Asian Journal of Chemistry; Vol. 26, No. 24 (2014), 8483-8487

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.18067

New and Efficient Synthesis of *N*-(4-Substituted phenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amines

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Received: 22 May 2014; *Accepted*: 25 August 2014; *Published online*: 1 December 2014; AJC-16387

The reaction of 2-isonicotinoyl-*N*-arylhydrazinecarbothioamide (**2a-c**) with chloroacetic acid in presence of anhydrous sodium acetate in absolute ethanol yields, in each case, a single product. The single crystal X-ray analysis confirmed the structure of these products as *N*-(4-aryl)-5-(pyridine-4-yl)-1,3,4-oxadiazol-2-amines (**4a-c**).

Keywords: Isoniazid, 1,3,4-oxadiazole, X-ray diffraction, Crystal structure and packing.

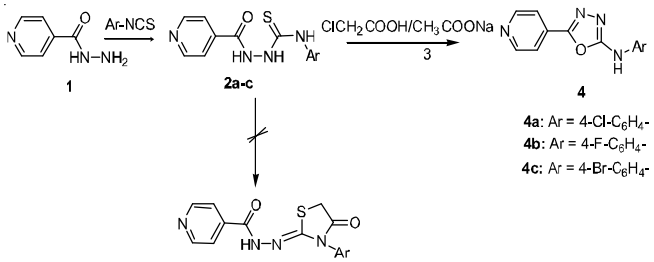
INTRODUCTION

1,3,4-Oxadiazole heterocycles are useful for the development of molecules of pharmaceutical interest. Substituted 1,3,4-oxadiazoles, have been the subject of extensive research due to its pharmacological activities. Literature survey revealed that minor modifications in the structure of 1,3,4-oxadiazole can lead to quantitative as well as qualitative changes in the biological activities. One of the most effective first-line anti-TB drugs is isoniazid (INH). Many analogues featuring the structure of isoniazid have been synthesized and tested as anti-mycobacterials. In a critical review published recently, the existence of more than 3000 compounds based on the isoniazid core was reported by Janin[1]. It has been reported by Wilder-Smith[2] and Mamolo *et al.*[3] that conversion of isoniazid to the corresponding 5-substituted-3*H*-1,3,4-oxadiazol-2-thione and 3*H*-1,3,4-oxadiazol-2-one and their 3-alkyl or aryl/alkyl derivatives, was characterized by their high activity against *M. tuberculosis* strain H37Rv. 1,3,4-Oxadiazoles conform to an important class of heterocyclic compounds with a wide range of biological activities such as antiviral[4], tyrosinase inhibitors[5], antimicrobial[6,7], cathepsin K inhibitors[8], fungicidal[9] and antineoplastic properties[10]. In continuation of our interest in the chemistry of 1,3,4-oxadiazoles[11], we aimed to study the reaction of isoniazid thiosemicarbazides (**2a-c**) with chloroacetic acid/anhydrous sodium acetate (**3**). This reaction did not afford possible 1,3,5-thiadiazolidinone where choroacetic acid acts as cyclodesulfurization agent for (**2a-c**) to produce corresponding 1,3,4-oxadiazoles (**4a-c**) **Scheme-I**. The most straightforward synthetic route involves the cyclodehydration of semicarbazides, which typically requires harsh reagents such as $POCl_3$[12] or concentrated sulfuric acid[13]. Alternatively, phosphonium salts and Burgess-type reagents[14] have been used to promote the cyclization. However, these reagents cause the formation of significant by-products and are only suitable for solid phase synthetic strategies. The reported cyclization protocols for thiosemicarbazides (**2a-c**) into 1,3,4-oxadiazoles (**4a-c**) were investigated using several desulfurization reagents including mercuric salts, lead oxide, I_2/NaOH, TsCl, DCC, EDC, polymer supported DCC, PS-carbodiimides, TBTU and hypervalent iodine(V)[15,16]. Most of these cyclization methods have several disadvantages such as handling of harsh and toxic reagents, elevated temperatures, long reaction time, *etc*. From literature survey, there is no report of using chloroacetic acid/anhydrous sodium acetate as cyclodesulfurization agent for the synthesis of 1,3,4-oxadiazoles.

