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# Crystal structure of 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile

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## RESEARCH ARTICLE



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## ABSTRACT

The crystal structure of the title compound, 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, were determined by single crystal X-ray structure analysis. The compound  $C_{14}H_{12}N_4O$  crystallizes in the triclinic crystal system with the *P*-1 space group (no. 2), having unit cell parameters  $a = 6.4788(7) \text{ \AA}$ ,  $b = 8.8433(7) \text{ \AA}$ ,  $c = 10.7377(9) \text{ \AA}$ ,  $\alpha = 103.456(7)^\circ$ ,  $\beta = 99.207(8)^\circ$ ,  $\gamma = 92.451(8)^\circ$ ,  $V = 588.55(9) \text{ \AA}^3$ ,  $Z = 2$ . The crystal structure was solved by direct methods using single-crystal X-ray diffraction data collected at room temperature and refined by full-matrix least-squares procedure with a final *R*-value of 0.0464 for 1432 observed reflections. The dihedral angle between the pyran ring and the pyrazole ring is  $178.08(6)^\circ$ , between the pyrazole ring and the benzene ring is  $98.92(6)^\circ$  and between the pyran ring and the benzene ring is  $97.10(5)^\circ$ . The molecules in the crystal are linked to an infinite two-dimensional network by N–H⋯N and C–H⋯π types of hydrogen bonds. Molecules are also reinforced by the  $\pi$ – $\pi$  interaction between the pyrazole ring and the pyran ring, respectively.

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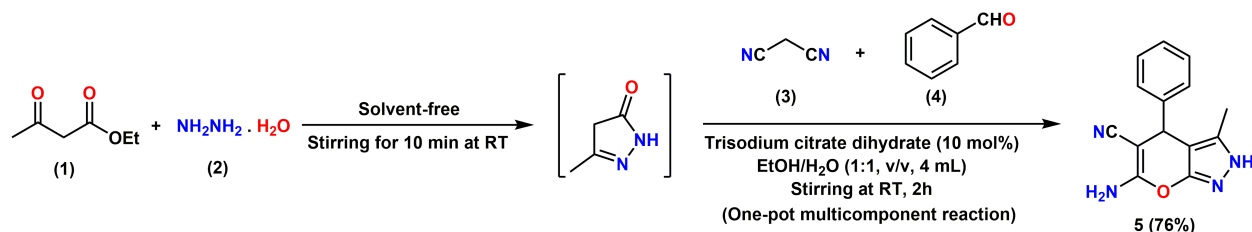
## 1. Introduction

Pyrano[2,3-c]pyrazole is a heterocyclic compound that has garnered significant attention in the field of organic chemistry due to its unique structural characteristics and a diverse range of potential applications. This fused-ring system consists of a pyrazole ring fused to a pyran ring, resulting in a complex yet intriguing molecular framework. The synthesis and characterization of pyrano[2,3-c]pyrazole derivatives have been the subject of extensive research efforts, driven by the promising biological activities of the compound and its potential pharmacological properties. The synthesis of pyrano[2,3-c]pyrazole derivatives has been the subject of intense investigation, with researchers exploring innovative synthetic methodologies to access structurally diverse compounds with enhanced biological properties. The development of efficient synthetic routes and strategies for the preparation of pyrano[2,3-c]pyrazole derivatives has been crucial in expanding the chemical space and exploring the structure-activity relationships of these compounds. Pyrano[2,3-c]pyrazole scaffolds represent a 'privileged' structural motif, well distributed in bioactive natural products and pharmaceutically potent synthetic heterocycles that possess a wide range of activities such as

