International Journal of Pure and Applied Researches http://ijopaar.com; 2017 Vol. 4(1); pp. 57-68, ISSN: 2455-474X

Comparative Analysis of One-Pot Facile Synthesis of Biologically Relevant Novel Tetrahydro-4H-Chromene-3-Carbonitrile and their X-Ray Crystallographic Behaviors

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Abstract

Syntheses and X-ray structural investigations have been compared for the three tetrahydro-4H-chromene-3-carbonitrile derivatives, 2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (I), 2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (II) and 2-Amino-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile hemihydrate (III) respectively. The compounds (I) and (III) crystallize in the monoclinic crystal system with space group C_2/c and compound (II) with space group P-1 crystallizes in the triclinic crystal system. The cyclohexene ring in all the compounds adopts sofa conformation. The pyran ring in compounds (I and II), deviates significantly from planarity and adopts boat conformation while the pyran ring in compound-III is almost planar. In the crystal structure of (I), (II) and (III), the molecules are linked by an elaborate system of N-H···O and N-H···N hydrogen bonds to generate a chain like construct. The crystal structures of all the three molecules were solved by direct method using single crystal X-ray diffraction data collected at room temperature and refined by full-matrix least-squares procedures. The X-ray crystallographic properties of these synthesized compounds of potential biological interests are compared herein.

Keywords: 4H-Pyran, single crystal, X-ray diffraction, Direct methods, Interactions.

1. Introduction

4*H*-Pyran-annulated heterocyclic scaffolds represent a "privileged" structural motif well distributed in naturally occurring compounds (Feuer, *et al*., 1974; Dean, 1963; Goel and Ram, 2009) with a broad spectrum of significant biological activities (Raj, *et al*., 2010; Flavin, *et al*., 1996; Morgan, *et al*., 2002; Kumar *et al*., 2009.). Recently, a series of synthetic 2-amino-3-cyano-4*H*-pyrans have been evaluated to possess potent anticancer (Skommer, *et al*., 2006; Kasibhatla, *et al*., 2004; Kamnitzer, *et al*., 2007; Bhavanarushi, *et al.,* 2013.), antibacterial and antifungal (Paliwal, *et al*., 2013; Kumar *et al*., 2009.), and anti-rheumatic (Smith, *et al*., 1995) properties. In this communication, I wish to present the comparative analysis of one-pot facile synthesis of a novel 4*H*-pyran-annelated heterocyclic compound, namely 2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (I), 2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (II) and 2-Amino-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile hemihydrates (III).

2. Experimental

2.1 Synthesis

2.1.1 2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (I)

An oven-dried screw cap test tube was charged with a magnetic stir bar, 3-bromobenzaldehyde (0.183 g, 1 mmol), malononitrile (0.066 g, 1.1 mmol), urea (0.007 g, 10 mol % as organo-catalyst), and EtOH:H_2O (1:1 v/v; 4 mL) in a sequential manner; the reaction mixture was then stirred vigorously at room temperature for about 20 min. After that, dimedone (0.140 g, 1 mmol) was added to the stirred reaction mixture, and the stirring was continued for 6 h (Brahmachari *et al*., 2014).

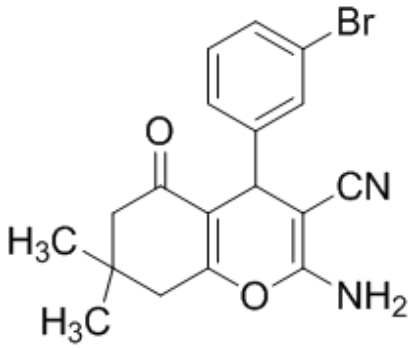

Figure-1 Chemical structure of the title compound-I

2.1.2 2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (II)

An oven-dried screw cap test tube was charged with a magnetic stir bar, 4-nitrobenzaldehyde (0.151 g, 1 mmol), malononitrile (0.066 g, 1.1 mmol), urea (0.007 g, 10 mol % as organo-catalyst), and EtOH:H2O (1:1 v/v; 4 mL) in a sequential manner; the reaction mixture was then stirred vigorously at room temperature for about 20 min. After that, dimedone (0.140 g, 1 mmol) was added to the stirred reaction mixture, and the stirring was continued for 5h (Brahmachari *et al*., 2014).

