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SYNTHESIS, SPECTRAL ANALYSIS AND SINGLE CRYSTAL STRUCTURE ELUCIDATION OF 1-ETHYL-2-(ETHYLAMINO)-4-(4-FLUOROPHENYL)-1,6-DIHYDRO-6-OXOPYRIMIDINE-5-CARBONITRILE

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ABSTRACT: A target compound 1-ethyl-2-(ethylamino)-4-(4-fluorophenyl)-1,6-dihydro-6-oxo pyrimidine-5-carbonitrile was prepared via reaction of ethyl amine with 1-ethyl-2-(ethylthio)-4-(4-fluorophenyl)-1,6-dihydro-6-oxo pyrimidine-5-carbonitrile. The structure elucidation of the new synthesized target was done using ^{1}H NMR, Mass, IR spectroscopy and single-crystal X-ray diffraction. The single crystal of the target compound was found to be monoclinic. The space group is P 21/n. The crystallographic parameters are *a* =10.9855(11) Å *b* = 10.7286(10) Å *c* =12.7136(10) Å, Z= 4 D_x, g cm^{-3} =1.272. α=90 β=93.545(5) γ=90. Molecular formula $C_{15}H_{15}FN_4O$ final R value was 0.0511.

Keywords: Pyrimidine analogues, amine derivative, single crystal, XRD.

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1.INTRODUCTION

Pyrimidine, a nitrogenous base is six membered aromatic ring found in cytosine, thymine and uracil and also known as 1,3-diazines. [1] In medicinal chemistry pyrimidine possess important place as a part of nucleic acids DNA and RNA.[2]. Pyrimidine derivatives are gaining more attention due to their broad spectrum of biological functions such as antitubercular,[3] antimalarial, [4] anti-inflammatory,[5] anti-viral,[6] antimicrobial and antioxidant activities.[7] Substituted 2-aminopyrimidines are prepared when halides or other leaving groups are displaced at C-2 position by metal- catalysed C-N bond forming reactions or nucleophilic aromatic substitution. Generally 2-

aminopyrimidines are synthesized by the nucleophilic substitution of labile groups by amino groups. [8] The literature has revealed 2-Amino-4-(2-thienyl) pyrimidines derivatives as potent antibacterial agents. especially 4-fluoro substituted compounds more effective than other halogenated substitutes.[9] 2-amino pyrimidines and N-alkylated compounds proved to exhibit excellent anticancer and antibacterial activities. [10] Furthermore, the amino group at C-5 position in pyrimidine derivatives containing nitrile and fluorine reported as ARO inhibitors.[11]. A detailed synthetic study and single crystal analysis of 1-ethyl-2-(ethylamino)-4-(4-fluorophenyl)-1,6-dihydro-6-oxo pyrimidine-5-carbonitrile is given below.

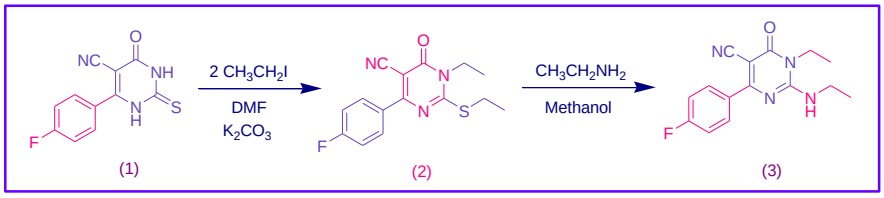
2. MATERIALS AND METHODS

Materials

For the synthesis purified reagents and solvents were used. Melting points were measured by open capillary and may be incorrect. The IR spectra was recorded on the Shimadzu-FTIR-8400 spectrometer using KBr (disc). Mass spectra were measured on the UC03-MASS spectrometer. ^{1}H NMR spectra recorded on a Bruker 400 MHz spectrometer using DMSO as a solvent and TMS (trimethyl silane) as internal standard. Compounds 1 and 2 are prepared by previously reported methods. [12-17]

Synthesis of 1-Ethyl-2-(Ethylamino)-4-(4-Fluorophenyl)-1,6-Dihydro-6-Oxopyrimidine-5-Carbonitrile (3)

For the For the preparation of compound (3), 1-ethyl-2-(ethylthio)-4-(4-fluorophenyl)-1,6-dihydro-6-oxo pyrimidine-5- carbonitrile (3.035 gm,0.01mol) and ethyl amine (≈ 1.5 ml) in methanol (30 ml) was added in round bottom flask and refluxed for 10 hours. When the reaction is complete (checked by TLC) the mixture is cooled at room temperature and poured into crushed ice. Formed solid product was filtered, dried and recrystallized using ethanol.



