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Synthesis and DFT Study of 7-Bromophenylnaphthopyran Moieties

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A one-pot, three-component reaction of 6-bromo-2-naphthol (**1**), *p*-chlorobenzaldehyde (**2**) and malononitrile or ethyl cyanoacetate (**3**) in ethanol/piperidine under reflux was performed to afford 4*H*-naphtho[2,1-*b*]pyrano-3-carbonitrile (**4a**) and ethyl 4*H*-naphtho[2,1-*b*]pyrano-3-carboxylate (**4b**) derivatives, respectively. The structure of these compounds was determined using IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopy and UV-Vis spectra. The molecular geometry of compounds **4a** and **4b** was determined at the B3LYP/631+G(d) level. The geometric optimization was performed on two tautomers and two conformers. Tautomers were separated by about 7.942 kcal/mol, while rotational conformers were separated by just 0.511 kcal/mol. The global electrophilicity, hardness, softness and local condensed Fukui functions were calculated and considered as molecular reactivity descriptors, moreover the frontier molecular orbitals (HOMO and LUMO) were also calculated.

Keywords: 6-Bromo-2-naphthol, 4-Chlorobenzaldehyde, Malononitrile, Ethyl cyanoacetate, Fukui functions, Density functional theory.

INTRODUCTION

The structural diversity of heterocyclic molecules has rendered them promising drug candidates [1,2]. Heterocyclic compounds containing oxygen atom/s, in particular, are of interest. One of the most intriguing groups of these materials is the benzopyran compounds, which provide researchers to improve their skills [3]. From a pharmaceutical and medical perspective, benzopyran compounds have been and continue to be considered a fruitful area of research [4-8]. Molecular engineering of these compounds was conducted with the hope of improving their biological, therapeutic and pharmacological properties.

The relevant literature on benzopyran compounds reveals that 4*H*-benzopyran and dihydropyrano[*c*]benzopyran and their derivatives are of considerable interest due to their wide range of pharmacological and biological activities [9-25], including antifungal [26], antitumor [27], anti-HIV [28], antimicrobial and antituberculous drugs [18] and muscle relaxants [29]. Depending on the pattern of substitution, these properties inspire numerous researchers to synthesize novel compounds with various aromatic rings bonded to the benzopyran moiety and acquire more active derivatives.

Following on from our earlier published works [30-38], herein we report the synthesis and characterization of new naphthopyran compounds. To further demonstrate the optical and biological results in terms of the synthesized compounds' structure activity relationships (SAR), density functional theory (DFT) is utilized to derive the theoretical parameters for the synthesized molecules [39-41].

EXPERIMENTAL

A Stuart Scientific Co., Ltd. device was used to determine melting points. On a Jasco FT/IR 460 additional spectrophotometer, IR spectra of KBr pellets were evaluated. A Bruker AV 400 MHz spectrometer was used to record ^{1}H and ^{13}C NMR spectra. A Shimadzu GC/MSQP5050A spectrometer was used to measure mass spectra. Sigma Aldrich or S.D. Fine Chemicals Ltd. provided all of the reagents and solvents, which were used without additional purification.

General steps for synthesizing of naphthopyran (4a-b)

Method A: A mixture 6-bromo-2-naphthol (**1**) (2.23 g, 0.01 mol), *p*-chlorobenzaldehyde (**2**) (1.40 g, 0.01 mol) and malononitrile (**3a**) or ethyl cyanoacetate (**3b**) (0.66 g, 0.01 mol

or 1.13 g, 0.01 mol), in absolute EtOH/piperidine (30 mL, 0.5 mL) was heated until precipitation was completed.

Method B: The condensation of 6-bromo-2-naphthol (**1**) (2.23 g, 0.01 mol), 2-(4-chlorobenzylidene)malononitrile (**5a**) or ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (**5b**) (1.88 g, 0.01 mol or 2.35 g, 0.01 mol) in absolute EtOH/piperidine (30 mL, 0.5 mL) was heated until precipitation was completed. The precipitated solid was removed, washed with methanol and recrystallized from dioxane.

2-Amino-7-bromo-4-(*p*-chlorophenyl)-4*H*-naphtho-[2,1-*b*]pyrane-3-carbonitrile (4a): Pale yellow crystals (dioxane); yield 92%, m.p.: 260 ¦C; IR (KBr, ν_{max}, cm^{-1}): 3350, 3321 (NH_2), 3184 (CH-arom.), 3081 (CH-aliph.), 2200 (C≡N), 1662 (C=C). ^{1}H NMR (DMSO-d_6, ppm) δ: 5.34 (s, 1H, pyran-CH), 7.10 (br, 2H, NH_2, exchangeable by D_2O), 7.18-78.14 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6, ppm) δ: 37.77 (C-4), 57.85 (C-3), 115.91 (C≡N), 118.60 (C-6), 118.71 (C-8), 120.73 (C-7), 126.24 (C-4a), 129.26, 129.40, 130.42, 130.75, 131.82 (Ar), 144.82 (C-5a), 147.60 (C-10a), 160.70 (C-2). MS *m/z* (%): 412 (M^+ + 3, 21.32), 410 (M^+ +1, 15.34), 409 (M^+ + 22.72), 169 (100). Anal. calcd. (found) % for $C_{20}H_{12}N_2OBrCl$ (*m.w.* 409.98): C, 58.35 (58.21); H, 2.94 (2.90); N, 6.80 (6.90).