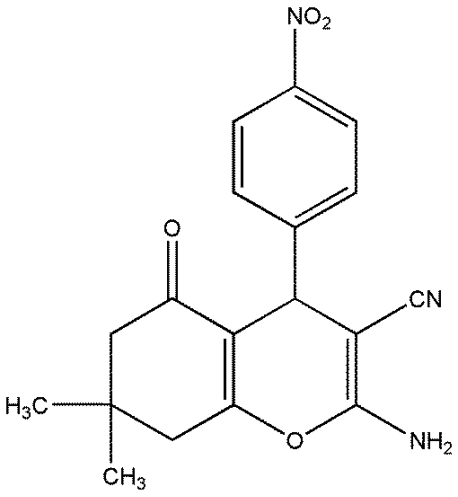

Figure-2 Chemical structure of the title compound-II

2.1.3 2-Amino-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile hemihydrate (III)

An oven-dried screw cap test tube was charged with a magnetic stir bar, pyridine-4-aldehyde (0.107 g, 1 mmol), malononitrile (0.066 g, 1.1 mmol), urea (0.007 g, 10 mol % as organo-catalyst), and EtOH:H_2O (1:1 v/v; 4 mL) in a sequential manner; the reaction mixture was then stirred vigorously at room temperature for about 20 min. After that, 5,5-Dimethylcyclohexane-1,3-dione (dimedone; 0.140 g, 1 mmol) was added to the stirred reaction mixture, and the stirring was continued for 6 hours (Brahmachari & Banerjee, 2013).

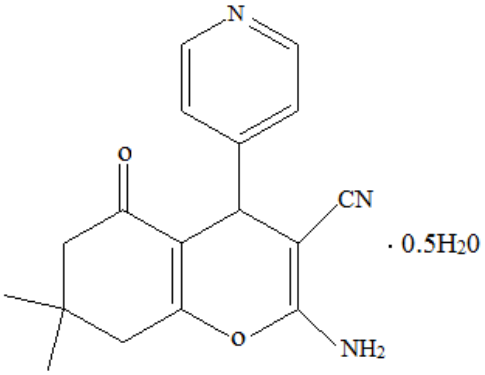

Figure-3 Chemical structure of the title compound-III

The progress of the reaction reported in all the compounds was monitored by TLC. On completion of the reaction, a solid mass precipitated out that was filtered off followed by washing with aqueous ethanol to obtain crude product which was purified just by recrystallization from ethanol without carrying out column chromatography. The structure of compounds I, II and III was confirmed by analytical as well as spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR, and TOF-MS.

Single crystal reported was obtained for all the compounds from DMSO as a solvent. For crystallization 50 mg of compound dissolved in 5 ml DMSO and left for several days at ambient temperature which yielded white block shaped crystals. The chemical structure of compound-I, compound-II and compound-III is given in Figure-1, Figure-2 and Figure-3 respectively.

2.2. Characterization

2.2.1 2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (I)

Infrared spectra were recorded using a Shimadzu (FT-IR 8400S) FT-IR spectrophotometer using KBr disc. ^{1}H and ^{13}CNMR spectra were obtained at 400 and 100 MHz, respectively, using a BrukerDRX-400 spectrometer and DMSO-d_6 as the solvent. Mass spectra (TOF-MS) were measured on a QTOF Micro mass spectrometer. Elemental analyses were performed with an Elementar Vario EL III Carlo Erba 1108 microanalyzer instrument. The melting point was recorded on a Chemiline CL-725 melting point apparatus and is uncorrected. Thin layer chromatography (TLC) was performed using silica gel 60 F254 (Merck) plates.

