Synthesis and Ab Initio Study of Pyrano[2,3-d]pyrimidine Derivatives

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ABSTRACT: *Tetrahydrobenzo[b]pyran derivatives 1 were utilized for the synthesis of several new pyrano[2,3-d]pyrimidine derivatives 2. Compound 2 was obtained in the presence of Ac_2O/H_2SO_4 (as a catalyst) and was confirmed by spectroscopic data such as IR, ^1H NMR and ^{13}C NMR. Ab initio calculation was carried out to study geometric optimization, thermodynamic parameters, aromaticity and dynamic process of conformational analysis for compound 2.*

KEY WORDS: *Pyrano[2,3-d]pyrimidine derivatives, Ab initio calculation, Aromaticity, Conformational analysis.*

INTRODUCTION

Benzopyrans have displayed an impressive bioassay of antibacterial (*Karnik et al.*, 2008 [1]), antioxidant (*Hwan et al.*, 2006 [2]) and cytotoxic activity (*Ren et al.*, 2009 [3]). The pyrimidine scaffold is the base of many bioactive molecular activities, such as antifungal (*Chen et al.*, 2003 [4]), antibacterial (*Cecile et al.*, 2003 [5]), antitumor (*Lin et al.*, 2009 [6]), anti-tubercular (*Deshmukh et al.*, 2009 [7]) and anti-herpes simplex virus type-1 (HSV-1) (*Rashad et al.*, 2009 [8]) agents. The synthesis methodology for preparation of novel pyranopyrimidine compounds and pyranopyrimidine derivatives which have been synthesized including pyrano[4,3-d]pyrimidine (*Bruno et al.*, 1999 [9]), 12H-chromon[2,3-d]pyrimidine (*Sabry et al.*, 2011 [10]), and pyrimidine[4́,5́:6,5]pyran derivatives (*Nahas et al.*, 2007 [11]) is of interest to researchers. Theoretical calculations have been done for such compounds (*Bigdeli et al.*, 2008 [12]; *Branowska et al.*, 2010 [13]; *Bigdeli et al.*, 2007 [14]).

The present research is comprised of two phases. The first is a report on the synthesis of novel pyrano[2,3-d]pyrimidine derivatives **2** from tetrahydrobenzo[b]pyran prepared using several methods (*Rashidian et al.*, 2010 [15]; *Mashkouri et al.*, 2009 [16]). The second phase is an ab initio study of HF/6-31G (d,p) levels for compound **2**. The energy, geometrical parameters, zero point vibrational energies, and Nucleus Independent Chemical Shift (NICS) values were calculated. A study of the dynamic processes of conformational analysis for compound **2** was performed.

EXPERIMENTAL SECTION

Instrumentation

All melting points were uncorrected and measured using capillary tubes on an electrothermal digital apparatus. Infrared (IR) spectra were recorded on a Shimadzo (FT-IR) 300 spectrophotometer in KBr.

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Brucker 500 MHz spectrometer in CDCl$_3$ with TMS as an internal standard. The progress of the reaction was monitored by Thin-Layer Chromatography (TLC) using CH$_2$Cl$_2$/EtOAc (3:1) as an eluent.

General procedure for synthesis of pyrano[2,3-d]pyrimidine derivatives

A solution of compound **1** (1 mmol) in Ac$_2$O (1.5 mL) with a catalytic amount of concentrated sulfuric acid was heated under reflux for 1 h. The reaction mixture was cooled at room temperature and kept for 1 day. The mixture was poured into water and the formed solid was filtrated, washed with water, and recrystallized using 2-propanol.

2,8,8-trimethyl-5-(3-Nitrophenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2a).

Pale Yellow solid; m.p>285°C; Yield 81%; IR (KBr) ν_{max} (cm^{-1}): 3439(NH), 2961(CH), 1773(C=O) and 1526(C=N). ^{1}H NMR (CDCl$_3$) δ ppm: 1.10, 1.16 (both s, 3H each, C(8) (CH$_3$)$_2$); 2.26 (s, 3H, C(2)-CH$_3$); 2.40 (m, 2H, CH$_2$); 2.65 (m, 2H, CH$_2$); 5.04 (s, 1H, H(5)); 7.40-8.21 (m, 4H, Ar-H) and 13.35 (br, 1H, NH).^{13}C NMR (CDCl$_3$) δ ppm: 21.46, 27.76, 29.23, 32.56, 33.52, 41.10, 50.77, 101.74, 113.72, 122.16, 123.81, 129.07, 134.80, 145.33, 148.29, 159.36, 161.27 165.27 and 195.53.

