

Synthesis, modeling and biological studies on 4-2'(2,3-dihydrobenzofuranyl)coumarins

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Abstract

Reaction of 4-bromomethyl coumarins with schiff's bases derived from salal and heterocyclic amines resulted in a tandem sequence leading to the formation of 3-heteroaryl amino 2-4'-coumarinyl 2,3-dihydrobenzofurans. The *cis/trans* diastereomeric ratio was estimated by ¹H-NMR. Quantum chemical modeling studies provided a proof for very low energy difference between them and accounted for the inseparable mixture of the diastereomers. The synthesized compounds have been subjected to DNA cleavage studies.

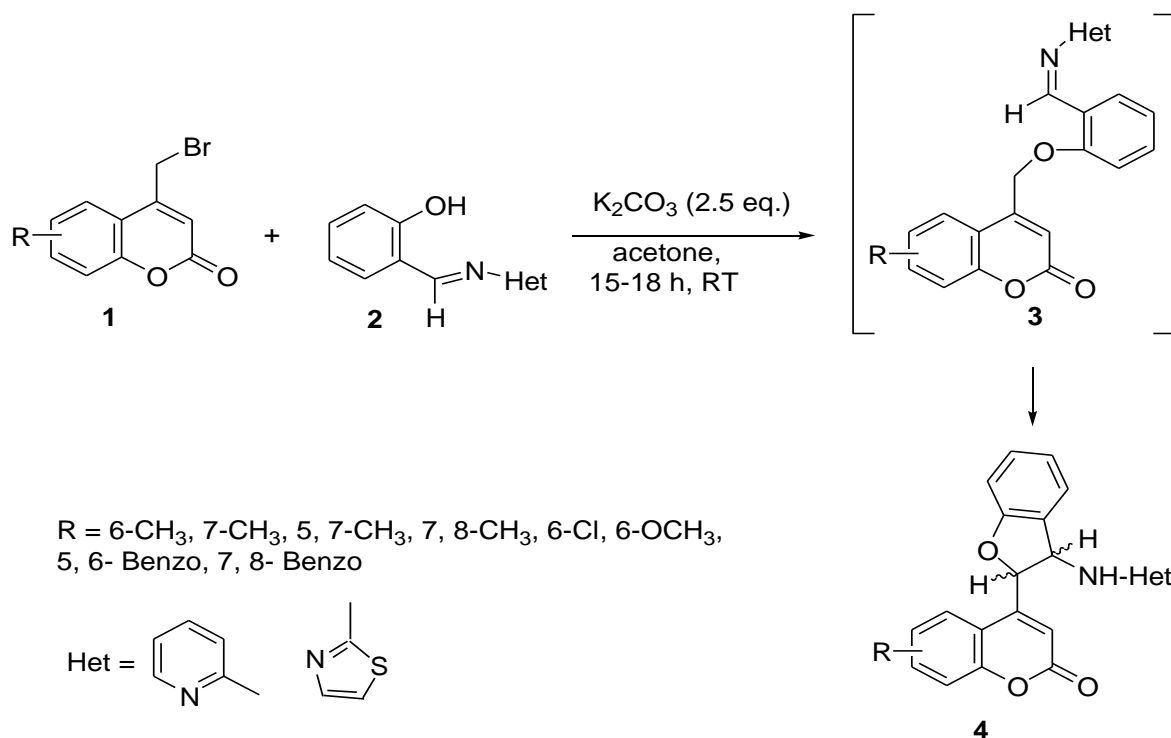
Keywords: Dihydrobenzofurans, intramolecular cyclization, 4-bromomethylcoumarins, DNA cleavage, gel electrophoresis

Introduction

Functionalized 2,3-dihydrobenzofurans have been found to exhibit wide ranging biological properties.¹⁻⁶ Recently 2,3-dihydrobenzofuran-5-ol has been shown to be more promising than vitamin E2 in inhibition of lipid per oxidation.⁷ This skeleton has been a part of number of naturally occurring oxygen heterocycles.⁸ In view of their secondary metabolite property and bio compatibility a number of synthetic approaches have been designed for 2,3-dihydrobenzofurans which make use of biomimetic approach,⁹ reductant metals,¹⁰ Lewis acids¹¹ and oxidation of phenol.¹² Recently we have reported first thermal method for 2,3-dihydro-3-benzofuranols,¹³ linked to a coumarin moiety under metal free conditions. During the present work aldimines derived from salal and pharmacophoric moieties like 2-amino thiazole and 2-amino pyridine have been reacted with 4-bromomethyl coumarins to obtain 3-heteroaryl amino 2,3-dihydrobenzofurans which have been screened for their ability to interact with DNA.