Thus newer and mild protocols for this privileged class of molecules are continuously sought. We have now focused on a simple and efficient protocol for the synthesis of *N*-(4-aryl)-5-(pyridine-4-yl)-1,3,4-oxadiazol-2-amines.

EXPERIMENTAL

All the solvents were obtained from Merck. The homogeneity of the compounds was checked by TLC performed on Silica gel G coated plates (Merck). Iodine chamber was used for visualization of TLC spots. The FT-IR spectra were recorded in KBr pellets on a (Spectrum BX) Perkin Elmer FT-IR spectrophotometer. Melting points were determined on a Gallenkamp melting point apparatus and thermometer was uncorrected. NMR Spectra were scanned in DMSO-d_6 on a Bruker NMR spectrophotometer operating at 500 MHz for ^{1}H



Scheme-I: Synthesis of compounds **4a-c**

and 125.76 MHz for ^{13}C at the Research Center, College of Pharmacy, King Saud University, Saudi Arabia. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard and D_2O was added to confirm the exchangeable protons. Mass spectra were measured on Jeol-JMS-700 HR MS. Crystals suitable for X-ray diffraction were mounted on glass fibers and their crystal data were collected using either Bruker SMART Apex II diffractometer. The data for these compounds were processed with SAINT and corrected for absorption using SADABS (Bruker[17]). The structures of the compounds were solved by direct method using the program SHELXTL (Sheldrick[18]) and were refined by full-matrix least squares technique on F^2 using anisotropic displacement parameters. The non-hydrogen atoms were refined anisotropically. In these compounds, all the H atoms were calculated geometrically with isotropic displacement parameters set to 1.2 (1.5 for methyl groups) times the equivalent isotropic U values of the parent carbon atoms. For methyl groups, a rotating group model was applied. The crystallographic data for the reported compounds are given in Table-1. H-bonding interactions are listed in Table-2.

General procedure for the synthesis of *N*-(4-aryl)-2-(pyridin-4-ylcarbonyl) hydrazinecarbothioamide (2a-c): Equimolar mixture of isonicotinic hydrazide (0.01 mol) and 4-aryl isothiocyanate in absolute ethanol (25 mL) was heated until a clear solution was obtained. The solution was refluxed for 3 h on water bath. The precipitated solid was filtered off and recrystallized from ethanol.

General procedure for the synthesis of *N*-(4-aryl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (4a-c): To a suspension of appropriate thiosemicarbazide **2a-c** (0.01 mol) in absolute ethanol (25 mL), chloroacetic acid (0.01 mol) and anhydrous sodium acetate (0.012 mol) was added. The mixture was refluxed on a water bath for 3 h, then left to cool. The separated solid was filtered off, washed with water and recrystallized from EtOH/DMF to give compounds **4a-c**, respectively.

***N*-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (4a):** Yield: 76 %; m.p.: 310-312 °C (EtOH/DMF) (Lit[19]. m.p.: 238-240 °C; IR (KBr, ν_{max}, cm^{-1}): 3250 (NH str.); ^1H NMR (500 MHz, DMSO-d_6) δ: 7.4 (2H, d, *J* = 8.5 Hz, Ar-H), 7.6 (2H, d, *J* = 8.5 Hz, Ar-H), 7.8 (2H, d, *J* = 4.2 Hz, pyridyl-H), 8.8 (2H, d, *J* = 4.2 Hz, pyridyl-H), 11.06 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 118.8, 119.2, 125.8, 129.0, 130.0, 137.3, 150.8, 156.3, 160.0; ESI *m/z* =273 $[M]^+$, 275 $[M + 1]^+$; HR MS: 271.9768[20].