2,8,8-trimethyl-5-(2-chlorophenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione (2b)

Pale yellow solid; m.p. 224-225 °C; Yield 50%; IR (KBr) ν_{max} (cm^{-1}): 3430 (NH), 2961 (CH), 1775 (C=O) and 1512(C=N). ^{1}H NMR (CDCl$_3$) δ ppm: 1.07, 1.15 (both s, 3H each, C(8) (CH$_3$)$_2$); 2.21(m, 2H, CH$_2$); 2.50(s, 3H, C(2)-CH$_3$); 2.57 (m, 2H, CH$_2$); 5.05 (s, 1H, H(5)); 7.01-7.50 (m, 4H, Ar-H) and 13.10 (br, 1H, NH). ^{13}C NMR (CDCl$_3$) δ ppm: 27.40, 29.52, 32.05, 32.25, 41.70, 40.09, 50.87, 113.87, 115.43, 126.56, 126.90, 127.91, 130.00, 130.37, 131.83, 133.12, 133.63, 140.06, 163.27 and 196.84.

Computational details

Ab initio calculations were carried out using the Gaussian 03 (*Frisch et al.*, 2004 [17]) program. The structural parameters, thermodynamic properties and stability energy for all compounds were fully optimized without symmetry constraints at the HF level with the 6-31G(d,p) basic set. Nucleus independent chemical shift NICS (0), (1) and (-1) calculations (*Buhl et al.*, 1995 [18]; *Schleyer et al.*, 1996 [19]) for all systems were performed using the Gauge Invariant Atomic Orbital (GIAO) approach at the B3LYP/6-311+G** levels. The study of conformational analysis for compound **2** using rigid rotation method and vibrational frequencies were considered at the HF level with the 6-31G (d,p) basic set. The frequencies were scaled by a factor of 0.9135 and were used to compute the zero-point vibrational energies; moreover, thermodynamic parameters and NICS values for all rings of isomers were calculated.

RESULTS AND DISCUSSION
Synthesis

The starting material tetrahydrobenzo[b]pyran derivatives **1(a-b)** were easily obtained using the one-pot reaction of malonitrile, dimedone and aromatic aldehyde in the presence of alum (*Mobinikhaledi et al.,* 2010 [20]). Compounds **1(a-b)** were used as precursors for the synthesis and new pyrano[2,3-d]pyrimidine derivatives. The newly synthesized compounds **2(a-b)** were characterized by IR, ^{1}H NMR, and ^{13}C NMR. The reaction of compounds **1(a-b)** with a mixture of acetic anhydride in the presence of sulfuric acid under reflux produced pyrano[2,3-d]pyrimidine derivatives **2(a-b)** (Scheme 1).

In the IR spectra of compounds **1(a-b)**, nitril and amin groups were observed in the region of 2190 and 3400 cm^{-1} (*Balalaie et al.*, 2007 [21]). When compounds **2(a-b)** were synthesized, the signals for the nitril and amin groups were not shown. A singlet broad peak for stretching vibrations of NH group was detected in the region of 3400 cm^{-1}, which corresponds to the pyrimidine fragment (in compound **2**) with strong hydrogen bonds. In the ^{1}H NMR spectra of compound **1**, the signal of NH$_2$ group appeared at about 6.6 ppm with two integrations. For compound **2**, the signal of NH group of the pyrimidine ring was observed in the region of 13 ppm with one integration. This is a result of hydrogen bonding between the NH of the pyrimidine ring with the C=O of the pyrimidine ring of another compound **2** (scheme 2); consequently, the signal of NH group appeared in the downfield of the ^{1}H NMR spectra.
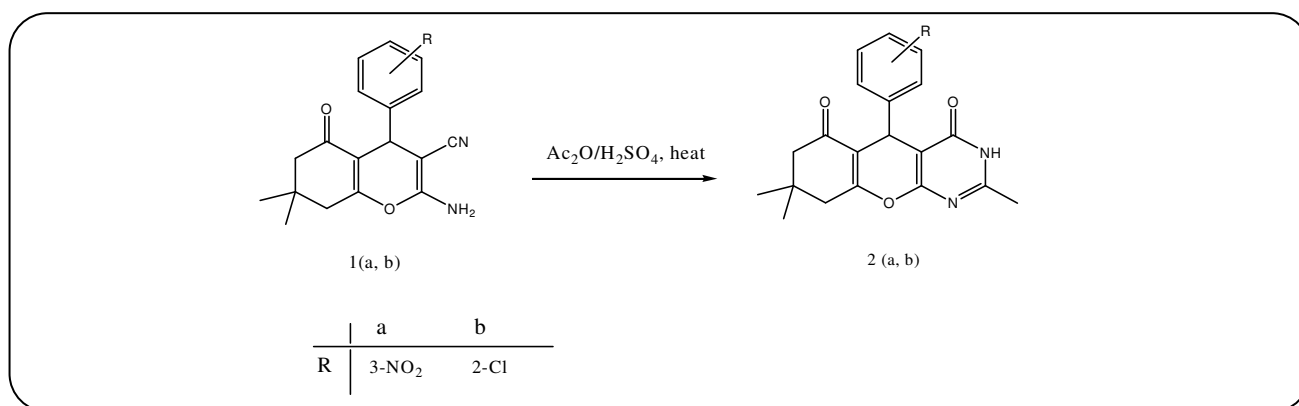
Scheme 1: Synthetic routs for pyrano[2,3-d]pyrimidine derivatives 2.
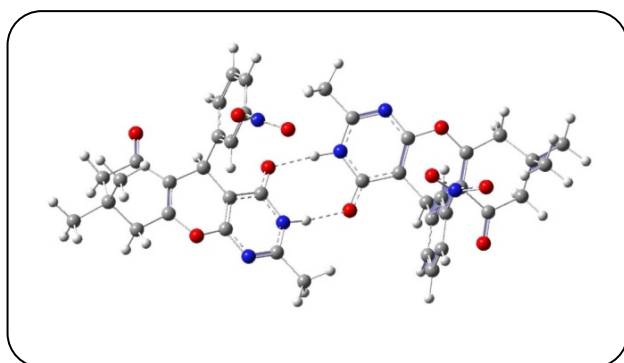
Scheme 2: Formation of hydrogen bonding in compounds 2.