Ethyl 2-amino-7-bromo-4-(*p*-chlorophenyl)-4*H*-naphtho-[2,1-*b*]pyrane-2-carboxylate (4b): Colourless needle crystals, (ethanol/benzene); yield 80%, m.p.: 145 ºC: IR (KBr, ν_{max}, cm^{-1}): 3458, 3324 (NH_2), 3010 (CH-arom.), 2970 (CH-aliph.), 1670 (C=O), 1622 (C=C). ^{1}H NMR (DMSO-d_6, ppm) δ: 1.28 (t, 3H, CH_3, *J* = 7.1 Hz), 4.03 (q, 2H, CH_2, *J* = 7.1 Hz), 5.47 (s, 1H, pyran-CH), 7.20 (br, 2H, NH_2, exchangeable by D_2O), 7.22-8.13 (m, 9H, Ar-H). ^{13}C NMR (DMSO-d_6, ppm) δ: 14.88 (CH_3-ester), 36.12 (C-4), 59.45 (C-3), 77.61 (CH_2-ester), 118.48 (C-7), 118.53 (C-6), 118.96 (C-8), 125.83 (C-4a), 128.55, 128.88, 129.29, 129.5, 130.37, 130.80, 131.07 (Ar), 116.00 (C-5a), 147.45 (C-10a), 160.70 (C-2), 168.38 (C=O). MS *m/z* (%): 460 (M^+ + 3, 6.35), 458 (M^+ +1, 11.46), 457 (M^+ + 16.202), 124 (100). Anal. calcd. (found) % for $C_{22}H_{17}NO_3BrCl$ (*m.w.* 457.01): C, 57.60 (57.49); H, 3.74 (3.52); N, 3.05 (2.81).

Computational details: Gaussian 16, a suite of DFT programs, was primarily used for this study [42]. After properly optimizing all geometric characteristics of all molecules, IR frequency calculations were performed to verify that the produced stationary sites were genuine potential energy minima. The Pople [43,44] basis sets were used in conjunction with the DFT method B3LYP [45,46] for the amino/imino system. The Gaussian-developed polarizable continuum model [47] (PCM) was used for the modeling in solution. Avogadro [48], a free program that uses the MMFF molecular mechanics force field, was used to perform conformational characterization of the synthesized compounds. The B3LYP/6-311+G(d,p) level of theory was used to optimize the lowest energy conformers.

RESULTS AND DISCUSSION

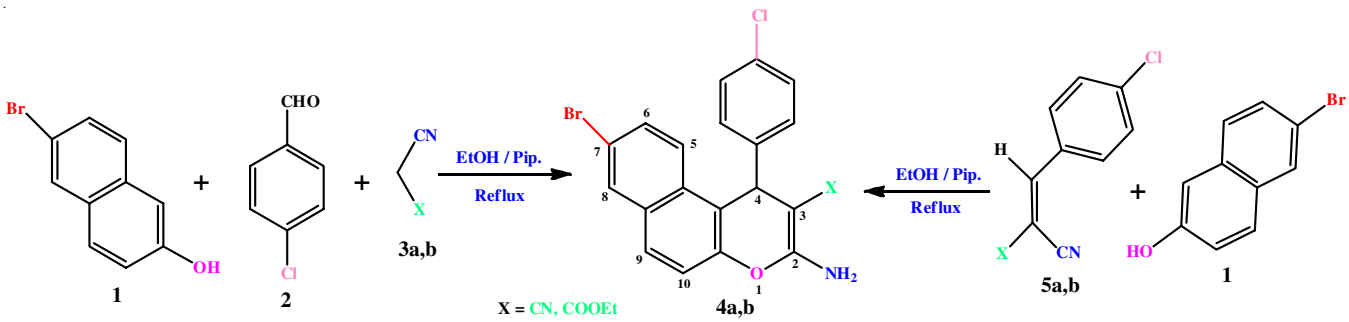
The condensation reaction of 6-bromo-2-naphthol (**1**) with *p*-chlorobenzaldehyde (**2**) and malononitrile or ethyl cyanoacetate (**3a-b**), in an EtOH/piperidine solution under reflux afforded 2-amino-7-bromo-4-(*p*-chlorophenyl)-4*H*-naphtho-[2,1-*b*]pyrane-3-carbonnitrile (**4a**) and ethyl 2-amino-7-bromo-4-(*p*-chlorophenyl)-4*H*-naphtho[2,1-*b*]pyrane-2-carboxylate (**4b**), respectively. The structure of compounds **4a** and **4b** was further supported by its independent synthesis from the reaction of compound **1** with 2-(4-chlorobenzylidene)malononitrile (**5a**) or ethyl 3-(4-chlorophenyl)-2-cyanoacrylate (**5b**) in an EtOH/piperidine solution under reflux (**Scheme-I**).

