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Syntheses and Antioxidant Activity of 1-Isonicotinoyl-4-phenylthiosemicarbazide and Crystal Structures of *N*-Phenyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine Hydrochloride and 4-Phenyl-3-(pyridin-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione derived from 1-Isonicotinoyl-4-phenylthiosemicarbazide

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Abstract

The title compound $C_{13}H_{12}N_4OS$ (**I**) is synthetized from isonicotinic hydrazide and isothiocynate. Compounds $C_{13}H_{11}N_4OCl$ (**II**) and $C_{13}H_{10}N_4S$ (**III**) where obtained upon reaction of (**I**) with Fe(II) or Mn(II) salts. Compound (**II**) is heterocyclic 1,3,4-oxadiazole while compound (**III**) is heterocyclic 1,2,4-triazole. The 1,3,4-oxadiazol derivative is almost planar with dihedral angle of 2.66 (8) and 5.14 (8)° between 1,3,4-oxadiazole ring and phenyl and pyridinium rings respectively; the dihedral angle between the phenyl and pyridinium rings is 3.92 (8)°. The 1,2,4-triazole derivative is non-planar. The phenyl and pyridyl rings form dihedral angles of 58.35 (5) and 58.33 (5)°, respectively, with the 1,2,4-triazole ring; the dihedral angle between the phenyl and pyridyl rings is 36.85 (4)°. In the compound (**II**) intramolecular hydrogen bonds of type N—H···Cl, C—H···N and C—H···Cl resulting in *S*(6) ring stabilize the structure. Intermolecular hydrogen bonds of type N—H···N, C—H···N, C—4···Cl link the molecule thus forming a three-dimensional network. In the structure of compound (**III**), intermolecular hydrogen bonds of type N—H···N, C—H···N, C—H···S1,link the monomer in a three-dimensional network.

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1. Introduction

Compounds containing heterocyclic rings has attracted a wide attention for the development of news drugs [1–4]. The oxadiazole and triazole derivatives take a large place in this category of drugs [5–8]. The 1,3,4-oxadiazoles derivatives are the basis of an important class of heterocyclic compounds with antimicrobial, antifungal, anti-inflammatory, anti-cancer and antihypertensive activities [9–13]. Several methods for the synthesis of 1,3,4-oxadiazoles have been reported in the literature. In nature the synthesis is systematically in several steps whereas the chemical synthesis can be done in a small number of steps [14–17]. Oxadiazole derivatives have great interest in industrial compounds and are used as organic electronics [18], as corrosion inhibitors [19], in energetic material [20] and in fluorescent nanofibrous material [21].

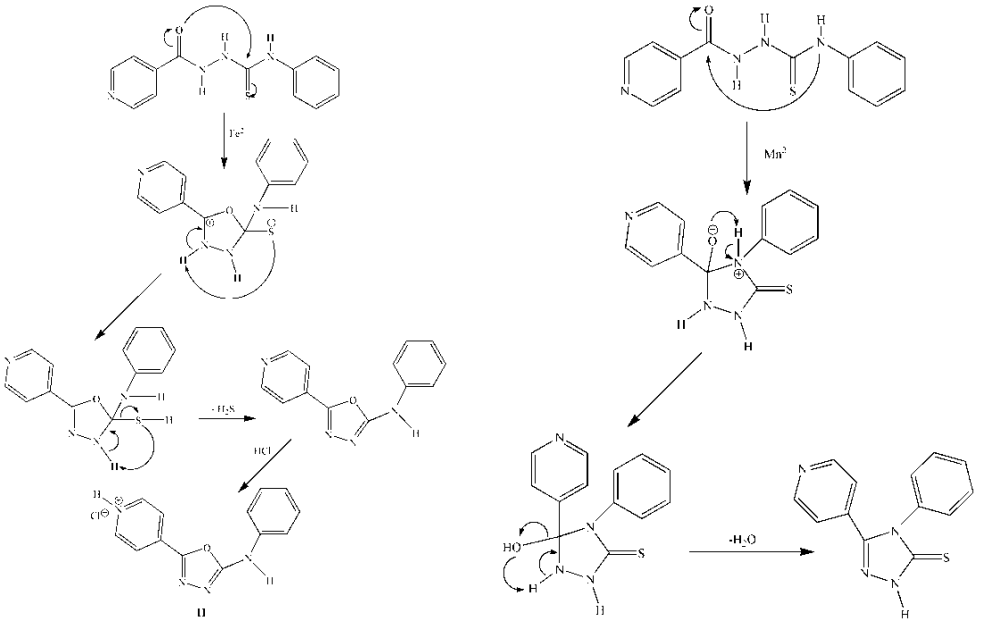
Several methods for the synthesis of 1,2,4-triazoles are developed in the literature. Microwave synthesis is widely used [22–24]. Cycloaddition of azinium-N-imine and nitrile [25], transition metal-catalyzed reaction [26, 27], starting from hydrazides [28], as well as Bronsted acid-catalyzed reaction [29] are good routes to yield 1,2,4-triazole derivatives. The 1,2,4-triazoles derivatives have been found to possess wide spectrum of biological activities [30–33]. Numerous triazole-based drugs has been developed as antibacterial [34], antifungal [35], anti-malarial [36], anticancer [37], antidiabetic [38].