Calculation

This study investigated the rotation barrier energies for compound **2** at the HF/6-31G (d,p) levels. Geometric and thermodynamic parameters, total energy, zero point energies, and NICS values of compounds **2(a-b)** and **3-5** were also calculated (scheme 3). NICS was calculated at the center of the rings (NICS (0)), at 1Å above the rings (NICS (1)), and at 1Å under the ring plane (NICS (-1)). According to Schreyer's convention (*Schleyer et al.*, 1996 [19]), rings with negative NICS values are quantified as aromatic (*Jiao et al.*, 1998 [22]; *Schleyer et al.*, 2000 [23]) and those with positive NICS values as anti-aromatic compounds.

Structural and thermodynamic parameters

The values of the energy, thermodynamic properties, and geometric parameters for compounds **2(a-b)** and **3-5** are summarized in Tables 1 and 2. In compounds **2(a-b)**, angle strain and steric hindrance caused bond angles and torsion angles; thus, the rings were quantitative and became out-of-plane in comparison with compounds **4** (Table 2).

Structural parameters and thermodynamic properties for conformers per compounds **2a** and **2b** are shown in Tables 3 and 4.

Conformational analysis

Conformational analysis of compounds **2a** and **2b** show four isomers for these compounds. The conformers and energy profiles of compounds **2a** and **2b** are shown in schemes 4 and 5. Rotation of the 3-nitrophenyl and 2-chlorophenyl rings around the covalent bond connecting the modular groups to the scaffold (responsible for conversion of G- to L-isomer) pass through T_1 and T_2 states. G and L configurations were found to have the lowest energy, whereas T_1 and T_2 configurations were found to have maximum energy. Energy calculation showed that G conformers were more stable for compounds **2a** and **2b**. To convert four conformers of compound **2a**, they should pass a lower barrier energy relative to compound **2b** together so the presence of the nitro group in the 3-position of the phenyl ring appears to cause less repulsion in T_1 and T_2 states of the isomers in comparison to the 2-position of chloro group on the phenyl ring. In compounds **2a** and **2b**, G- and L-isomers show little difference in energy level and T_1- and T_2-isomer energy values were very close.

### Aromaticity

The NICS values calculated for compounds **2-5** and the benzene ring are given in Table 5. Compounds **2-5** and benzene ring were used as a reference for compression of NICS with compound **2**. The NICS values of compound **3** reflect the paratropicity of the local current. The calculations showed some aromatic character for compound **4** and a high degree of aromatic character

Table 1: Geometric and thermodynamic parameters of compound 3-5.

Feature	3	4	5
HF/6-31G**//HF/6-31G**	-573.00000	-378.8969108	-378.8935738
G^o_{298}	-572.934560	-378.8969108	-378.8935738
H^o_{298}	-572.778534	-378.779468	-378.776387
S^o	321.044	82.113	83.413
ZPVE(NIMAG)	129.39025(0)	68.80977(0)	68.61168(0)
r_{21}	1.360	1.305	1.337
r_{32}	1.383	1.365	1.346
r_{43}	1.510	1.417	1.329
r_{54}	1.510	1.448	1.401
r_{65}	1.383	1.362	1.383
r_{16}	1.360	1.375	1.345
θ_{321}	122.48	122.38	125.50
θ_{432}	120.55	124.98	116.89
θ_{543}	111.65	111.34	122.83
θ_{654}	120.55	119.90	115.13
θ_{165}	122.48	125.09	123.54
θ_{216}	120.02	116.27	116.08
Φ_{4321}	1.177	0.00	-0.02
Φ_{5432}	-12.35	0.00	0.00
Φ_{6543}	12.35	0.00	0.01
Φ_{1654}	-1.17	0.00	0.01
Φ_{2165}	-11.52	0.00	0.00
Φ_{3216}	11.52	0.00	0.02