Results and Discussion

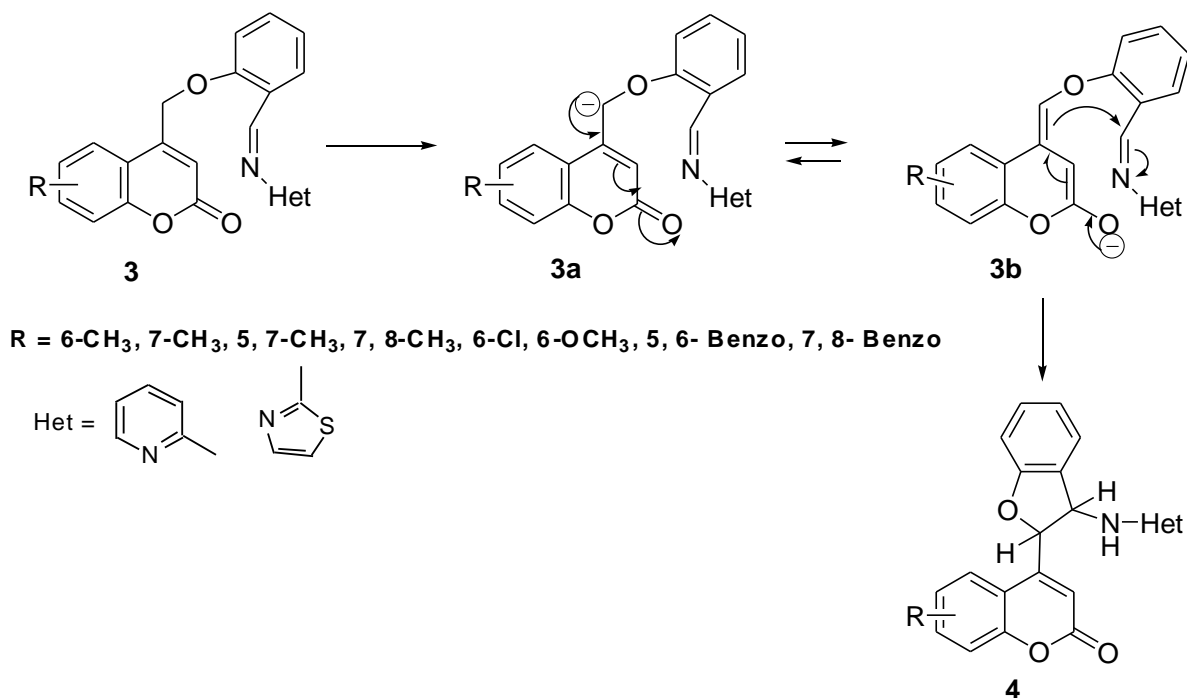
The required 4-bromomethylcoumarins were prepared using phenols and 4-bromoethylacetoacetate under Pechmann cyclization conditions.¹⁴ The heteroaryl aldimines were obtained from salal and 2-amino pyridine/2-amino thiazole according to reported methods.¹⁵ The reaction of **1** and **2** in acetone at room temperature resulted in the formation of colorless crystalline solids isolated by the usual work up (Scheme 1). The absence of the methylene protons around 5.2 - 5.4 δ ppm lead us to conclude that the initially formed ethers probably underwent a further intramolecular carbanion addition across the azomethine group located at close spatial proximity (*ortho* position) leading to the formation of 2,3-Dihydrobenzofurans (Table 1). The proposed intermediacy of ethers is supported by our earlier work.¹⁶ The reactivity of active C4-methylene group in 4-aryloxymethyl coumarins has been used to synthesize biologically active 4-2' benzofuranyl coumarins by an intramolecular aldol addition followed by dehydration¹⁷⁻¹⁹ by our group.



Scheme 1. Synthesis of 4-[3-(Pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-ones **4a-4h** and 4-[3-(Thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-ones **4i-4p**.

A plausible mechanistic pathway for the formation of coumarinyl dihydrobenzofurans **4** is indicated in (Scheme 2). The initially formed ethers **3** (which were not isolated) can easily

generate a carbanion under the experimental conditions (acetone/ K_2CO_3) which is stabilized as the enolate due to its conjugation with the lactone carbonyl. In the next step, formation of C-C bond is proposed due to the nucleophilic attack on the azomethine carbon. Due to the lack of control of stereochemistry of the carbanion, it is likely that the coumarinyl 2,3-dihydro benzofurans are obtained as mixture of *cis* and *trans* diastereomers.



Scheme 2. Mechanism of formation of coumarinyl 2, 3-dihydrobenzofurans **4a-4p**.

The 1H NMR of all the compounds, **4** exhibited two sets of peaks for C_2' and C_3' protons with J values in the range of 2.4-4.3 and 7.4-8.4 Hz which are characteristic of *cis* and *trans* isomers reported for 2, 3-dihydrobenzofurans.^{20, 21}

IR spectrum of 7-methyl-4-[3-(pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one **4b** exhibited carbonyl frequency at 1712 cm^{-1} , NH stretching at 3432 cm^{-1} . Two doublets obtained for compound **4b** recorded on a 400 MHz 1H -NMR spectrometer ($CDCl_3$) at 6.28 and 6.14 δ ppm were due to C_2' H and C_3' H of *trans* isomer with coupling constants 8.5 and 8.4 Hz and additional two doublets obtained at 5.97, 5.86 ppm with coupling constants 4.3 and 4.4 Hz, were due to C_2' H and C_3' H of the *cis* isomer. In addition two singlets for the C_6 -CH₃ groups at 2.38 and 2.31 ppm and two singlets for the C_3 -H of coumarin at 6.43 and 6.23 ppm. The aromatic region from 7.90 to 6.54 ppm integrated to a total of 24 protons thus indicating the presence of two diastereomers. The ratio estimated from the peak heights in the 1H -NMR spectra was (1:1). The LCMS spectrum exhibited a m/z peak at 370.9 which confirmed the formation of compound. In some of the compounds the C_2' and C_3' protons were not distinguishable and appeared as complex multiplet.

Table 1. Newly synthesized coumarinyl 2, 3-dihydrobenzofurans **4a-4p**

Compd.	R	Het	M.P. (°C)	Reaction time (h)
4a	6-CH ₃	2-Pyridyl	148-150	15
4b	7-CH ₃	2-Pyridyl	160-162	15
4c	5,7-CH ₃	2-Pyridyl	160-162	15
4d	7,8-CH ₃	2-Pyridyl	184-186	15
4e	6-OCH ₃	2-Pyridyl	167-168	15
4f	6-Cl	2-Pyridyl	222-224	18
4g	5,6 – benzo	2-Pyridyl	196-198	18
4h	7,8 – benzo	2-Pyridyl	202-204	18
4i	6-CH ₃	2-Thiazolyl	168-170	17
4j	7-CH ₃	2-Thiazolyl	174-176	17
4k	5,7-CH ₃	2-Thiazolyl	178-180	17
4l	7,8-CH ₃	2-Thiazolyl	182-184	18
4m	6-OCH ₃	2-Thiazolyl	186-188	18
4n	6-Cl	2-Thiazolyl	196-198	18
4o	5,6 – benzo	2-Thiazolyl	188-190	18
4p	7,8 – benzo	2-Thiazolyl	194-196	18

Experimental methods to separate these diastereomers by techniques like TLC, column chromatography, HPLC did not yield any fruitful results. In view of this, it was thought worthwhile to estimate the energy difference between these diastereomers and it was observed that the energy difference between *cis*- and *trans*-diastereomers is too close to each other, very less in comparison with the energy difference between the chair and boat conformations of cyclohexane (7.61 kcal/mol) and hence *cis* and *trans* diastereomers were found to be inseparable.