In the present study, we have firstly synthesized a 1-isonicotinoyl-4-phenylthiosemicarbazide which was used to synthetize *N*-phenyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine in presence of iron chloride and 4-phenyl-3-(pyridin-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione in presence of manganese (Scheme 1) that were characterized by spectroscopic studies an X-ray diffraction study (XRD).

2. Experimental Section

2.1. Starting materials and instrumentation

Isonicotinic hydrazide, phenyl isothiocynate, iron chloride tetrahydrate and manganese acetate tetrahydrate were purchased from Sigma-Aldrich and used as received without further purification. All solvents used were of reagent grade. Elemental analyses of C, H and N were recorded on a VxRio EL Instrument. Infrared spectra were obtained on a FTIR Spectrum Two of Perkin Elmer spectrometer in the 4000-400 cm^{-1} region.



Scheme 1. Proposed mecanism for the synthesis of **II** and **III** from **I**.

2.2. Synthesis of 1-isonicotinoyl-4-phenylthiosemicarbazide (I)

For the synthesis of 1-isonicotinoyl-4-phenylthiosemicarbazide, (I), a mixture of isonicotinic hydrazide (0.01 mol) and phenyl isothiocynate (0.01 mol) in absolute ethanol was refluxed for 12 h. The solid material obtained on cooling was filtered, washed with diethyl ether, air-dried.

Yield: 80 %. Elemental Anal. $C_{13}H_{12}N_4OS$, Found (Calcd.) (%): C, 57.34 (57.31); H, 4.44 (4.42); N, 20.57 (20.55); S, 11.77 (11.73). IR (ν, cm^{-1}): 3210, 3113 (N-H), 1682 (C=O), 1254 (C=S). ^{1}H NMR (DMSO-d_6, δ(ppm)):10.82 (S, 1H, NH), 9.86 (S, 1H, NH), 9.79 (S, 1H, NH), 8.78-7.32 (m, 9H, Ar-H).

2.3. Synthesis of N-phenyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine hydrochloride (II)

For the synthesis of (II), a stirred mixture of (I) (272.3 mg, 1 mmol) and $FeCl_2{\cdot}4H_2O$ (198.8 mg, 1 mmol)in ethanol was refluxed for 2 h. After cooling, the solution was filtered off and the precipitate was then crystallized from a methanol. Yield 55%. Elemental Anal. $C_{13}H_{11}N_4OCl$, Found (Calcd.) (%): C, 56.84 (56.82); H, 4.04 (4.02); N,

20.40 (20.38); Cl, 12.91 (12.88). IR (n, cm^{-1}): 1615, 1569, 1558, 1497, 1488, 832, 791, 755, 688, 677, 512.

2.4. Synthesis of 4-phenyl-3-(pyridin-4-yl)-1H-1,2,4-triazole-5(4H)-thione(III)

For the synthesis of (III), a stirred mixture of (I) (272.3 mg, 1 mmol) and $Mn(OAc)_2 \cdot 4H_2O$ (245.09 mg, 1 mmol) in ethanol was refluxed for 2 h. After cooling, the solution was filtered off and the precipitate was then crystallized from a methanol. Yield 51%. Elemental Anal. $C_{13}H_{10}N_4S$, Found (Calcd.) (%): C, 61.40 (61.37); H, 3.96 (3.93); N, 22.03 (22.00); S, 12.61 (12.58). IR (ν, cm^{-1}): 1615, 1585, 1564, 1537,1480, 1451, 1415,1240, 1215, 1183, 1092, 1051, 898, 857, 746, 722, 684, 563, 524, 499.