antiviral [1], insecticidal [2], molluscicidal [3], antimicrobial [4], analgesic [5], hypotensive [6], hypoglycemic and anticancer agents [7-9]. Pyrano[2,3-c]pyrazole framework present in natural and synthetic organic compounds is reported to be responsible for imparting potent biological properties, anti-inflammatory [10,11], antimicrobial [12-14], anti-angiogenesis [15], Chk1 inhibitor activity [16], and analgesic [17], and molluscicidal activity [18]. The present communication aims to disclose the crystal structure of a member of this series of biologically important scaffolds, 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile [19,20]. This research publication aims to provide a comprehensive overview of the synthesis, structural characterization, and biological evaluation of pyrano[2,3-c]pyrazole derivatives. By highlighting the synthetic strategies employed, the structural modifications made, and the pharmacological potential exhibited by the pyrano[2,3-c]pyrazole derivatives, this study contributes to the growing body of knowledge on heterocyclic chemistry and drug discovery. Exploring of pyrano[2,3-c]pyrazole derivatives as potential drug candidates holds great promise for the development of novel therapeutic agents with improved efficacy and reduced side effects, thus addressing unmet medical needs and advancing the field of medicinal chemistry.

**Table 1.** Crystallographic characteristics, details of X-ray data collection, and structure refinement parameters for the title compound.

Empirical formula	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O
Formula weight (g/mol)	252.28
Temperature (K)	293(2)
Crystal system	Triclinic
Space group	P-1
a, (Å)	6.4788(7)
b, (Å)	8.8433(7)
c, (Å)	10.7377(9)
α (°)	103.456(7)
β (°)	99.207(8)
γ (°)	92.451(8)
Volume (Å <sup>3</sup> )	588.55(9)
Z	2
ρ <sub>calc</sub> (g/cm <sup>3</sup> )	1.424
μ (mm <sup>-1</sup> )	0.095
F(000)	264.0
Crystal size (mm <sup>3</sup> )	0.3 × 0.2 × 0.2
Radiation	MoKα (λ = 0.71073)
2θ range for data collection (°)	6.88 to 49.98
Index ranges	-4 ≤ h ≤ 7, -10 ≤ k ≤ 10, -12 ≤ l ≤ 12
Reflections collected	3695
Independent reflections	2073 [R <sub>int</sub> = 0.0304, R <sub>sigma</sub> = 0.0645]
Data/restraints/parameters	2073/0/185
Goodness-of-fit on F <sup>2</sup>	0.996
Final R indexes [I ≥ 2σ (I)]	R <sub>1</sub> = 0.0464, wR <sub>2</sub> = 0.0966
Final R indexes [all data]	R <sub>1</sub> = 0.0768, wR <sub>2</sub> = 0.1104
Largest diff. peak/hole (e.Å <sup>-3</sup> )	0.21/-0.22

**Scheme 1.** Synthesis of 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, 5.

## 2. Experimental

### 2.1. Synthesis of 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5)

An oven-dried screw-cap test tube was sequentially charged with a magnetic stirrer bar, ethyl acetoacetate (**1**, 1 mmol) and hydrazine hydrate (**2**, 1 mmol) (Scheme 1). The reaction mixture was vigorously stirred at room temperature for about 10 minutes to generate the corresponding pyrazole derivative **3** *in situ*. The resulting reaction mixture was then added with malononitrile (**3**, 1.1 mmol), benzaldehyde (**4**, 1 mmol), trisodium citrate dihydrate (10 mol%), and EtOH/H<sub>2</sub>O (1:1, v/v, 4 mL), followed by vigorous stirring at room temperature for another 2 h. The progress of the reaction was monitored by TLC. At the end of the reaction, a solid mass was precipitated, which was filtered off and washed with aqueous ethanol to obtain the crude product 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile, **5**. The product was purified (with 76% yield) by recrystallization from ethanol, upon which we obtained single crystals.

### 2.2. Synthesis of single crystal

A single crystal was obtained using dimethyl sulfoxide (DMSO) as a solvent. For crystallization, 50 mg of the compound, 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (molecular formula C<sub>14</sub>H<sub>12</sub>N<sub>4</sub>O) was dissolved in 5 ml of DMSO and left for several days at room temperature, which produced block-shaped crystals suitable for XRD analysis.

