SYNTHESIS OF AMINOACETAMIDE SUBSTITUTED NAPHTHALIMIDE DERIVATIVES

A thesis submitted in partial fulfillment of the requirements for the award of the Degree of

MASTER OF SCIENCE

IN

CHEMISTRY

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July 2015

CANDIDATE'S DECLARATION

I hearby declare that the work being presented in the thesis entitled "SYNTHESIS OF AMINOACETAMIDE SUBSTITUTED NAPHTHALIMIDE DERIVATIVES", in partial fulfilment of the requirement for the award of degree of Masters of Science in Chemistry and being submitted to Thapar University, Patiala, is my own work during the period of January to July 2015 under the supervison of Dr.Kamadeep Paul, Associate Professor, School of Chemsirty and Biochemistry, Thapar University, Patiala. I have not submitted the matter embodied in this thesis work for the award of any degree.

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Date: 15.07.2015

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In my capacity as supervisor of the candidate's thesis, I certify that the above statements are true to the best of my knowledge.

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CERTIFICATE

This is to certify that the thesis "SYNTHESIS OF AMINOACETAMIDE SUBSTITUTED NAPHTHALIMIDE DERIVATIVES" being submitted by Sheryl Sharma for the partial fulfillment of requirements for the award of degree of Master's in Science in Chemistry in School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonafide work carried out under the supervision of Dr. Kamaldeep Paul and that no part of the thesis has been submitted for the award of any degree.

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ACKNOWLEDGEMENT

I gratefully acknowledge the support and guidance of all the faculty members presently working in the School of Chemistry and Biochemistry at Thapar Univeristy, Patiala, Punjab. Most particularly, I would like to thank my thesis advisor, Dr. Kamaldeep Paul, without his thoughtful encouragement and careful supervision, my thesis would never have taken shape. Also, I would like to thank Dr.Vijay Luxami and Dr. Bonamali Pal for their timely support and help. I would also like to acknowledge the support of my mentor Ms. Richa Goel and other members of the lab with whom I worked in close acquaintance during my time for guiding me through every elementary step. Their extended knowledge and experience about working in an Organic Chemistry Lab has greatly helped me in learning various skills like column chromatography ,Microwave reaction techniques, Filtration, Crystallization, Melting Point, Distillation, TLC (Thin Layer Chromatography), Extraction etc. The Lab staff in the Chemistry Department, further made sure to provide me with the necessary tools required for the completion of this work.

I would also like to extend my gratitude towards the SAI Labs Facility at Thapar University for providing me with various structure determination techniques like ^{1}H, ^{13}C NMR etc. to authenticate my work.

Furthermore, I am also grateful to my friends, family and fellow students who encouraged me with productive crtiques, which provided me with new ideas to work.

At last, I would like to thank the large number of open sources and related projects that critically facilitated this project.

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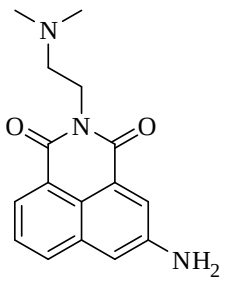
Introduction

Heterocyclic chemistry has profound impact on medicinal chemistry, with the majority of them now being used in the pharmaceutical industry because of their inherent biological activity. Being chemically more flexible, they are better able to respond to the many demands of a biochemical system and hence, continue to be exploited with great advantage by the drug industry. Various heterocyclic moieties are selected as the basis of most biological systems by nature. All these natural and synthetic heterocyclic compounds can be seen participating in various chemical reactions inside the human body. Also, their ability to produce stable complexes with metal ions further imparts them with great biochemical significance. Apart from being used in the drug industry, many heterocycles are also used in synthetic applications like fungicides, herbicides, anticorrosive agents, photo stabilizers, agrochemicals, dyestuff, copolymer, photographic developers, and fluorescent flavoring agents etc.[1]

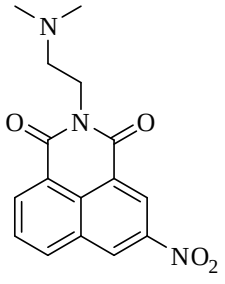
Naphthalimide is one such moiety that has recently gained advances in the field of cancer research because of their ability to target biomolecules and in particular nucleic acids.[2-5] The planar nature of the aromatic core has suggested that the molecule intercalates itself between the base-pairs of DNA, thus inhibiting the activity of an enzyme called topoisomerase II.[6] These are also known to stabilize double stranded DNA against heat denaturation.[7,8] Easy substitution at 3- or 4-position by amino or nitro groups not only allows the introduction of other functional groups, which can be used for targeting biomolecules, but can have a major effect on the electronic properties with a consequent influence on the chemical, photochemical and spectroscopic properties.[9] Extending the aromatic ring system to create aromatic- or heteroaromatic-fused derivatives help to control their properties better. The optical and photo physical properties of 1,8-naphthalimides are also very sensitive to substitution in the aromatic ring, functionalization with an amine group at 3-, 4-, 5- or 6-position of the ring produces

compounds which possess internal charge transfer (ICT) transitions giving them a strong fluorescence. By altering the nature of the ring substituent or that of the imide, the position of the resultant emission band can be varied. This yields particularly attractive derivatives since they can partially overcome auto-fluorescence and light scattering from any biological environments. These tunable photophysical properties thus make them excellent compounds to probe the microenvironment of biological systems as well as finding applications in the field of supramolecular chemistry as well as medicinal chemistry.[10] Sulfonated derivatives of 1,8-naphthalimides have recently being recognized as antiviral agents with selective *in vitro* activity against the human immunodeficiency virus, HIV-1.[11] Bromination of 1,8-naphthalimides at the 3- and 4-positions of the ring have been proposed as good candidates for the photo chemotherapeutic inhibition of enveloped viruses in blood and in blood products. Existing research results confirmed that the substituent in 5-position of the naphthalene ring is also key to antitumor activity of the naphthalimides.[2,4] The presence of a basic terminal group in the side chain and of two or three methylene units separating the terminal nitrogen of the side chain from the naphthalene ring was shown to play a key role in their anticancer activities.[7a]

Amonafide (3-amino-1,8-naphthlimide), and mitonafide (3-nitro-1,8-naphthalimide), two leading members were found to exhibit high antitumour activity with IC_{50} values (the concentration of a drug required to inhibit a given biological/biochemical process by 50%) of 0.47 µM and 8.80 µM, respectively, against HeLa cell lines and therefore reached phase II of the clinical trials [2,7a] but have failed, thus far to enter clinical phase III because of dose-limiting bone marrow toxicity.[2-4] Amonafide's toxicity, which is highly variable, is linked to its metabolism. It can be metabolized by *N*-oxidation (via CYP1A2) to generate a rapidly eliminated inactive metabolite.[12] Alternatively, it can be metabolized by the enzyme *N*-acetyltransferase 2 (NAT2) to *N*-acetylamonafide, a metabolite that is no longer a substrate for CYP1A2, but displays *in vitro* cytotoxicity similar to that of amonafide.[13]