Table 2. ¹H NMR (CDCl₃, 400 MHz) data for selected diastereomeric coumarinyl dihydrobenzofurans **4**

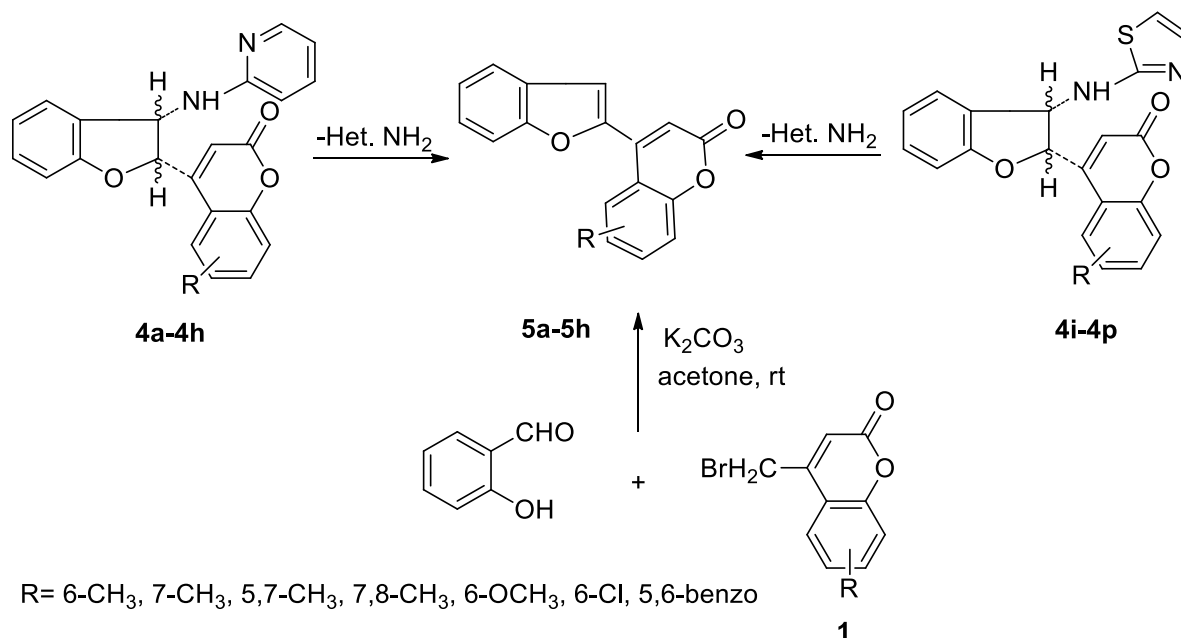
Compd.	R	Het	<i>Cis</i>		<i>Trans</i>	
			C _{2'} -H (J Hz)	C _{3'} -H (J Hz)	C _{2'} -H (J Hz)	C _{3'} -H (J Hz)
4a	6-CH ₃	2-Pyridyl	5.90 (3.1)	5.72 (3.2)	6.22 (8.2)	6.08 (8.3)
4b	7-CH ₃	2-Pyridyl	5.97 (4.3)	5.86 (4.4)	6.28 (8.5)	6.14 (8.4)
4c	5,7-CH ₃	2-Pyridyl	6.05 (2.4)	5.76 (2.4)	6.29 (8.4)	6.07 (8.3)
4f	6-Cl	2-Pyridyl	6.73 (5.8)	6.48 (5.5)	5.83 (7.5)	4.75 (7.6)
4g	5,6 -benzo	2-Pyridyl	5.92 (4.8)	5.86 (4.3)	6.42 (8.36)	6.07 (8.32)
4k	5,7-CH ₃	2-Thiazolyl	6.0 (4.3)	5.62 (4.3)	6.62 (8.3)	6.55 (8.2)
4l	7,8-CH ₃	2-Thiazolyl	6.02 (4.2)	5.57 (4.2)	6.46 (7.5)	6.31 (7.4)

It can be seen from (Table 2) that the coupled C_{2'} and C_{3'} proton chemical shifts differed by 0.04-0.18 ppm with the *J* values varying from 2.4-8 Hz in *cis* and *trans* diastereomers.

Reactivity of coumarinyl dihydrobenzofurans (4a-4p)

Coumarinyl dihydrobenzofurans **4** when refluxed in acetone K₂CO₃ quickly underwent β -elimination leading to the formation of 4-2'-benzofuranyl coumarins²² **5**. The identity of the product **5** (Scheme 3) was confirmed by an independent synthesis using 4-bromomethyl coumarins **1** and salal. The m.p, IR, ¹H NMR was identical with the sample obtained in the earlier route. Similarly, compounds **4i-4p** also yielded identical compound **5** under refluxing conditions in acetone and anhydrous potassium carbonate.

It can be seen that all the compounds exhibited the expulsion of Het-NH₂ fragment in their GCMS spectra leading to the formation of benzofuranyl coumarins.



Scheme 3. Formation of 4-2'-benzofuranyl coumarins **5** from diastereomeric dihydrobenzofuranyl coumarins **4**.

Quantum-chemical modeling studies

Quantum-chemical modeling studies were performed by robust DFT method utilizing B3LYP hybrid exchange-correlation functional, consisting of non-local hybrid exchange part as defined by Becke's three parameters equation²³ and the nonlocal Lee–Yang–Parr correlation functional.²⁴ Split-valence Gaussian basis sets 6-311G (d) and 6-311+G (d, p) were used. Geometry optimization of the studied molecules was performed without applying any restrictions on the molecular symmetry. All calculations were done with the GAUSSIAN 03 program.²⁵

To ensure good quality of the quantum-chemical modeling, we used DFT method at the B3LYP/6-311G- (d) level of theory for energy minimization. Energies for several isomers were calculated and are presented hereunder (Figures 1-8). Rows differ by conformation of coumarin moiety (as it is seen from the table orientation of H3' towards furan oxygen is more preferable than of H5' both for *cis*- and *trans* isomers). Energies are given (in kcal/mole) relative to the most stable isomer in the series.