Scheme 1 schematic presentation of target compound

Yield: 67 % MP = 180 °C Mass (M^{+}) 287; IR (KBr) (cm^{-1}) 1095 (C-F str.),.1666 (C=O), 2214 (CN), 2978 (C-H aliphatic), 3333 (secondary. amine NH-str.); ^{1}H NMR (δ ppm) (400 MHz, DMSO); δ 1.2 (m 3H, N-CH_2-CH_3), 1.2 (m 3H, NH-CH_2-CH_3), 3.5 (q 2H, NH-CH_2-CH_3), 4.0 (q 2H, N-CH_2-CH_3), 7.3-7.9 (m 4H, Ar-H), 8.2 (t 1H, NH). R_f = 0.13 (6:4, ethyl acetate: hexane).

X-ray Diffraction Analysis

For the single crystal analysis, Kappa APEX- II (Bruker AXS) diffractometer, having an X-ray tube with targeted molybdenum used. For intensity recording of the peaks CCD of the graphite base was used. Data was corrected and reduced by using APEX- II. Elucidation of the structure was accomplished using SHELXTL software. To represent asymmetric units in the compound graphically the ORTEP technique is used. For presenting hydrogen bonding PLATON was utilized. The crystallographic details are given below.

Table 1. Crystal data and single-crystal X-ray diffraction refinement details for the target compound

Formula	**$C_{15}H_{15}FN_4O$**
Formula weight	286.31
T, K	296(2) K
Wavelength Å	0.71073
Crystal system	Monoclinic
Space group	P 21/n
a, Å	10.9855(11)
b, Å	10.7286(10)
c, Å	12.7136(10)
β, deg	93.545(5)
V Å^3	1495.5(2)
Z; Calculated density, Mg/m^3	4; 1.272
μ, mm^{-1}	0.092
F (000)	600
Crystal size, mm	0.500 x 0.450 x 0.400
θ range for data collection, deg	2.486 - 28.397
Limiting indices	-9<=h<=14, -14<=k<=12, 16<=l<=16
Reflections collected / unique	10832 / 3667 [*R*(int) = 0.0356]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.964 and 0.955
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3667 / 0 / 194
Goodness-of-fit on F^2	1.009
Final R indices [$I>2\sigma(I)$]	R1 = 0.0511, *w*R2 = 0.1469
R indices (all data)	R1 = 0.0922, *w*R2 = 0.1791

Extinction coefficient	0.011(4)
Largest diff. peak and hole, e $Å^{-3}$	0.253 and -0.208

Table 2. Bond lengths [Å]

Bond	Length, Å	Bond	Length, Å
C1-C2	1.381(3)	C9-O1	1.220(2)
C1-C6	1.394(2)	C9-N3	1.403(2)
C2-C3	1.357(3)	C10-N1	1.331(2)
C3-F1	1.361(2)	C10-N2	1.334(2)
C3-C4	1.370(3)	C10-N3	1.366(2)
C4-C5	1.376(3)	C11-C12	1.462(4)
C5-C6	1.385(3)	C11-N2	1.452(2)
C7-N1	1.344(2)	C13-C14	1.497(3)
C7-C8	1.383(2)	C15-N4	1.144(2)
C8-C9	1.436(2)	N2-H(2A)	0.88(2)

Table 3. Bond angles (deg)

Bond	Angle, deg	Bond	Angle, deg
C2-C1-C6	120.46(18)	C15-C8-C9	115.30(15)
C3-C2-C1	118.68(19)	O1-C9-N3	120.25(16)
C2-C3-F1	118.9(2)	O1-C9-C8	125.40(16)
C2-C3-C4	123.0(2)	N3-C9-C8	114.34(14)
F1-C3-C4	118.1(2)	N1-C10-N2	118.32(15)
C3-C4-C5	118.0(2)	N1-C10-N3	123.36(14)
C4-C5-C6	121.26(19)	N2-C10-N3	118.30(16)
C5-C6-C1	118.57(17)	C12-C11-N2	112.4(2)