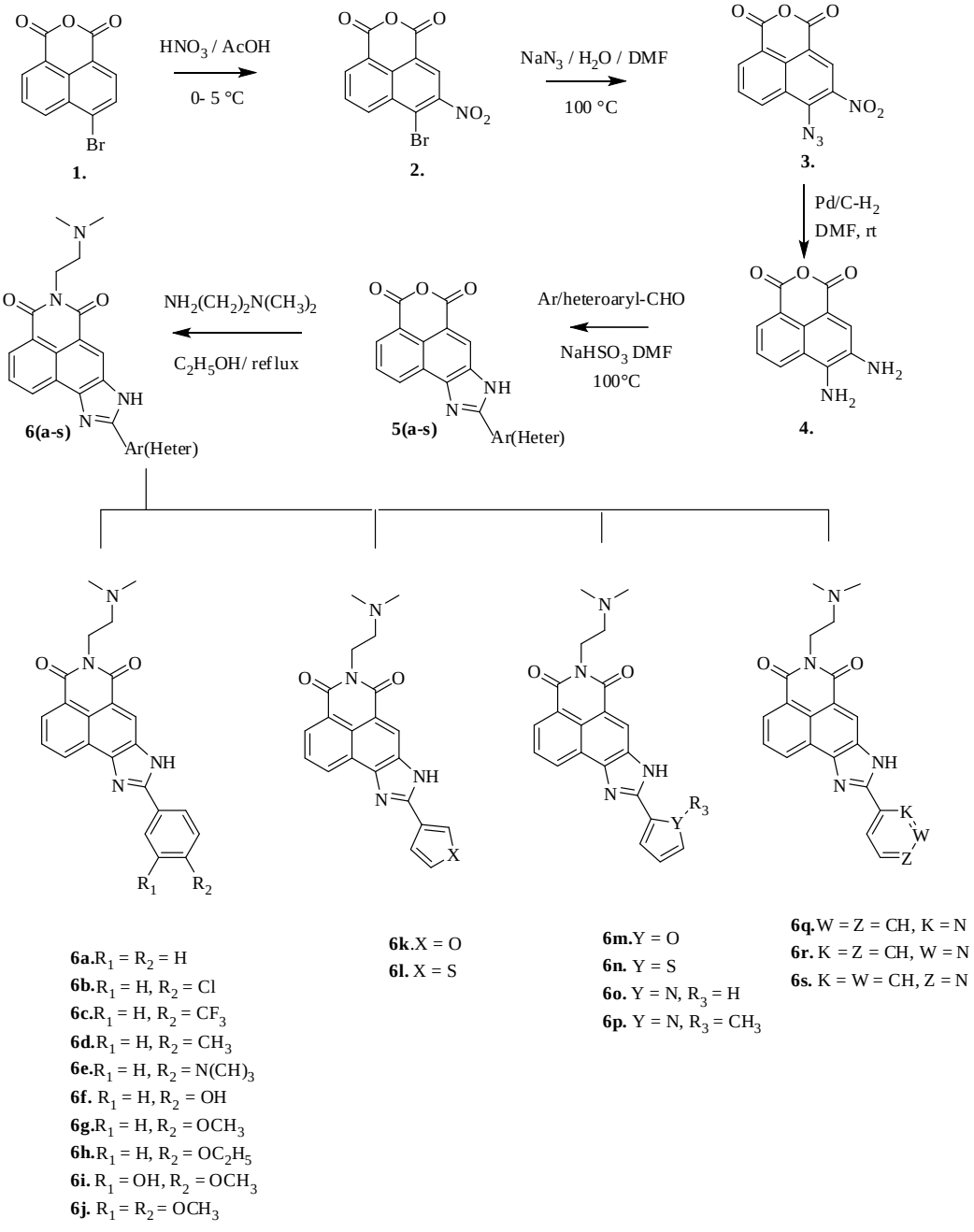
Amonafide



Mitonafide

Review of literature

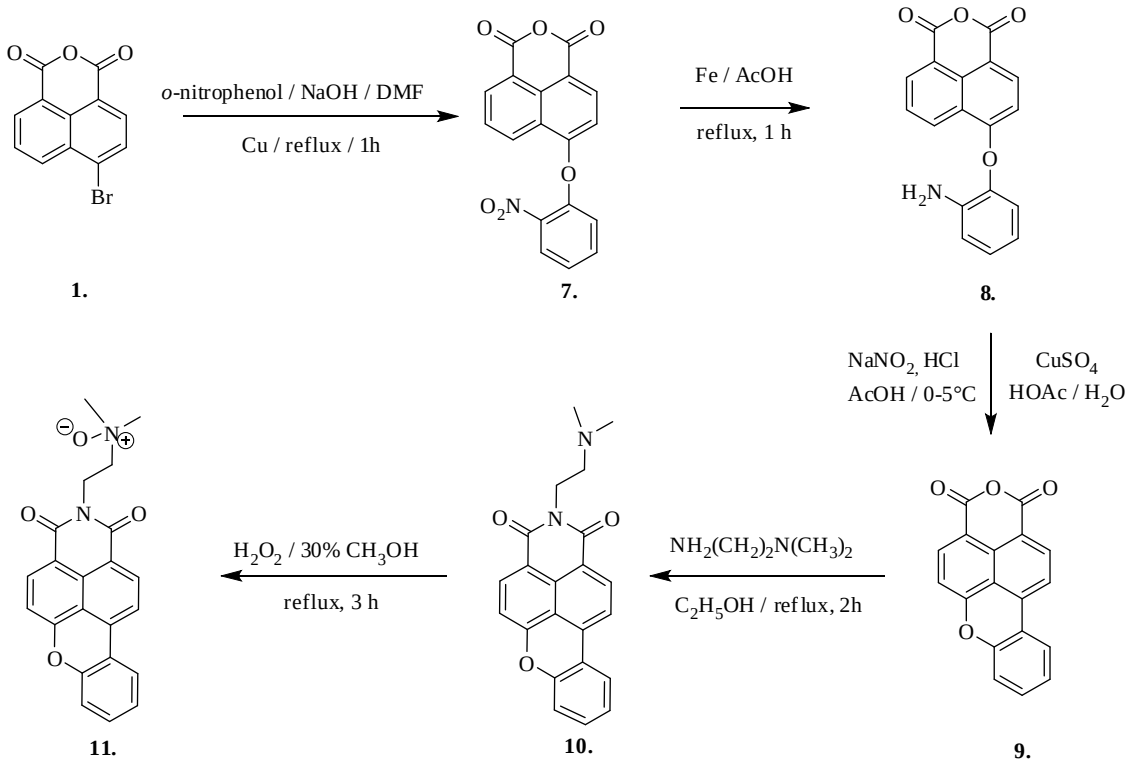
In the preparation of biologically active naphthalimde moieties, 3,4-diamino-naphthalene-1,8-dicarboxylic anhydride (**4**) played a chief intermediate (**Scheme-1**). Feng Li and co-workers



Scheme 1. Synthesis of aryl/heteroaryl- 1,8-dicarboxylic anhydrides

suggested an alternatively shorter route for the synthesis of diamine (**4**). First step involved the nitration of 4-bromo-naphthalene-1,8-dicarboxylic anhydride (**1**), the resulting **2** when treated with sodium azide in DMF at 100 ^{0}C to obtain compound **3**, which was then reduced by hydrogenation over Pd/C to the desired diamine **4**. The last two steps were obtained in nearly quantitative yield without any purification. Condensation of diamine (**4**) and aldehydes using sodium bisulfite as the oxidant in presence of DMF at 100 ^{0}C gave the corresponding aryl/heteroaryl-naphthalene-1,8-dicarboxylic anhydrides **5(a–s)**. The final step involved the treatment of the corresponding anhydrides **5(a–s)** with *N*,*N*-dimethylethane-1,2-diamine in ethanol at reflux temperature to give a series of target aryl/heteroaryl-imidazonaphthalimides **6(a–s)**.[14]

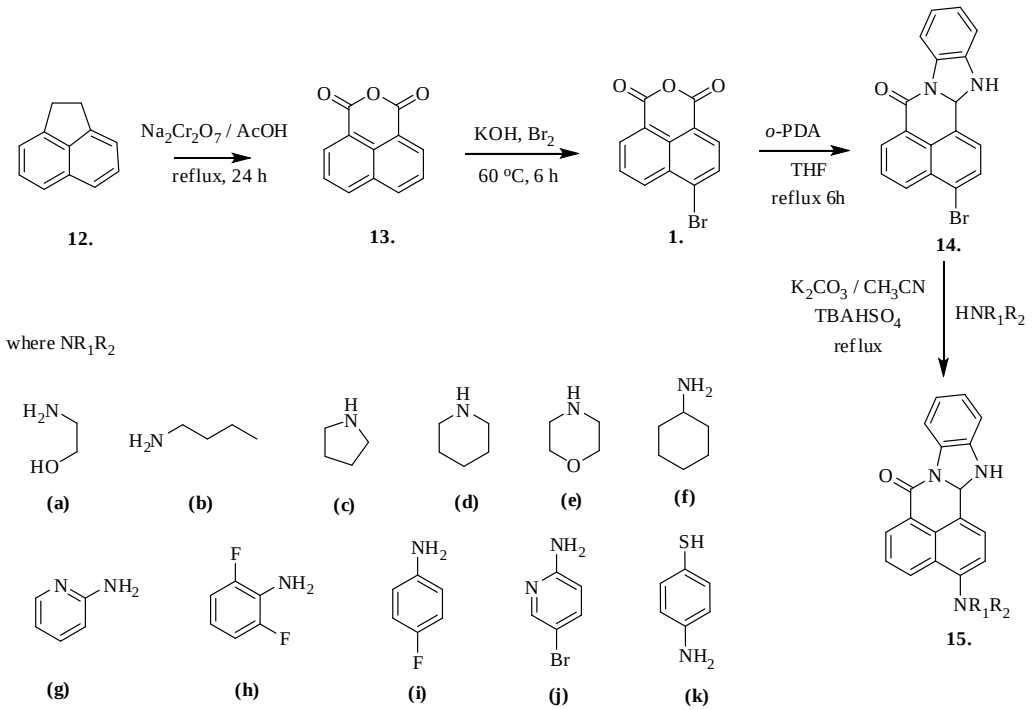
Hong Yin and co-workers has been synthesized N-oxide of naphthalimide (**11**) derivative using 4-bromonaphthalic anhydride as a starting material (**Scheme-2**). 4-Bromonaphthalic anhydride was dissolved in DMF along with *o*-nitrophenol and stirred for 1 h under reflux temperature with NaOH and Cu as catalysts. The solid obtained (**7**) was again refluxed for another 1 h in the