The IR spectra of compounds **4a-b** showed the absorption peaks at 3350, 3321 and 3458, 3324 cm^{-1} (NH_2), 2200 cm^{-1} (C≡N), 1670 cm^{-1} (C=O), while ^{1}H NMR and ^{13}C NMR spectra of compounds **4a-b**, which showed 4*H*-pyran at δ 5.34 and 5.47 and C-4 at δ 37.77 and 36.42 ppm. The mass spectra of compounds **4a-b** showed the corresponding molecular ion peaks of compound **4a** at *m/z* 412 (M^+ + 3, 21.32), 410 (M^+ +1, 15.34), 409 (M^+ + 22.72) and base peak at 232 (100), while compound **4b** at 460 (M^+ + 3, 6.35), 458 (M^+ +1, 11.46), 457 (M^+ + 16.202) and base peak at 124 (100).

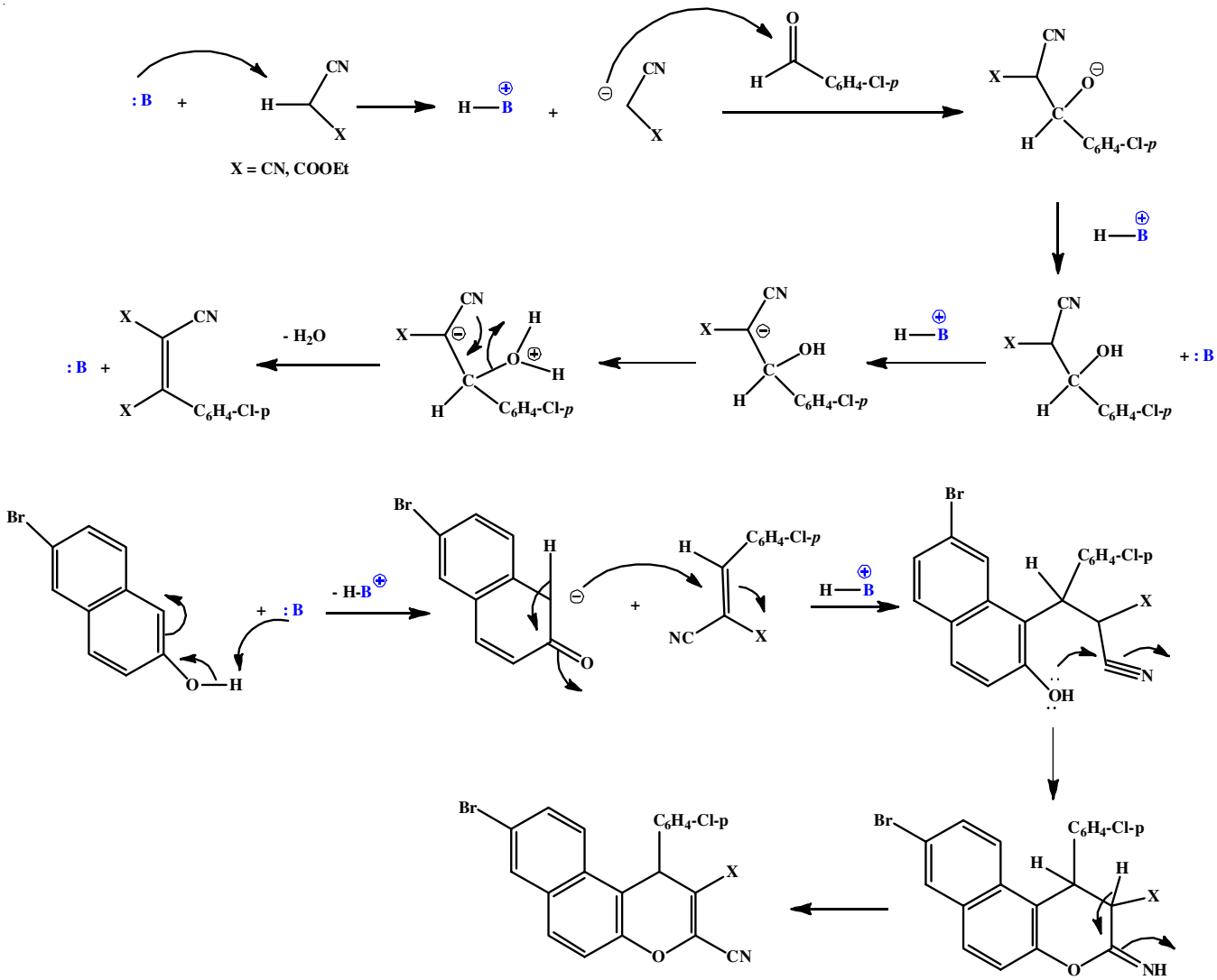
Mechanism: Scheme-II depicts a plausible mechanism for the formation of compounds **4a** and **4b** derivatives. In presence of piperidine, Knoevenagel reaction is initiated by the formation of 2-(4-chlorobenzylidene)malononitrile or ethyl 3-(4-chlorophenyl)-2-cyanoacrylate, following the elimination of one water molecule from the condensation of *p*-chlorobenzaldehyde and malononitrile or ethyl cyanoacetate. Tautomerization of 6-bromo-2-naphthol generates the enolate, which then reacts with 2-(4-chlorobenzylidene)malononitrile or ethyl-3-(4-chlorophenyl)-2-cyanoacrylate as a Michael acceptor to produce an intermediate, which was used to produce 7-bromonaphthopyrans (**4a-b**) by intramolecular cyclization and rearrangement.