***N*-(4-Flourophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (4b):** Yield: 67 %; m.p.: 250-252 °C (EtOH/DMF); IR (KBr, ν_{max}, cm^{-1}): 3279 (NH); ^1H NMR (500 MHz, DMSO-d_6) δ: 7.1 (2H, d, *J* = 8.5 Hz, Ar-H), 7.6 (2H, d, *J* = 8.5 Hz, Ar-H), 7.7 (2H, d, *J* = 4.2 Hz, pyridyl-H), 8.7 (2H, d, *J* = 4.2 Hz, pyridyl-H), 11.06 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 115.5, 118.9, 119.8, 130.7, 134.7, 150.6, 156.1, 156.5, 158.4, 160.4; ESI *m/z* = 257.1 $[M + 1]^+$; HR MS: 255.9877.

TABLE-1
CRYSTAL DATA AND PARAMETERS FOR STRUCTURE REFINEMENT OF **4a**, **4b** AND **4c**

Compound	**4a**	**4b**	**4c**
Molecular formula	$C_{13}H_9N_4OCl$	$C_{13}H_9N_4OF$	$C_{13}H_9N_4OBr$
Molecular weight	272.69	256.24	317.14
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P*21/*c*	*P*21/*c*	$P2_1/c$
a/Å	7.0865 (2)	6.8862 (2)	7.1990 (2)
b/Å	14.2650 (3)	14.2190	14.2364 (5)
c/Å	13.3863 (4)	13.3656 (3)	13.5100 (5)
α/°	90	90	90
β/°	115.973 (2)	116.577 (2)	115.886 (3)
γ/°	90	90	90
V/Å^3	1216.53 (6)	1170.41 (5)	1245.69 (8)
Z	4	4	4
Dcalc (g cm^{-3})	1.489	1.454	1.691
Crystal dimensions (mm)	0.90 × 0.62 × 0.34	0.12 × 0.14 × 0.66	0.17 × 0.12 × 0.10
μ/mm^{-1}	2.77	0.91	4.49
Radiation γ (Å)	1.54178	1.54178	1.54178
Reflections measured	8459	8049	8578
Ranges/indices (h, k, l)	-8, 6; -17, 13; -16, 16	-7, 7; -17, 16; -16, 15	-8, 8; -17, 15; -15, 16
θ limit (°)	4.8-70.0	6.2-69.8	4.8-69.8
Unique reflections	2227	2145	2331
Observed reflections (I > 2σ(I))	1965	1833	1651
Parameters	173	173	172
Goodness of fit on F2	1.06	1.06	1.05
R1, wR2 (I ≥ 2σ(I))	0.033, 0.096	0.038, 0.114	0.043, 0.120

TABLE-2
HYDROGEN BOND GEOMETRIES FOR COMPOUNDS **4a**, **4b** AND **4c**

D-H···A	d(D-H) (Å)	d(H···A) (Å)	d(D···A) (Å)	Angle (D-H···A) (°)
		(4a)		
N4-H1N···N1^{i}	0.86	2.05	2.9056 (19)	174.00
C12-H12A···N2^{ii}	0.93	2.53	3.376 (2)	151.00
C13-H13A···N3	0.95	2.29	2.925 (2)	125.00
		(4b)		
N4-H4N···N1^{iii}	0.88	2.05	2.9235 (19)	174.00
C12-H12A···N2^{iv}	0.93	2.51	3.316 (2)	145.00
C13-H13A···N3	0.93	2.28	2.918 (2)	125.00
		(4c)		
N1A-H1···N5A^{v}	0.86	2.09	2.915 (4)	162.00
C2A-H3···N3A^{ii}	0.93	2.53	3.392 (5)	155.00
C1A-H2···N2A	0.93	2.31	2.938 (5)	125.00
C11A-H11A···Br1A	0.93	3.04	3.819(14)	142.90