Total energies in Hartree and zero-point vibrational energy is in kcal/mol
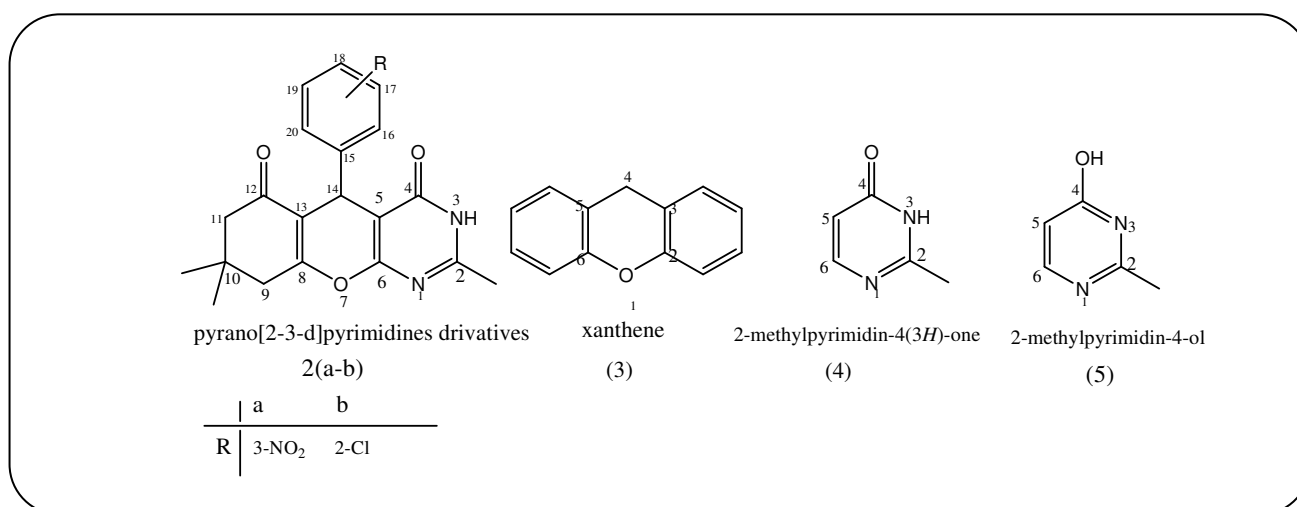
Scheme 3: The structure of scaffolds

Table 2: Comparison of compounds 2(a-b) with compounds 3 and 4 for geometric and thermodynamic parameters.

Feature	2a	2b	3 and 4(as refrence)
HF/6-31G**//HF/6-31G**	-1306.0560486	-1561.4766088	378.8969108
G^o_{298}	-1305.713511	-1561.144287	-378.818482
H^o_{298}	-1305.635936	-1561.071634	-378.779468
S^o	163.269	152.911	82.113
ZPVE(NIMAG)	248.80895 (0)	240.17569(0)	68.80977(0)
r_{21}	1.279	1.279	1.360
r_{32}	1.352	1.351	1.383
r_{43}	1.392	1.393	1.510
r_{54}	1.446	1.445	1.510
r_{65}	1.347	1.346	1.383
$r_{16}= r_{76}= r_{87}$	1.359	1.360	1.360
$r_{8,13}$	1.329	1.328	1.333
$r_{14,13}= r_{14,5}$	1.513	1.514	1.509
θ_{321}	122.56	122.56	122.48
θ_{432}	124.08	124.09	120.55
θ_{543}	113.18	113.13	111.65
θ_{654}	117.39	117.37	120.55
θ_{165}	126.19	126.23	122.48
θ_{216}	116.54	116.49	120.02
$\theta_{567}= \theta_{7,8,13}$	122.21	122.26	124.92
θ_{678}	119.28	119.37	115.71
Φ_{4321}	0.64	0.62	1.17
Φ_{5432}	1.14	1.81	-12.35
Φ_{6543}	-2.67	-3.66	12.35
Φ_{1654}	2.86	-1.20	-1.17
Φ_{2165}	-1.06	-1.06	-11.52
Φ_{3216}	-0.78	2.74	11.52
$\Phi_{14,567}$	3.11	-11.66	0.00
$\Phi_{13,14,56}$	-12.08	-11.66	0.00
$\Phi_{8,13, 14, 5}$	11.19	10.80	0.0
$\Phi_{78,13, 14}$	-1.32	-1.00	0.00
$\Phi_{678,13}$	-11.50	-9.75	0.00
Φ_{5678}	10.44	8.81	0.00

Total energies in Hartree and zero-point vibrational energy is in kcal/mol

Table 3: Geometric and thermodynamic parameters for isomers of compound 2a.