Fragmentation patterns of compounds **4a-b**, respectively is shown in **Scheme-III**.

Computational study: Since the 6-311+G(d,p) basis set includes a polarization p-function for hydrogen atoms in addition



Scheme-I: Synthesis of 7-bromonaphthopyran derivatives



Scheme-II: Plausible mechanism for the formation of 7-bromonaphthopyran derivatives

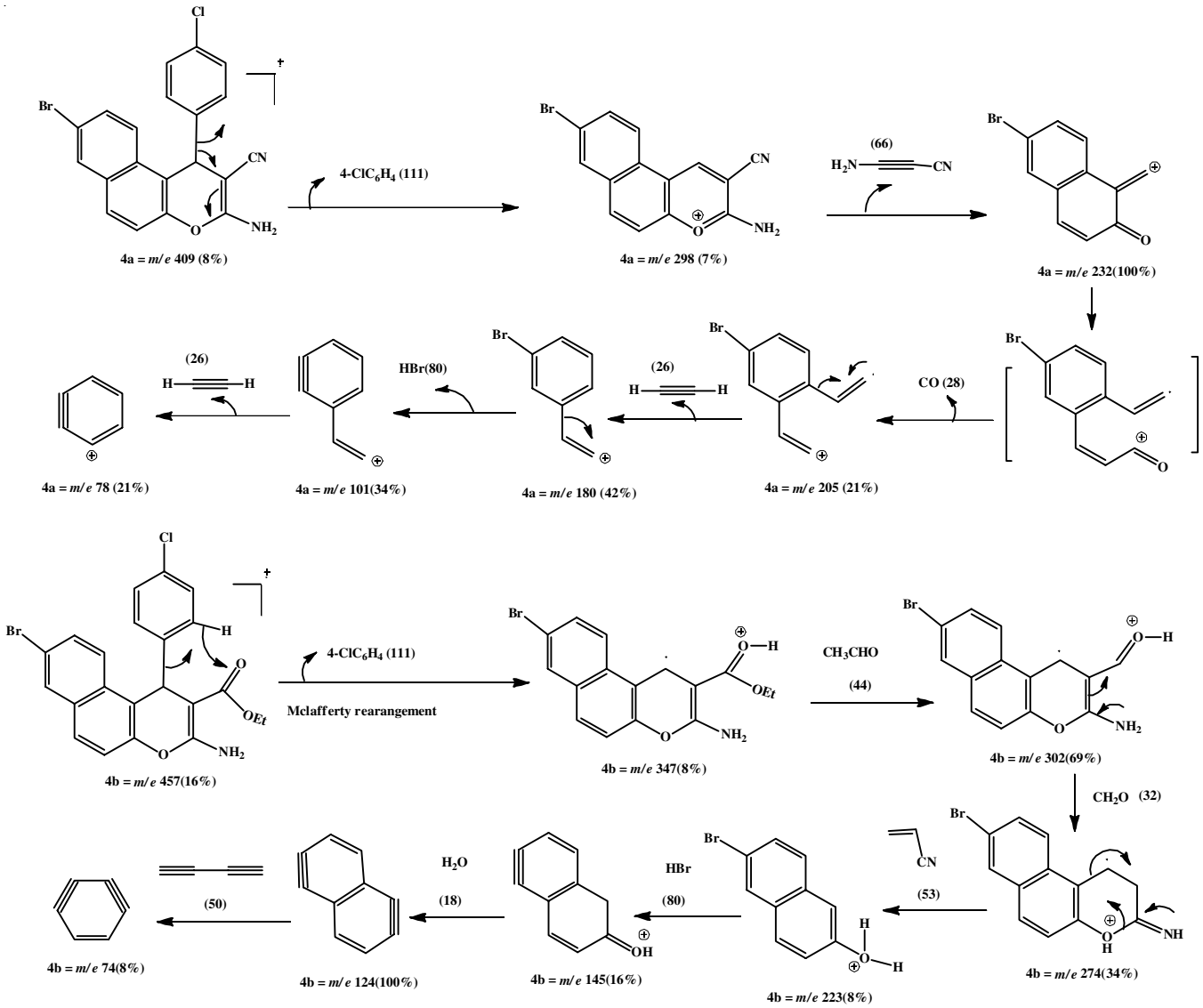
to the normal 6-31G(d) basis set, it is more appropriate for modeling proton transfer and prototropic tautomerism. The initial structure of compound **4b** was drawn by chem draw and the other possible tautomeric form **4b′** was built by proper shifts of the proton. As compound **4b** contains some rotatable single bonds, it is essential to execute a conformational analysis to find the lowest energy conformations of all tautomers (**Scheme-IV**).

