A Simple, Convenient, and Efficient Synthetic Route for The Preparation of (*Z*)-3,5-Dichloro-*N*-(3-(4-substitutedphenyl)-4-phenylthiazole-2(3*H*)-ylide)benzamide Heterocyclic Compounds from Aroyl Thiourea Derivatives via *S*-cyclization Mechanism

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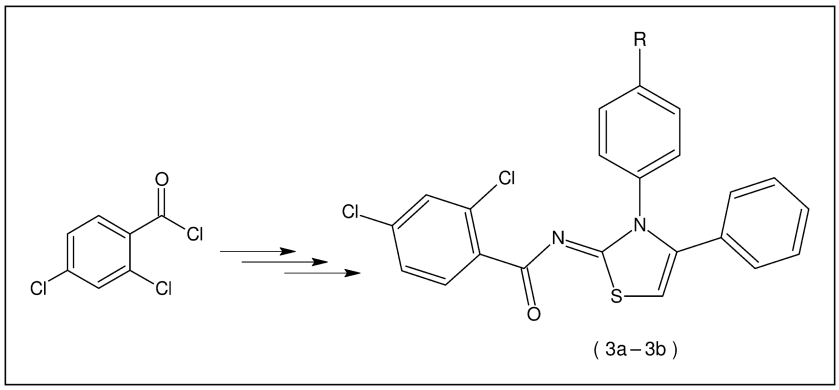

A series of variously substituted 1,3-thiazole heterocyclic compounds (**3a**–**3d**) were prepared by base-catalyzed *S*-cyclization of corresponding 2,4-dichloro-*N*-{[(4-substitutedphenyl)amino]carbonothioyl}benzamide (**2a**–**2d**) with acetophenone in the presence of bromine. The structure of all compounds was established by IR, ^{1}H-NMR, ^{13}C-NMR, elemental analysis, and X-ray crystallographic analysis.

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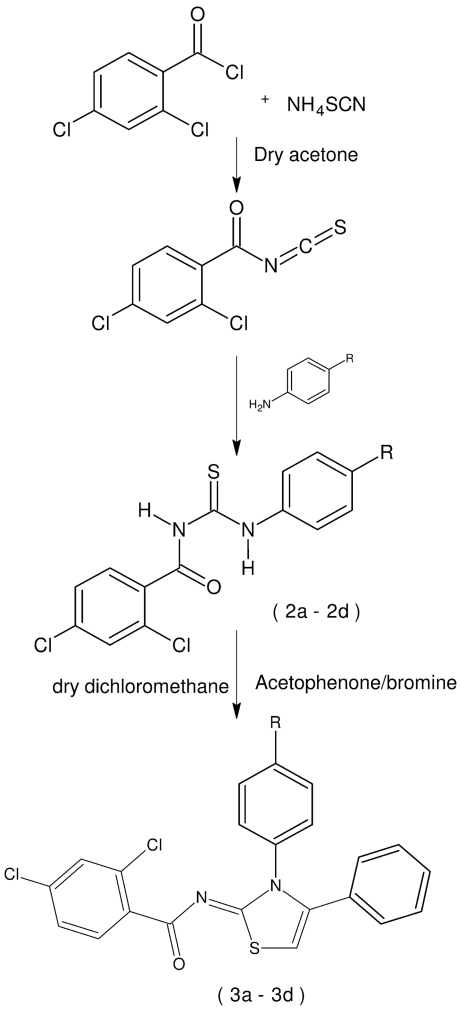
INTRODUCTION