Feature	G	T_1	L	T_2
HF/6-31G**//HF/6-31G**	-1306.0560486	-1306.0463352	-1306.0538176	-1306.0460993
E_{rel}	(0.0)	(5.72)	(0.98)	(5.87)
G^o_{298}	-1305.713511	-1305.700622	-1305.711149	-1305.700436
E_{rel}	(0.0)	(8.14)	(1.44)	(8.22)
H^o_{298}	-1305.635936	-1305.627173	-1305.633756	-1305.626933
Erel	(0.0)	(5.51)	(1.33)	(5.66)
S^o	163.269	154.585	162.888	154.700
ZPVE(NIMAG)	248.80895(0)	248.82495(1)	248.77279(0)	248.82791(1)
r_{21}	1.279	1.279	1.279	1.279
r_{32}	1.352	1.350	1.352	1.351
r_{43}	1.392	1.391	1.392	1.393
r_{54}	1.446	1.445	1.446	1.445
r_{65}	1.347	1.347	1.347	1.347
$r_{16} = r_{76} = r_{87}$	1.359	1.359	1.360	1.359
$r_{8,13}$	1.329	1.328	1.329	1.329
$r_{14,13} = r_{14,5}$	1.513	1.516	1.513	1.519
θ_{321}	122.56	122.43	122.57	122.46
θ_{432}	124.08	124.26	124.10	124.26
θ_{543}	113.18	113.15	113.15	113.10
θ_{654}	117.39	117.03	117.37	117.16
θ_{165}	126.19	126.61	126.24	126.53
θ_{216}	116.54	117.34	116.51	116.34
θ_{567}	122.21	119.09	122.19	121.39
θ_{678}	119.28	117.97	119.18	117.97
$\theta_{7,8,13}$	123.04	122.03	123.03	122.01
$\theta_{8,13,14}$	122.59	121.12	122.60	121.02
$\theta_{13,14,5}$	108.20	106.72	108.14	106.68
$\theta_{14,5,6}$	122.91	121.20	122.95	121.23
$\theta_{13,8,9}$	125.83	126.16	125.86	126.16
$\theta_{8,9,10}$	113.34	112.90	113.34	112.90
$\theta_{9,10,11}$	108.51	108.47	108.49	108.47
$\theta_{10,11,12}$	113.68	114.18	113.68	114.18

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Table 3: Geometric and thermodynamic parameters for isomers of compound 2a (Continued).

$\theta_{11,12,13}$	117.27	117.44	117.29	117.44
$\theta_{12,13,8}$	119.01	118.65	118.98	118.54
$\theta_{12,13,14}$	118.39	120.25	118.41	120.32
$\theta_{20,15,14} = \theta_{16,15,14}$	120.77	120.53	121.04	120.60
$\theta_{15,14,13} = \theta_{15,14,5}$	111.90	113.11	111.95	112.61
Φ_{4321}	0.64	2.52	0.59	1.92
Φ_{5432}	1.14	0.33	0.92	-0.23
Φ_{6543}	-2.67	-3.95	-2.46	-2.75
Φ_{1654}	2.86	5.89	2.91	4.69
Φ_{2165}	-1.06	-3.13	-1.40	-3.09
Φ_{3216}	-0.78	-1.36	-0.46	-0.36
$\Phi_{14,567}$	3.11	5.68	2.91	4.58
$\Phi_{13,14,56}$	-12.08	-27.25	-12.23	-26.45
$\Phi_{8,13,14,5}$	11.19	25.58	11.25	26.08
$\Phi_{78,13,14}$	-1.32	-2.90	-0.93	-3.90
$\Phi_{678,13}$	-9.57	-22.53	-10.33	-22.13
Φ_{5678}	8.61	20.87	9.26	21.67
$\Phi_{12,13,89}$	-3.23	-4.76	-3.04	-6.92
$\Phi_{11,12,13,8}$	11.02	10.01	10.83	12.21
$\Phi_{10,11,12,13}$	-37.47	-35.76	-37.39	-36.56
$\Phi_{9,10,11,12}$	53.21	52.06	53.25	52.29
$\Phi_{89,10,11}$	-44.59	-45.56	-44.65	-45.46
$\Phi_{13,89,10}$	21.62	25.11	21.57	25.20
$\Phi_{12,13,14,15}$	68.46	84.33	68.75	84.93
$\Phi_{13,14,15,16}$	58.55	156.74	-120.13	-37.09
$\Phi_{13,14,15,20}$	-121.68	-27.06	60.07	144.76
$\Phi_{20,15,14,5}$	116.67	-148.56	-61.57	23.59
$\Phi_{16,15,14,5}$	-63.10	33.67	118.23	-158.26
Φ_{9876}	171.19	157.32	170.37	157.83
Φ_{8761}	-170.90	-156.53	-170.34	-156.83

Relative energies are with respect to the most stable conformation. Total energies in Hartree and relative energies (including zero-point energy) are in kcal/mol. Zero-point vibrational energy is scaled by a factor of 0.9135 eliminate known systematic error in calculations

Table 4: Geometric and thermodynamic parameters for isomers of compound 2b.