The influence on the final result should be minimal, but this step is necessary, if we are to obtain the true lowest energy tautomers. Molecular Mechanics' MMFF force field was used to do a comprehensive rotor search on the two tautomers, rotating all single bonds and generating every feasible conformer. The resulting conformers were sorted by energy, with the 5 least energetic conformers for each tautomer being selected for optimization in the gas phase at the B3LYP/6-31G(d,p) level. The compound **4b** tautomer of the chemical was found to be the most stable. The largest difference in energy between it and **4b′** tautomer is 6.98 kcal/mol, which may be because compound **4b** tautomer can form an intramolecular hydrogen bond between the N-H_2 of the pyran ring and O from the ethoxy group of the ester group, as depicted in Fig. 1.

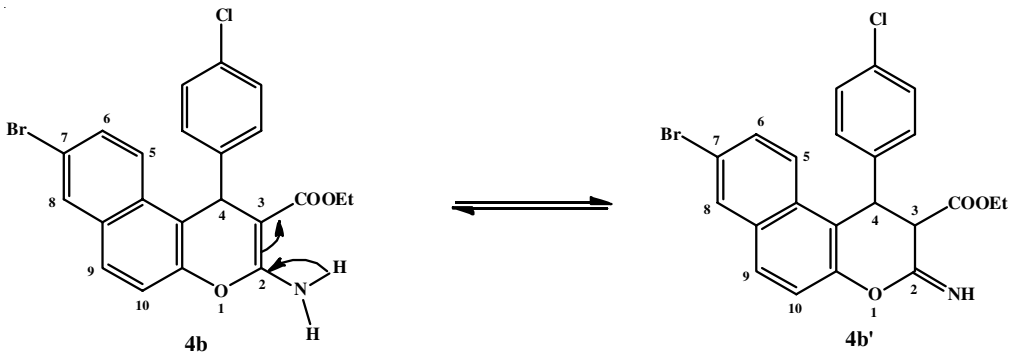
UV-visible absorption studies: The electronic absorption spectrum of compound **4b** was enrolled in acetone at ambient temperature in the range of 800 nm to 200 nm. The absorption bands were observed at 295 nm. The energy difference between the outermost molecular orbitals can be deduced from these electronic absorption spectra [48]. The UV-Vis spectra of compound **4b** in acetone, as computed by TDDFT, are shown in Fig. 2. The experimentally obtained spectra show a strong correlation with the TDDFT calculations in Table-1, both in terms of the absorption band and the peak positions.

The bond lengths and bond angles for compound **4b** (Fig. 3) were measured and recorded in Table-2 for further structural analysis.

Quantum chemical calculations: Single-point energy calculations were performed using the DFT method and the 6-311++G (d,p) basis set to determine the frontier molecular orbitals (FMO). The following equations [49] were used to estimate fundamental quantum parameters: energy gap ($\Delta E = E_{LUMO} - E_{HOMO}$), absolute electronegativities ($\chi = -E_{HOMO} + E_{LUMO}/2$), absolute hardness ($\eta = E_{LUMO} - E_{HOMO}/2$), absolute softness ($\sigma = 1/\eta$), chemical potentials ($\mu = -\chi$) and global electrophilicity ($\omega = X2/2\eta$).



Scheme-III: The fragmentation patterns of 7-bromo-4-(*p*-chlorophenyl)- naphthopyran derivatives (**4a,b**)



Scheme-IV: Tautomers of compound **4b**

TABLE-1
CALCULATED AND EXPERIMENTAL ABSORPTION WAVELENGTHS (λ, nm), POLARIZABILITY AND DIPOLE MOMENT (μ) OF COMPOUNDS **4b** AND **4b′**

Compound	Assignments	λ^a (nm)	λ^b (nm)	μ (Debye)	Polarizability (a.u.)
4b	H → L	298, 310	295	3.667922	317.457667
4b′	H → L	250, 3	–	1.948092	313.091000

[a]The calculated absorption wavelength at TD-B3LYP/6-311+G*(d, p) in acetone; [b]The experimental absorption wavelength in acetone.