2.5. X-ray crystallography

Crystals suitable for X-diffraction, of the reported compound, were grown by slow evaporation of MeOH solution of the complex. Details of the X-rays crystal structure solution and refinement are given in Table 1. Diffraction data were collected using a SuperNova Rigaku Oxford Diffraction diffractometer single diffractometer with graphite monochromatized Cu$K\alpha$ radiation (λ = 1.54184 Å). All data were corrected for Lorentz and polarization effects. No absorption correction was applied. Complex scattering factors were taken from the program package *SHELXTL* [39]. The structures were solved by direct methods which revealed the position of all non-hydrogen atoms. All the structures were refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement parameters for all non-hydrogen atoms [40]. The hydrogen atoms were geometrically optimized and refined as riding model by AFIX instructions. Molecular graphics were generated using *ORTEP-3* [41].

2.6. DPPH free radical scavenging

Antioxidant capacities of compound (I) was measured according to Akhtar et al. [42] with modifications. 3.8 mL of the methanol solution of DPPH• (40 mg/L) was added to test compound (200 µL) at different concentrations. The mixture was shaken vigorously and incubated in dark for 30 min at room temperature. After the incubation time, the absorbance of the solution was measured at 517 nm by using UV-visspectrophotometer Perkin two. The DPPH• radical scavenger effect was calculated using the Equation (1):

$$Scavenging\ activity\ (\%\ control) = \frac{Absorbance_{control} - Absorbance_{sample}}{Absorbance_{control}}\ x\ 100$$

where $A_{control}$ is the absorbance of the control reaction and A_{sample} is the absorbance of the test compound. The tests were carried out in triplicate. Trolox was used as positive control.

Table 1. Crystal data and structure refinement details for **II** and **III**.

Chemical formula	$C_{13}H_{11}N_4OCl$	$C_{13}H_{10}N_4S$
*M*r	274.71	254.31
Crystal system	Monoclinic	Orthorhombic
Space group	*I*2/*a*	*Pbcn*
Temperature (K)	293	293
a (Å)	14.9090 (2)	11.2967 (2)
b (Å)	11.6000 (1)	12.7600 (1)
c (Å)	15.1001 (3)	17.5797 (2)
β (°)	112.143 (2)	
V (Å^3)	2418.87 (7)	2534.04 (6)
Z	5	4
Radiation type	Cu Kα	Cu *K*α
μ (mm^{-1})	1.75	2.20
Crystal size (mm)	0.05 × 0.08 × 0.09	0.06 × 0.07 × 0.09
T_{min}, T_{max}	0.775, 1.000	0.753, 1.000
No. of measured reflections	15578	15362
No. of independent reflections	2532	2643
No. of observed [I > 2σ(I)] reflections	2351	2407
R_{int}	0.030	0.026
$R[F^2 > 2\sigma(F^2)]$	0.047	0.038
$wR(F^2)$	0.127	0.115
S	1.06	1.08
No. of reflections	2532	2643

No. of parameters/restraints	172/0	163/0
$\Delta\rho max, \Delta\rho_{min}$ (e Å^{-3})	0.28, −0.41	0.26, −0.20

3. Results and Discussion

In the present study, the compound 1-isonicotinoyl-4-phenylthiosemicarbazide **(I)** was synthesized by the reaction of phenyl isothiocyanate and nicotinic hydrazide. Compounds **II** and **III** were obtained during our attempt to synthesize complexes using Fe(II) or Mn(II) salts, respectively. The reaction sequences depicted in the scheme**1** were followed to obtain **II** and **III** respectively.

3.1. Spectroscopic study

The NMR spectra of compound **I** are recorded in dmso-d_6 (Figure 1). The ^{1}H NMR spectrum shows characteristic signals at 10.85 ppm, 9.86 ppm and 9.79 ppm. attributed to the three N—H moieties present in the molecule. The signals due to the aromatic protons are in the rang 7.32-8.78 ppm. The ^{13}C NMR spectrum exhibits two signals at 181.71 ppm and 164.95 ppm characteristic of C=S and C=O, respectively. Additional signals attributed to the aromatic carbon atoms are pointed in the range 151-140 ppm. The infrared spectrum of compound **I** exhibited characteristic bands. The bands of medium intensities appearing at 3210 cm^{-1} and 3113 cm^{-1} are attributed to N—H stretching vibration. The bands pointed at 1682 cm^{-1} is attributed to the C=O linked to the pyridyl ring, while the band at 1667 cm^{-1} is due to the C=O engaged in hydrogen bonding with H—N in β position. The band due to the N—N and C=S moieties are respectively pointed at 1444 cm^{-1} and 1215 cm^{-1}[43]. Additional band pointed in the regions 1600-1400 cm^{-1} are attributed to the phenyl and the pyridyl ring. Bands at 753 cm^{-1} and 688 cm^{-1}are indicative of the presence of monosubstituted aromatic rings.