C5-C6-C7	119.83(16)	N3-C13-C14	112.18(16)
C1-C6-C7	121.59(16)	N4-C15-C8	176.9(2)
N1-C7-C8	121.77(15)	C10-N1-C7	118.21(14)
N1-C7-C6	115.13(14)	C10-N2-C11	124.28(17)
C8-C7-C6	123.09(15)	C10-N3-C9	120.89(14)
C7-C8-C15	123.93(16)	C10-N3-C13	122.35(14)
C7-C8-C9	120.63(14)	C9-N3-C13	116.42(14)

3. RESULTS AND DISCUSSION

The target compound 1-ethyl-2-(ethylamino)-4-(4-fluorophenyl)-1,6-dihydro-6-oxo pyrimidine-5-carbonitrile (3) was prepared by the reaction of ethyl amine with 1-ethyl-2-(ethylthio)-4-(4-fluorophenyl)-1,6-dihydro-6-oxo pyrimidine-5-carbonitrile (2) as given in scheme-1. The title compound (3) was examined by IR, ^{1}H NMR and Mass spectroscopy. Thus, the IR spectrum showed a strong C=O stretching band at 1666 cm^{-1} and a strong absorption band for C≡N at 2214 cm^{-1} and a strong NH band at a range of 3070-3333 cm^{-1} and 2978 cm^{-1} for aliphatic C-H bonds. ^{1}H NMR spectra showed an up-field signals for aliphatic protons in the range of δ 1.2 - 4.0 ppm and down-field signals for some proton (aromatic region) in the range of δ 7.3 – 7.9 ppm and signal for -NH at δ 8.2 ppm.For single crystal diffraction the diffraction intensities are distributed in 3D space, and the indexing is carried out by searching orientation matrix. The crystal structure was refined by using full-matrix least squares based on F^2 with the program SHELXTL. In the process of collecting single crystal diffraction data indexing results were received with a tetragonal cell, space group is P 21/n and lattice parameters a =10.9855(11) Å b = 10.7286(10) Å c =12.7136(10) Å, Z= 4 D_x, g cm^{-3} =1.272. α=90 β=93.545(5) γ=90. X-ray diffraction method was applied for exploration of structure of $C_{15}H_{15}FN_4O$. The structure refinement data are given in Table 1. The bond lengths and bond angles are given in Table 2 and 3. The molecule is crystallized in space group, monoclinic system. The molecular structure of $C_{15}H_{15}FN_4O$ and PLATON diagram for target compound are shown in figs.1 and 2. The crystal packing diagram of title compound shown in fig.3. Crystallographic details for this structure are submitted to Cambridge Crystallographic Data Centre (Deposition No. CCDC 2153894). The data can be obtained free via http:/www.ccdc.cam.ac.uk/perl/catreq.cgi (or from The Cambridge Crystallographic Data Centre 12 Union Road Cambridge CB2 1EZ United Kingdom F: +44 (0)1223 336033 e-mail: deposit@ccdc.cam.ac.uk).

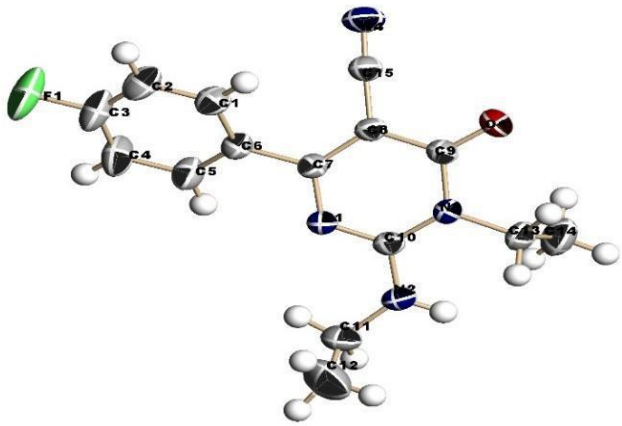


Fig.1. Molecular **s**tructure of title compound (3)