Minimum energy conformations in (Figure 1) and (Figure 3) for the *cis* diastereomers indicate the dihedral angle to be very close to 0°. Whereas (Figure. 2) and (Figure 4) for the *trans* diastereomers show the anti periplanar relation between H₂ and H₃ indicating the dihedral angle to be around 180°. Energy difference between the most stable *cis*- and *trans*- isomers is small – 0.42 kcal/mole only.

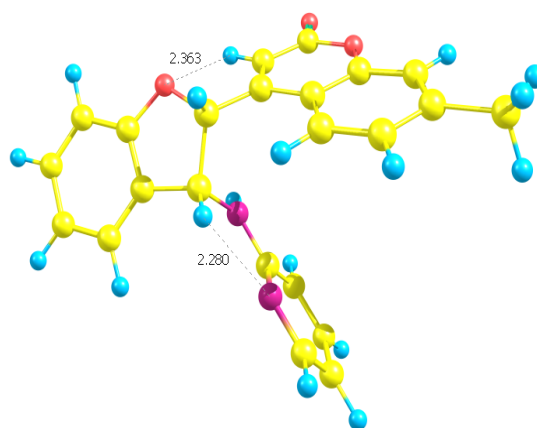


Figure 1. *cis*-Conformation of compound **4b** (+0.42 kcal/mole).

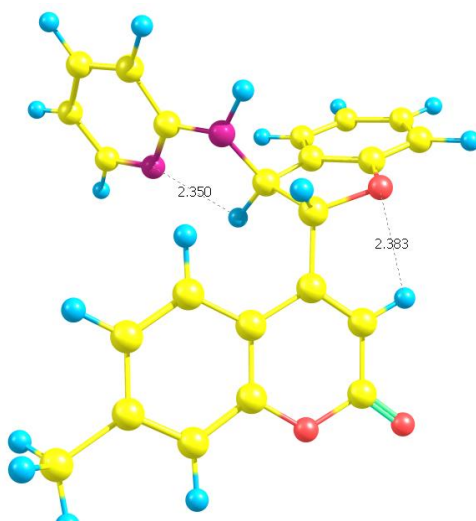


Figure 2. *trans*-Conformation of compound **4b** (0.0 kcal/mole).

For thiazole derivative picture is the same, but energy difference between *cis*- and *trans*-isomers is slightly higher (+0.88 kcal/mole). The conformation of coumarin moiety was chosen the same as in the most stable isomers of pyridine derivative. Isomers in rows differ in orientation of thiazole ring.

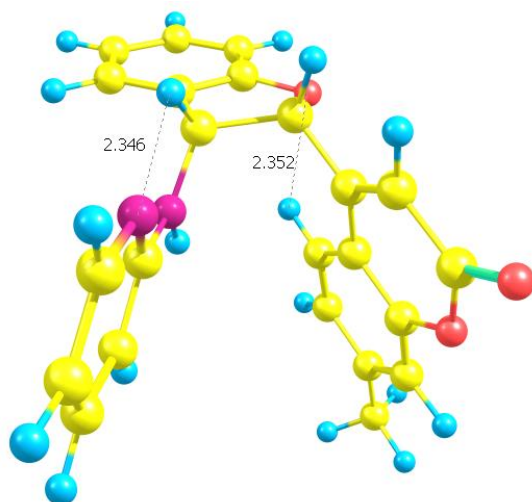


Figure 3. *cis*-Conformation of compound **4b** (+2.13 kcal/mole).

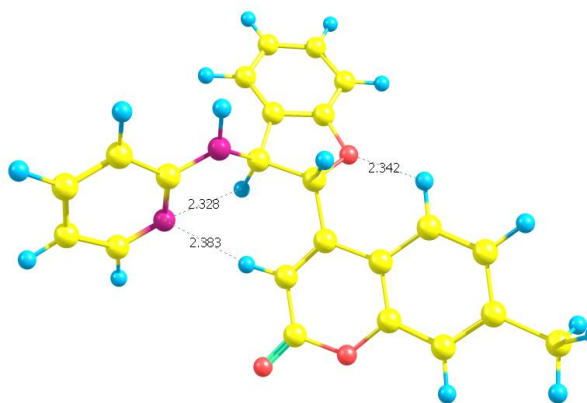


Figure 4. *trans*-Conformation of compound **4b** (+1.3 kcal/mole).

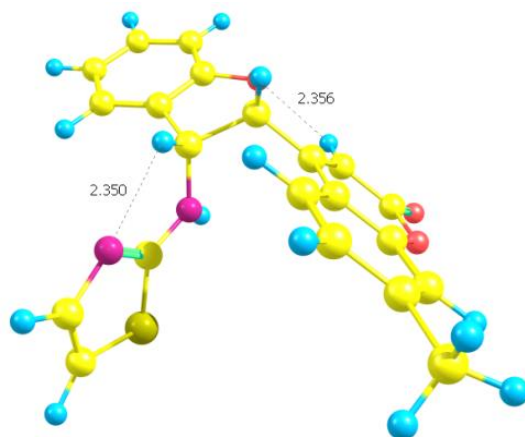


Figure 5. *cis*-Conformation of compound **4j** (+0.88 kcal/mole).