Upon reaction of **I** with Fe(II) and Mn(II), organic compounds **II** and **III** are respectively isolated. It seems that the metal cation act as catalyst. The infrared spectra of **II** and **III** are strongly different from the spectrum of **I**. Both spectra of **II** and **III** present bands due to aromatic rings. The infrared spectrum of compound **II** shows also bands at 1159 cm^{-1} and 1444 cm^{-1} attributed to the oxadiazole C—O—C and the N—N moieties, respectively [44]. Compound **III** presents three bands at 1537, 1480 and 1451 cm^{-1} which are indicative of a triazole ring [45].The band due to the thione group (C=S) present in compound **III** is pointed at 1215 cm^{-1}.

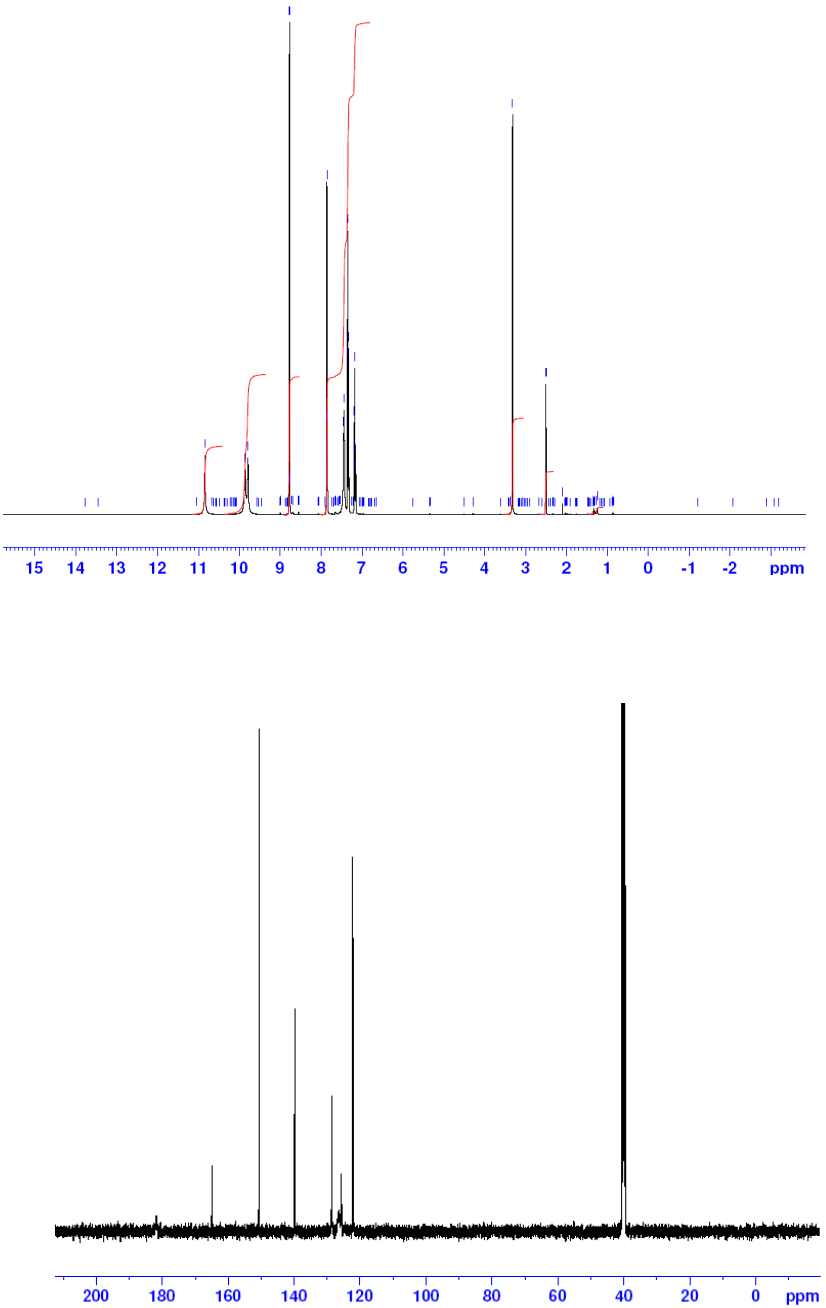


Figure 1. ^{1}H and ^{13}C NMR spectra of compound **I**.