White solid. Yield 86%. Mp: 227-228°C. IR (KBr) ν_{max}/cm^{-1}: 3331, 3304, 3128, 3035, 2945, 2326, 2189, 1670, 1664, 1601, 1583, 1373, 1364, 1231, 1144, 1034, 876, 862, 631. ^{1}HNMR (400 MHz, DMSO-d_6) δ/ppm: 7.39 (1H, d, J = 8.4 Hz, aromatic H), 7.31 (1H, t, J = 1.6 Hz, aromatic H), 7.27 (1H, t, J = 8.0 & 7.6 Hz, aromatic H), 7.16 (1H, d, J = 7.6 Hz, aromatic H), 7.09 (2H, s, NH_2), 4.21 (1H, s, C*H*), 2.53 (2H, s, CH_2), 2.26 (1H, d, J = 16.4 Hz,), 2.13 (1H, d, J = 16.0 Hz), 1.04 (3H, s, CH_3), 0.96 (3H, s, CH_3). ^{13}CNMR (100 MHz, DMSO-d_6)δ/ppm: 196.16, 163.30, 158.95, 147.87,

131.05, 130.34, 129.95, 126.77, 121.97, 119.92, 112.51, 58.07, 50.33, 35.75, 32.25 (2C), 28.73, 27.19. TOF-MS: 395.0364 $[M+Na]^+$. Elemental analysis: Calcd. (%) for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.51; found: C, 57.88; H, 4.56; N, 7.53.

2.2.2 2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (II)

Infrared spectra were recorded using a Shimadzu [FT-IR 8400S] FT-IR spectrophotometer using KBr disc. ^{1}H and ^{13}CNMR spectra were obtained at 400 and 100 MHz, respectively, using a BrukerDRX-400 spectrometer and DMSO-d_6 as the solvent. Mass spectra [TOF-MS] were measured on a QTOF Micro mass spectrometer. Elemental analyses were performed with an ElementarVario EL III Carlo Erba 1108 microanalyzer instrument. The melting point was recorded on a Chemiline CL-725 melting point apparatus and is uncorrected. Thin layer chromatography [TLC] was performed using silica gel 60 F254 [Merck] plates.

White solid. Yield 92%. Mp: 183-185°C. IR (KBr) ν_{max}/cm^{-1}: 3373, 3304, 3177, 2953, 2872, 2303, 2181, 1647, 1612, 1607, 1595, 1510, 1348, 1223, 1138, 1022, 849, 721, 555. ^{1}HNMR (400 MHz, DMSO-d_6) δ/ppm: 8.17 (2H, d, J = 8.4 Hz, aromatic H), 7.45 (2H, d, J = 8.4 Hz, aromatic H), 7.19 (2H, s, NH_2), 4.37 (1H, s, CH), 2.54 (2H, s, CH_2), 2.26 (1H, d, J = 16.0 Hz), 2.11 (1H, d, J = 16.0 Hz), 1.04 (3H, s, CH_3), 0.96 (3H, s, CH_3). ^{13}CNMR (100 MHz, DMSO-d_6) δ/ppm: 196.18, 163.56, 158.99, 152.71, 146.67, 129.03 (2C), 124.10 (2C), 119.75, 112.13, 57.39, 50.26, 36.06, 32.24 (2C), 28.66, 27.35. TOF-MS: 362.1117 $[M+Na]^+$. Elemental analysis: Calcd. (%) for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38; found: C, 63.68; H, 5.07; N, 12.41.

2.2.3 2-Amino-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile hemihydrate (III)

White solid. Yield 92% (0.272 g). Mp: 214–216° C. IR (KBr) ν_{max}/cm^{-1}: 3389, 3312, 3038, 2962, 2878, 2341, 2330, 2183, 1674, 1653, 1599, 1529, 1479, 1360, 1213, 1149, 1041, 922, 852, 787, 658. ^{1}HNMR (400 MHz, DMSO-d_6) δ/ppm: 8.49 (2H, d, J = 5.6 Hz, aromatic H), 7.19 (2H, s, NH_2), 7.18 (2H, d, J = 1.2 Hz, aromatic H), 4.23 (1H, s, CH), 2.54 (2H, s, CH_2), 2.27 (1H, d, J = 16.0 Hz), 2.14 (1H, d, J = 16.4 Hz), 1.04 (3H, s, CH_3), 0.97 (3H, s, CH_3). ^{13}CNMR (100 MHz, DMSO-d_6) δ/ppm: 196.11, 163.69, 159.11, 153.45, 150.12 (2C), 122.93 (2C), 119.78, 111.84, 57.17, 50.27, 35.58, 32.23 (2C), 28.68, 27.36. TOF-MS: 296.0589 [M + H]+. Elemental analysis: Calcd. (%) for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23; found: C, 69.18; H, 5.81; N, 14.21.

