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Research Article

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Synthesis, characterization, antifungal activity and crystal structure of 1-(2-chlorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazole-4-carboxaldehyde

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ABSTRACT

*1-(2-Chlorophenyl)-3-(thiophen-2-yl)-1H-pyrazole-4-carboxaldehyde (**3**) was synthesized by the reaction of (Z)-1-(2-chlorophenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**2**) and Vilsmeier-Haack (DMF, $POCl_3$) reaction. The synthesised compound was characterized by spectroscopy and elemental analysis. The crystal structure was determined from single crystal X-ray diffraction data. It crystallizes in the triclinic crystal system with the space group P-1 and with unit cell parameters a= a = 7.2562(12) Å, b= 8.6896(11) Å, c =11.4407(16) Å ; α = 109.168(7)º, β= 105.648(7)º, γ = 94.4099(8)º and Z = 2. The crystal structure is stabilized by intramolecular C---H...O hydrogen bonds.*

Keywords: Antifungal, diffusion, packing, spectral studies, X-ray diffraction.

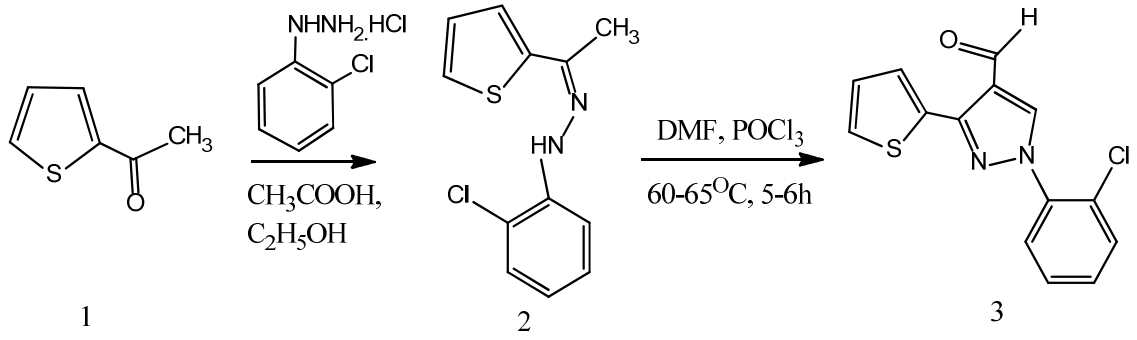
INTRODUCTION

Pyrazoles and its derivatives, a class of well known nitrogen heterocycles, occupy a prime position in medicinal and pesticide chemistry for their diverse biological activities such as antioxidant [1,2], anticancer [3], anti-inflammatory [4], anticonvulsant [5], antipyretic [6], antimicrobial activities [7, 8]. Literature survey reveals that formylation of hydrazones yield formyl pyrazoles [1]. Formylation is a key process in organic synthesis in which the resulting aldehyde function acts as a crossroads intermediate, hence a large number of methods have been developed for this reaction. The Vilsmeier-Haack reaction is useful; method for the synthesis of 4-formyl pyrazoles, which can further be used as building blocks in the synthesis of complex molecules and biological active compounds. In view of this observation, we took the present task of synthesizing formyl pyrazoles with an in intention of getting more biological potency.

EXPERIMENTAL SECTION

The condensation of 2-acetyl thiophene (**1**) with 2-chloro phenylhydrazine hydrochloride in ethyl alcohol and a catalytic amount of acetic acid at water bath reflux condition produced (Z)-1-(2-chlorophenyl)-2-(1-(thiophen-2-yl)ethylidene)hydrazine (**2**). Then, compound (**2**) was added to the Vilsmeier-Haack reagent prepared by drop-wise addition of $POCl_3$ (1.2 mL) in ice cooled DMF (10 mL). The mixture was stirred at 60-65 ^oC for 6 h. The progress of

the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water, neutralized with $NaHCO_3$, the solid separated was filtered, washed with ice cold water and recrystallized from ethanol to obtain target molecule 1-(2-chlorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazole-4-carboxaldehyde (**3**) in 92% yield (Scheme-1). The product was purified by column chromatography using hexane:ethyl acetate (9:1 v/v) as eluent. Pure single crystal (light yellow) of the product was crystallized by the slow evaporation method using ethanol as a solvent, m.p. 134-135 °C.