Since the initial isolation of the polypyrrole netropsin in 1951 and distamycin in 1964, the interest in this class of compounds has been increased [1].These natural antibiotics showed anticancer and antiviral activities by DNA binding [2]. Bleomycins, a group of anticancer antibiotics, also have a dithiazole moiety along with the imidazole and pyrimidine ring systems [3]. Thiazole heterocycle is a commonly occurring substructure in organic chemistry, found in a variety of structurally and biologically interesting natural products such as mirabazoles, thiangazole, and tantazoles, which display selective cytotoxicity against murine solid tumors and are potent and selective inhibitors of HIV-1 [4,5]. Synthetic thiazoline derivatives are useful medicaments showing antifungal [6,7], anti-tumor [8], anti-allergic [9], anti-inflammatory [10], anti-hypertension [11], analgesic, anti-bacterials, anti-rheumatic, anti-pyretic, and anti-HIV [12] activities. Some fused thiazolines find applications in the treatment of allergies, hypertension, inflammation, schizophrenia, and bacterial and HIV infections [13]. 2-Thiazolylimino-5-arylidene-4-thiazolidinones show marked antimicrobial activity against bacteria, yeasts, and molds [14]. Some cyclic chiral oligothiazolines, having a wheel-like architecture containing a linear array of thiazoline rings, are well-known supramolecules [15]. 2-(Tetrahydronaphthalen-1-yl) iminothiazolidine exhibits pronounced antidepressant activity [16], and β-(hydrooxyethyl)thiazolidines are effective antihypertensives [17]. 3-Substituted 2-(cyanoimino) thiazolidines can be used in agriculture due to their neonicotinoid insecticidal activity [18]. 3-Substituted thiazolidines show radioprotective properties against γ-radiations [19]. 2-Imino-1,3-thiazolines derivatives have shown antifungal activity against the rice blast fungus *Pyricularia oryzae* [20] and thus can be used fungicides. 2-Imino-1,3-thiazoline derivatives significantly inhibit melanin production in a dose-dependant manner, thus acting as a skin whitening agent [21], and pifithrin-α is a reversible inhibitor of p53-mediated apoptosis and p53-dependant gene transcription [22].

Scheme 1. Synthetic route of compounds **3a–3d**: R=OCH_3 (a), CH_3 (b), Cl (c), and NO_2 (d).



Taking into consideration the aforementioned biological and synthetic significance of 2-imino-1,3-thiazolines, we designed the synthesis of some new 1,3-thiazolines having three points of structural diversity for systematic evaluation of biological activities and establishment of structure activity relationship (SAR) in depth. Herein, the synthesis of some 1,3-thiazoline derivatives is described.

RESULTS AND DISCUSSION

2,4-Dichloro-*N*-{[(4-substitutedphenyl)amino]carbonothioyl}benzamide (**2a–2d**) were prepared according to the published procedure involving treatment of aroyl chloride with ammonium thiocyanate in anhydrous acetone followed by reaction with suitably substituted anilines [23–26] as shown in Scheme 1. The use of phase transfer catalysts as a method of agitating a heterogeneous reaction system is gaining recognition [27,28].

In search of improved methods to prepare the 2,4-dichloro-*N*-{[(4-substitutedphenyl)amino]carbonothioyl}benzamides by reacting isothiocyanates with nucleophiles, we have found the use of tetrabutylammonium bromide (TBAB) as a phase transfer catalyst (PTC) can afford aroyl isothiocyanates in good yield, as reported here. The compounds (**2a–2d**) showed absorptions at 3351 and 3200 cm^{-1} for free and associated NH, at ~1660 for carbonyl, and at 1230–1226 cm^{-1} for thiocarbonyl groups in IR spectra and singlets at δ 9.39–9.32 and 12.02–11.95 (ppm) for NH (1) and NH (3) and peaks at 166–164 and 180.0–175.1 (ppm) for carbonyl and thiocarbonyl were observed in ^{1}H- and ^{13}C-NMR spectra, respectively. The cyclocondensation of 2,4-dichloro-*N*-{[(4-substitutedphenyl)amino]carbonothioyl}benzamide with acetophenone was achieved in the presence of bromine and base. Thus, triethyl amine was added to a solution of 2,4-dichloro-*N*-{[(4-substitutedphenyl)amino]carbonothioyl}benzamide in anhydrous dichloromethane, followed by the treatment with a mixture of acetophenone and bromine under an inert atmosphere to afford heterocyclic (*Z*)-3,5-dichloro-*N*-(3-(4-substitutedphenyl)-4-phenylthiazole-2(3*H*)-ylide)benzamide derivatives. The absence of N—H peaks at 3200–3400 cm^{-1}, slight shifting of C=O absorptions to 1630–1650 cm^{-1}, and appearance of characteristic C=N at 1450–1495 cm^{-1} were observed in the IR spectra. ^{1}H-NMR spectra showed the disappearance of N—H peaks and emergence of a ^{1}H characteristic singlet at δ 6.85–6.75 due to C=C—H of the thiazole ring. In ^{13}C-NMR, the characteristic peak for olefinic carbon at δ 107.5–107.8 (ppm) confirmed the formation of (*Z*)-3,5-dichloro-*N*-(3-(4-substitutedphenyl)-4-phenylthiazole-2(3*H*)-ylide) benzamide derivatives (**3a–3d**).