3. X-ray data collection and structure refinement

The title compounds (I-III) were synthesized following a simple, straightforward and highly efficient multicomponent one-pot protocol at ambient conditions. The structures of the compounds (I), (II) and (III) were determined by single-crystal X-ray diffraction analysis. X-ray data of compounds (I), (II) and (III) were collected on a X'calibur system-Oxford diffraction using Mo$K\alpha$ (λ=0.71069 Å) at room temperature. The solution was obtained by direct methods and refined by full-matrix least-squares refinement methods (Sheldrick, 2008) based on F2, using SHELXL97. All non-H atoms were refined anisotropically. All H atoms were fixed geometrically with their U_{iso} values 1.2 times their phenyl C atoms and 1.5 times their terminal methyl C atoms. The geometry of the molecule was calculated using the WinGX (Farrugia, 2012), PARST (Nardelli, 1995) and PLATON (Spek, 2009) softwares. Crystallographic data and details of the data collection and structure solution and refinement are listed in Table-1.

Table-1

Summary of the crystal structure, data collection and structure refinement parameters for compounds (I), (II) and (III).
Experiments were carried out at 293 K with Mo*Kα* (0.71073 Å) radiation using a X'calibur system – Oxford diffraction make, U.K.

Compound	*(I)*	*(II)*	*(III)*
Crystal data			
Chemical formula	$C_{18}H_{17}BrN_2O_2$	$C_{20}H_{23}N_3O_5S$	$C_{17}H_{17}N_3O_2.0.5H_2O$
Crystal system, space group	Monoclinic, C_2/c	Triclinic, P-1	Monoclinic, C_2/c
a, *b*, *c* (Å)	23.557(2), 9.2963(7) 15.7502(12)	8.21(7), 9.22(7), 14.55(11)	22.010(6),11.0364(10), 17.147(4)
α, β, γ (°)	90, 93.43(8), 90	74.89(6), 87.39(6), 78.55(7)	90, 130.37(4), 90
h, k, l ranges	-28≤ h ≤16, -11≤ k ≤ 11, -17≤ l ≤19	-7 ≤ h ≤ 10, -11 ≤ k ≤11, -17 ≤ l ≤ 17	-27 ≤ h ≤27, -13 ≤ k ≤ 13, -21 ≤ l ≤ 21
V(Å^3)	3443.0(5)	1044.09(14)	3173.4(12)
μ (mm^{-1})	2.398	0.191	0.087
Crystal size (mm)	0.3 × 0.2 × 0.2	0.3 × 0.2 × 0.2	0.3 × 0.3 × 0.2
Z	8	2	8
Data collection			
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Reflections observed(I > 2σ(I))	1411	2250	2377
R_{int}	0.0617	0.0347	0.0417
Refinement			
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, *S*	0.058, 0.1056, 0.934	0.061, 0.1358, 1.023	0.043, 0.1152, 1.069
Reflections collected / unique	6665 / 3385	7317/4095	18015/3110
No. of parameters	210	298	218
$\Delta\rho_{max}$, $\Delta\rho_{min}$, (e Å^{-3})	-0.528, -0.491	0.338, -0.311	-0.247, 0.179

Computer programs: *CrysAlis PRO* (Oxford Diffraction,2010), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), *ORTEP-3* (Farrugia, 2012), *PLATON* (Spek,2009).

4. Results and Discussion

The X-ray analyses showed that the molecules of all three compounds have slightly different structures. There is only one molecule in an asymmetric unit cell in all the three compounds. The crystal structure reveals the presence of a DMSO solvent in compounds (II) and water solvent is present in compound (III). There are no any significant differences found between bond lengths and bond angles of all the three compounds despite of different substituent's at some positions. The X-ray crystal structure analysis reveals that the final refinement converged to the R-values of 0.058 (I), 0.061 (II) and 0.043 (III). The goodness of fit (GOOF) is 0.934 (I), 1.023 (II) and 1.069 (III). These values are an indicator of quality determination of atomic peaks/locations. In the molecules, the expected geometric parameters are observed. The overall molecular geometry of all the compounds, including bond distances (Allen *et al*., 1987) has a normal range and corresponds to those observed in related structures (Tu *et al.*, 2001; Wang, 2011; Mohamed *et al.*, 2012; Hu *et al*., 2012; Kant *et al.,* 2013).