(i) -x + 3, y + 1/2, -z + 1/2; (ii) -x + 1, -y-1, -z; (iii) -x + 2, y + 1/2, -z-1/2; (iv) -x, -y-1, -z-1; (v) –x-1, y + 1/2, -z-1/2

***N*-(4-Bromophenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine (4c):** Yield: 70 %; m.p.: 290-292 °C; IR (KBr, ν_{max}, cm^{-1}): 3190 (NH); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.5 (2H, d, *J* = 8.5 Hz, Ar-H), 7.6 (2H, d, *J* = 8.5 Hz, Ar-H), 7.8 (2H, d, *J* = 4.2 Hz, pyridyl-H), 8.8 (2H, d, *J* = 4.2 Hz, pyridyl-H), 11.06 (s, D_2O exch., 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6) δ:168.4, 163.3, 160.2, 156.3, 152.7, 150.6, 146.6, 138.0, 132.0, 125.0, 129.9, 121.4, 119.4, 113.7, 56.0; HR MS: 315.9593 [M^+], 317.9696 [M^+].

RESULTS AND DISCUSSION

The reaction of isonicotinichydrazide (**1**) with aryl isothiocyanates in absolute ethanol afforded thiosemicarbazides **2a-c** which was then treated with chloroacetic acid in presence of anhydrous sodium acetate **3** in absolute ethanol to yield, in each case, a single product as examined by TLC. However, the intermolecular cyclization of thiosemicarbazides similar to **2a-c** *via* losing of H_2S molecule to give 1,3,4-oxadiazoles were reported with different procedures[21]. The structures of compounds *N*-4-aryl-5-(pyridine-4-yl)-1,3,4-oxadiazol-2-amines **4a-c** were confirmed by single crystal X-ray analysis. **Scheme-I** illustrates the synthetic pathways used for the preparation of target compounds. Starting materials thiosemicarbazides (**2a-c**) were used to produce the final compounds *N*-(4-aryl)-5-(pyridine-4-yl)-1,3,4-oxadiazol-2-amines (**4a-c**). In IR spectra of all compounds NH stretching were observed at about 3219-3190 cm^{-1}. In the ^{1}H NMR spectra of the compounds **4a-c** that are taken in DMSO-d_6, D_2O exchangeable NH proton was seen as broad singlet at 11 ppm. The aromatic protons appear as multiplet at 7.1-8.8 ppm. High resolution mass (HR MS) of the compounds **4a**, **4b** and **4c** showed 273.9650, 256.9855 and 315.9593 mass, respectively in agreement with their molecular formula.

Crystal structure of compound 4a: The molecular structure of **4a** is depicted in (Fig. 1 4a). The oxadiazole ring (N2/N3/C6-C7/O1) is planar with a maximum deviation of -0.0033(12) Å for O1, forming the dihedral angle of 5.61(8)° and 3.42(8)° with the pyridine ring system (N1/C1-C5) and to that of the chloro-substituted phenyl ring (C8-C13), respectively. In the crystal packing of **4a**, occurrence of N-H···N, C-H···N intermolecular and an intramolecular C-H···N hydrogen bonds (Table-2. 4a) are observed. These H-bond patterns are of significance, in which rings are the most prominent features. The N4 of the secondary amine group of one molecule is linked to N1 of the pyridine ring of the other molecule *via* N4-H1N···N1 (symmetry code: -x + 3, y + 1/2, -z + 1/2) hydrogen bond. These head-to-tail arrangements of hydrogen bonds link the molecules into a supramolecular chain along the crystallographic axis b. Furthermore these chains are interconnected into a two dimensional structure *via* a pair of C12-H12A···N2 (symmetry code: -x + 1, -y-1, -z) intermolecular H-bonds generating $R_2^2(16)$ ring motif. The crystal packing is, as expected, dominated by these hydrogen bonds. In the molecule, an intramolecular C13-H13A···N3 hydrogen bond forms a six-membered ring, producing an S(6) ring motif. The observed C(11)-Cl(1) bond length is 1.7487 (17) Å. Bond lengths and bond angles are within the normal ranges.