Although the same mesomeric anionic thiourea intermediate may furnish either imino-1,3-thiazoles (*S*-cyclization products) or isomeric imidazole-2-thiones (*N*-cyclization products), it has already equally demonstrated [29] that under these conditions the thermodynamically stable

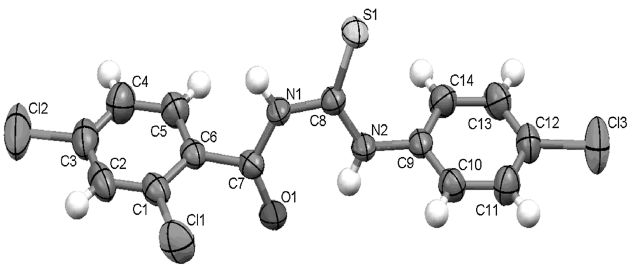


Figure 1. Molecular structure and crystallographic numbering scheme for compound 2c. Selected bond lengths (Å): C11–C1 1.722(2); C12–C3 1.739(2); S1–C8 1.6718(18); O1–C7 1.215(2); N1–C7 1.369(2); N1–C8 1.388(2); N2–H2N 0.8594; C11–C12 1.371(3). Selected bond angles (°): C7–N1–C8 129.13(15); C7–N1–H1N 113.1; C8–N1–H1N 117.8; C8–N2–C9 124.97(15); C8–N2–H2N 118.7; O1–C7–N1 123.18(17); O1–C7–C6 122.58(17); N2–C8–S1 125.55(14); N1–C8–S1 118.19(13).

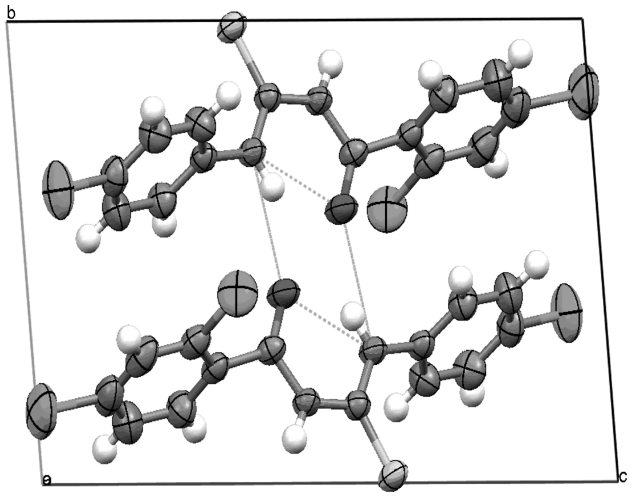


Figure 2. The packing diagram of the unit cell of the compound **2c** was projected down the *a*-axis and shown at 50% probability thermal ellipsoids.

imino-1,3-thiazoles are the exclusive products as reported the previous papers [30,31].

Single crystals of **2c** suitable for X-ray diffraction studies were obtained by evaporation from dichloromethane/ethanol. The molecular structure is shown in Figure 1. The compound (**2c**), 2,4-dichloro-*N*-{[(4-chlorophenyl) amino]carbonothioyl}benzamide, crystallizes in a triclinic primitive space group, $P - 1$ (#2). Like its other analogue, the molecule is not planar. The amido group is 63.52(7)° from the 2,4-dichloro-benzyl ring plane of C1—C6/C11/C12. The thiourea group is slightly twisted (13.11(11)°) from the amido group. The 4-chloro-phenyl ring plane, C9—C14/C13, makes a dihedral angle of 10.03(11)° with the 2,4-dichloro-benzyl ring plane, C1—C6/C11/C12. There are intermolecular N—H···O and N—H···S H-bond interactions. The intermolecular N—H···O H-bond interactions link the molecules to form dimers, whereas N—H···S H-bond interactions link the molecules to form 1D chains along the *b*-axis in the crystal lattice (Fig. 2). There are also π···π interactions between neighboring benzene rings in the crystal lattice.