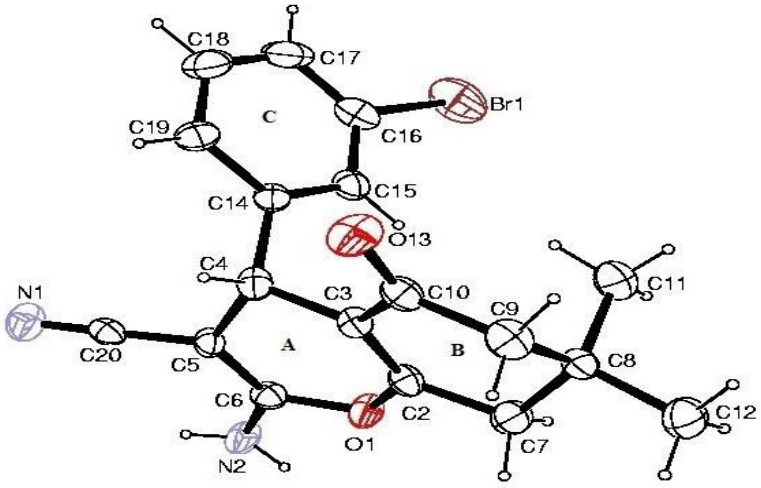

Figure-4 Molecular structure of 2-Amino-4-(3-bromophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (I) with displacement ellipsoids drawn at 40% probability level.

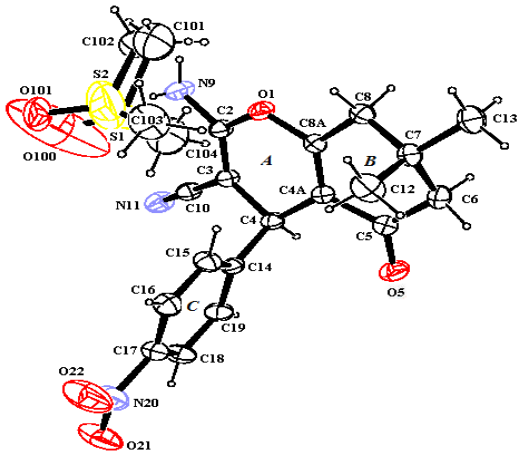

Figure-5 Molecular structure of 2-Amino-7,7-dimethyl-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (II) with displacement ellipsoids drawn at 40% probability level.

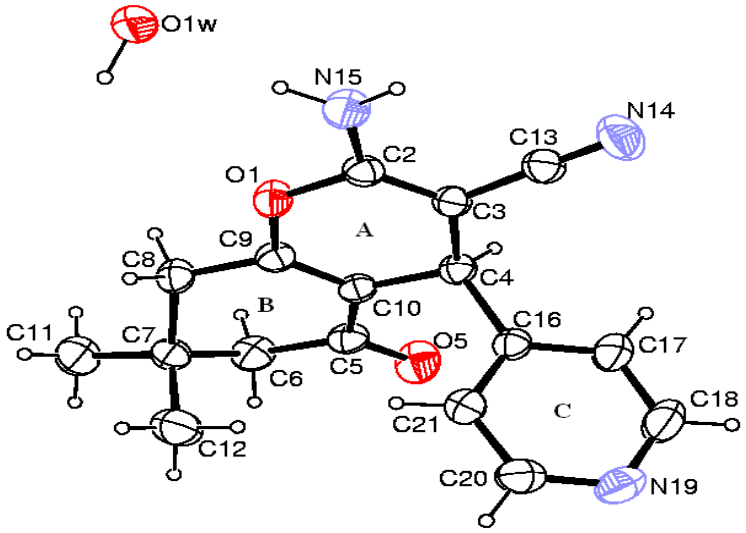

Figure-6 Molecular structure of methyl 2-Amino-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile hemihydrate (III) with displacement ellipsoids drawn at 40% probability level.