3.2. Antioxidant activity of compound 1

The method of scavenging the DPPH• radical is largely used to evaluate the antioxidant activity of organic or inorganic compounds [46, 47]. The antioxidant activity of the compound **I** has been substantially investigated. Figure 2 shows the plots of DPPH• free radical scavenging activity (%) for Trolox and compound **I**. The DPPH• is a stable free radical and becomes a stable molecule when it accepts an electron or hydrogen radical. The antioxidant molecules scavenge the DPPH• radical by hydrogen donating ability. It is observed that the scavenging activity increases with increasing the concentration in the range tested (100-500 µmol/L). Compound **I** have scavenging activity between 17.53±0.26 and 74.46±0.06 % within the investigated concentration range due to the NH groups which can react with DPPH• radical by the typical H-abstraction reaction to form a stable radical. Comparatively to the scavenging activity of Trolox (9.86±0.67 - 49.66±0.28 %), the values observed for compound **I** are higher than those of Trolox for all the studied concentrations. When increasing the concentration (100 to 500 µM), the scavenging activity of compound **I** increases more rapidly than that of Trolox.

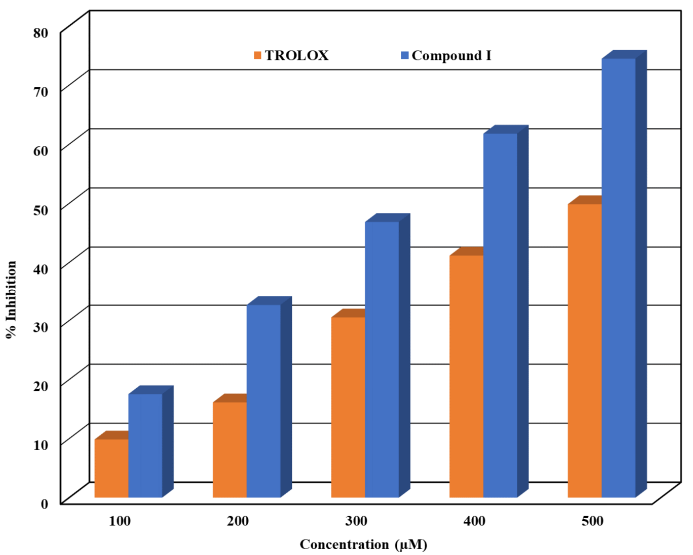


Figure 2. Antioxidant activity of (**I**).

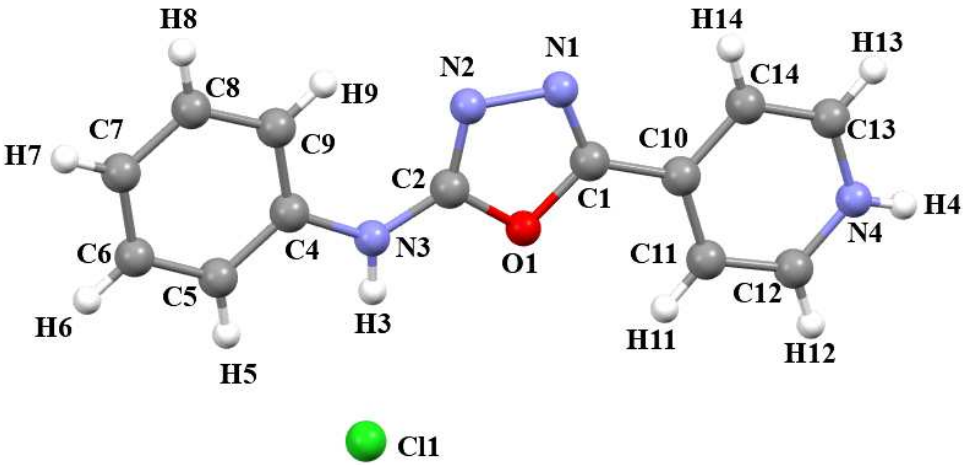
3.3. X-ray structures determination

Crystals suitable for X-ray determination were grown from slow evaporation of methanol solution of **II** and **III**.