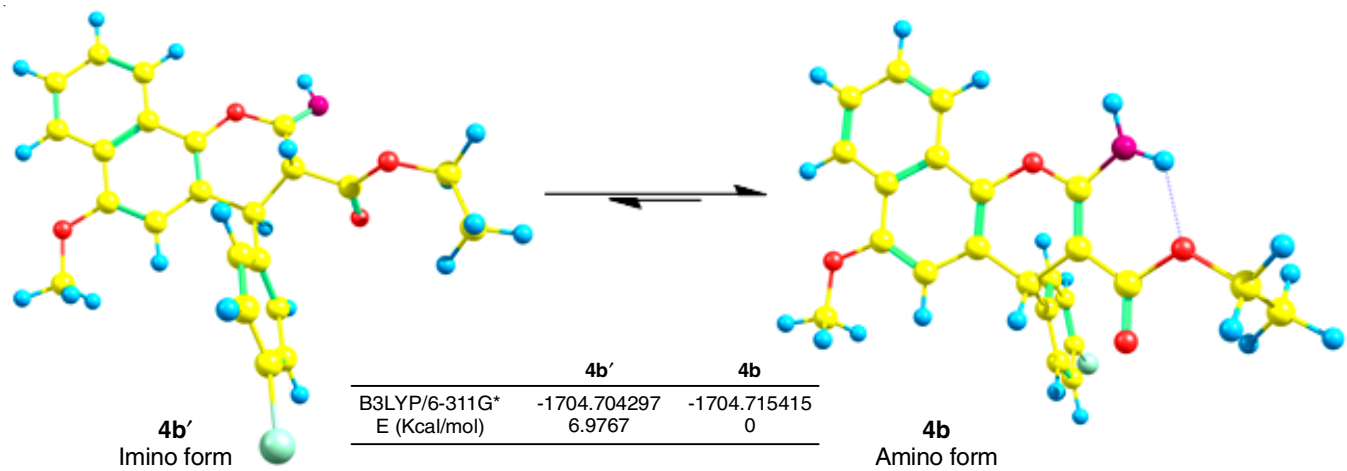


Fig. 1. 3D models of compounds **4b** and **4b′** optimized at the B3LYP/6-311+G(d,p) level of theory

TABLE-2
OPTIMIZED GEOMETRICAL PARAMETERS OF INVESTIGATED COMPOUND **4b** AT B3LYP/6-311G* LEVEL OF THEORY

Bond lengths (Å)							
R(1,2)	1.3769	R(7,28)	1.3626	R(15,36)	1.0079	R(22,23)	1.3917
R(1,6)	1.4105	R(8,9)	1.4201	R(15,37)	1.0094	R(22,43)	1.0846
R(1,30)	1.084	R(8,34)	1.0817	R(16,17)	1.2172	R(23,24)	1.3917
R(2,3)	1.4151	R(9,10)	1.3662	R(16,18)	1.3761	R(23,44)	1.0827
R(2,31)	1.0818	R(9,11)	1.5135	R(18,19)	1.4507	R(24,25)	1.3892
R(3,4)	1.4268	R(10,14)	1.3917	R(19,20)	1.5196	R(24,27)	1.7625
R(3,7)	1.4337	R(11,12)	1.5234	R(19,38)	1.0899	R(25,26)	1.3945
R(4,5)	1.4169	R(11,21)	1.5348	R(19,39)	1.0913	R(25,45)	1.0827
R(4,10)	1.4231	R(11,35)	1.0933	R(20,40)	1.0942	R(26,46)	1.0837
R(5,6)	1.3766	R(12,13)	1.3696	R(20,41)	1.0909	R(28,29)	1.4221
R(5,32)	1.082	R(12,16)	1.4541	R(20,42)	1.0928	R(29,47)	1.0952
R(6,33)	1.0843	R(13,14)	1.3594	R(21,22)	1.399	R(29,48)	1.0886
R(7,8)	1.3745	R(13,15)	1.3583	R(21,26)	1.3969	R(29,49)	1.0950
Bond angles (°)							
A(2,1,6)	120.2497	A(7,8,34)	121.084	A(13,15,37)	116.3267	A(21,22,43)	120.0113
A(2,1,30)	119.9563	A(9,8,34)	117.8848	A(36,15,37)	118.9338	A(23,22,43)	118.7458
A(6,1,30)	119.794	A(8,9,10)	119.0009	A(12,16,17)	123.9818	(22,23,24)	119.0827
A(1,2,3)	120.6823	A(8,9,11)	120.5831	A(12,16,18)	114.7734	(22,23,44)	120.7495
A(1,2,31)	120.7328	A(10,9,11)	120.4061	A(17,16,18)	121.2403	A(24,23,44)	120.1674
A(3,2,31)	118.5849	A(4,10,9)	122.5134	A(16,18,19)	116.8589	A(23,24,25)	121.0259
A(2,3,4)	119.0622	A(4,10,14)	115.8168	A(18,19,20)	111.6284	A(23,24,27)	119.4211
A(2,3,7)	122.0293	A(9,10,14)	121.6691	A(18,19,38)	108.6471	A(25,24,27)	119.5529
A(4,3,7)	118.9083	A(9,11,12)	110.4631	A(18,19,39)	104.2281	(24,25,26)	119.08
A(3,4,5)	119.007	A(9,11,21)	111.8857	A(20,19,38)	111.3434	A(24,25,45)	120.2222
A(3,4,10)	118.1354	A(9,11,35)	108.1937	A(20,19,39)	111.4333	A(26,25,45)	120.6974
A(5,4,10)	122.8575	A(12,11,21)	112.2647	A(38,19,39)	109.2863	A(21,26,25)	121.2226
A(4,5,6)	120.5722	A(12,11,35)	107.2041	A(19,20,40)	109.5565	A(21,26,46)	119.3866
A(4,5,32)	118.934	A(21,11,35)	106.5581	A(19,20,41)	110.8027	A(25,26,46)	119.3752
A(6,5,32)	120.4932	A(11,12,13)	120.0028	A(19,20,42)	111.0189	A(7,28,29)	118.5228
A(1,6,5)	120.4266	A(11,12,16)	115.3179	A(40,20,41)	108.2519	A(28,29,47)	111.2385
A(1,6,33)	119.7504	A(13,12,16)	124.6792	A(40,20,42)	108.2019	A(28,29,48)	105.8295
A(5,6,33)	119.823	A(12,13,14)	122.2274	A(41,20,42)	108.9283	A(28,29,49)	111.2437
A(3,7,8)	120.4105	A(12,13,15)	128.1395	A(11,21,22)	121.3805	A(47,29,48)	109.4353
A(3,7,28)	115.0215	A(14,13,15)	109.6058	A(11,21,26)	120.2658	A(47,29,49)	109.5411
A(8,7,28)	124.5678	A(10,14,13)	119.303	A(22,21,26)	118.3475	A(48,29,49)	109.4718
A(7,8,9)	121.0273	A(13,15,36)	116.6707	A(21,22,23)	121.2412		