Within the pyran rings of the three compounds, the lengths of the C-O bonds differ by only 0.004 Å in compound (I), 0.014 Å in compound (II) and 0.003 Å in compound (III), even though these are formally single bonds, respectively. Similarly, the C2-C3 and C5-C6 distances differ by 0.024 Å in compound (I), 0.018 Å in compound (II) and 0.015 Å in compound (III), even though these are formally double bonds. These observations are consistent with a significant degree of aromatic-type electronic delocalization within the pyran rings.

The length of the double bond C10 = O13 [1.215(5) Å] in compound (I), C5 = O5 [1.224(3) Å] in compound (II) and C5 = O5 [1.221(3) Å] in compound (III), is longer than that observed for carbonyl bonds [1.19 Å], probably because the carbonyl oxygen atom are involved in an intermolecular N-H…O hydrogen bond and is comparable with the related structure (Abdel-Aziz *et al*. 2012; Xu *et al.,* 2012).

The bond length (C20-N11) = 1.137(5)Å for compound (I), (C10-N11) = 1.148(3)Å for compound (II) and (C13-N14) = 1.145(3)Å for compound (III) and bond angle (C5-C20-N1) = 176.7(5)° in compound (I), (C3-C10-N11) = 179.0(3)° in compound (II) and (C3-C13-N14) = 179.1(2)° in compound (III), are almost same in all the three compounds and shows linear character of the carbonitrile group, a feature observed in carbonitrile compounds (Mohamed *et al.*, 2012). The average endocyclic bond angles of the cyclohexene {[116.03(4)° compound-I], [116.3(2)° compound-II], [116.3(2)° compound-III]} and pyran rings {[119.1(4)° compound-I], [119.5(4)° compound-II], [119.95(2)° compound-III]}, for all the three compounds are almost same and agree well with the structure of its kind "2-Amino-7,7-dimethyl-5-oxo-4-[3-(trifluoromethyl)phenyl]-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile". The C-Br distance [(C16-Br1 = 1.888(6) Å] in substituted benzene ring in compound (I), is in good agreement with the literature value (Allen *et al*., 1987).

The cyanide group with pyrano ring [(O1-C6-C5-C20) = -176.9(4)° (I)] and [(O1-C2-C3-C10) = -177.0(2)° (II)] orients in -anti-periplanar (*-ap*) conformation. Also, the amino group [(C2-O1-C6-N2) = -170.0(4)°] and [(C8A-O1-C2-N9) = -170.0(4)°] orients in-anti-periplanar (*-ap)* conformation for compounds (I) and (II), while in compound (III), both the cyanide and amino groups orients in (+*ap*) conformation with pyrano ring as indicated by tortional angles [(O1-C2-C3-C13) = 177.8(3)° and (C9-O1-C2-N15) = 178.6(2)°].

The pyran ring in compounds (I and II), deviates significantly from planarity and adopts boat conformation with asymmetry parameters [ΔC_S (O1) = 3.706, ΔC_2 (C2-C3) = 14.00 (compound-I)] and [ΔC_S (O1) = 1.74, ΔC_2 (C2-C3) = 8.99 (compound-II)]. But the pyran ring in compound-III is almost planar and deviate slightly from planarity with maximum torsion angle equals to -6.1° for C3/C4/C10/C9. Cyclohexene ring in all the three compounds adopts sofa conformation with asymmetry parameters [ΔC_S (C3) = 9.987 for compound-I, ΔC_S (C4A) = 8.32 for compound-II and ΔC_S (C4A) = 8.32 for compound-III] (Duax & Norton, 1975).

The principal motifs in the crystal structures of compounds (I) and (II) are constructed by means of N-H···O and N-H···N hydrogen bonds while in compound (III), supramolecular aggregation depends on just N-H…O hydrogen bonds. Both the active H atoms of the NH_2 group [compounds (I) and (II)] participate in intermolecular N-H…N and N-H…O hydrogen bonds.