Scheme-1: Synthetic pathway for the preparation of formylpyrazole derivative

Melting point was determined by open capillary method and ia uncorrected. ^{1}H NMR spectrum was recorded on Agilent vnmrs400MHz spectrometer using $CDCl_3$ as a solvent and TMS as internal standard The Chemical shifts are expressed in δ ppm. Mass spectra were obtained on Shimadzu LCMS-2010A spectrophotometer (Chemical Ionization). Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyzer. Chromatographic separations were carried out on silica gel (70-230 mesh, Merck) column using hexane: ethyl acetate (9:1) as eluent.

Spectral analysis

In ^{1}H NMR spectrum, synthesized compound 1-(2-chlorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazole-4-carboxaldehyde, (**3**) showed sharp singlet at δ 9.62 ppm. due to -CHO proton. A singlet for one proton absorbed at δ 8.46 ppm. was assigned to pyrazole ring proton. An array of signals observed as multiplet for seven protons in the region δ 7.20-7.72 ppm. was due to aromatic benzene and thiophene rings protons. In its ^{13}C NMR spectrum, compound, (**3**) showed an absorption signal due to -CHO carbon at δ 186.2 ppm. Signals observed at δ 136.1, 114.6 and 129.4 ppm. were due to C_3-, C_4- and C_5-carbons of newly formed pyrazole ring. Four carbons of thiophene ring and six carbons of benzene ring showed the absorption signals at δ 127.1, 128.0, 129.3, 140.8 ppm. and δ 119.1, 122.4, 127.7, 130.7, 133.9, 142.5 ppm. respectively.

The mass spectrum of compound, (**3**) showed peak at m/z 290 with the relative intensity of 33%, which corresponds to molecular mass with ^{37}Cl isotope. The base peak observed at m/z 288 corresponding to molecular ion with ^{35}Cl atom. These peaks in the mass spectrum were in agreement with the molecular formula $C_{14}H_9ClN_2OS$ of the synthesized compound. Further, it showed satisfactorily analytical data for C, H and N atoms. Anal. Calcd. for $C_{14}H_9ClN_2OS$: C, 58.23; H, 3.14; N, 9.70%; Found: C, 58.18; H, 3.17; N, 9.65%.

The spectral and elemental analysis data proves the structure of 1-(2-chlorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazole-4-carboxaldehyde, (**3**). The structure proof was further confirmed by X-ray diffraction studies.

X-Ray Data Collection, Structure Refinement and Crystal structure determination

A light yellow rectangle shaped single crystal of dimensions 0.20×0.20×0.20 mm of the title compound was chosen for an X-ray diffraction study. X-ray intensity data were collected for the title compound at temperature 296 K on a Bruker Proteum2 CCD diffractometer with X-ray generator operating at 45 kV and 10 mA, using CuK_α radiation of wavelength 1.54178 Å. Data were collected for 24 frames per set with different settings of φ (0° and 90°), keeping the scan width of 0.5°, exposure time of 5 s, the sample to detector distance of 45.10 mm and 2θ value at 46.6°. A complete data set was processed using *SAINT PLUS* [9]. The structure was solved by direct methods and refined by

full-matrix least squares method on F^2 using *SHELXS* and *SHELXL* programs [10]. All the non-hydrogen atoms were revealed in the first difference Fourier map itself. All hydrogen atoms were positioned geometrically (C–H = 0.93 Å) and refined using a riding model with U_{iso}(H) = 1.2 U_{eq} (C) and $\underline{U}_{iso}$(H) = 1.5 U_{eq} (O) for hydroxy group. After several cycles of refinement, the final difference Fourier map showed peaks of no chemical significance and the residual is saturated. The geometrical calculations were carried out using the program *PLATON* [11]. The molecular and packing diagrams were generated using the software *MERCURY* [12]. The details of the crystal structure and data refinement are given in Table 1. The list of bond lengths and bond angles and torsion angle of the non-hydrogen atoms are given in Table 2, 3, 4, 5, 6 and Table 7. Figure-1 represents the ORTEP of the molecule with thermal ellipsoids drawn at 50% probability.