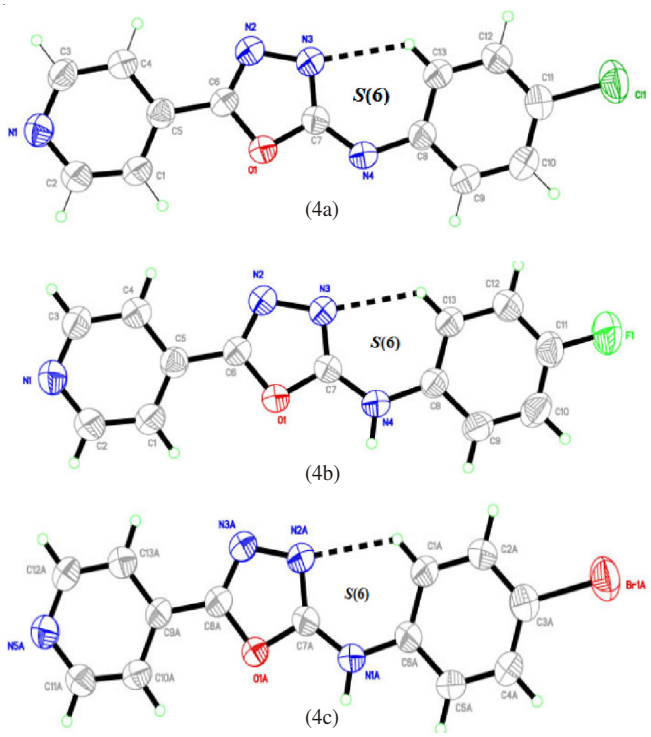
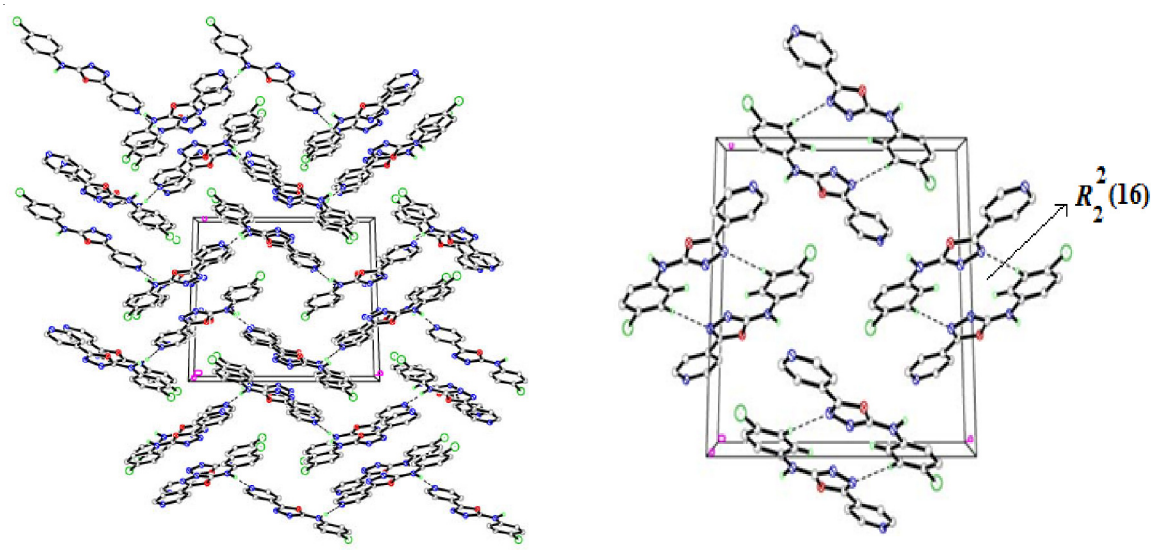