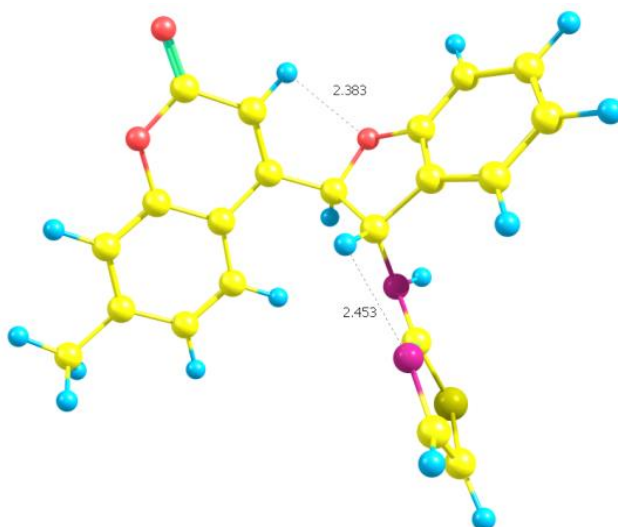


Figure 6. *trans*-Conformation of compound **4j** (0.0 kcal/mole).

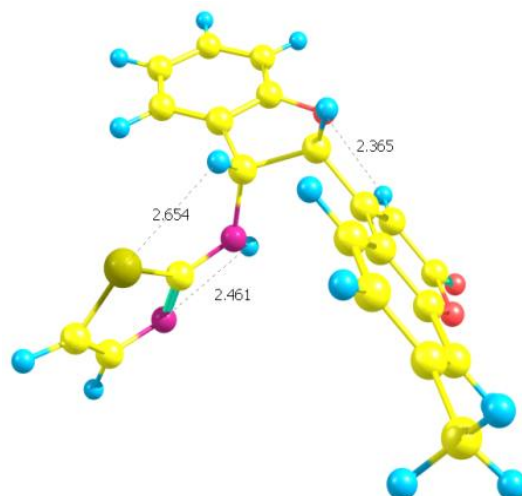


Figure 7. *cis*-Conformation of compound **4j** (+3.05 kcal/mole).

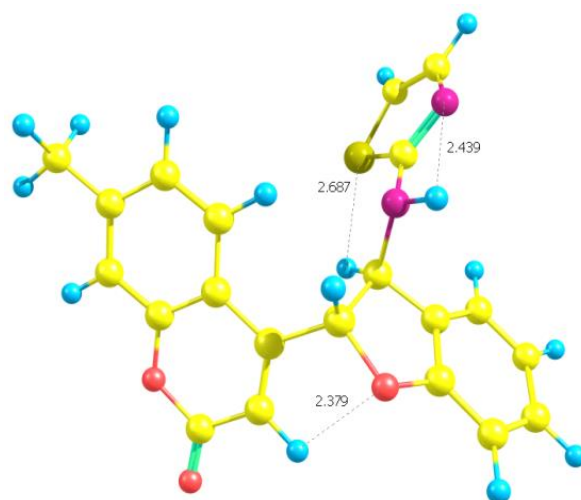


Figure 8. *trans*-Conformation of compound **4j** (+1.26 kcal/mole).

The energies of the most stable structures were refined employing 6-311+G (d, p). For energy difference between *I-cis* and *I-trans* isomers in this basis set the value obtained is 0.25 kcal/mole and it is even lower than calculated with 6-311G (d) basis set. For the thiazole derivative with the extended basis set 6-311+G (d, p) extended with polarization *p*-functions on hydrogen atoms and diffuse functions. For energy difference between *cis* and *trans* isomers in this basis set the value obtained is 0.25 kcal/mole and it is even lower than calculated with 6-

311G (d) basis set. For the thiazole derivative with the extended basis set 6-311+G (d, p) the relative stability is also lower and is equal to 0.56 kcal/mole. Lower energy is for trans-isomer.

Biological Studies

The DNA cleavage studies of all the reported 4-[3-(pyridin-4-ylamino)-2, 3-dihydro-benzofuran-2-yl]-chromen-2-ones **4a-4f** and 4-[3-(thiazol-2-ylamino)-2, 3-dihydro-benzofuran-2-yl]-chromen-2-ones **4i-4n** have been carried out against *E. coli* by agarose gel electrophoresis method.

Gel electrophoresis technique is based on the migration of DNA under the influence of electric potential. The photograph (Figures 9 and 10) show the molecular weight difference compared to control and is the differentiating criterion for the DNA cleaving ability of the tested compound with *E. coli*, control experiments using DNA alone does not indicate any significant cleavage of DNA even after long exposure time. After marker M and control C, the first six lanes correspond to 4-[3-(pyridin-4-ylamino)-2, 3-dihydro-benzofuran-2-yl]-chromen-2-ones **4a-4f**, (Figure 9) and in this series the gel used for the analysis of DNA treated with **4a-4f** samples show streak indicating only a partial cleavage. But an extract band of high molecular weight DNA was found in all these samples treated DNA. This is because of strong binding of the compounds to DNA by which its molecular weight was found to be increased. In all samples two bands were seen, compounds corresponding to the band and free DNA which is concentration dependent. The DNA bound with compound formed a high molecular weight band and unbound DNA migrated as in control. In **4f**, only high molecular weight band was observed possibly because the concentration of compound used was enough to bind with the DNA used for treatment. Like **4f**, in **4c** treated DNA lane also, the low molecular weight band was missing, but high molecular weight band was could not be clearly seen because of the fluorescence of compound left in wells under UV.

After marker M and control C, the first six lanes in Figure 10 correspond to 4-[3-(Thiazol-2-ylamino)-2, 3-dihydro-benzofuran-2-yl]-chromen-2-ones **4i-4n**, and in this series the similar behavior of samples was noted as compared with **4a-4f**. In conclusion it can be seen that all the synthesized compounds which were screened against *E. coli* for DNA studies show, that they have the ability to partially cleave the DNA and as well strongly bind with DNA. In conclusion all compounds have better DNA binding property than DNA cleavage.