Feature	G	T_1	L	T_2
HF/6-31G**//HF/6-31G**	-1561.4766088	-1561.4565449	-1561.4744816	-1561.4574515
E_{rel}	(0.0)	(12.44)	(1.25)	(11.93)
G^o_{298}	-1561.144287	-1561.122510	-1561.142695	-1561.123213
E_{rel}	(0.0)	(13.52)	(0.92)	(13.13)
H^o_{298}	-1561.071634	-1561.052776	-1561.069569	-1561.053598
Erel	(0.0)	(11.69)	(1.21)	(11.23)
S^o	152.911	146.767	153.906	146.516
ZPVE(NIMAG)	240.17569(0)	240.01689 (1)	240.08780 (0)	240.07726 (1)
r_{21}	1.279	1.27946	1.28	1.28
r_{32}	1.351	1.35211	1.35	1.35
r_{43}	1.393	1.39507	1.40	1.39
r_{54}	1.445	1.44756	1.45	1.44
r_{65}	1.346	1.34462	1.35	1.35
$r_{16}= r_{76}= r_{87}$	1.360	1.35876	1.36	1.36
$r_{8,13}$	1.328	1.32942	1.33	1.33
$r_{14,13}= r_{14,5}$	1.513	1.52222	1.517	1.52
θ_{321}	122.56	122.50	122.49	122.52
θ_{432}	124.09	124.46	124.19	124.40
θ_{543}	113.13	112.53	113.21	112.83
θ_{654}	117.37	116.85	117.10	117.33
θ_{165}	126.23	126.78	126.45	126.58
θ_{216}	116.49	115.861	116.53	116.12
θ_{567}	122.26	120.45	122.36	120.66
θ_{678}	119.36	116.42	119.29	116.39
$\theta_{7,8,13}$	123.10	121.27	123.18	121.06
$\theta_{8,13,14}$	122.40	119.57	122.73	119.96
$\theta_{13,14,5}$	108.42	104.71	108.10	104.81
$\theta_{14,5,6}$	122.71	119.98	123.03	119.83
$\theta_{13,8,9}$	125.91	126.13	126.11	126.36
$\theta_{8,9,10}$	113.43	112.53	113.45	112.63
$\theta_{9,10,11}$	108.44	108.52	108.26	108.64
$\theta_{10,11,12}$	113.54	114.63	113.70	113.47

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Table 4: Geometric and thermodynamic parameters for isomers of compound 2b (Continued).

$\theta_{11,12,13}$	117.15	117.261	117.34	116.57
$\theta_{12,13,8}$	118.87	119.00	118.60	118.13
$\theta_{12,13,14}$	118.69	121.39	118.66	121.19
$\theta_{20,15,14}=\theta_{16,15,14}$	117.671	127.08	118.94	117.91
$\theta_{15,14,13}=\theta_{15,14,5}$	113.60	110.92	111.49	116.08
Φ_{4321}	0.62	2.88	0.51	2.61
Φ_{5432}	1.81	3.57	0.63	-0.77
Φ_{6543}	-3.66	-10.08	-1.81	-2.90
Φ_{1654}	-1.20	12.09	2.17	5.47
Φ_{2165}	-1.06	-5.59	-1.02	-3.75
Φ_{3216}	2.74	-2.31	-0.40	-0.45
$\Phi_{14,567}$	-11.66	7.56	2.51	6.47
$\Phi_{13,14,56}$	-11.66	-36.19	-10.14	-35.24
$\Phi_{8,13,14,5}$	10.80	34.86	9.15	34.52
$\Phi_{78,13,14}$	-1.00	-5.02	-0.50	-5.10
$\Phi_{678,13}$	-9.75	-29.09	-8.753	-29.10
Φ_{5678}	8.81	27.67	7.68	28.19
$\Phi_{12,13,89}$	-4.66	-6.04	-2.40	-12.90
$\Phi_{11,12,13,8}$	12.95	9.83	10.70	19.68
$\Phi_{10,11,12,13}$	-38.83	-34.35	-37.80	-41.67
$\Phi_{9,10,11,12}$	53.43	51.77	53.54	53.53
$\Phi_{89,10,11}$	-44.28	-46.13	-44.50	-44.74
$\Phi_{13,89,10}$	21.93	25.82	20.98	26.93
$\Phi_{12,13,14,15}$	65.77	90.92	67.17	101.33
$\Phi_{13,14,15,16}$	62.47	154.56	-120.77	-35.74
$\Phi_{13,14,15,20}$	-117.56	-28.24	59.38	147.33
$\Phi_{20,15,14,5}$	117.77	-147.64	-61.58	27.59
$\Phi_{16,15,14,5}$	-62.19	35.16	118.25	-155.47
Φ_{9876}	171.27	149.98	172.06	149.26
Φ_{8761}	-170.49	-149.88	-171.95	-150.03