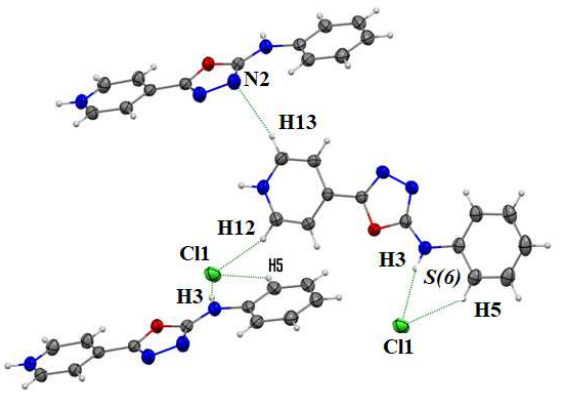
3.3.1. Structure of N-phenyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-amine hydrochloride (II)

Compound **II** crystallizes in the monoclinic space group *I*2/*a*. The asymmetric unit contains one protonated *N*-phenyl-5-(pyridin-4-yl)-1,3,4-oxadiazol-2-ammonium cation and one chloride anion (Figure 3a). Selected bonds distances are listed in Table 2. The central 1,3,4-oxadiazol ring C1/N1/N2/C2/O1 is almost planar [rms 0.009 Å] with short distances C1=N1 [1.2801(18)Å] and C2=N2 [1.3013(18) Å] indicating double-bond character. The distances C1—O1 [1.3725(15) Å] and C2—O1 [1.3623 (15) Å] are compatible with single-bond character. These values are in accordance with those reported for compound with 1,3,4-oxadiazol moiety [48]. The molecular structure of **II** is almost planar (Figure 3a). The phenyl and pyridinium rings form dihedral angles of 2.66 (8) and 5.14 (8)°, respectively, with the central five-membered ring 1,3,4-oxadiazole ring. The dihedral angle between the phenyl and pyridinium rings is 3.92 (8)°. The torsion angle N1—C1—C10—C14 between the pyridinium ring attached to -C1 of 1,3,4-oxadiazol moiety is -4.4 (2)° and the torsion angle N2—C2—N3—C4 of -2.9 (2)° show that the rings are quite coplanar. The whole cation moiety is almost planar with rms deviation of 0.0433 Å. The largest deviation from the mean plane of the cation unit of 0.0825 (1) Å is observed for the atom N3.

The almost planar geometry of the oxadiazole molecule is stabilized by the intramolecular N3–H3···Cl1 and C5–H5···Cl1 hydrogen bonds forming the usual six-membered *S*(6) ring, as shown in Figure 3b (Table 3). Intermolecular hydrogen bonds of type N–H···N (N4—H4···N4^{iii}), C–H···Cl (C12—H12···Cl1^{ii}) and C–H···N (C13—H13···N2^{i}) (Table 3, Figure 4) link the molecule in a tridimensional network.



(a)



(b)

Figure 3. The molecular structure of the compound **II**(**a**), showing the atom numbering scheme and the intramolecular N–H···N hydrogen contacts forming *S*(6) motifs (**b**).