Frontier molecular orbitals (FMOs) parameters: The nucleophilicity (electron donation) and electrophilicity (electron acceptance) of a molecule are displayed by the HOMO and LUMO states, respectively. The energy of the orbitals was determined using DFT techniques at the ground state. The HOMO and LUMO charge densities are seen to be uniformly distributed throughout the molecule in Fig. 4a-b. Table-3 provides a overview of the quantum chemical descriptors. The DFT/HOMO

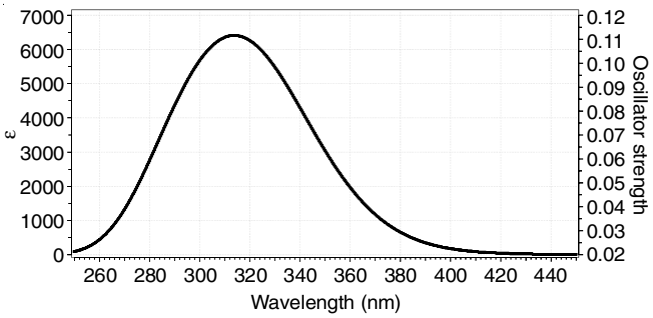


Fig. 2. UV-Vis spectra of compound **4b** as obtained by theoretical calculations

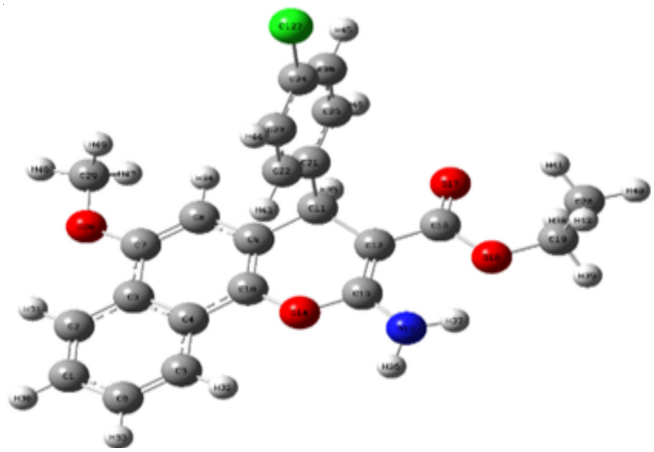


Fig. 3. Optimized structure of compound **4b**

values for compounds **4a** and **4b** are –6.38 and –6.212 eV, respectively while the values of LUMO orbitals are –2.07 and –1.83 eV.

The computational factors used to characterize a molecule include its chemical hardness, chemical softness, electronegativity and chemical potential, all of which are calculated using the energy gap (ΔE) between the HOMO and LUMO. The synthesized naphthopyran derivatives with a low kinetic stability were found to have a small energy gap (ΔE), indicating a strong reactivity [50]. In addition, the molecule exhibits significant reactivity, which can be interpreted as biological activity, as measured by its softness values (σ) [51], moreover naphthopyran derivatives have a negative chemical potential (μ) that implies spontaneous reaction [52].