Relative energies are with respect to the most stable conformation. Total energies in Hartree and relative energies (including zero-point energy) are in kcal/mol. Zero-point vibrational energy is scaled by a factor of 0.9135 eliminate known systematic error in calculations
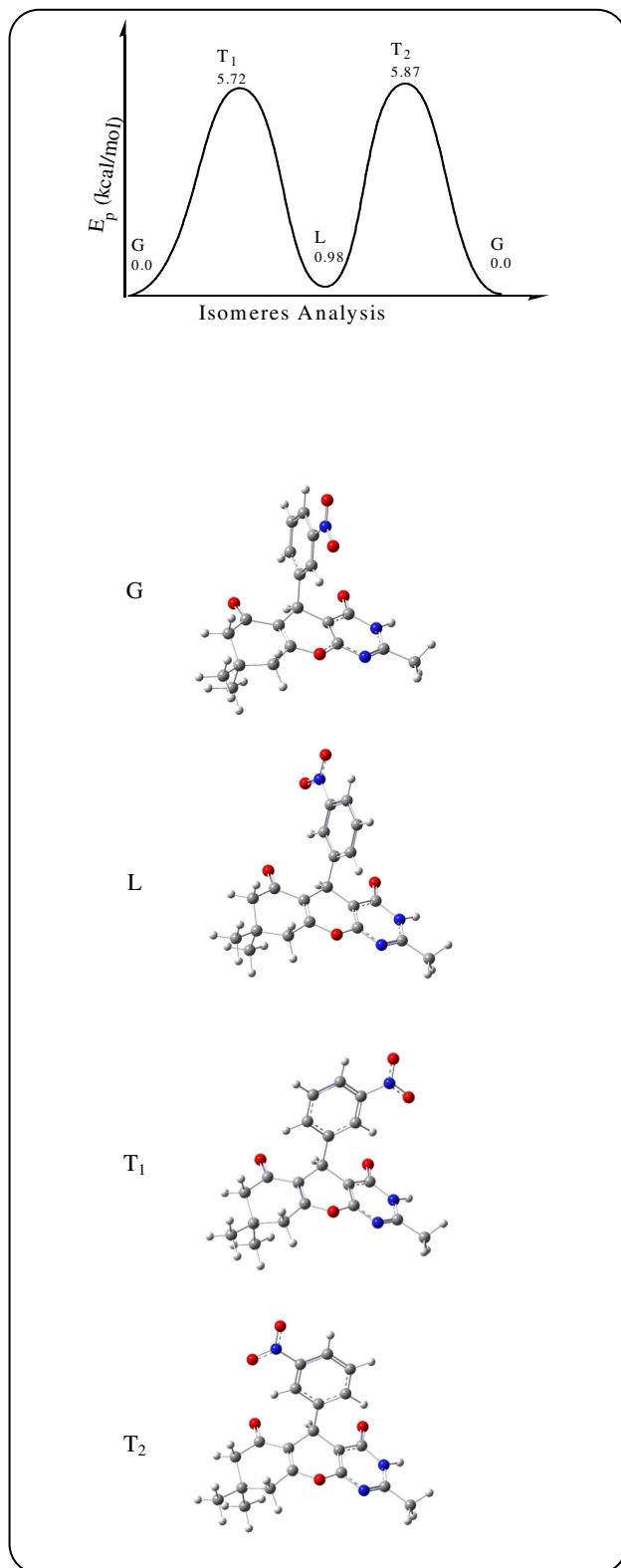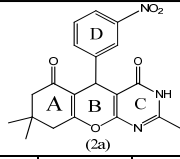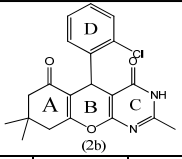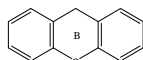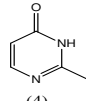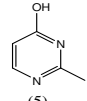
Scheme 4: Calculated HF/6-31G(d,p) strain energy (kcal/mol) profile, four conformers 2,8,8-trimethyl-5-(3-Nitrophenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione complete structure parameters are in Table 3.
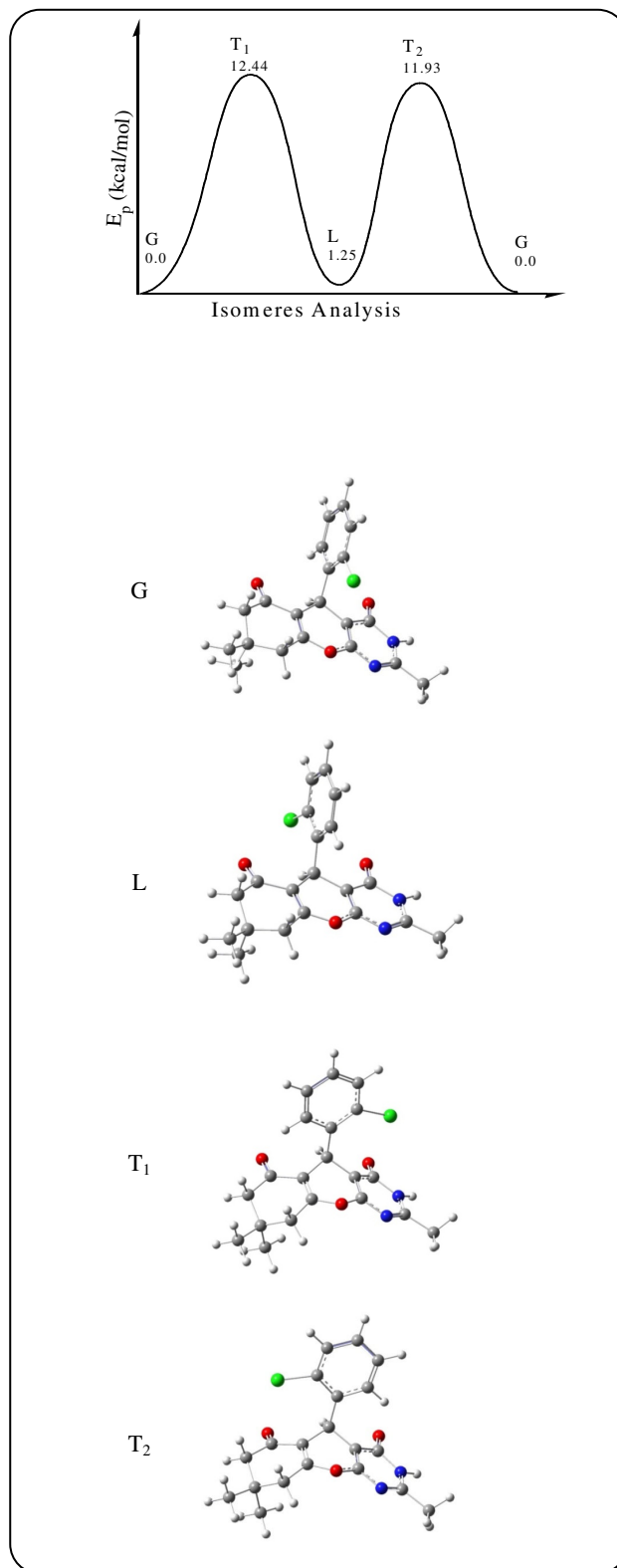
Scheme 5: Calculated HF/6-31G(d,p) strain energy (kcal/mol) profile, four conformers 2,8,8-trimethyl-5-(2-cholorophenyl)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione complete structure parameters are in Table 4.