Fig. 1. ORTEP diagram of (**4a-c**), 50 % probability ellipsoid



(4a) (4a)

Fig. 2. Crystal packing of compound **4a**

Crystal structure of compound 4b: (Fig. 1. 4b) shows the molecular structure of **4b**. The oxadiazole ring (N2/N3/C6-C7/O1), with the maximum deviation of 0.0023(16) Å for C6, is planar. It forms the dihedral angle of 7.27(8) and 3.71(8) with the pyridine ring system (C1/C2/N1/C3/C4/C5) and to the fluoro-substituted phenyl ring (C8-C13) respectively. Bond lengths and bond angles are within the normal ranges. The crystal packing of **4b** is shown in (Fig. 3). The intermolecular N-H···N hydrogen bonds link the molecules into zig-zag chains along the *b* axis (Table-2. 4b). These chains are further interconnected *via* pair of C-H···N intermolecular H-bonds generating $R_2^2(16)$ ring motif. In the molecule, an intramolecular C13-H13A···N3 hydrogen bond forms a six-membered ring, producing the ring motif with graph-set notation of S(6). The observed C(11)-F(1) bond length is 1.366(2) Å.

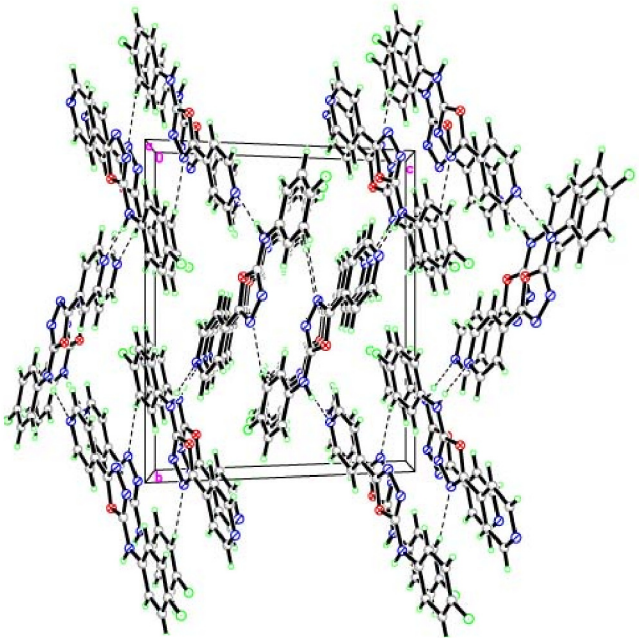


Fig. 3. Crystal packing of compound **4b**

Crystal structure of compound 4c: The molecular structure of **4c** is depicted in (Fig. 4). The oxadiazole ring (C7A/O1A/C8AN3A/N2A), with the r.m.s deviation of -0.0033(12) Å for O1, is planar. It forms the dihedral angle of 5.61(8)° and 3.42(8)° with the pyridine ring system (C9A/C10A/C11A/N5A/C12A/C13A) and to the bromo-substituted phenyl ring (C1A-C6A) respectively, which is identical to that of compound **4a**. Bond lengths and bond angles are within the normal ranges. In the crystal packing of **4c**, occurrence of N-H···N, C-H···N intermolecular hydrogen bonds and C-H···N intramolecular hydrogen bonds are observed (Table-2. 4c). The N1A of the secondary amine group of one molecule is linked to N5A of the pyridine ring of the other molecule *via* N1A-H1···N5A hydrogen bond. These hydrogen bonds link the molecules into a zig-zag chain running parallel to the crystallographic axis b. Further the molecules are held together *via* pair of C-H···N intermolecular H-bonds generating $R_2^2(16)$ ring motif (Fig. 1. 4a). In the molecule (Fig. 1. 4c), an intramolecular C1A-H2···N2A hydrogen bond forms a six-membered ring, producing an S(6) ring motif. Unlike the crystal packing of **4a** and **4b**, for **4c** in addition to the above, intermolecular C11A-H11A···Br1A and N1A-H1···N5A interactions is observed (Fig. 1. 4b) generating an additional $R_2^2(20)$ ring motif.