EXPERIMENTAL

All reagents were used as received unless otherwise stated. Reagent-grade dry acetone, ethanol, ethyl acetate, triethylamine, acetophenone, tetrabutylammonium bromide (TBAB), and 2,4-dichlorobenzoyl chloride were obtained from Merck Chemical Co. Acetone and dichloromethane were dried according to standard procedures and distilled before use. Melting points were recorded on Electrothermal IA9000 series digital melting point apparatus. The proton NMR and ^{13}C spectra were recorded in DMSO-d_6 solvent on Bruker 300 MHz spectrophotometer using tetramethylsilane as an internal reference, respectively. The apparent resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), and m (multiplet). Infrared measurements were recorded in the range 400–4000 cm^{-1} on spectrum 2000 by Perkin Elmer. Elemental analysis was carried out using Perkin Elmer CHNS/O 2400. Obtained results were within 0.4% of the theoretical values. A thin layer chromatography (TLC) analysis were carried out on 5 × 20 cm^2 plate coated with silica gel GF_{254} type 60 (25–250 mesh) using an ethyl acetate-petroleum ether mixture (1:2) as solvent.

General method for the preparation of 2,4-dichloro-*N*-{[(4-substitutedphenyl)amino]carbonothioyl}benzamide (2a–2d). In a 250-mL round-bottom flask, 80 mL of anhydrous acetone and 1.46 g (0.01 mol) of 2,4-dichlorobenzoyl chloride were placed. The mixture was allowed to stir until the solid dissolved. Then, a solution of 3% tetrabutylammonium bromide (TBAB) and 0.76 g (0.01 mol) of ammonium thiocyanate in dry acetone was added dropwise in the round-bottom flask, and the reaction mixture was refluxed for 45 min. After cooling to room temperature, a solution of substituted aromatic primary amine (0.01 mol) in acetone (25 mL) was added and the resulting mixture refluxed for 2.5 h. The reaction mixture was poured into five times its volume of cold water to precipitate the product, which was recrystallized from ethanol as an intense yellow powder.

2,4-Dichloro-N-{[(4-methoxyphenyl)amino]carbonothioyl}benzamide (2a). This compound was obtained as colorless powder, yield: 1.41 g (90%), m.p. 162–163°C; IR (KBr pellet) in cm^{-1}: 1531 (benzene ring), 1403 (C—N stretching), 1143 (C=S); ^{1}H-NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 12.01 (1H, s, broad, NH), 9.32 (1H, s, broad, NH), 7.85 (2H, d, *J* = 8.15), 7.21 (2H, d, *J* = 7.5), 3.46 (3H, s, —OCH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) in δ (ppm): 180.1 (C=S), 165.0 (C), 162.7 (C), 150.4 (C), 145.5 (C), 140.7 (C), 135.3 (C), 127.8 (C), 55.0 (C). Anal. Calcd. for $C_{15}H_{12}Cl_2N_2O_2S$ (355.23): C, 50.72; H, 3.40; N, 7.89; S, 9.03. Found: C, 50.72; H, 3.42; N, 7.88; S, 9.01.

2,4-Dichloro-N-{[(4-methylphenyl)amino]carbonothioyl}benzamide (2b). This compound was obtained as colorless powder, yield: 1.38 g (92%), m.p. 175–176°C; IR (KBr pellet) in cm^{-1}: 1535 (benzene ring), 1403 (C—N stretching), 1141 (C=S); ^{1}H-NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 11.95 (1H, s, broad, NH), 9.41 (1H, s, broad, NH),7.80 (2H, d, *J* = 8.09), 7.24 (2H, d, *J* = 7.2), 2.46 (3H, s, —CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) in δ (ppm): 180.0 (C=S), 166.0 (C), 162.7 (C), 150.4 (C), 145.5 (C), 140.7 (C), 135.3 (C), 127.8 (C), 25.0 (C). Anal. Calcd. for $C_{15}H_{12}Cl_2N_2OS$ (339.23): C, 50.11; H, 3.57; N, 8.26; S, 9.45. Found: C, 50.13; H, 3.59; N, 8.23; S, 9.45.