Table 5: The NICS (0), (1) and (-1) values (ppm) were calculated by ab initio study in B3LYP/6-311+G** level of theory.

structure										
	B	C	D	B	C	D	3	4	5	benzene
$NICS(1)_{zz}$	5.3	-3.0	-19.5	3.2	-2.0	-24.1	7.9	-9.1	-21.9	-29.0
$NICS(0)_{zz}$	17.7	0.6	-10.1	17.3	6.5	-12.5	32.4	9.3	-5.5	-14.5
$NICS(-1)_{zz}$	5.8	-5.0	-18.6	5.2	-4.9	-24.1	2.7	-9.3	-21.9	-29.0

for compound **5**; benzene was determined by the NICS values. The resulting structure **5** shows that aromaticity decreased relative to the benzene ring because two nitrogen atoms which are electronegative have been located in the benzene ring.

The NICS values for compounds **2a** and **2b** indicate that ring B had less paratropicity of the local current than compound **3** and ring C decreased the ring current because of adjacent ring pressure as compared to compound **4**. Electron withdrawing groups (nitro and chloro groups i.e.) in ring D for compound **2** decreased the ring current relative to the benzene ring so NICS values for ring D decreased. Positive $NICS_{zz}$ values cannot reflect the ring current and these values result from local diatropic current which cause the NICS values to become positive. The observed high $NICS(0)_{zz}$ values for ring B result from local diatropic current (*Ranjbar et al.,* 2013 [24]). Calculations of structures **4** and **5** determined by amidic form (**4**) are preferable to phenolic form (**5**) caused by energy and aromaticity.

CONCLUSIONS

This study investigated the new synthesis of 2,8,8-trimethyl-5-(substituted)-5,7,8,9-tetrahydro-4H-chromno-[2,3-d]pyrimidine-4,6(3H)-dione bearing 3-nitro phenyl (**2a**) and 2-chloro phenyl (**2b**) rings at the 5-position of parent pyrano[2,3-d]pyrimidine. Theoretical calculations were performed for compounds **2**-**5**. Ab initio calculation provided an image of conformational analysis and stability energy for compounds **2**(**a**-**b**). Conformational analysis confirmed four conformers for compounds **2a** and **2b**.

In compound **2a,** nitro group showed less hindrance than the chloro group in compound **2b.** Thus, reduction rotation of the barrier energy was observed in the calculations. The results show that hindrance of the chloro group in compound **2b** increased rotation barrier energy.

The NICS values of compound **2** reveal that ring B has paratropicity of the local current and high positive NICD(0)zz values for ring B result from local diatropic current and ring C has a ring current. Locating the electron withdrawing groups (nitro and chloro groups) in the benzene ring decreased the NICS values for ring D at compound **2** relative to the benzene ring. The results showed that the amidic form in structure **4** is more stable than the phenolic forms in structure **5**, and the NICS values show better aromaticity in the phenolic form. The experimental results confirm the amidic structure because in compound **2** the amidic oxygen atoms in the carbonyl groups tend to allocate sp^2 hybrids and the electronegative atom prefer this hybrid.

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