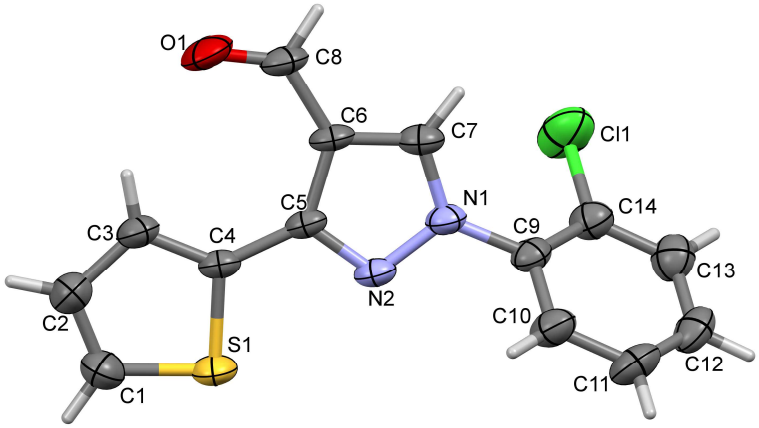


Figure-1: ORTEP diagram of the molecule with thermal ellipsoids drawn at 50% probability

RESULTS AND DISCUSSION

In the molecular structure of the title compound, the bond lengths and bond angles do not show large deviations and are comparable with the standard values. The dihedral angle between the mean planes of thiophene ring (S1/C3/C4/C1/C2) and the phenyl ring (C9/C10/C12/C14/C13/C11) is 52.98°. The dihedral angle between the mean planes of the thiophene ring (S1/C3/C4/C1/C2) and the pyrazole ring (N1/N2/C6/C7/C5) is 3.99°. The dihedral angle between the mean planes of the phenyl ring (C9/C10/C12/C14/C13/C11) and the pyrazole ring (N1/N2/C6/C7/C5) is 48.99°.The bond length between C14-Cl1, C8-O1, N1-N2, C4-C5, N1-C9, C1-S1, S1-C4 AND C6-C8 are 1.731 Å, 1.205 Å, 1.363 Å, 1.460 Å, 1.421 Å, 1.703 Å, 1.717 Å and 1.450 Å respectively. The bond angle between C1-S1-C4, C4-C5-N2, C5-N2-N1, N2-N1-C9, O1-C8-C6, C9-C14-Cl1 and C3-C4-C5 are 91.771°, 117.35°, 105.59°, 118.68°, 128.19°, 120.86° and 131.04° respectively. The torsion angle between C4-C5-N2-N1, N1-C9-C14-Cl1, C1-S1-C4-C5 and O1-C8-C6-C7 are 117.12°, -0.23°, -178.95° and -174.01° respectively. The crystal structure is stabilized by intramolecular C---H...O hydrogen bonds. Figure-2 represents the packing diagram of the molecule when viewed down along the *α* axis.