2,4-Dichloro-N-{[(4-chlorophenyl)amino]carbonothioyl}benzamide (2c). This compound was obtained as colorless block crystals (ethanol:dichloromethane 1:2), yield: 1.55 g (92%), m.p. 165–166°C; IR (KBr pellet) in cm^{-1}: 1534 (benzene ring), 1403 (C—N stretching), 1140 (C=S); ^{1}H-NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 12.03 (1H, s, broad, NH), 9.39 (1H, s, broad, NH), 7.65 (2H, d, *J* = 8.11), 7.24 (2H, d, *J* = 7.5); ^{13}C-NMR (300 MHz, DMSO-d_6) in δ (ppm): 175.1 (C=S), 164.0 (C), 150.4 (C), 140.7 (C), 135.3 (C), 127.8 (C). Anal. Calcd. for $C_{14}H_9Cl_3N_2OS$ (359.65): C, 46.75; H, 2.52; N, 7.79; S, 8.92. Found: C, 46.74; H, 2.53; N, 7.78; S, 8.93.

2,4-Dichloro-N-{[(4-nitrophenyl)amino]carbonothioyl}benzamide (2d). This compound was obtained as light yellow powder, yield: 1.62 g (89%), m.p. 196°C; IR (KBr

pellet) in cm^{-1}: 1536 (benzene ring), 1406 (C—N stretching), 1143 (C=S); ^{1}H-NMR (300 MHz, DMSO-d_6) in δ (ppm) and *J* (Hz): 12.02 (1H, s, broad, NH), 9.32 (1H, s, broad, NH), 8.28 (2H, d, *J* = 8.31), 7.24 (2H, d, *J* = 8.5); ^{13}C-NMR (300 MHz, DMSO-d_6) in δ (ppm): 179.1 (C=S), 165.0 (C), 162.7 (C), 150.4 (C), 145.5 (C), 140.7 (C), 135.3 (C), 127.8 (C). Anal. Calcd. for $C_{14}H_9Cl_2N_3O_3S$ (370.21): C, 45.42; H, 2.45; N, 11.35; S, 8.66. Found: C, 45.44; H, 2.47; N, 11.35; S, 8.65.

General method for the preparation of (*Z*)-3,5-dichloro-*N*-(3-(4-substitutedphenyl)-4-phenylthiazole-2(3*H*)-ylide) benzamide (3a–3d). Triethylamine (0.01 mol) was added to a stirred solution of 1-aroyl-3-arylthiourea (0.01 mol) in dry dichloromethane (30 mL), followed by drop-wise addition of a solution of bromine (0.01 mol) in acetophenone (0.01 mol) under nitrogen. The reaction mixture was stirred for 1–2 h, and progress of the reaction was monitored by thin layer chromatography (hexane:ethyl acetate 4:1). After the reaction was complete, the mixture was filtered; the filtrate was concentrated to afford thiazole derivatives, which were purified by recrystallization from ethanol.

(Z)-3,5-Dichloro-N-(3-(4-methoxyphenyl)-4-phenylthiazole-2 (3H)-ylide)benzamide (3a). Yield: 1.49 g (71%), m.p. 169–170° C; IR (KBr pellet) in cm^{-1}: 1641 (C=O), 1531 (benzene ring), 1452 (C=N stretching), 1275 (C—S), 1155 (C—N); ^{1}H-NMR (300 MHz, DMSO-d_6) in δ (ppm): 8.36–7.15 (m, 12H, Ar—H), 6.85 (s, CH=C), 3.66 (s, 3H, OCH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) in δ (ppm): 171.1, 165.0, 162.7, 139.4, 135.5, 132.7, 130.3, 129.8, 128.4, 128.0, 126.5, 107.2, 56.4. Anal. Calcd. for $C_{23}H_{16}Cl_2N_2O_2S$ (455.35): C, 60.67; H, 3.54; N, 6.15; S, 7.04. Found: C, 60.68; H, 3.57; N, 6.12; S, 7.02.

(Z)-3,5-Dichloro-N-(3-(4-methylphenyl)-4-phenylthiazole-2 (3H)-ylide)benzamide (3b). Yield: 1.61 g (75%), m.p. 158–159° C; IR (KBr pellet) in cm^{-1}: 1643 (C=O), 1585 (benzene ring), 1450 (C=N stretching), 1262 (C—S), 1151 (C—N); ^{1}H-NMR (300 MHz, DMSO-d_6) in δ (ppm): 8.14–7.13 (m, 12H, Ar—H), 6.84 (s, CH=C), 2.51 (s, 3H, CH_3); ^{13}C-NMR (300 MHz, DMSO-d_6) in δ (ppm): 170.1, 168.0, 142.2, 138.5, 137.3, 136.7, 133.1, 131.9, 130.2, 129.4, 128.4, 128.0, 122.2, 107.6, 21.4. Anal. Calcd. for $C_{23}H_{16}Cl_2N_2OS$ (439.35): C, 62.88; H, 3.67; N, 6.38; S, 7.30. Found: C, 62.86; H, 3.42; N, 6.36; S, 7.28.