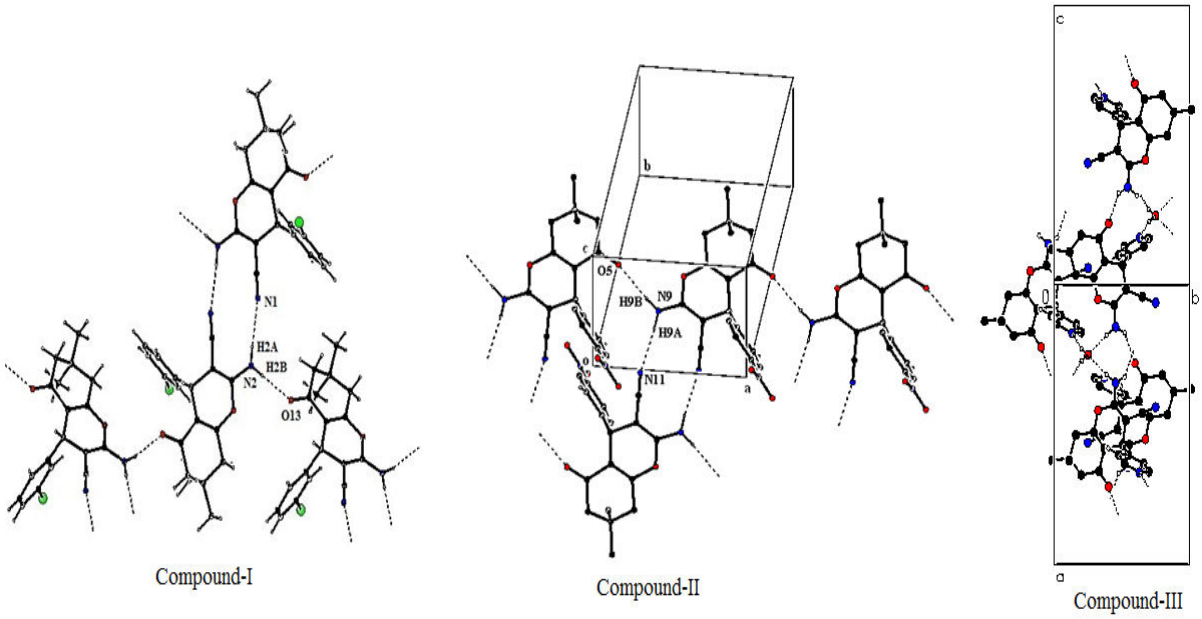

Figure-7 Partial view of intermolecular hydrogen interactions between the molecules (I,II,III)

The formation of the two-dimentional supramolecular structure is readily analysed in terms of centrosymmetric dimer as the basic building block. A pair of intermolecular N2-H2A…N1 and N2-H2B…O13 hydrogen bonds in compound (I) and N9-H9A…N11 and N9-H9B…O5 hydrogen bonds in compounds (II) generates a chain of rings. Atom N2 in the molecule acts as a donar to atoms N1 and O13 [compound (I)] and atom N9 in the molecule acts as a donar to atoms N11 and O5 [compound (I)], so forming a centrosymmetric $R_2^2(12)$ dimmers and chains having graph-set motif of C(8) for compounds (I) and (II) while in compound (III), intermolecular N15-H15…O5 hydrogen bond link the molecules into chains having graph-set motif of C(8). The propagation of these motifs generates infinite chain of rings. The best packing view for compounds (I) and (III) is obtained along b-axis forming a chain like patterns where as for compound (II), the best view has been obtained along c-axis also forming chains as illustrated in the figures 4, 5 and 6. Water solvent molecule in compound (III) also takes part in intramolecular interactions thus helps in forming the supramolecular structures (Tables 5, 6 and 7). In addition to this π–π electron interactions are observed in crystal structure of compound (III) (Table 8) that too plays a decisive role in the crystal organization while such interactions are absent in the compounds (I) and (II) respectively.

Table-2
Selected bonds lengths (Å) and angles (°) for compound (I)

O1-C2	1.366(5)	O1-C6	1.370(5)
N1-C20	1.137(5)	N2-C6	1.338(5)
C5-C20	1.419(6)	C16-Br1	1.888(6)
C10-O13	1.215(5)	C8-C11	1.534(7)
C2-O1-C6	118.5(3)	C3-C2-O1	122.8(4)
O13-C10-C3	120.4(4)	O13-C10-C9	122.9(4)
C3-C10-C9	116.6(4)	N1-C20-C5	176.7(5)
N2-C6-C5	127.6(4)	N2-C6-O1	110.8(4)

Table-3
Selected bonds lengths (Å) and angles (°) for compound (II)