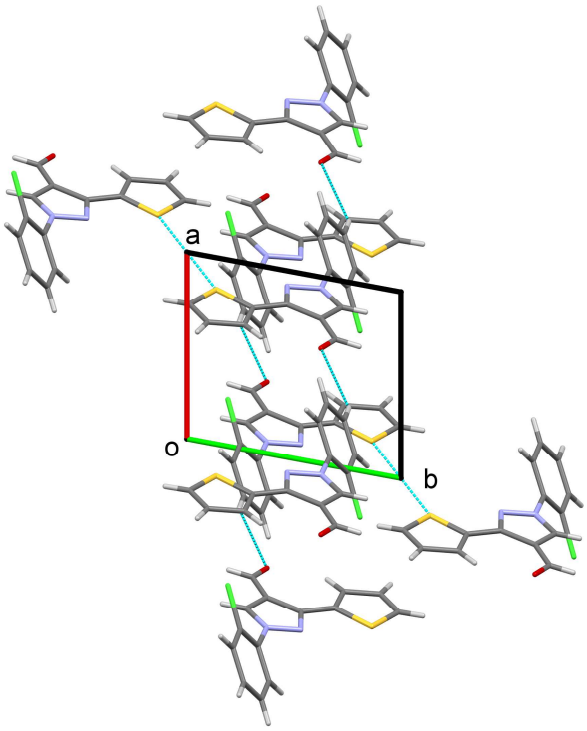


Figure 2: Packing diagram of the molecules when viewed down along the *a* axis

Table 1. Crystal data and structure refinement details of molecule	
Empirical formula	$C_{14}H_9ClN_2OS$
Formula weight	288.75
Temperature	296K
Wavelength	1.54178 Å
Reflns. for cell determination	3359
θ Range for above	4.31º to 64.49 º
Crystal system	Triclinic
Space group	*P*-1
Cell dimensions	α= 7.2562(12) Å β= 8.6896(11) Å *c* =11.4407(16) Å α= 109.168(7) º *β*= 105.648(7) º ɣ= 94.4099(8) º
Volume	645.18(17) $Å^3$
Z	2
Density(calculated)	1.486 Mgm^{-3}
Absorption coefficient	4.068 mm^{-1}
F_{000}	296
Crystal size	0.200× 0.200×0.200 mm
θ range for data collection	4.31º to 64.49 º
Index ranges	$-3 \le h \le 8$ $-9 \le k \le 10$ $-13 \le l \le 12$
Reflections collected	3359
Independent reflections	1979 [R_{int} = 0.0431]
Absorption correction	Multi-scan
Refinement method	Full matrix least-squares on F^2
Data/ restraints/ parameters	1979 / 0 / 173
Goodness-of-fit on F^2	1.031
Final [$I > 2\sigma(I)$]	$R1$ = 0.0658, ω$R2$ = 0.1710
R indices (all data)	$R1$ = 0.0773, ω$R2$ = 0.1821
Extinction coefficient	0.017(3)
Largest diff. peak and hole	0.555 and -0.473e $Å^{-3}$

Table 2: Atomic coordinates and equivalent thermal parameters of the non-hydrogen toms

Atom	x	Y	z	U_{eq}
Cl1	0.25000(16)	0.19150(17)	0.03204(11)	0.0793(5)
S1	0.17129(14)	0.86380(10)	0.50892(9)	0.0482(3)
O1	0.3831(4)	0.3738(3)	0.6354(3)	0.0603(10)
N1	0.0608(4)	0.3730(3)	0.2314(3)	0.0353(8)
N2	0.0826(4)	0.5314(3)	0.3154(3)	0.0340(8)
C1	0.2772(6)	0.9879(4)	0.6682(4)	0.0531(11)
C2	0.3563(6)	0.9030(5)	0.7417(4)	0.0536(12)
C3	0.3340(5)	0.7322(4)	0.6684(3)	0.0425(11)
C4	0.2350(4)	0.6916(4)	0.5401(3)	0.0321(10)
C5	0.1821(4)	0.5331(4)	0.4312(3)	0.0303(9)
C6	0.2237(4)	0.3726(4)	0.4228(3)	0.0358(10)
C7	0.1435(5)	0.2778(4)	0.2941(3)	0.0390(11)
C8	0.3201(5)	0.3054(4)	0.5187(4)	0.0443(11)
C9	-0.0461(5)	0.3315(4)	0.0980(3)	0.0365(10)
C10	0.0241(5)	0.2490(4)	-0.0013(3)	0.0430(11)
C11	-0.0812 (6)	0.2151 (5)	-0.1301 (4)	0.0524 (12)
C12	-0.2561 (6)	0.2654 (5)	-0.1599(4)	0.0509(12)
C13	-0.3273(6)	0.3476(5)	-0.0624(4)	0.0555(14)
C14	-0:2235(5)	0:3829(5)	0:0669(4)	0:0480(12)

Table-3: Atomic coordinates and equivalent thermal parameters of the hydrogen atom

Atom	x	Y	z	U_{eq}
H1	0.27990	1.10150	0.70040	0.0630
H2	0.41890	0.95100	0.83100	0.0640
H3	0.38200	0.65590	0.70420	0.0510
H7	0.14580	0.16580	0.25610	0.0470
H8	0.33500	0.19560	0.48600	0.0530
H10	-0.27220	0.44060	0.13260	0.0580
H11	-0.44720	0.38030	-0.08310	0.0660
H12	-0.32640	0.24380	-0.24640	0.0610
H13	-0.03300	0.15810	-0.19640	0.0630