Scheme 2. Synthesis of tertiary anime *N*-oxides of 1,8-naphthalimides

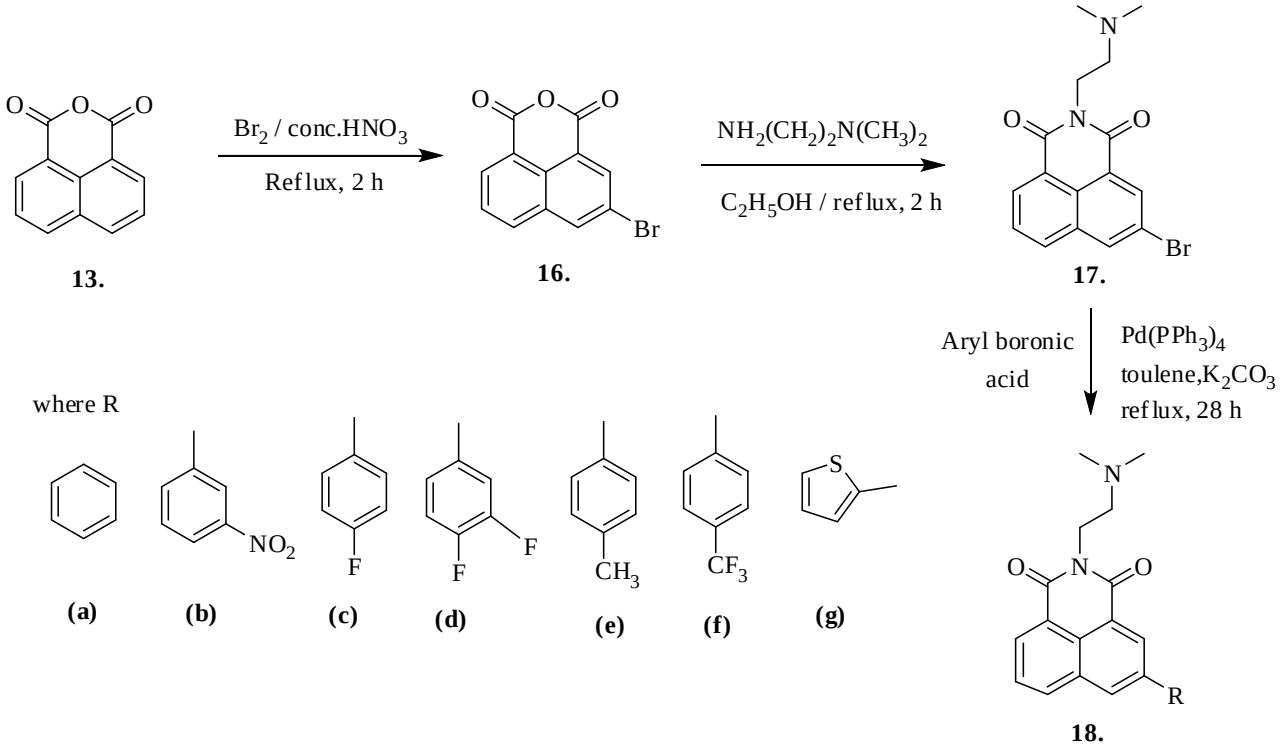
presence of Fe powder and glacial acetic acid to afford solid compound **8**. Compound **8** was then added into the solution of hydrochloric acid and sodium nitrite at 0–5 ^{0}C for 1 h, followed by the addition of $CuSO_4$ solution. Refluxing for another half an hour gave a yellow solid of benzo (k, l)xanthene-3,4-dicarboxylic anhydride (**9**), which when mixed with *N*,*N*-dimethyl ethylenediamine in ethanol and refluxed for 3 h gave the intermediate product **10**. Oxidation of **10** with H_2O_2 (30%) in CH_2Cl_2 or methanol under refluxing condition for 3 h, introduced the NO group and finally the removal of the solvent gave the desired compound **11**.[15]

The synthesis of the target naphthalimide derivative (**15**) was achieved using commercially available acenaphthene derivative as a starting material (**Scheme-3**). Acenaphthene was oxidized using acetic acid and sodium dichromate at 75 ^{0}C for 8 h to give 1,8-naphthalic anhydride (**13**) followed by bromination with Br_2 and KOH at 60 ^{0}C for 6 h, resulted in compound **1**. Refluxing of compound **1** with *o*-phenylenediamine (*o*-PDA) in THF for 6 h lead to the formation of a brown coloured powdered compound bromo-benzo[*de*]benzo[4,5]imidazo [2,1-*a*]isoquinoline-7-one (**14**). It was refluxed with various primary and secondary amines in the presence of phase transfer catalyst (K_2CO_3, CH_3CN and $TBAHSO_4$) for 8 to 12 h to give compounds **15(a-k)**.[16]



Scheme 3. Synthesis of substituted-benzo[*de*]benzo[4,5]imidazo[2,1-*a*]isoquinolin-7-one

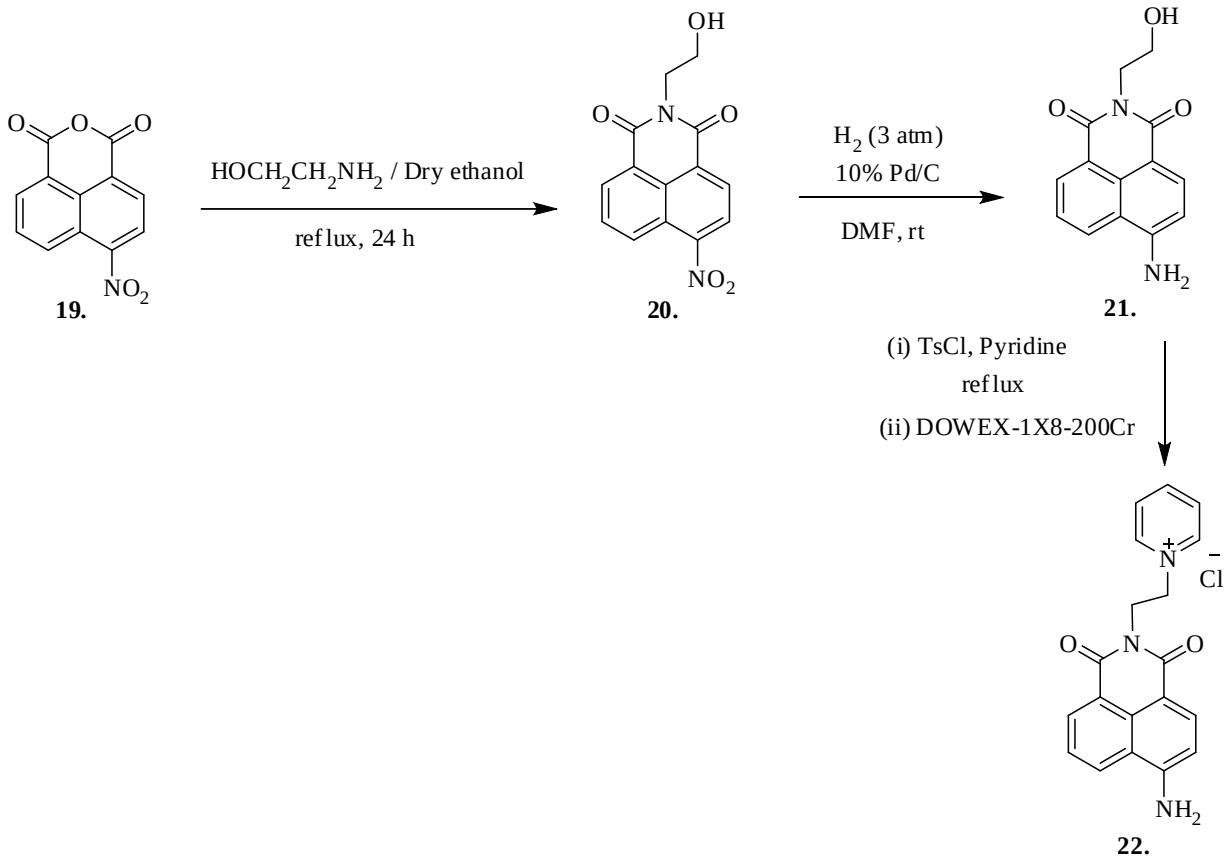
Xuhong Qian *et. al.* was able to synthesize a series of naphthalimide compounds **18**(**a-g**) using the Suzuki–Miyaura cross-coupling reactions (**Scheme-4**). Using naphthalic anhydride **(13)** as an initial substrate, the target compounds were synthesized in a 3 step series of bromination, amination and carbon-carbon coupling Suzuki reaction with Pd and K_2PO_4 as a catalyst and a base respectively. The effect of toulene and 1,4-dioxane as solvents were similar on the yields, as a result toluene was chosen because of its lower toxicity in the lab. Using $Pd(PPh_3)_4$ as a catalyst under refluxing condition, the reaction time was greatly reduced and maximum amount of yield was obtained as the dissociation of PPh_3 is easiest during the reductive elimination procedure of the Suzuki reaction mechanism.[17]



