( 9089)

S = 1.032               Npar= 539
```

```
The following ALERTS were generated. Each ALERT has the format
       test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.
```

Alert level C

```
ABSTY02_ALERT_1_C  An _exptl_absorpt_correction_type has been given without
            a literature citation. This should be contained in the
            _exptl_absorpt_process_details field.
            Absorption correction given as multi-scan
```

```
PLAT242_ALERT_2_C Check Low       Ueq as Compared to Neighbors for      C24_2
PLAT790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd.  #          1
              C22 H34 N6 O
```

Alert level G

```
PLAT005_ALERT_5_G No _iucr_refine_instructions_details  in the CIF          ?
PLAT154_ALERT_1_G The su’s on the Cell Angles are Equal ..........    0.00100 Deg.
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels ..........        126
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   3 ALERT level C = Check. Ensure it is not caused by an omission or oversight
   3 ALERT level G = General information/check it is not something unexpected

   2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   1 ALERT type 2 Indicator that the structure model may be wrong or deficient
   0 ALERT type 3 Indicator that the structure quality may be low
   2 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

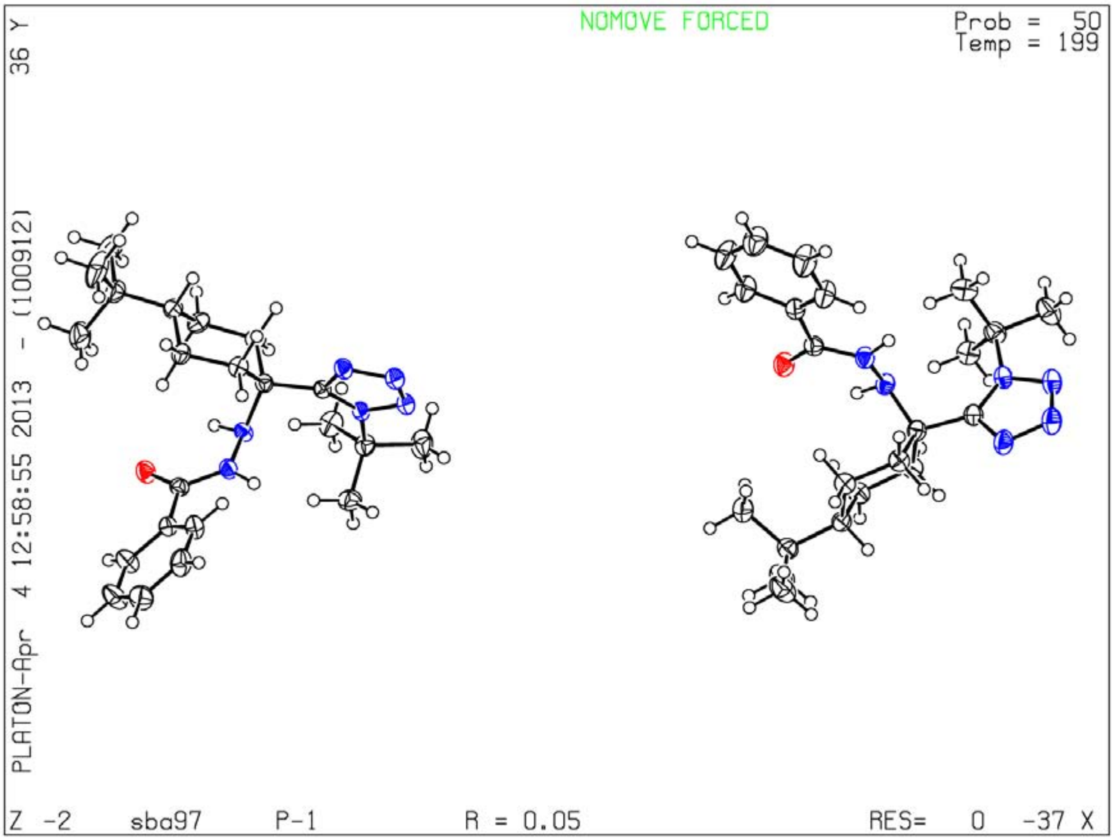
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 05/11/2012; check.def file version of 05/11/2012

Datablock sba97 - ellipsoid plot



checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

No syntax errors found.   CIF dictionary   Interpreting this report

Datablock: sba98

```
Bond precision:  C-C = 0.0020 A          Wavelength=0.71073

Cell:            a=12.1572(8)     b=11.6707(8)     c=33.725(2)
                 alpha=90         beta=90          gamma=90
Temperature:     200 K

                Calculated                 Reported
Volume          4785.0(5)                  4784.9(6)
Space group     P b c a                    Pbca
Hall group      -P 2ac 2ab                 ?
Moiety formula  C24 H36 N6 O               ?
Sum formula     C24 H36 N6 O               C24 H36 N6 O
Mr              424.59                     424.59
Dx,g cm-3       1.179                      1.179
Z               8                          8
Mu (mm-1)       0.075                      0.075
F000            1840.0                     1840.0
F000’           1840.58
h,k,lmax        16,15,45                   16,15,45
Nref            6324                       6241
Tmin,Tmax       0.974,0.984                0.955,0.984
Tmin’           0.955

Correction method= MULTI-SCAN

Data completeness= 0.987          Theta(max)= 28.950

R(reflections)= 0.0480( 4739)     wR2(reflections)= 0.1152( 6241)

S = 1.036                Npar= 291
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

● Alert level C

```
ABSTY02_ALERT_1_C  An _exptl_absorpt_correction_type has been given without
            a literature citation. This should be contained in the
            _exptl_absorpt_process_details field.
            Absorption correction given as multi-scan
```

Alert level G

```
PLAT005_ALERT_5_G No _iucr_refine_instructions_details  in the CIF          ?
PLAT063_ALERT_4_G Crystal Size Likely too Large for Beam Size ....       0.62 mm
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   1 ALERT level C = Check. Ensure it is not caused by an omission or oversight
   2 ALERT level G = General information/check it is not something unexpected

   1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   0 ALERT type 2 Indicator that the structure model may be wrong or deficient
   0 ALERT type 3 Indicator that the structure quality may be low
   1 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 05/11/2012; check.def file version of 05/11/2012

Datablock sba98 - ellipsoid plot