Table 4: Anisotropic thermal parameters of the non-hydrogen atoms

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	0.0654(8)	0.1217(11)	0.0616(8)	0.0332(7)	0.0267(6)	0.0546(7)
S1	0.0604(6)	0.0385(6)	0.0487(6)	0.0250(4)	0.0081(4)	0.01759(4)
O1	0.0658(18)	0.0632(17)	0.0589(19)	0.0422(15)	0.0029(14)	0.0227(13)
N1	0.0402(15)	0.0338(14)	0.0381(15)	0.0209(12)	0.0105(12)	0.0133(11)
N2	0.0358(14)	0.0365(14)	0.0382(15)	0.0230(12)	0.0114(12)	0.0139(11)
C1	0.060(2)	0.0371(18)	0.056(2)	0.0151(17)	0.0101(19)	0.0113(16)
C2	0.058(2)	0.053(2)	0.043(2)	0.0163(17)	0.0048(18)	0.0170(17)
C3	0.0467(19)	0.0440(18)	0.042(2)	0.0237(15)	0.0091(15)	0.0191(14)
C4	0.0309(16)	0.0339(16)	0.0400(18)	0.0216(14)	0.0122(13)	0.0130(12)
C5	0.0283(15)	0.0375(16)	0.0364(17)	0.0239(14)	0.0127(13)	0.0139(12)
C6	0.0364(17)	0.0366(17)	0.046(2)	0.0282(15)	0.0122(15)	0.0164(13)
C7	0.0424(18)	0.0371(17)	0.049(2)	0.0261(16)	0.0169(16)	0.0158(14)
C8	0.046(2)	0.0430(19)	0.054(2)	0.0319(18)	0.0107(18)	0.0192(15)
C9	0.0388(17)	0.0371(16)	0.0380(18)	0.0217(14)	0.0090(14)	0.0075(13)
C10	0.0431(19)	0.048(2)	0.044(2)	0.0224(17)	0.0152(16)	0.0126(15)
C11	0.058(2)	0.057(2)	0.043(2)	0.0192(18)	0.0167(18)	0.0079(18)
C12	0.053(2)	0.060(2)	0.039(2)	0.0282(18)	0.0031(17)	0.0011(17)
C13	0.043(2)	0.072(3)	0.056(2)	0.038(2)	0.0034(18)	0.0146(18)
C14	0.046(2)	0.061(2)	0.046(2)	0.0285(18)	0.0140(17)	0.0217(17)

Table 5: Bond lengths (Å).

Atoms	Length	Atoms	Length	Atoms	Length	Atoms	Length
Cl1-C10	1.731(4)	C4-C5	1.460(5)	C1-C2	1.339(6)	C12-C13	1.366(6)
S1-C1	1.703(4)	C5-C6	1.428(5)	C2-C3	1.416(6)	C13-C14	1.384(6)
S1-C4	1.717(4)	C6-C7	1.361(4)	C3-C4	1.359(4)		
O1-C8	1.205(5)	C6-C8	1.450(5)	C1-H1	0.9300	C11-H13	0.9300
N1-N2	1.364(4)	C9-C10	1.378(5)	C2-H2	0.9300	C12-H12	0.9300
N1-C7	1.339(5)	C9-C14	1.389(5)	C3-H3	0.9300	C13-H11	0.9300
N1-C9	1.421(4)	C10-C11	1.384(5)	C7-H7	0.9300	C14-H10	0.9300
N2-C5	1.321(4)	C11-C12	1.367(6)	C8-H8	0.9300		

Table 6: Bond angles (º)

Atoms	Angle	Atoms	Angle	Atoms	Angle	Atoms	Angle
C1-S1-C4	91.77(17)	C5-C6-C8	133.4(3)	C4-C5-C6	132.0(3)	C9-C14-C13	119.6(4)
N2-N1-C7	111.1(3)	C7-C6-C8	122.4(3)	C5-C6-C7	104.2(3)		
N2-N1-C9	118.7(3)	N1-C7-C6	108.5(3)	N2-C5-C6	110.6(3)	C12-C13-C14	120.9(4)
C7-N1-C9	130.2(3)	O1-C8-C6	128.2(4)	S1-C1-H1	124.00	C6-C8-H8	116.00
N1-N2-C5	105.6(3)	N1-C9-C10	122.3(3)	C2-C1-H1	124.00	C10-C11-H13	120.00
S1-C1-C2	112.2(3)	N1-C9-C14	118.7(3)	C1-C2-H2	124.00	C12-C11-H13	120.00
C1-C2-C3	112.5(4)	C10-C9-C14	118.8(3)	C3-C2-H2	124.00	C11-C12-H12	120.00
C2-C3-C4	112.8(3)	C11-C10-C9	120.9(3)	C2-C3-H3	124.00	C13-C12-H12	120.00
S1-C4-C3	110.7(3)	C11-C10-C11	118.3(3)	C4-C3-H3	124.00	C12-C13-H11	120.00
S1-C4-C5	118.2(2)	C9-C10-C11	120.8(4)	N1-C7-H7	126.00	C14-C13-H11	119.00
C3-C4-C5	131.0(3)	C10-C11-C12	120.0(4)	C6-C7-H7	126.00	C9-C14-H10	120.00
N2-C5-C4	117.4(3)	C11-C12-C13	119.8(4)	O1-C8-H8	116.00	C13-C14-H10	120.00