O1-C2	1.367(3)	O1-C8A	1.380(3)
C2-N9	1.332(3)	C4A-C8A	1.330(4)
C10-N11	147(3)	C5-O5	1.223(3)
C7-C12	1.526(4)	C7-C13	1.528(4)
C5-C4A-C4	118.4(2)	O5-C5-C4A	120.5(3)
O5-C5-C6	121.9(3)	O1-C8A-C8	111.2(2)
N11-C10-C3	178.9(3)	O21-N20-O22	123.3(3)
O21-N20-C17	118.6(3)	O22-N20-C17	118.1(3)

Table-4
Selected bonds lengths (Å) and angles (°) for compound (III)

O1-C2	1.372(2)	C5-O5	1.221(3)
C9-C10	1.335(3)	N19-C20	1.327(3)
O1-C9	1.369(2)	C18-N19	1.333(3)
C2-N15	1.333(3)	C13-N14	1.145(3)
C2-O1-C9	119.0(2)	O1-C9-C8	110.7(2)
C3-C13-N14	179.1(2)	C4-C10-C5	118.9(2)
C11-C7-C12	109.2(2)	C16-C21-C20	119.7(2)
O1-C9-C10	123.1(2)	C3-C4-C10	109.0(2)

Table-5
Geometry of intermolecular interactions for compound (I)

D–H…A	D–H(Å)	H…A(Å)	D…A(Å)	D–H…A(°)
N2-H2A…N1[i]	0.86	2.17	3.019(5)	168
N2-H2B…O13[ii]	0.86	2.05	2.871(5)	159

Symmetry code(s): (i) –x, 1-y, 1-z (ii) x,-y, 1/2+z

Table-6
Geometry intermolecular interactions for compound (II)

D–H…A	D–H(Å)	H…A(Å)	D…A(Å)	D–H…A(°)
N9-H9A…N11[i]	0.86	2.30	3.1452	169
N9-H9B…O5[ii]	0.86	2.18	3.0275	168
C19-H19…N11[iii]	0.93	2.50	3.2539	138

Symmetry code(s): (i) –x+1,-y,-z (ii) x-1, y, z (iii) –x+2,-y,-z

Table-7
Geometry of intermolecular and intramolecular interactions for compound (III)

D–H…A	D–H(Å)	H…A(Å)	D…A(Å)	D–H…A(°)
N15-H151…O1W	0.91(3)	2.09(3)	2.992(3)	174(3)
O1W-H11...N19[i]	0.92(3)	1.98(4)	2.881(3)	167(3)
N15- H152…O5[ii]	0.85(2)	2.18(2)	2.888(2)	142(2)

Symmetry code(s): (i) –x+1/2, y-1/2, -z+1/2 (ii) x, -y+2, z+1/2

Table-8

Geometry of π–π interactions. Cg1 represents the center of gravity of the ring (A). CgI…CgJ represents the distance between the ring centroids; CgI…P, the perpendicular distance of the centroid of one ring from the plane of the other. α is the dihedral angle between the planes of rings I and J; β is the angle between normal to the centroid of ring I and the line joining ring centroids; Δ is the displacement of the centroid of ring J relative to the intersection point of the normal to the centroid of ring I and the least-squares plane of ring J.

CgI	CgJ	CgI…CgJ(Å)	CgI…P(Å)	α (°)	β(°)	Δ (Å)
1	1[i]	3.8547(2)	3.555	0.00	22.75	1.49

Symmetry code(s): (i) 1-x, 1-y, 1-z

5. Conclusion

In conclusion, three biologically relevant tetrahydro-4H-chromene-3-carbonitrile derivatives (**I-III**) were synthesized following a simple, straightforward and highly efficient multicomponent one-pot protocol at ambient conditions, and the molecules were fully compared in regard to their detailed spectral and X-ray crystallographic behavior. 4*H*-pyran-annelated heterocyclic compounds are very important in the drug-discovery studies and investigations have shown that the structural features of biologically relevant tetrahydrobenzo [*b*] pyran derivatives is of both scientific and practical interest. The result of the single-crystal X-ray structure analysis establishes the structural aspects of these compounds. Hydrogen bonding plays a key role in molecular recognition. These are the main non-covalent interactions in the molecule that influences the crystal packing.

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