(Z)-3,5-Dichloro-N-(3-(4-chlorophenyl)-4-phenylthiazole-2 (3H)-ylide)benzamide (3c). Yield: 1.50 g (79%), m.p. 182–183° C; IR (KBr pellet) in cm^{-1}: 1647 (C=O), 1541 (benzene ring), 1452 (C=N stretching), 1255 (C—S), 1150 (C—N); ^{1}H-NMR (300 MHz, DMSO-d_6) in δ (ppm): 8.37–7.65 (m, 12H, Ar—H), 6.77 (s, CH=C); ^{13}C-NMR (300 MHz, DMSO-d_6) in δ (ppm): 173.1, 170.4, 139.4, 137.1, 135.5, 132.7, 131.3, 129.8, 128.8, 128.0, 126.5, 107.6. Anal. Calcd. for $C_{23}H_{13}Cl_3N_2OS$ (459.77): C, 57.47; H, 2.85; N, 6.09; S, 6.97. Found: C, 57.47; H, 2.88; N, 6.11; S, 6.95.

(Z)-3,5-Dichloro-N-(3-(4-nitrophenyl)-4-phenylthiazole-2(3H)-ylide)benzamide (3d). Yield: 69%, m.p. 203–204°C; IR (KBr pellet) in cm^{-1}: 1638 (C=O), 1562 (benzene ring), 1454 (C=N stretching), 1271 (C—S), 1157 (C—N); ^{1}H-NMR (300 MHz, DMSO-d_6) in δ (ppm): 8.21–7.11 (m, 12H, Ar—H), 6.75 (s, CH=C); ^{13}C-NMR (300 MHz, DMSO-d_6) in δ (ppm): 174.1, 169.0, 162.7, 139.4, 135.5, 132.7, 130.3, 129.8, 128.4, 128.0, 126.3, 107.0. Anal. Calcd. for $C_{22}H_{13}Cl_2N_3O_3S$ (470.32): C, 56.18; H, 2.79; N, 8.93; S, 6.82. Found: C, 56.20; H, 2.81; N, 8.90; S, 6.79.

Single crystal X-ray diffraction analysis of 2c. A colorless block crystal having dimensions of 0.07 × 0.26 × 0.49 mm^3 was mounted in glass capillary. All measurements were made on a Bruker SMART 1000 CCD detector with graphite monochromated Mo-Kα radiation. Indexing was performed from 60 images that were exposed for 10 s for a preliminary unit cell determination. Of which, 33 out of total of 56 reflections were successfully indexed. The crystal-to-detector distance was 50.00 mm. Cell constants and an orientation matrix for data collection corresponded to a primitive triclinic cell with dimensions: a = 6.0436(4) Å, α = 93.208(1)°, b = 9.5906(7) Å, β = 98.912(1)°, V = 788.29(10) $Å^3$, c = 14.0673(10) Å, γ = 100.772(1)°. For Z = 2 and F.W. = 359.64, the calculated density is 1.515 g/cm^3. The data were collected at a temperature of 33(1)°C to a maximum 2θ value of 50.05°. A total of 1421 oscillation images were collected in four runs. A sweep of data was done using ω scans from 330.0° to 148.2° in −0.3° step, at χ = 54.7° and φ = 0.0°. The exposure rate was 50.0 (s/°). The detector swing angle was −30.00°. A second sweep was performed using ω scans from 330.0° to 201.5° in −0.3° step, at χ = 54.7° and φ = 90.0°. The detector swing angle was −30.00°. Another sweep was performed using ω scans from 330.0° to 261° in −0.3° step, at χ = 54.7° and φ = 180.0°. A final sweep was performed using ω scans from 330.0° to 285° in −0.3° step, at χ = 54.7° and φ = 270.0°. CCDC 795456 contains the supplementary crystallographic data for this article. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CBZ IEZ, UK. Facsimile (44)-01223-336-033, E-mail: deposit@ccdc.cam.ac.uk (or) http://www.ccdc.cam.ac.uk/deposit.

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