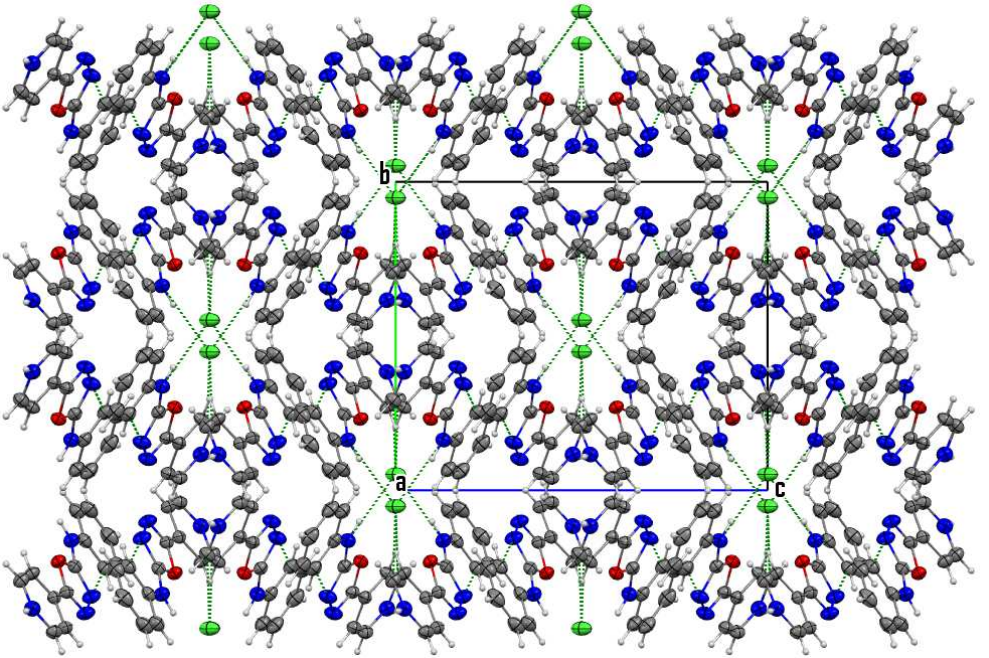


Figure 4. The crystal packing of (**II**) viewed along *a* axis.

Table 2. Selected bond lengths (Å).

II		**III**	
Bond	**Bong lengths [Å]**	**Bond**	**Bong lengths [Å]**
O1—C2	1.3623 (15)	S1—C7	1.6689 (13)
O1—C1	1.3725 (15)	N3—C8	1.3807 (16)
N3—C2	1.3340 (17)	N3—C7	1.3867 (16)
N3—C4	1.4099 (17)	N3—C1	1.4342 (16)
N1—C1	1.2801 (18)	N1—C7	1.3375 (18)
N1—N2	1.3975 (18)	N1—N2	1.3693 (15)
N2—C2	1.3013 (18)	N2—C8	1.2972 (17)

Table 3. Hydrogen-bonding geometry (Å, °) of compound **II**.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3···Cl1	0.86	2.27	3.1243 (12)	169.5
C13—H13···N2^{i}	0.93	2.53	3.4296 (19)	164.1
C5—H5···Cl1	0.93	2.85	3.6158 (17)	140.7
C12—H12···Cl1^{ii}	0.93	2.75	3.4075 (15)	128.1
C9—H9···N2	0.93	2.31	2.937(2)	124.4
N4—H4···N4^{iii}	0.90(3)	1.79(3)	2.682(2)	172(3)

Symmetry codes: (i) *x*−1/2, −*y*+2, *z*; (ii) −*x*+1, −*y*+1, −*z*+1; (iii) −*x*+1/2, *y*, −*z*+1.

3.3.2. Structure of 4-phenyl-3-(pyridin-4-yl)-1H-1,2,4-triazole-5(4H)-thione(III)

Compound **III** crystallizes in the orthorhombic space group *Pbcn*. The asymmetric unit contains one 4-phenyl-3-(pyridin-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (Figure 5). Selected bonds distances are listed in Table 2. The central 1,2,4-triazole ring N1/N2/C8/N3/C7 is almost planar [rms 0.009 Å] with long distances C7—N1 [1.3375 (18)Å], C7—N3 [1.3867 (16)Å] and C8—N3 [1.3807 (16) Å] indicating single-bond character. The short distance C8=N2 [1.2972 (17) Å] is compatible with double-bond character. These values are in accordance with those reported for compound with 1,2,4-triazolemoiety [49]. The distance C7=S1 of 1.6689 (13) Å, compatible with double-bond character [50] indicates that the compound exists only in its thione form. The molecular structure of (III) is non-planar (Figure 3). The phenyl and pyridyl rings form dihedral angles of 58.35 (5) and 58.33 (5)°, respectively, with the central five-membered ring 1,2,4-triazole ring. The dihedral angle between the phenyl and pyridyl rings is 36.85 (4)°. Three types of intermolecular hydrogen bonds, N1—H1···N4^{i}, C2—H2···N2^{ii} and C12—H12···S1^{iii}, are observed in the crystal which link the molecule in three dimensional network (Table 4, Figure 6).