### 2.3. Crystal structure determination and refinement

X-ray intensity data of 3695 reflections (of which 2073 unique) were collected on X'calibur CCD area-detector diffractometer equipped with graphite monochromated MoKα radiation (λ = 0.71073 Å). The crystal used for data collection was of dimensions 0.30×0.20×0.20 mm. The cell dimensions were determined by least-squares fit of angular settings of 1276 reflections in the θ range 3.81 to 28.61°. The intensities were measured by ω scan mode for θ ranges 3.44 to 24.99°. 2073 reflections were treated as observed (I > 2σ(I)). Data were corrected for Lorentz, polarization, and absorption factors. The structure was solved by direct methods using SHELXS97 [21]. The positions of the amino and H2 attached to the N2 atoms were determined from a difference Fourier map and refined isotropically. All remaining H atoms were geometrically fixed and allowed to ride on their parent C atoms with C-H = 0.93-0.98 Å, and U<sub>iso</sub>(H) = 1.5 U<sub>eq</sub>(C) of the attached C atoms for the methyl H atoms and 1.2 U<sub>eq</sub> for the other H atoms. Full-matrix least squares refinement was carried out using SHELXL97 [21]. The final refinement cycles converged to an R = 0.0464 and wR(F<sup>2</sup>) = 0.1104 for the observed data. Residual electron densities ranged from -0.220 to 0.209 e.Å<sup>-3</sup>. The crystallographic data for the title compound are summarized in Table 1.

## 3. Results and discussion

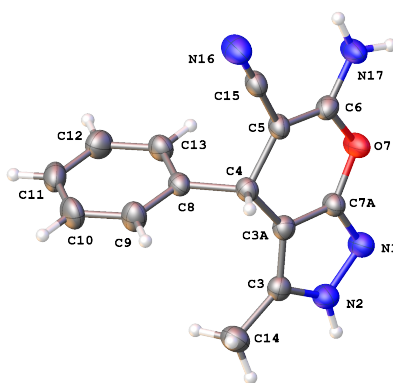
The crystal structure consists of a three-ring system, the pyran ring, the pyrazole ring, and the benzene ring (Figure 1). The benzene ring and the pyrazole ring are nearly planar with a maximum deviation of 0.0027 Å for the benzene C13 atom and 0.0038 Å for the pyrazole C7A atom.

**Table 2.** Bond lengths for the title compound.

Atom	Atom	Length (Å)	Atom	Atom	Length (Å)
N1	N2	1.364(2)	C6	O7	1.377(2)
N1	C7A	1.320(3)	C6	N17	1.348(3)
N2	C3	1.355(3)	O7	C7A	1.374(2)
C3	C3A	1.380(3)	C8	C9	1.384(3)
C3	C14	1.488(3)	C8	C13	1.382(3)
C3A	C4	1.500(3)	C9	C10	1.387(3)
C3A	C7A	1.382(3)	C10	C11	1.377(3)
C4	C5	1.526(3)	C11	C12	1.372(3)
C4	C8	1.526(3)	C12	C13	1.386(3)
C5	C6	1.354(3)	C15	N16	1.149(3)
C5	C15	1.415(3)			

**Table 3.** Bond angles for the title compound.

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
C7A	N1	N2	101.42(17)	C6	C5	C5	127.4(2)
C3	N2	N1	113.87(18)	N17	N17	O7	108.99(19)
N2	C3	C3A	105.66(18)	C7A	O7	C6	114.57(17)
N2	C3	C14	122.21(19)	N1	C7A	C3A	115.17(18)
C3A	C3	C14	132.1(2)	N1	C7A	O7	118.77(18)
C3	C3A	C4	132.80(19)	O7	C7A	C3A	126.05(19)
C3	C3A	C7A	103.87(18)	C9	C8	C4	120.3(2)
C7A	C3A	C4	123.33(18)	C13	C8	C4	121.55(19)
C3A	C4	C5	106.05(16)	C13	C8	C9	118.09(19)
C3A	C4	C8	112.18(15)	C8	C9	C10	120.9(2)
C8	C4	C5	112.05(16)	C11	C10	C9	120.2(2)
C6	C5	C4	126.15(18)	C12	C11	C10	119.5(2)
C6	C5	C15	116.96(18)	C11	C12	C13	120.1(2)
C15	C5	C4	116.88(18)	C8	C13	C12	121.2(2)
C5	C6	O7	123.62(18)	N16	C15	C5	178.9(2)

**Figure 1.** The molecular structure of the title compound, displacement ellipsoids were drawn at 40% probability level.