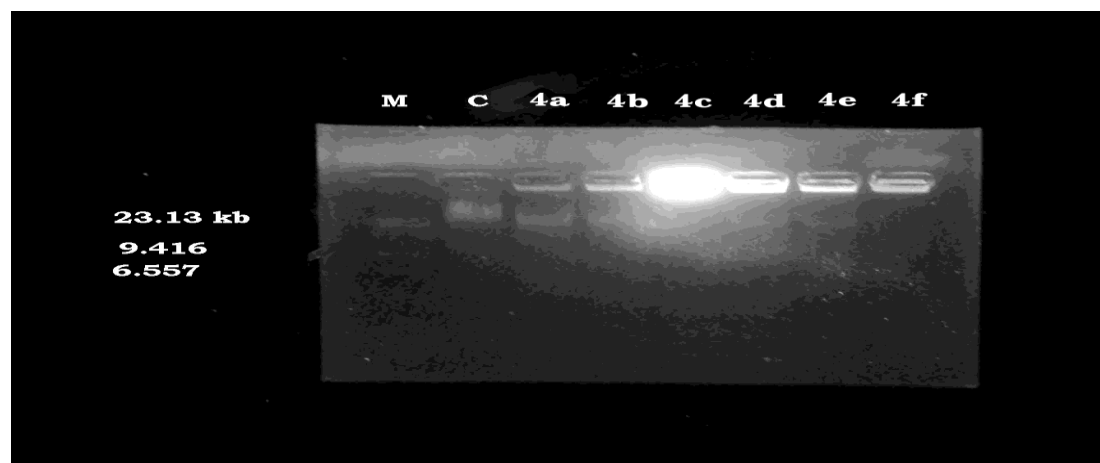


Figure 9. Gel electrophoresis picture of 4-[3-(pyridin-4-ylamino)-2, 3-dihydro-benzofuran-2-yl]-chromen-2-ones **4a-4f**. Photograph showing the effect of representative compounds on DNA of *E.coli*. Lane M: DNA marker, Lane C: untreated DNA.

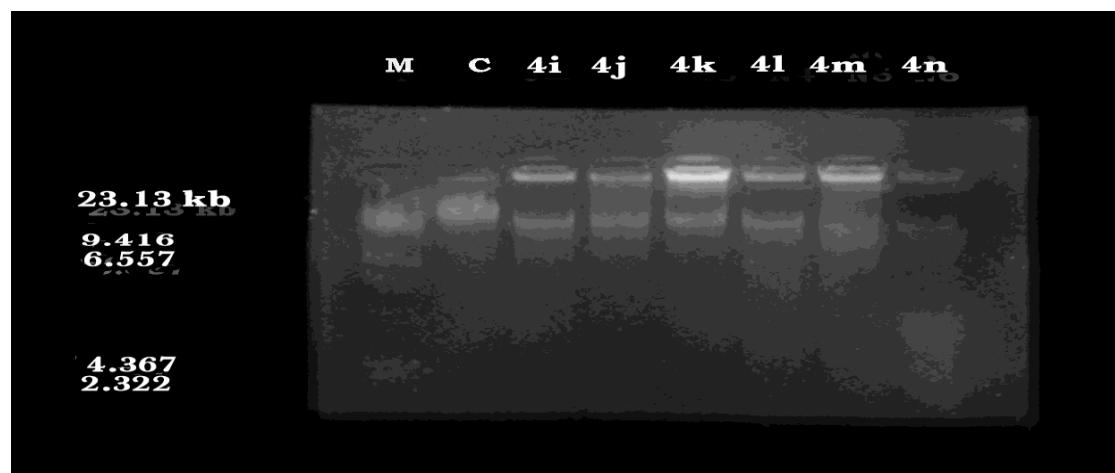


Figure 10. Gel electrophoresis picture of 4-[3-(thiazolyl-4-ylamino)-2, 3-dihydro-benzofuran-2-yl]-chromen-2-ones **4i-4n**. Photograph showing the effect of representative compounds on DNA of *E.coli*. Lane M: DNA marker, Lane C: untreated DNA.

Conclusions

A series of 4-[3-(pyridin/thiazol-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-ones **4a-4p** were synthesized via intermediates **3** and were well characterized and evaluated for DNA cleavage studies by agarose gel electrophoresis method against *E. Coli*. The results show that

compounds exhibit both DNA cleavage and binding activity against *E. Coli*, in specific DNA binding was prominently observed with all the compounds. Their ability to exist in the conformers makes them good candidate for interactive studies with DNA.

Experimental Section

General. The melting points were determined by open capillaries and are uncorrected. All the commercial samples were purified before use. TLC analyses were performed on commercial Kieselgel 60 F254 silica gel plates. IR Spectra were recorded on a Bruker EQUINOX 55 FTIR. NMR spectra were obtained on Bruker spectrometer using CDCl₃ as solvent, with proton resonances at 300 and 400 MHz, respectively. Mass spectral data (LCMS) were recorded on Agilent Single Quartz mass spectrometer. The elemental analysis was carried out using Heraeus CHN rapid analyzer. Quantum-chemical modeling studies were performed by robust DFT method utilizing B3LYP hybrid exchange-correlation functional, consisting of non-local hybrid exchange part as defined by Becke's three parameters equation [23] and the nonlocal Lee–Yang–Parr correlation functional. Split-valence Gaussian basis sets 6-311G (d) and 6-311+G (d, p) were used. Geometry optimization of the studied molecules was performed without applying any restrictions on the molecular symmetry. All calculations were done with the GAUSSIAN'03 program.

4-[3-(Pyridin/thiazol-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-ones (4a-4p). A mixture of anhydrous potassium carbonate (0.00625 mol) and *o*-hydroxybenzylidenepyridine/*o*-hydroxybenzylidenethiazole (0.0025 mol) were stirred for half an hour in dry acetone (30 mL). To this 4-bromomethyl coumarins (0.0025 mol) were added and the stirring was continued for 16-20 h at room temperature. The mixture was diluted with crushed ice. Separated solid was filtered and washed with water, then with dilute HCl (1:1) and with water thoroughly. Solids were crystallized from ethyl alcohol.