Conclusion

The reaction of thiosemicarbazides **2a-c** with cholroacetic acid/anhydrous sodium acetate yields, in each case, a single product. The FT IR, ^{1}H NMR, ^{13}C NMR, HR MS and single crystal X-ray crystallography analysis confirmed the structure of these products as N-(4-aryl)-5-(pyridine-4-yl)-1,3,4-oxadiazol-2-amines, **4a-c**. In the crystal structure studies of these reported compounds **4a-c**, H-bond patterns are of significance, in which rings are the most prominent features. The ring motifs with the graph-set notation of S(6), $R_2^2(16)$ in **4a-c** and $R_2^2(20)$ in **4c** have been observed and discussed.

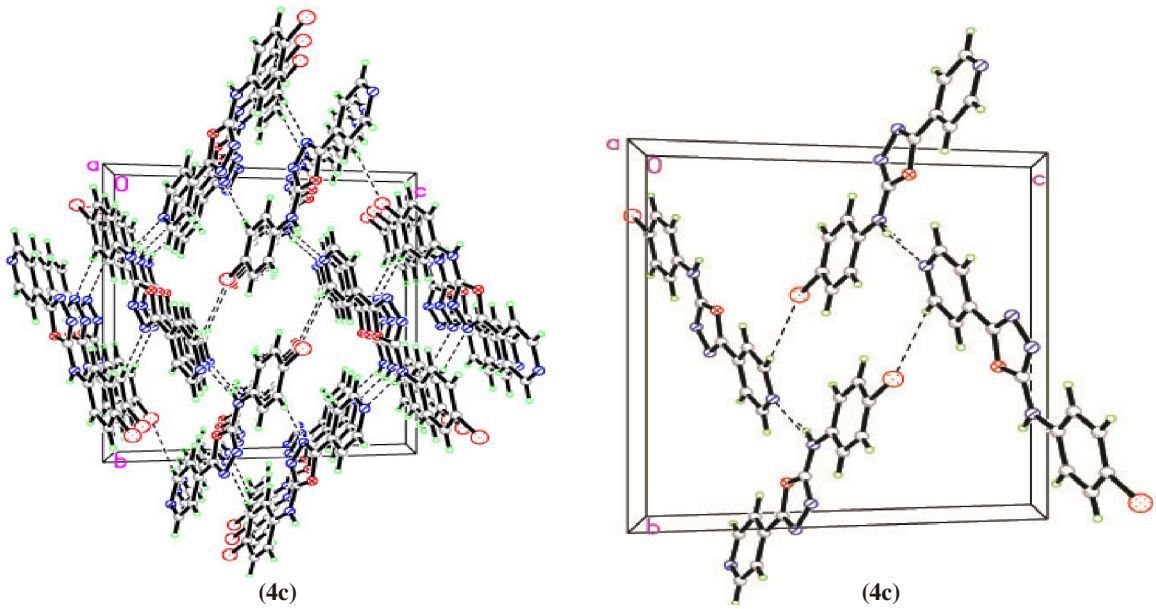


Fig. 4. Crystal packing of compound **4c**

Supplementary details

Cambridge Crystallographic Data Center (CCDC) numbers 922285, 922286 and 924114 contains crystallographic data for the structures **4a**, **4b** and **4c**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk/ http://www.ccdc.cam.ac.uk).

ACKNOWLEDGEMENTS

The authors are thankful to Deanship of Scientific Research and Research Center, College of Pharmacy, King Saud University.

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