Scheme 4. Synthesis of 2-(2-(dimethylamino)ethyl)-5-aryl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione

The target molecule **22**, synthesized by Swagata Banerjee and co-workers required three steps as shown (**Scheme 5)**. The first step involved the condensation reaction between 4-nitro-1,8-naphthalic anhydride **(19)** and ethanolamine in dry ethanol under reflux condition and inert atmosphere. It was then reduced to compound **20** using catalytic hydrogenation by 10% Pd/C in DMF at 3 atm H_2. Compound **21** was then treated with *p*-toluene sulfonyl chloride (*p*-TsCl) in

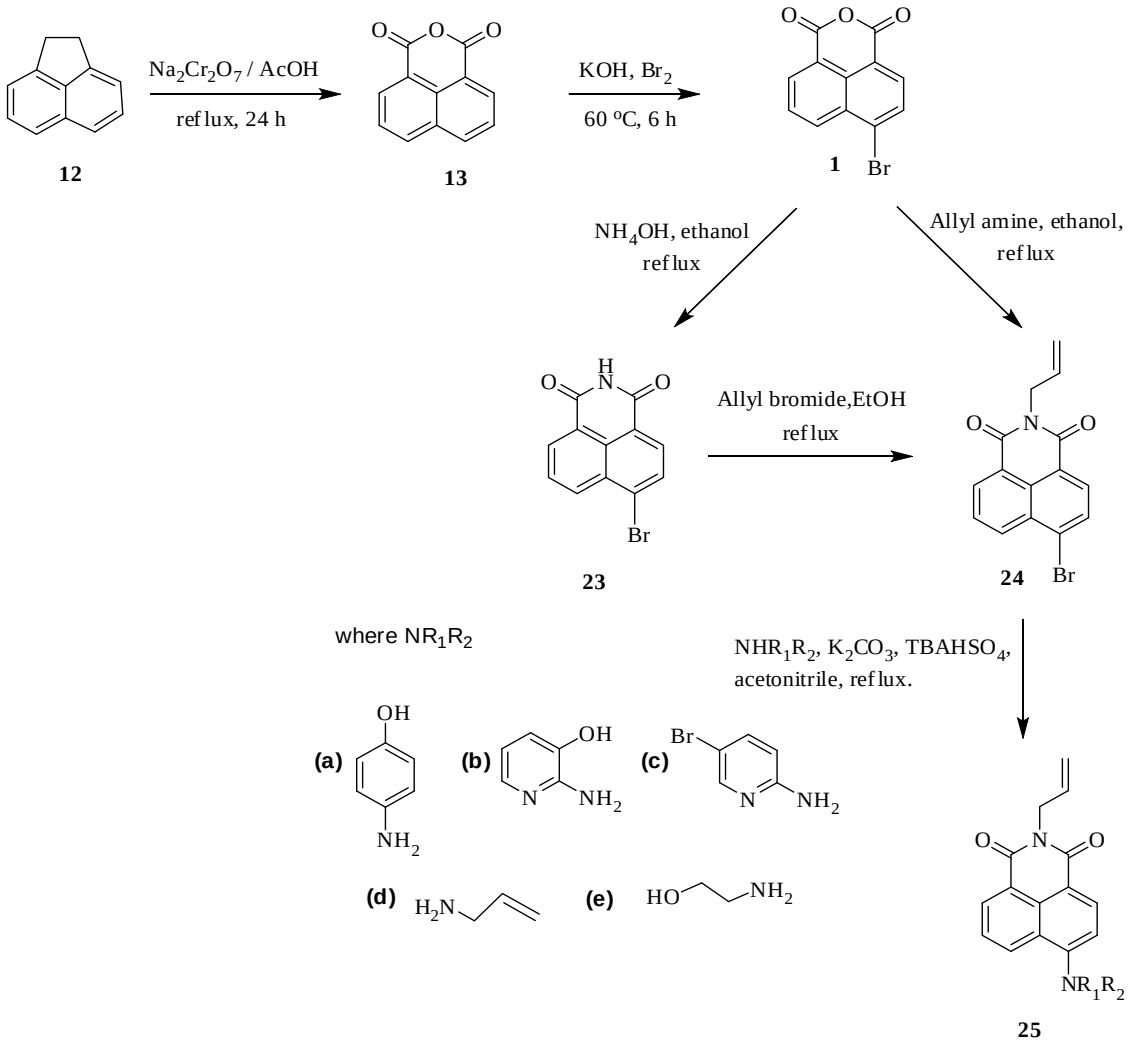
pyridine at reflux temperature, the tosylate salt of the target compound was obtained. Work up was done with water, washed with CH_2Cl_2 and purified using silica flash column chromatography. The product was then precipitated as its PF^{6-} salt using NH_4PF_6 and converted to the chloride salt of **22** by the treatment with DOWEX-1 × 8–200 ion exchange resin.[18]



Scheme 5. Synthesis of 1-(2-(6-amino-1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)ethyl) pyridinium chloride

Synthesis of the desired target naphthalimide analogues **25(a–e)** was achieved (**Scheme-6**) via multistep reactions using commercially available starting material acenaphthene (**12**). Oxidation of acenaphthene with acetic acid and sodium dichromate at 75 ^{0}C for 8 h gave compound **13**. Compound **13** on treatment with bromine in the presence of KOH solution at 60 ^{0}C for 6 h resulted in the formation of a white solid of 6-bromo-benzo[*de*]-isochromene-1,3-dione (**1**). Refluxing of compound **1** with allylamine and ethanol for 8 h gave 2-allyl-6-bromo-benzo[de]isoquinoline-1,3-dione (**24**). Alternatively, compound **24** was also synthesized by the refluxing of compound **1** with ammonium hydroxide in ethanol to get 6-bromo-