Furthermore, in the molecule, the pyran ring is essentially planar and deviates slightly from the planarity with a maximum torsion angle equal to  $5.2(3)^\circ$  for C3A/C4/C5/C6. The pyran and pyrazole rings are fused through the common atoms C7a and C3a. In the molecule, the expected geometric parameters are observed. The overall molecular geometry of the title compound, including bond distances [22], has a normal range and corresponds to those observed in related structures [23–26]. The six C–C bond lengths in the benzene ring range from  $1.372(4)$  to  $1.387(4)$  Å with an average value of  $1.381(4)$  Å (Table 2). The bond angles in this benzene ring vary from  $118.1(2)$  to  $121.2(3)^\circ$  with an average value of  $120(3)^\circ$ , which coincides exactly with the theoretical value of  $sp^2$ -hybridization (Table 3).

The dihedral angle between the pyran ring and the pyrazole ring is  $178.08(6)^\circ$ , between the pyrazole ring and the benzene ring is  $98.92(6)^\circ$  and between the pyran ring and the benzene ring is  $97.10(5)^\circ$  (Table 4). From the dihedral angle between the pyrazole ring and pyran ring, it shows that these rings are nearly coplanar to each other. The torsion angle  $C15-C5-C6-O7 = 176.31(18)^\circ$  and  $N17-C6-O7-C7A = 179.87(17)^\circ$  conveys that the carbon atom C15 and the nitrogen atom of the amino group lie almost in the plane of the pyran ring. In addition, the torsion angle  $C14-C3-C3A-C4 = 0.5(4)^\circ$  shows that the C14 atom of the

methyl group lies in the plane of the pyrazole ring. The exocyclic bond angles at the ring junction, that is, at C3a and C7a, are  $132.8(2)$  and  $118.8(2)^\circ$ , respectively.

The length of the bond  $C15-N16 = 1.149(3)$  Å and the angle of the bond  $C5-C15-N16 = 178.9(2)^\circ$ , shows linear character of the carbonitrile group, a characteristic observed in carbonitrile compounds [27]. The values of the C–O bonds ( $C7A-O7 = 1.374(2)$  Å,  $C6-O7 = 1.377(2)$  Å) in the pyran ring are in good agreement with the value of the literature and the related structure [23–26]. The bond distances  $C3-C3A = 1.380(3)$ ,  $N1-C7A = 1.320(3)$ ,  $C3-N2 = 1.355(3)$  Å in the pyrazole ring and  $C6-C5 = 1.354(3)$ ,  $C5-C4 = 1.526(3)$ ,  $C4-C3A = 1.500(3)$  Å in the pyran ring also agree well with the standard values [22] and with some related structures [23–26]. Furthermore,  $C4-C8 = 1.526(3)$  Å conveys the presence of a single C–C bond. Some other important torsion angles are given in Table 4.

Intermolecular interactions are responsible for the stability of molecules within the unit cell. A pair of intermolecular  $N17-H171\dots N1$  and  $N17-H172\dots N16$  hydrogen bonds link the molecules to inversion dimers that generate  $R^2_2(23)$  graph-set motifs for N–H $\cdots$ N interactions [28,29] (Figure 2). These dimers are arranged in a manner to form chains of rings parallel to the (110) direction.