Conclusion

An efficient one-pot, three-component approach for the synthesis of 4*H*-naphthopyran derivatives by the reaction of aldehydes, malononitrile or ethyl cyanoacetate cyano ester/arylidines and 6-bromol-2-naphthol catalyzed by piperidine is presented. The molecular geometry of compounds **4a** and **4b** were calculated using density functional theory at the B3LYP/6-31+G(d) level of theory.The most stable tautomer of this chemical appears to be **4b**. Most notably, it differs from the **4b** tautomer by a significant amount of energy (6.98 kcal/mol).The electrophilicity, hardness and softness of molecules on a global scale, as well as their local condensed Fukui functions, were calculated.

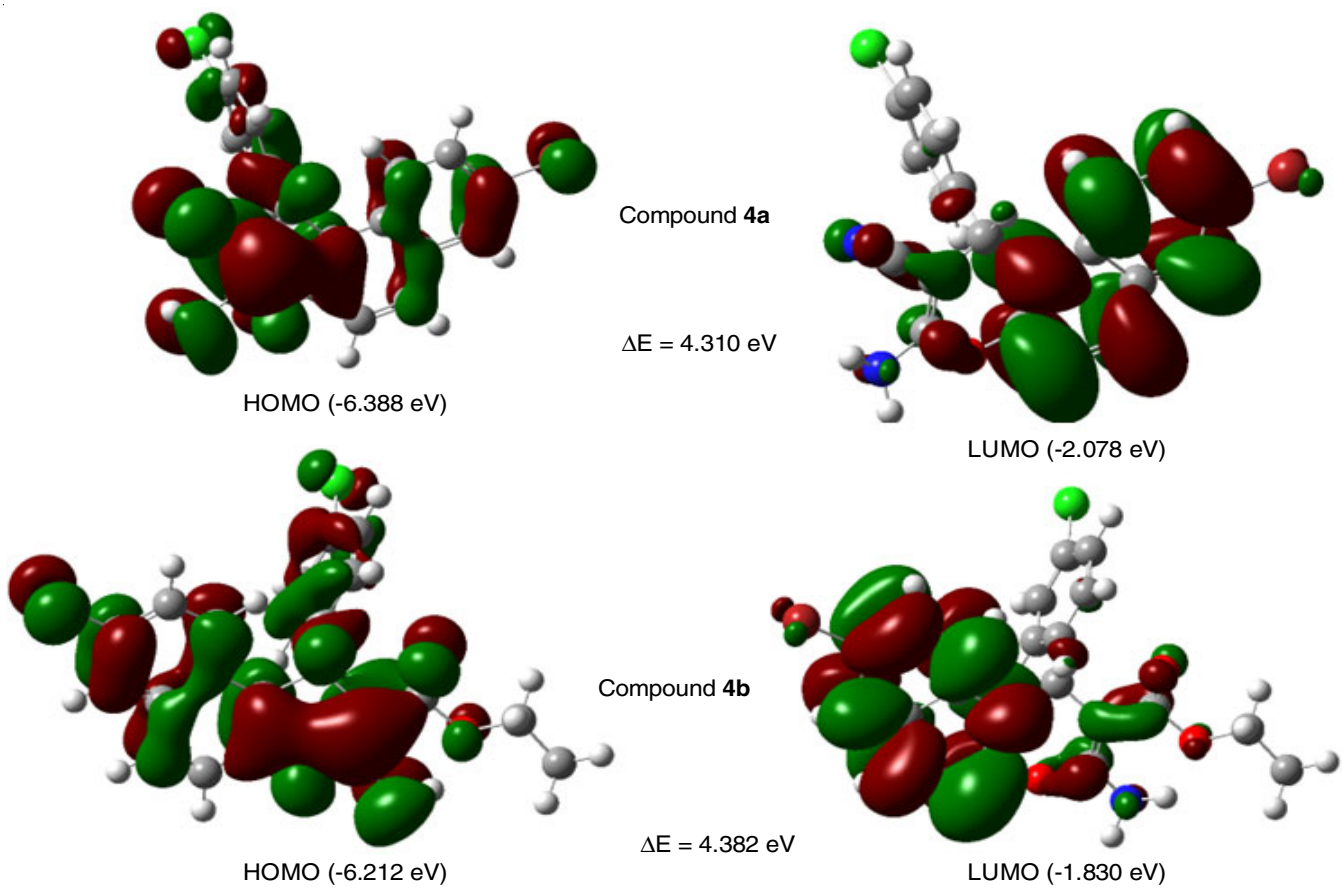


Fig. 4. Frontier molecular orbital of the compound **4a,b**

TABLE-3
QUANTUM CHEMICAL PARAMETERS FOR NAPHTHOPYRAN DERIVATIVES CALCULATED AT THE DFT LEVEL

Method	Compd.	HOMO	LUMO	ΔE	I	A	χ	μ	η	σ	ω
DFT/B3LYP	**4a**	-6.388	-2.078	4.310	6.388	2.078	4.233	-4.233	2.155	0.464	4.158
	4b	-6.212	-1.830	4.382	6.212	1.83	4.021	-4.021	2.191	0.456	3.690

ΔE: energy gap, χ: electronegativity, μ: Chemical potential, η: global hardness, σ: global softness, ω: global electrophilicity index.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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