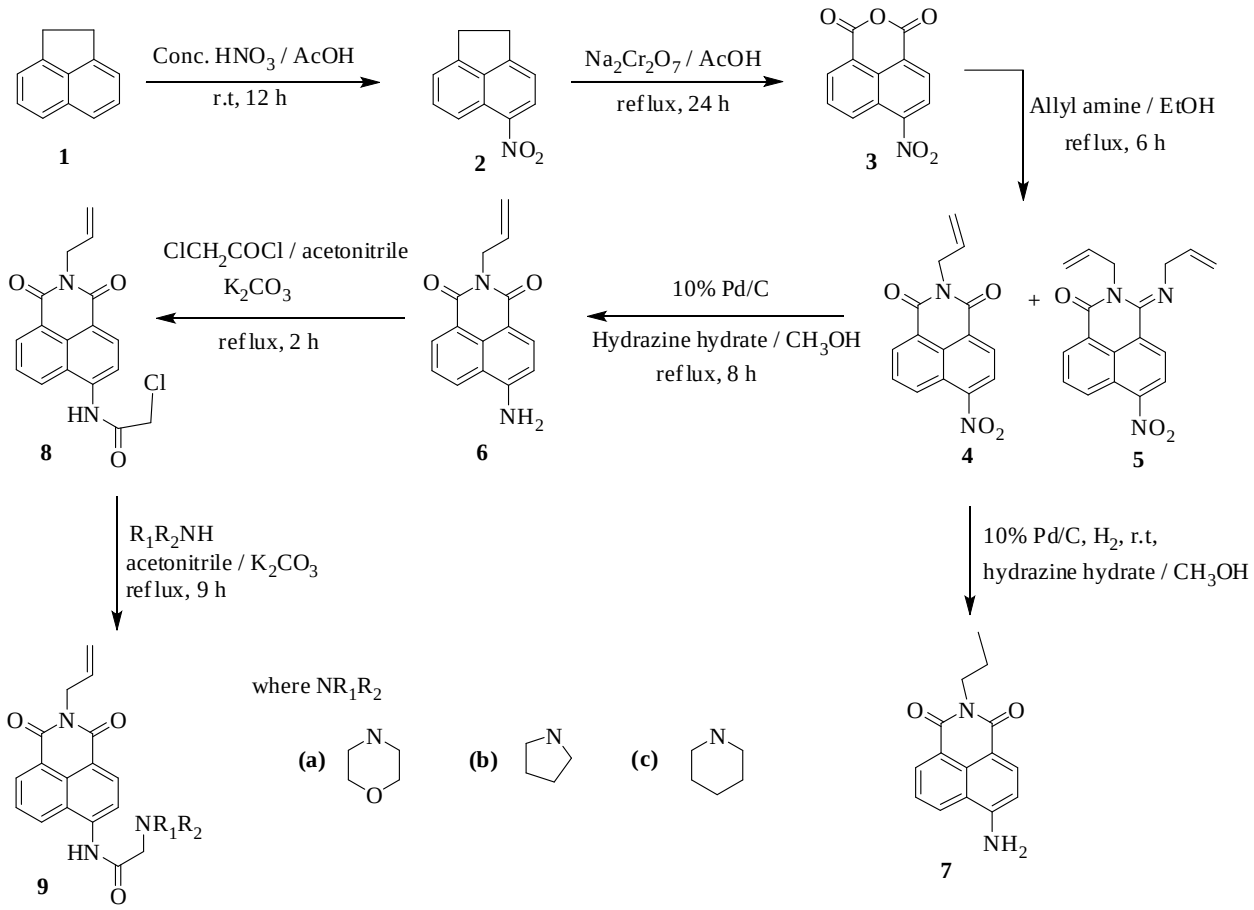
benzo[*de*]isoquinoline-1,3-dione (**23**) followed by treatment with allyl bromide in the presence of ethanol at reflux condition for 8 h. The crude product was purified through column chromatography to get pure compound **24**. Compound **24** was further refluxed with primary and secondary amines in the presence of K_2CO_3 and CH_3CN using $TBAHSO_4$ as catalyst for 8–12 h to get the crude product which was then purified through column chromatography to get the pure target compounds **25(a-e)**.[19]



Scheme 6. Synthesis of 2-allyl-6-substituted amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione

Results and Discussion

Using commercially available acenaphthene (**1**) as an initial substrate, naphthalimide derivatives (**9a-c**) were synthesized according to the **scheme 1**. Treatment of compound **1** with concentrated nitric acid and acetic acid at room temperature for 12 h, gave yellow colored powder of 5-nitro-1,2-dihydroacenaphthylene (**2**). It was then recrystallized using ethanol. Under refluxing conditions, oxidation of the product **2** was done with sodium dichromate and acetic acid for 24 h, gave an orange colored powder of 6-nitrobenzo[*de*]isochromene-1,3-dione (**3**). The crude of **3** was directly used for the next step without any further purification.[20,21] On treating compound **3** with allyl amine and ethanol under refluxing conditions for 6 h, two products, 2-allyl-6-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**4**) and 2-allyl-3-(allylimino)-6-nitro-2,3-dihydro-1*H*-



Scheme 1. Synthesis of *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-aminoacetamide (9a-c)

benzo[*de*]isoquinolin-1-one (**5**) were obtained. Allylated nitro derivatives (**4** and **5)** were well characterized by ^{1}H and ^{13}C NMR spectrometry. ^{1}H NMR spectrum of compound **4** showed two triplets at δ 4.81 and δ 4.83 ppm corresponding to N-CH_2 protons, two double doublets at δ 5.24-5.27 and 5.33-5.38 of allylic-CH_2. Multiplet of allylic-CH was observed at δ 5.94-6.04 ppm. Aromatic protons of naphthalimide showed wide range of splitting pattern ranging from δ 7.98-8.86 ppm corresponding to five protons. ^{13}C NMR spectrum showed the distinctive allylic-NCH_2 at δ 42.6 ppm and the two carbonyl groups at δ 162.0 ppm and 162.8 ppm. So, ^{1}H and ^{13}C NMR spectra analysis confirmed the formation of 2-allyl-6-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**4)** (**Figures-1,2**).

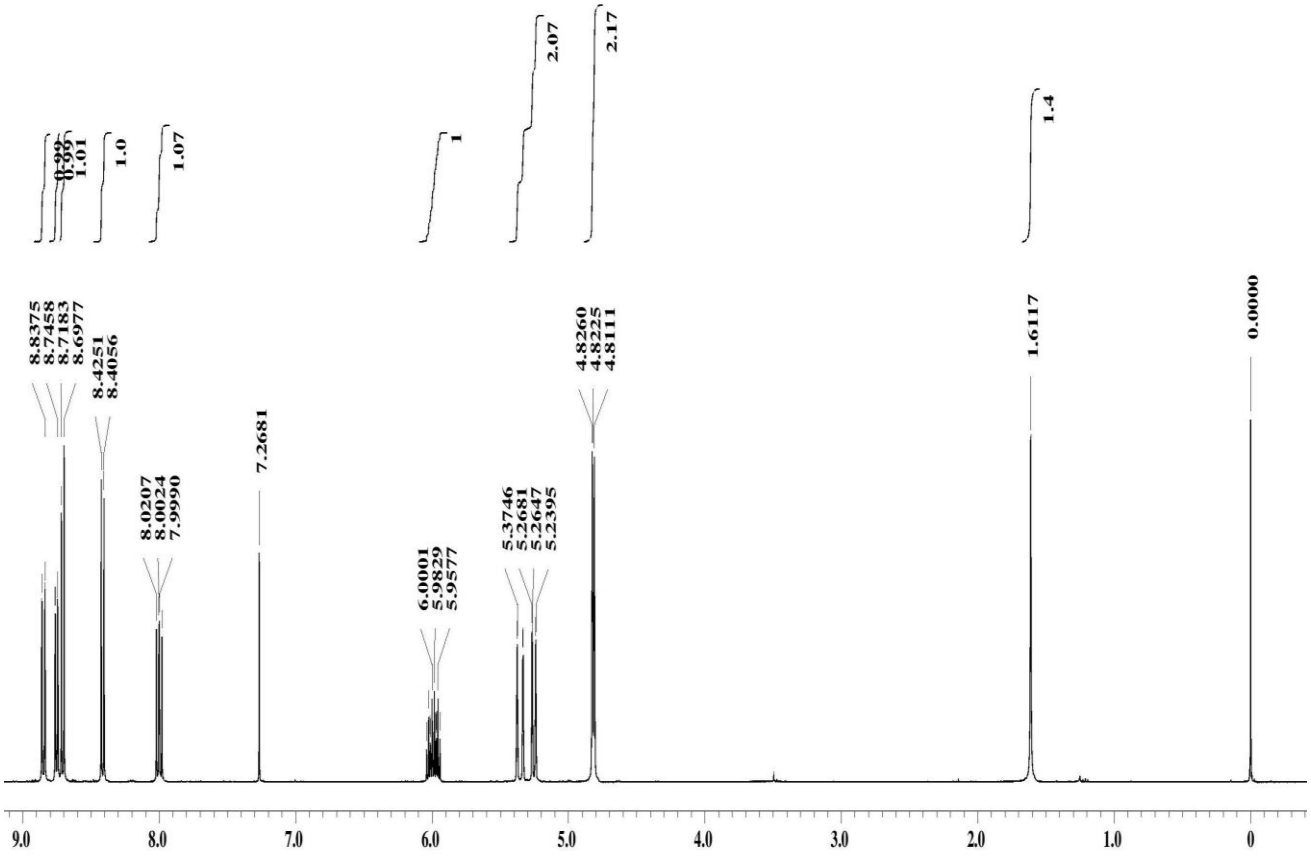


Figure 1. ^{1}H NMR spectrum of 2-allyl-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4)