**Table 4.** Torsion angles for the title compound.

A	B	C	D	Angle (°)	A	B	C	D	Angle (°)
N1	N2	C3	C3A	-0.1(2)	C5	C4	C8	C13	47.0(3)
N1	N2	C3	C14	179.74(18)	C5	C6	O7	C7A	-1.1(3)
N2	N1	C7A	C3A	0.6(2)	C6	C5	C15	N16	152(14)
N2	N1	C7A	O7	-179.32(17)	C6	O7	C7A	N1	-176.90(18)
N2	C3	C3A	C4	-179.6(2)	C6	O7	C7A	C3A	3.2(3)
N2	C3	C3A	C7A	0.5(2)	C7A	N1	N2	C3	-0.3(2)
C3	C3A	C4	C5	177.0(2)	C7A	C3A	C4	C5	-3.1(3)
C3	C3A	C4	C8	-60.4(3)	C7A	C3A	C4	C8	119.5(2)
C3	C3A	C7A	N1	-0.7(2)	C8	C4	C5	C6	-117.6(2)
C3	C3A	C7A	O7	179.20(19)	C8	C4	C5	C15	62.7(2)
C3A	C4	C5	C6	5.2(3)	C8	C9	C10	C11	-0.2(3)
C3A	C4	C5	C15	-174.55(18)	C9	C8	C13	C12	-0.7(3)
C3A	C4	C8	C9	106.9(2)	C9	C10	C11	C12	0.0(4)
C3A	C4	C8	C13	-72.2(2)	C10	C11	C12	C13	-0.1(3)
C4	C3A	C7A	N1	179.32(18)	C11	C12	C13	C8	0.5(3)
C4	C3A	C7A	O7	-0.7(3)	C13	C8	C9	C10	0.6(3)
C4	C5	C6	O7	-3.4(3)	C14	C3	C3A	C4	0.5(4)
C4	C5	C6	N17	175.4(2)	C14	C3	C3A	C7A	-179.4(2)
C4	C5	C15	N16	-28(14)	C15	C5	C6	O7	176.31(18)
C4	C8	C9	C10	-178.52(18)	C15	C5	C6	N17	-4.9(3)
C4	C8	C13	C12	178.39(18)	N17	C6	O7	C7A	179.87(17)
C5	C4	C8	C9	-134.0(2)					

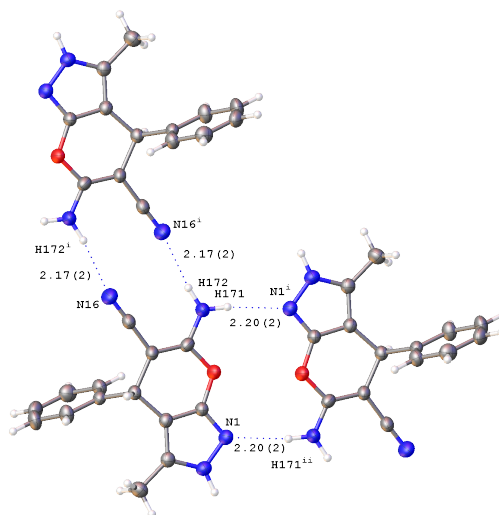
**Table 5.** Geometry of intermolecular interactions of the title compound.

D-H...A	D-H, Å	H...A, Å	D...A, Å	$\theta$ (D-H...A), °
N17-H171...N1 <sup>i</sup>	0.89(2)	2.20	3.080(3)	171.6
N17-H172...N16 <sup>ii</sup>	0.92(2)	2.17	3.079(3)	171
N2-H2...Cg3 <sup>iii</sup>	0.92(3)	2.55	3.38(2)	149

Symmetry codes: (i)  $-x-1, -y+1, -z$ ; (ii)  $-x, -y+1, -z+1$ ; (iii)  $-x, -y+2, -z$ .**Table 6.** Geometry of  $\pi$ - $\pi$  interactions for the title compound\*.