6-Methyl-4-[3-(pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4a). Yield: (0.83 g, 91%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3430 (NH stretching), 1713 (C=O of lactone); ¹H NMR 400 MHz (CDCl₃) δ : 7.93-6.68 (m, 24H, Ar-H), 6.67 (s, 1H, C₃-H), 6.47 (s, 1H, C₃-H), 6.21 (d, $J = 8.2$ Hz, 1H, C₂), 6.04 (d, $J = 8.3$ Hz, 1H, C₃), 5.93 (d, $J = 3.1$ Hz, 1H, C₂), 5.71 (d, $J = 3.2$ Hz, 1H, C₃), 2.26 (s, 3H, CH₃), 2.20 (s, 3H, CH₃); MS (LCMS) m/z : 371 (M+H); Anal calcd. for C₂₃H₁₈N₂O₃ C: 74.58, H: 4.90, N: 7.56 Found C: 74.50, H: 4.86, N: 7.47.

7-Methyl-4-[3-(pyridin-4-yl amino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4b). Yield: (0.81 g, 89%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3432 (NH stretching), 1712 (C=O of lactone); ¹H NMR 400 MHz (CDCl₃) δ : 7.90- 6.54 (m, 24H, Ar-H), 6.43 (s, 1H, C₃-H), 6.28 (d, $J = 8.5$ Hz, 1H, C₂), 6.23 (s, 1H, C₃-H), 6.14 (d, $J = 8.4$ Hz, 1H, C₃), 5.97 (d, $J = 4.3$ Hz, 1H, C₂), 5.86 (d, $J = 4.4$ Hz, 1H, C₃), 2.38 (s, 3H, CH₃), 2.31 (s, 3H, CH₃); MS (LCMS) m/z : 370.9 (M+H); Anal calcd. for C₂₃H₁₈N₂O₃ C: 74.58, H: 4.90, N: 7.56 Found C: 74.55, H: 4.92, N: 7.55.

5,7-Dimethyl-4-[3-(pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4c).

Yield: (0.77 g, 81%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3432 (NH stretching), 1714 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.00-6.38 (m, 22H, Ar-H), 6.53 (s, 1H, C₃-H), 6.40 (s, 1H, C₃-H), 6.29 (d, $J = 8.4$ Hz, 1H, C₂'), 6.07 (d, $J = 8.3$ Hz, 1H, C₃'), 6.05 (d, $J = 2.42$ Hz, 1H, C₂'), 5.76 (d, $J = 2.4$ Hz, 1H, C₃'), 2.85 (s, 3H, CH₃), 2.67 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 2.31 (s, 3H, CH₃); MS (LCMS) m/z : 385 (M+H); Anal calcd. for C₂₄H₂₀N₂O₃ C: 74.98, H: 5.24 N: 7.29 Found C: 74.84 H: 5.32, N: 7.86.

7,8-Dimethyl-4-[3-(pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4d).

Yield: (0.78 g, 82%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3428 (NH stretching), 1715 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.51- 5.36 (m, 26H, Ar-H), 6.45 (s, 1H, C₃-H), 6.10 (s, 1H, C₃-H), 2.47 (s, 3H, CH₃), 2.37 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 2.29 (s, 3H, CH₃); MS (LCMS) m/z : 385 (M+H); Anal calcd. for C₂₄H₂₀N₂O₃ C: 74.98, H: 5.24 N: 7.29 Found C: 74.92, H: 5.26, N: 7.34. (The C₂' and C₃' protons were merged in the multiplet in the range of 6.54-5.36 ppm and could not be distinguished separately).

6-Methoxy-4-[3-(pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4e).

Yield: (0.77 g, 80%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3427 (NH stretching), 1718 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 7.34- 5.77 (m, 28H, Ar-H), 6.69 (s, 1H, C₃-H), 6.51 (s, 1H, C₃-H), 3.84 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃); MS (LCMS) m/z : 387 (M+H); Anal calcd. for C₂₃H₁₈N₂O₄ C: 71.49, H: 4.70, N: 7.25 Found C: 71.44 H: 4.86, N: 7.22. (The C₂' and C₃' protons were merged in the multiplet in the range 6.70- 5.77 ppm and could not be distinguished separately).

6-Chloro-4-[3-(pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4f).

Yield: (0.74 g, 76%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3430 (NH stretching), 1718 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 7.70-6.98 (m, 24H, Ar-H), 6.73 (d, $J = 5.84$ Hz, 1H, C₂'), 6.68 (s, 1H, C₃-H), 6.48 (d, $J = 5.5$ Hz, 1H, C₃'), 6.44 (s, 1H, C₃-H), 5.83 (d, $J = 7.5$ Hz, 1H, C₂'), 4.75 (d, $J = 7.6$ Hz, 1H, C₃'); MS (LCMS) m/z : 391(M+H), 393.2 (M+2+H); Anal calcd. for C₂₂H₁₅ClN₂O₃ C: 67.61, H: 3.87, N: 7.17 Found C: 67.66, H: 3.95, N: 7.26.

5,6-Benzo-4-[3-(pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4g).

Yield: (0.71 g, 70%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3428 (NH stretching), 1720 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.05-6.02 (m, 30H, Ar-H), 6.96 (s, 1H, C₃-H), 6.88 (s, 1H, C₃-H), 6.42 (d, $J = 8.36$ Hz, 1H, C₂'), 6.07 (d, $J = 8.32$ Hz, 1H, C₃'), 5.92 (d, $J = 4.8$ Hz, 1H, C₂'), 5.86 (d, $J = 4.3$ Hz, 1H, C₃'); MS (LCMS) m/z : 407 (M+H); Anal calcd. for C₂₆H₁₈N₂O₃ C: 76.83, H: 4.46, N: 6.89 Found C: 76.82, H: 4.52, N: 6.82.

7,8-Benzo-Methyl-4-[3-(pyridin-4-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4h).

Yield: (0.63 g, 62%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3432 (NH stretching), 1719 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.52-5.22 (m, 34H, Ar-H), 6.73 (s, 1H, C₃-H), 6.66 (s, 1H, C₃-H); MS (LCMS) m/z : 407 (M+H); Anal calcd. for C₂₆H₁₈N₂O₃ C: 76.83, H: 4.46, N: 6.89 Found C: 76.90, H: 4.48, N: 6.76 (The C₂' and C₃' protons were merged in the multiplet in the range 6.92- 5.22 ppm and could not be distinguished separately).