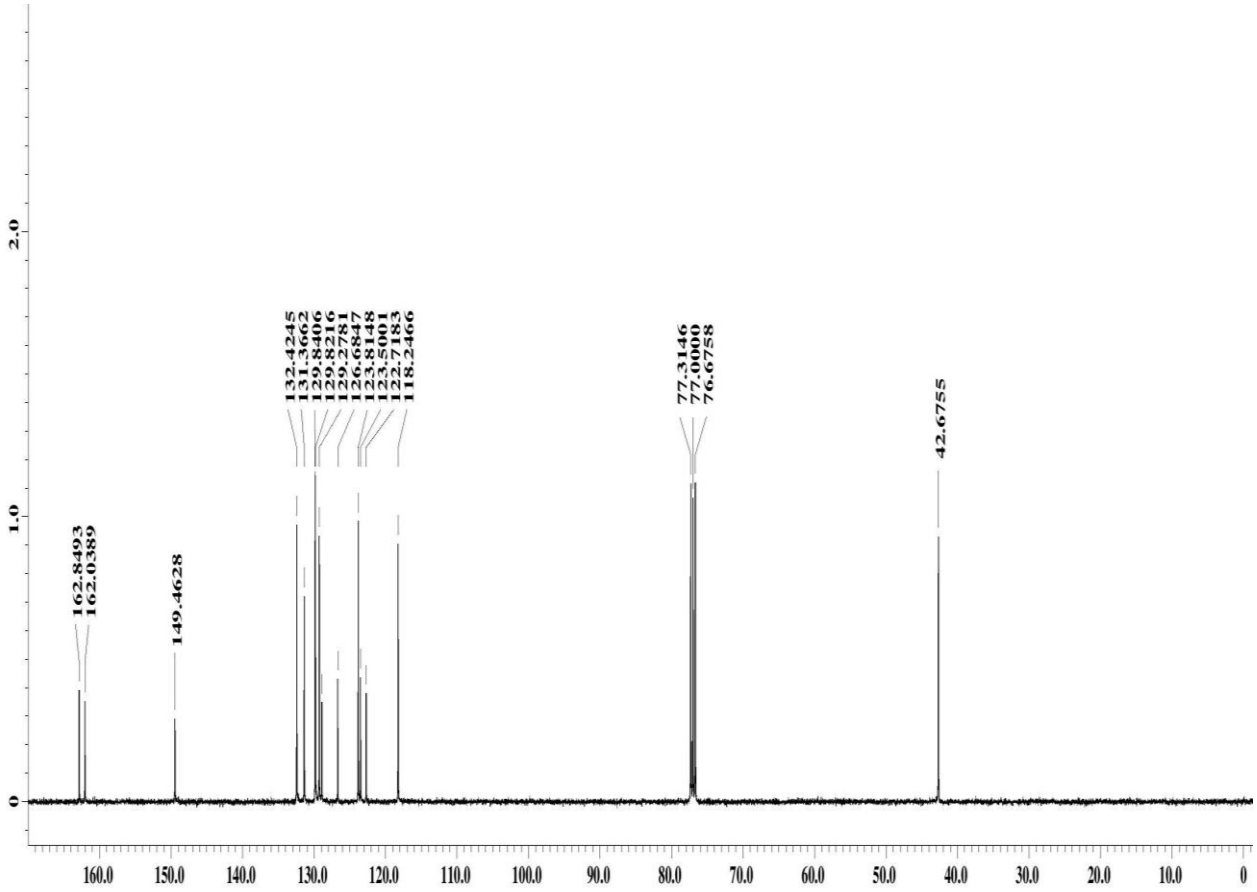


Figure 2. ^{13}C NMR spectrum of 2-allyl-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4)

^{1}H NMR spectrum of compound **5** showed one triplet at δ 4.09 and one doublet δ 4.80 ppm corresponding to four N-CH_2 protons, one mutiplet at δ 5.17-5.47 corresponds to four protons of two allyl-CH_2. Multiplet of two allylic-CH was observed at δ 5.96-6.09 ppm. Aromatic protons of naphthalimide showed wide range of splitting pattern ranging from δ 6.73-8.60 ppm corresponding to five protons. ^{13}C NMR spectrum showed the two distinctive N-CH_2 at δ 42.1 ppm and 46.0 ppm, one C=N group at δ 163.7 ppm and one carbonyl group at δ 164.3 ppm. Thus, ^{1}H and ^{13}C NMR spectra analysis confirmed the formation of 2-allyl-3-(allylimino)-7-nitro-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-1-one (**5)** (**Figures-3**,**4**).

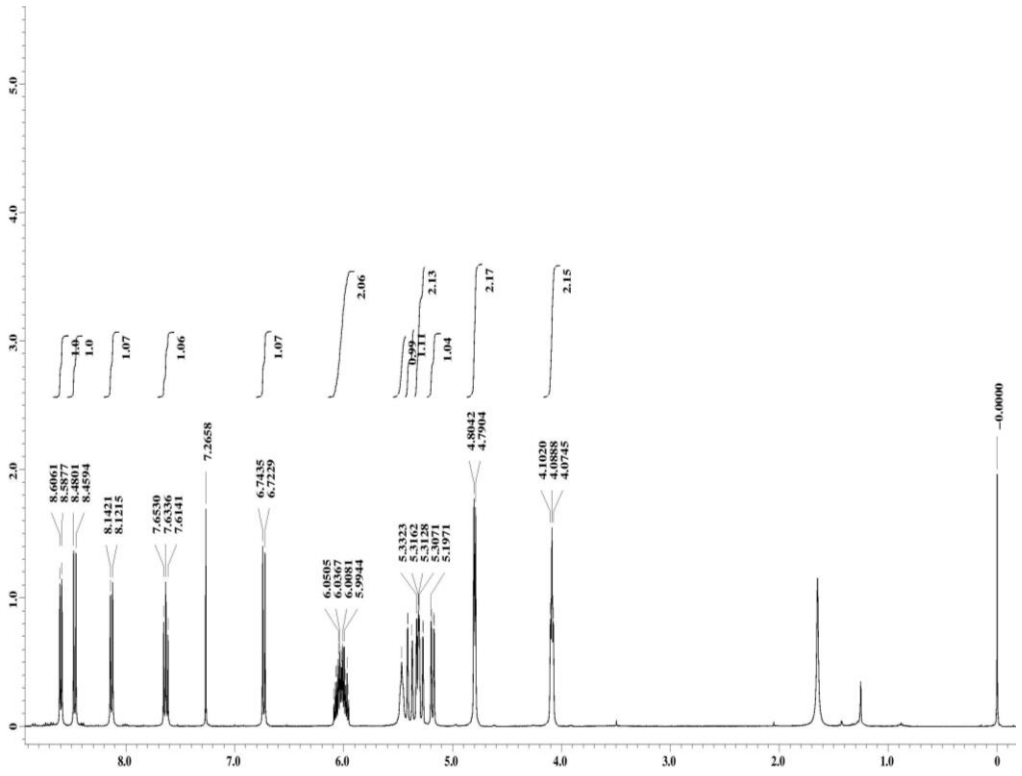


Figure 3. ^{1}H NMR spectrum of 2-allyl-3-(allylimino)-7-nitro-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-1-one (5)

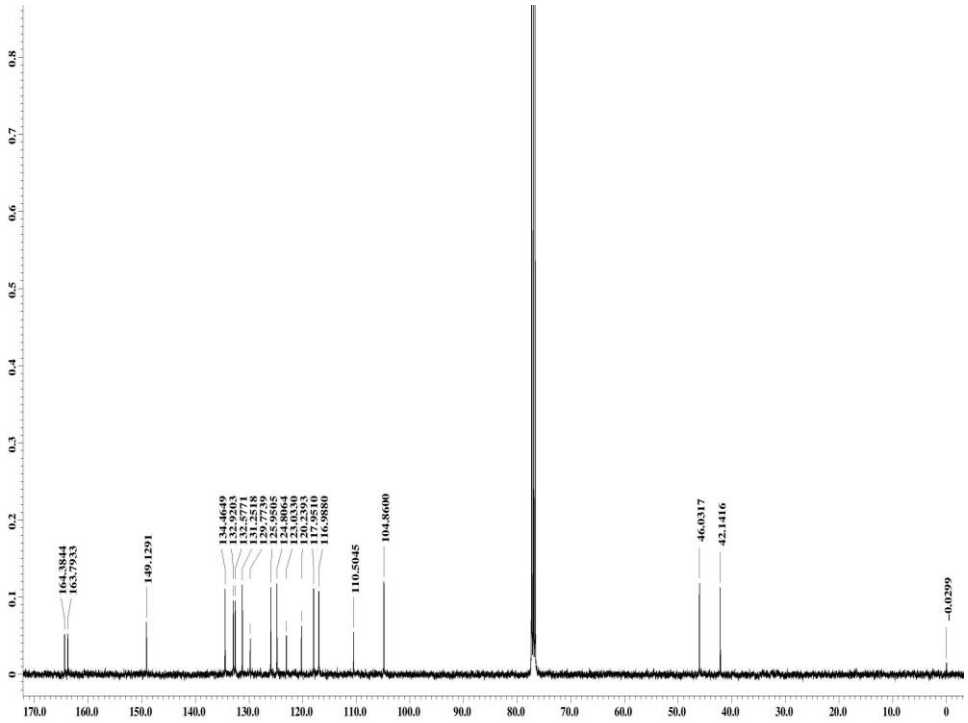


Figure 4. ^{13}C NMR spectrum of 2-allyl-3-(allylimino)-7-nitro-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-1-one (5)