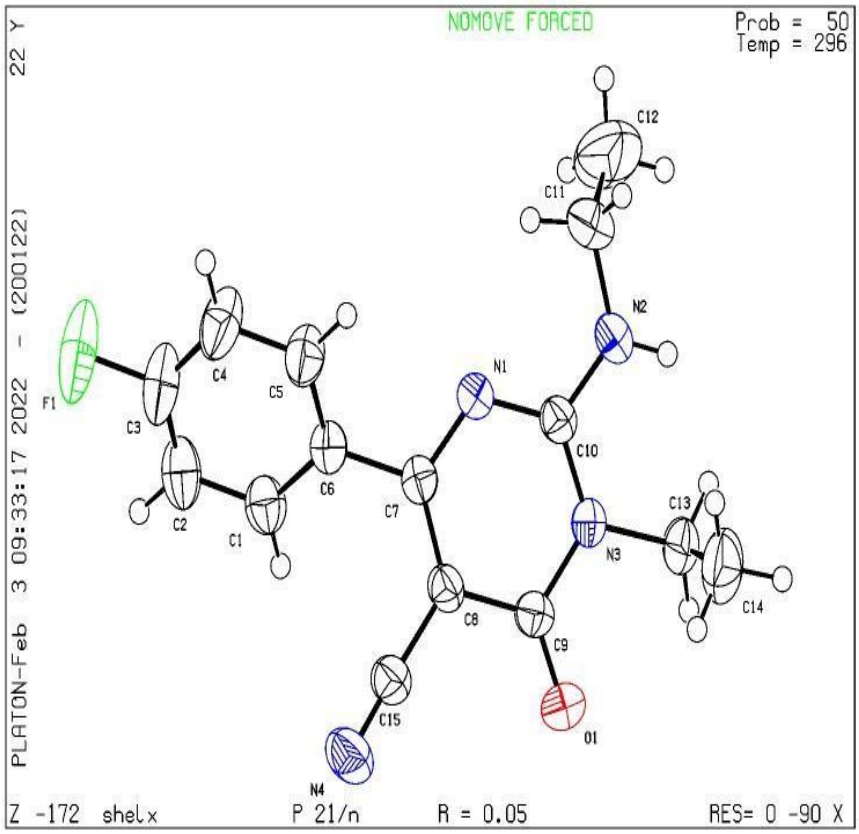


Fig.2. PLATON diagram of title compound (3)

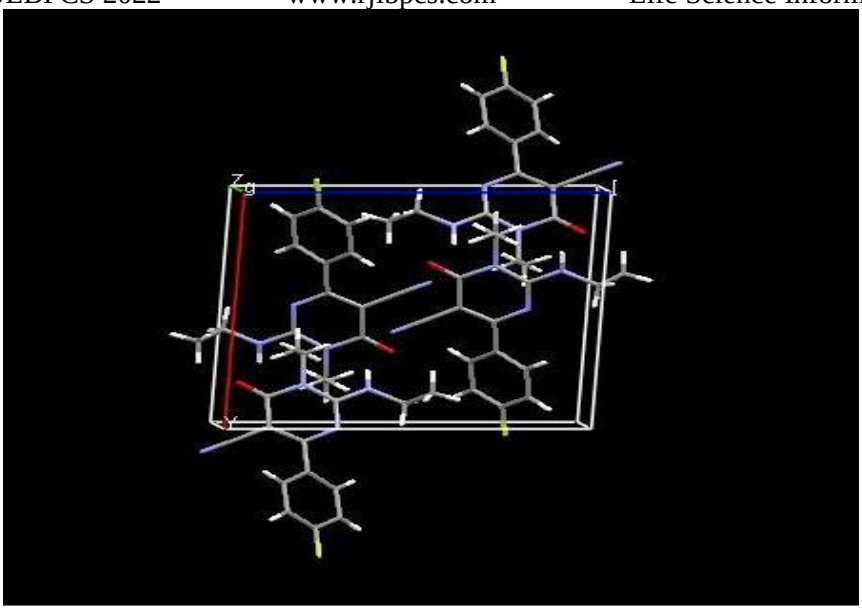


Fig.3. Crystal packing diagram of title compound (3)

4. CONCLUSION

In this article we have described the preparation of 1-ethyl-2-(ethylamino)-4-(4-fluorophenyl)-1,6-dihydro-6-oxo pyrimidine-5-carbonitrile using conventional method. The single crystal was developed by a slow evaporation method. The structure of the title compound is confirmed by different spectroscopic methods and SC-XRD.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

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CONFLICT OF INTEREST

The authors announce that there is no conflict of interests.

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