6-Methyl-4-[3-(thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4i). Yield: (0.72 g, 76%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3426 (NH stretching), 1713 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 7.41-5.58 (m, 24H, Ar-H), 6.40 (s, 1H, C₃-H), 6.33 (s, 1H, C₃-H), 2.48 (s, 3H, CH₃), 2.32 (s, 3H, CH₃); MS (LCMS) m/z : 377 (M+H); Anal calcd. for C₂₁H₁₆N₂O₃S: 67.00, H: 4.28, N: 7.44 Found C: 67.14, H: 4.22, N:7.47. (The C₂' and C₃' protons were merged in the multiplet in the range 6.92-5.58 ppm and could not be distinguished separately).

7-Methyl-4-[3-(thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4j). Yield: (0.60 g, 83%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3424 (NH stretching), 1712 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 7.71-5.51(m, 24H, Ar-H), 6.41 (s, 1H, C₃-H), 6.32 (s, 1H, C₃-H), 2.50 (s, 3H, CH₃), 2.45 (s, 3H, CH₃); MS (LCMS) m/z : 377 (M+H); Anal calcd. for C₂₁H₁₆N₂O₃S: 67.00, H: 4.28, N: 7.44; Found C: 67.10, H: 4.32, N:7.46. (The C₂' and C₃' protons were merged in the multiplet in the range 6.80-5.51 ppm and could not be distinguished separately).

5,7-Methyl-4-[3-(thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4k). Yield: (0.72 g, 76%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3430 (NH stretching), 1715 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.65- 6.93 (m,18H, Ar-H), 6.62 (d, $J = 8.2$ Hz, 1H, C₂'), 6.55 (d, $J = 8.2$ Hz, 1H, C₃'), 6.40 (s,1H, C₃-H), 6.23 (s, 1H, C₃-H), 6.00 (d, $J = 4.3$ Hz, 1H, C₂'), 5.62 (d, $J = 4.3$ Hz, 1H, C₃'), 2.36 (s, 3H, CH₃), 2.32 (s, 3H, CH₃), 2.28 (s, 3H, CH₃), 2.26 (s, 3H, CH₃); MS (LCMS) m/z : 391 (M+H); Anal calcd. for C₂₂H₁₈N₂O₃S: 67.67, H: 4.65, N:7.17 Found C: 67.65, H: 4.69, N: 7.24.

7,8-Methyl-4-[3-(thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4l). Yield: (0.65 g, 68%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3428 (NH stretching), 1714 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.56- 6.85 (m, 18H, Ar-H), 6.46 (d, $J = 7.4$ Hz, 1H, C₂'), 6.31 (d, $J = 7.4$ Hz, 1H, C₃'), 6.28 (s, 1H, C₃-H), 6.23 (s, 1H, C₃-H), 6.02 (d, $J = 4.2$ Hz, 1H, C₂'), 5.57 (d, $J = 4.2$ Hz, 1H, C₃'), 2.33 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 2.27 (s, 3H, CH₃), 2.24 (s, 3H, CH₃); MS (LCMS) m/z : 391 (M+H); Anal calcd. for C₂₂H₁₈N₂O₃S: 67.67, H: 4.65, N: 7.17 Found C: 67.71, H: 4.68, N:7.20.

6-Methoxy-4-[3-(thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-ones (4m). Yield: (0.62 g, 65%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3432 (NH stretching), 1718 (C= O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.62- 6.28 (m, 24H, Ar-H), 6.32 (s, 1H, C₃-H), 6.28 (s, 1H, C₃-H), 3.85 (s, 3H, OCH₃), 3.72 (s, 3H, OCH₃); MS (LCMS) m/z : 393 (M+H); Anal calcd. for C₂₁H₁₆N₂O₄S: 64.27, H: 4.11, N:7.14 Found C: 64.30, H: 4.17, N: 7.24. (The C₂' and C₃' protons were merged in the multiplet in the range 6.28-5.22 ppm and could not be distinguished separately).

6-Chloro-4-[3-(thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4n). Yield: (0.58 g, 60%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3434 (NH stretching), 1717 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.96- 6.32 (m, 24H, Ar-H), 6.62 (s, 1H, C₃-H), 6.38 (s, 1H, C₃-H); MS (LCMS) m/z : 397 (M+H), 399 (M+2+H); Anal calcd. for C₂₀H₁₃ClN₂O₃S: 60.53, H: 3.30, N: 7.06 Found C: 60.55, H: 3.34, N: 7.10. (The C₂' and C₃' protons were merged in the multiplet in the range 6.32-5.36 ppm and could not be distinguished separately)

5,6-Benzo-4-[3-(thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4o).

Yield: (0.62 g, 62%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3430 (NH stretching), 1719 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 5.44-8.12 (m, 30H, Ar-H), 6.46 (s, 1H, C₃-H), 6.38 (s, 1H, C₃-H), MS (LCMS) m/z : 413 (M+H); Anal calcd. for $\text{C}_{24}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$: 69.89, H: 3.91, N: 6.79 Found C: 69.88, H: 3.76, N: 6.78. (The C₂' and C₃' protons were merged in the multiplet in the range 6.76-5.44 ppm and could not be distinguished separately).

7,8-Benzo-4-[3-(thiazol-2-ylamino)-2,3-dihydro-benzofuran-2-yl]-chromen-2-one (4p).

Yield: (0.58 g, 58%); IR (KBr) $\nu_{\max}/\text{cm}^{-1}$: 3429 (NH stretching), 1716 (C=O of lactone); ^1H NMR 400 MHz (CDCl_3) δ : 8.36-5.55 (m, 30H, Ar-H), 6.39 (s, 1H, C₃-H), 6.27 (s, 1H, C₃-H); MS (LCMS) m/z : 413 (M+H); Anal calcd. for $\text{C}_{24}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$: 69.89, H: 3.91, N: 6.79 Found C: 69.82, H: 3.88, N: 6.82. (The C₂' and C₃' protons were merged in the multiplet in the range 6.92-5.55 ppm and could not be distinguished separately).

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