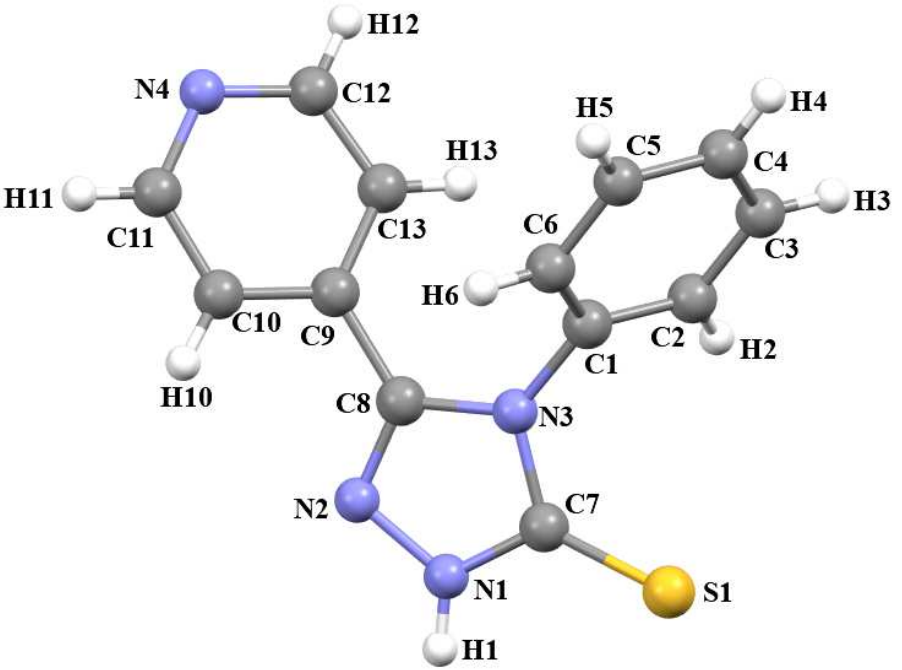


Figure 5. The molecular structure of the compound **III**, showing the atom numbering scheme.

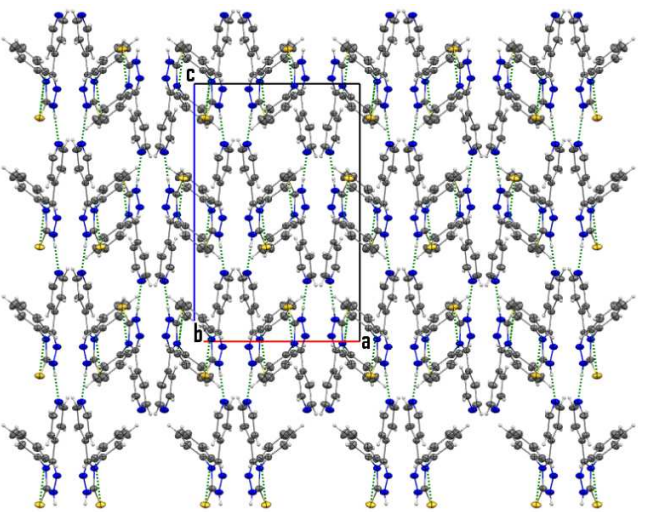


Figure 6. The crystal packing of (**III**) viewed along the *b* axis.

Table 4. Hydrogen-bonding geometry (Å, °) of compound **III**.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1···N4^{i}	0.86	1.97	2.8304 (16)	179.4
C2—H2···N2^{ii}	0.93	2.70	3.4889 (19)	143.4
C12—H12···S1^{iii}	0.93	2.94	3.7711 (16)	148.9

Symmetry codes: (i) x, $-y+1$, $z-1/2$; (ii) $-x+1/2$, $y+1/2$, z; (iii) $-x+1/2$, $-y+3/2$, $z+1/2$.

Conclusion

Compound (**I**) synthesized from the reaction between isonicotinic hydrazide and isothiocynate yields compounds **II** and **III** when it reacts with Fe(II) or Mn(II). With iron(II) an 1,3,4-oxadiazole derivative is formed whereas with manganese(II) a 1,2,4-triazole derivate is formed. It appears that the action of the metal is determinate in the direction of the reaction. The structure of compound **I** is confirmed by elemental analysis and spectroscopic techniques (FT-IR, ^{1}H and ^{13}C NMR). The molecular structures of compounds **II** and **III** are determined by X-ray diffraction. Compound **I** shows a good antioxidant power superior to that of TROLOX, which is used as a reference, in the concentration range 100-500µM.

Supplementary Materials:

CCDC-2215920 and 2215921 contain the supplementary crystallographic data for complex (**II**) and complex (**III**) respectively. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

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