CgI	CgJ	CgI...CgJ, Å	CgI...P, Å	$\alpha$ , °	$\beta$ , °	$\Delta$ , Å
Cg1	Cg2 <sup>i</sup>	3.523	3.444	1.81	10.38	0.74

\* Symmetric code: (i)  $-x, -y, -z$ . Cg1 represents the center of gravity of the pyrazole ring, and Cg2 represents the center of gravity of the pyran ring. CgI...CgJ represents the distance between the ring centroid; CgI...P represents the perpendicular distance of the centroid of one ring from the plane of the other;  $\alpha$  is the dihedral angle between the planes of rings I and J;  $\beta$  is the angle between the normal to the centroid of ring I and the line joining the ring centroids;  $\Delta$  is the displacement of the centroid of rings J relative to the intersection point of the normal to the centroid of ring I and the least squares plane of ring J.

**Figure 2.** Dimer structure of the title compound. Symmetry codes: (i)  $-x, 1-y, 1-z$ ; (ii)  $1-x, 1-y, 2-z$ .

Furthermore, molecules are reinforced by  $\pi$ ... $\pi$  interaction between pyrazole and pyran rings (I and J): the distance between the ring centroids Cg1...Cg2 ( $-x, 1-y, -z$ ) is 3.523 Å; the perpendicular distance of the centroid of ring I from the plane of ring J (Cg1...P is 3.444 Å); the dihedral angle between the planes of rings ( $\alpha$  is 1.81°); the angle between normal to the centroid of ring I and the line joining ring centroids ( $\beta$  is 10.38°); and the displacement of the centroid of ring J relative to the intersection point of the normal to the ring I and the least squares plane of ring J ( $\Delta$  is 0.74 Å). The geometry of N-H...N

and N-H... $\pi$  type of intermolecular hydrogen bonding is given in Table 5.

Crystal packing analysis showed that there exist intermolecular hydrogen bonds of N-H...N and N-H... $\pi$  type, along with  $\pi$ - $\pi$  interactions; which play an important role in crystal structure stabilization. The pack view of molecules within the unit cell was generated using OLEX2 [30] and is viewed down to the  $a$ -axis as shown in Figure 3. The molecules are organized in the crystal lattice, forming ladder-like patterns. The geometry of these interactions is presented in Tables 5 and 6.

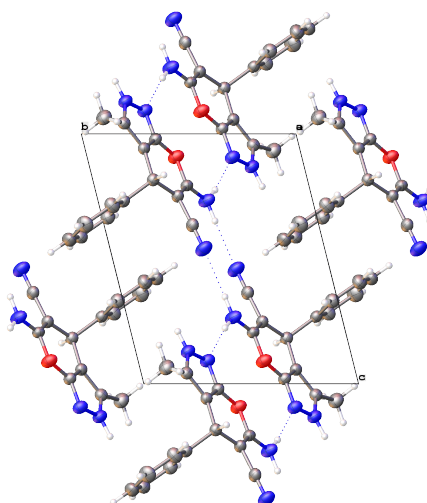


Figure 3. Packing view of molecules down to the *a* axis for hydrogen interactions.

#### 4. Conclusion

The biologically important scaffold, 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile, was synthesized using DMSO as a solvent under ambient conditions, and characterized by means of single X-ray crystallographic studies in order to elucidate the crystal structure and understand the behavior of the title molecule in the presence of different hydrogen bond modes and  $\pi\cdots\pi$  interactions stabilization. Intermolecular interactions are responsible for the stability of molecules within the unit cell.

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#### Supporting information

CCDC-971311 contains the supplementary crystallographic data for this article. 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](mailto: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.

#### Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.  
 Author contributions: All authors contributed equally to this work.  
 Ethical approval: All ethical guidelines have been adhered to.  
 Sample availability: Samples of the compound are available from the author.


#### CRedit authorship contribution statement

Conceptualization: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Methodology: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Software: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Validation: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Formal Analysis: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Investigation: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Resources: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Data Curation: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Writing - Original Draft: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Writing - Review and Editing: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Visualization: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Supervision: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta; Project Administration: Naresh Sharma, Indrajit Karmakar, Goutam Brahmachari, Vivek Kumar Gupta.

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