Table 7: Torsion angles (º)

Atoms	Angle	Atoms	Angle
C4-S1-C1-C2	-0.3(4)	C3-C4-C5-C6	-3.1(6)
C1-S1-C4-C3	-0.2(3)	N2-C5-C6-C7	0.6(4)
C1-S1-C4-C5	-179.0(3)	N2-C5-C6-C8	-177.5(4)
C7-N1-N2-C5	0.6(4)	C4-C5-C6-C7	-176.8(3)
C9-N1-N2-C5	178.5(3)	C4-C5-C6-C8	5.1(6)
N2-N1-C7-C6	-0.2(4)	C5-C6-C7-N1	-0.2(4)
C9-N1-C7-C6	-177.8(3)	C8-C6-C7-N1	178.1(3)
N2-N1-C9-C10	130.5(4)	C5-C6-C8-O1	3.8(7)
N2-N1-C9-C14	-46.3(5)	C7-C6-C8-O1	-174.0(4)
C7-N1-C9-C10	-52.1(6)	N1-C9-C10-Cl1	-0.2(5)
C7-N1-C9-C14	131.0(4)	N1-C9-C10-Cl1	-178.0(4)
N1-N2-C5-C4	177.1(3)	C14-C9-C10-Cl1	176.6(3)
N1-N2-C5-C6	-0.8(4)	C14-C9-C10-Cl1	-1.1(6)
S1-C1-C2-C3	0.7(5)	N1-C9-C14-C13	178.3(4)
C1-C2-C3-C4	-0.9(5)	C10-C9-C14-C13	1.3(6)
C2-C3-C4-S1	0.6(4)	Cl1-C10-C11-C12	-177.0(4)
C2-C3-C4-C5	179.2(4)	C9-C10-C11-C12	0.8(6)
S1-C4-C5-N2	-2.0(4)	C10-C11-C12-C13	-0.7(7)
S1-C4-C5-C6	175.3(3)	C11-C12-C13-C14	0.9(7)
C3-C4-C5-N2	179.5(4)	C12-C13-C14-C9	-1.2(7)

Antimicrobial activity

Antimicrobial activity of the synthesized compounds was done by paper disc diffusion method [13]. The compound (**3**) at the concentration of 50 µg/mL in methanol in the nutrient agar media were screened for their antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *C. albicans*, *Fusarium oxysporium*. The antibiotic nystatin was used as positive reference drug. The screening tests were performed in triplicate and the results were taken as a mean of three determinations and were summarized in Table 8.

Minimum inhibitory concentrations (MICs) were determined by broth dilution technique [14]. The nutrient broth, which contain logarithmic serially two-fold diluted amount of test compound and controls were inoculated with approximately 5 x 10^5 cfu of actively dividing bacteria cells. The fungal cultures were incubated for 72 hrs at 37 °C, the growth was monitored spectrophotometrically. The experiments were carried out in triplicate; the results were taken as a mean of three determinations and were summarized in Table 8.

Table-8: Zone of Inhibition (diameter) at 25 µg/mL concentrations (X) in mm and MICs (Y) in µg/mL of the synthesized compound, (3) tested against fungal stains by disc diffusion method and micro dilution method respectively

Compound	*A. niger*		*A. flavus*		*C. albicans*	
	X	Y	X	Y	X	Y
3	18	23	20	24	17	36
nystatin	35	20	30	18	32	22
The results are expressed as mean of three determinations (n=3); nystatin (50 µg per disc) = positive control						

CONCLUSION

In the present work, a new molecule 1-(2-chlorophenyl)-3-(thiophen-2-yl)-1*H*-pyrazole-4-carboxaldehyde synthesized and characterized by spectral and crystallographic studies. The molecule was evaluated for its antifungal activity against tested fungal strains.

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