After separating from column chromatography, 2-allyl-6-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**4**) was then reduced to 2-allyl-6-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **(6)** via catalytic hydrogenation by 10% Pd/C along with hydrazine hydrate and HPLC grade methanol in refluxing conditions for 8 h. ^{1}H NMR spectrum of compound **6** showed one broad singlet at δ 4.97 ppm corresponding to two protons of the NH_2 group. Aromatic protons of naphthalimide showed wide range of splitting pattern ranging from δ 6.90-8.63 ppm corresponding to five protons. Therefore, ^{1}H NMR spectrum analysis confirmed the formation of 2-allyl-6-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**Figure**-**5**)

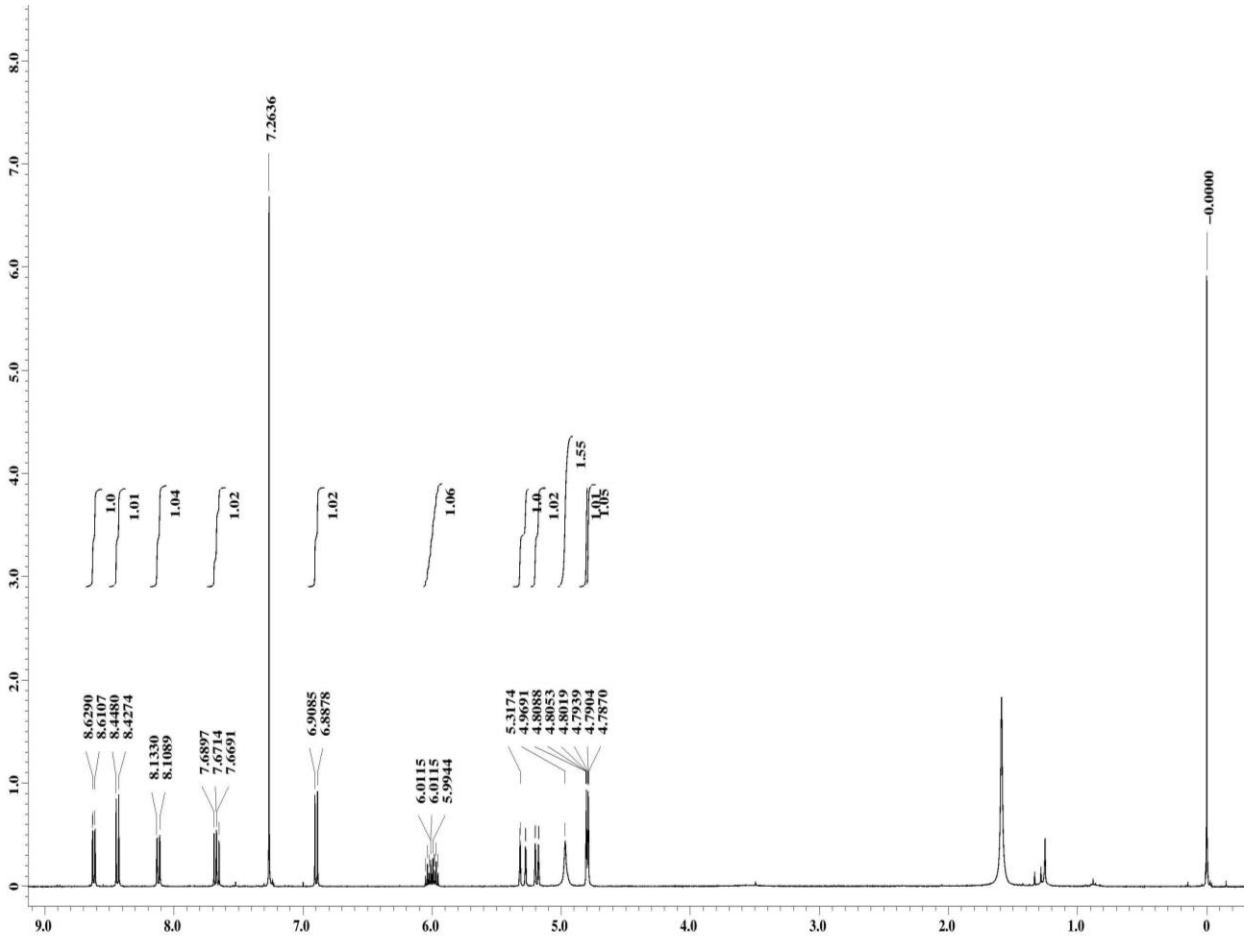


Figure 5. ^{1}H NMR spectrum of 2-allyl-6-amino-1H-benzo[*de*]isoquinoline-1,3(2H)-dione (**6**)

But, when compound **4** was treated with 10% Pd/C in simultaneous presence of H_2 and hydrazine hydrate in methanol at room temperatue, allyl group was also reduced with nitro group to give 6-amino-2-propyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**7**) in 78% yield. ^{1}H NMR spectrum of **7** showed one triplet at δ 0.97 ppm of three methyl protons, a multiplet at δ 1.72 ppm

of 2H protons corresponding to the methylene group, a triplet at δ 4.10 ppm of two protons of N-CH_2 group and 2H broad singlet at δ 6.29 ppm of NH_2 group. Aromatic protons of naphthalimide showed wide range of splitting pattern ranging from δ 6.86-8.54 ppm corresponding to five protons. ^{13}C NMR spectrum showed the distinctive peaks for two methyl protons at δ 10.9 ppm and δ 20.7 ppm, one N-CH_2 group at δ 40.7 ppm and the two carbonyl groups at δ 163.3 ppm and δ 164.0 ppm. Therefore, ^{1}H and ^{13}C NMR spectra analysis confirmed the formation of reduced allyl product, 6-amino-2-propyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**7**) (**Figures-6**,**7**).

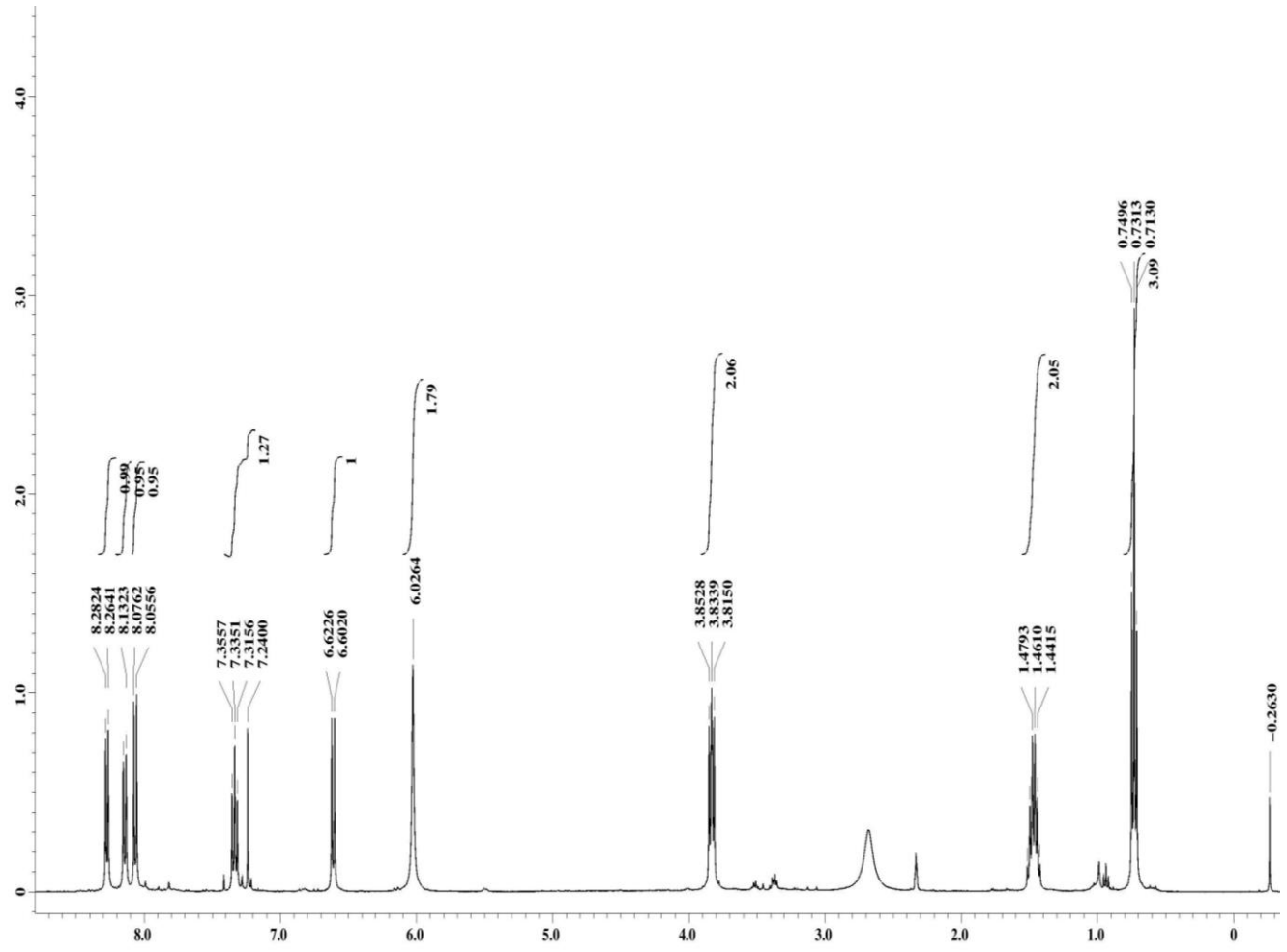


Figure 6. ^{1}H NMR spectrum of 6-amino-2-propyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione

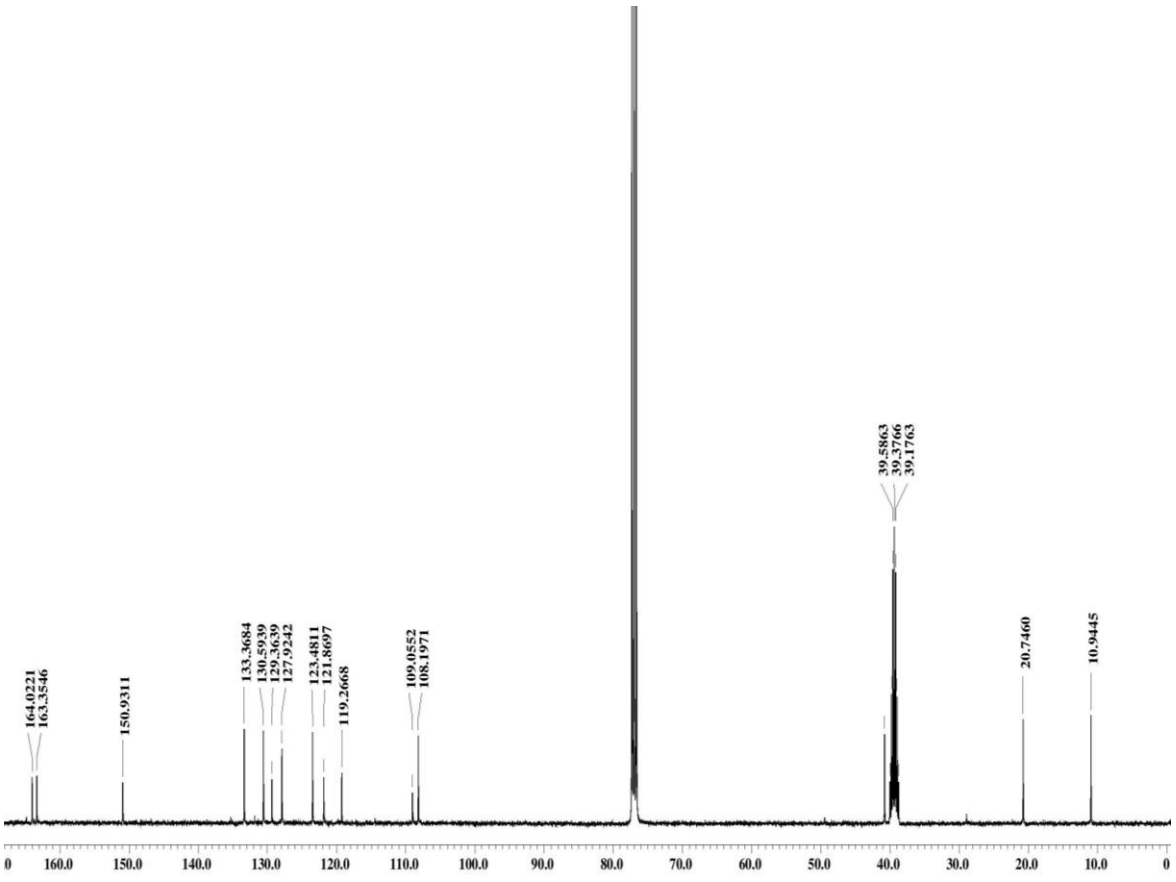


Figure 7. ^{13}C NMR spectrum of 6-amino-2-propyl-1H-benzo[*de*]isoquinoline-1,3(2H)-dione

On further treatment of compound **6** with chloroacetyl chloride, K_2CO_3 and acetonitrile for 2 h, white colored precipitates of compound *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-chloroacetamide **(8)** in 62% yield was obtained. ^{1}H NMR spectrum of compound **8** showed one singlet at δ 4.40 ppm of two protons of $COCH_2$, three doublets at δ 4.81, 5.22 and 5.33 ppm of two protons of N-CH_2 and one proton of each of the allyl-CH_2 group. A multiplet at δ 5.95-6.05 ppm of one proton of the allyl-CH group was also observed. Aromatic protons of naphthalimide showed wide range of splitting pattern ranging from δ 7.85-8.67 ppm corresponding to five protons. A broad singlet at δ 9.57 ppm of one proton of the NH was also observed. ^{13}C NMR spectrum showed the distinctive peaks at δ 42.4 ppm for $COCH_2$ and at δ 43.4 ppm for the N-CH_2 group. The three carbonyl groups were further observed at δ 163.1, 163.6 and 164.1 ppm. Therefore, ^{1}H and ^{13}C NMR spectra analysis confirmed the formation of *N*-(2-allyl-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-chloroacetamide (**8**) (**Figures-8,9**)

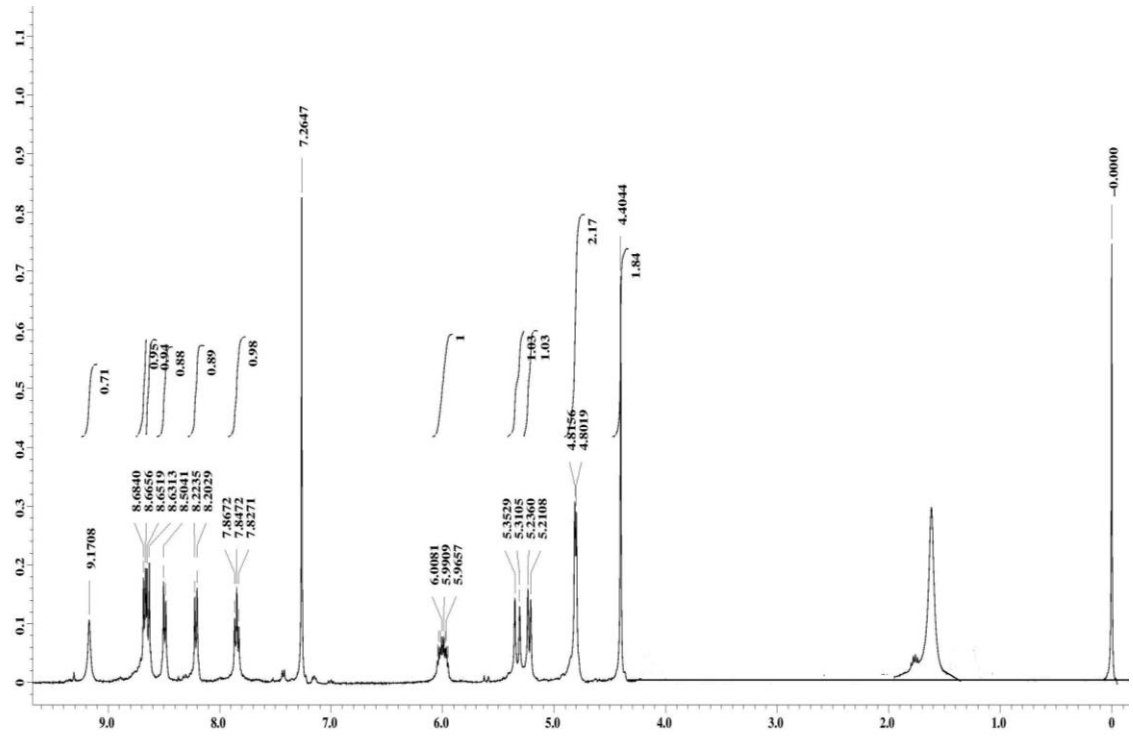


Figure 8. ^{1}H NMR spectrum of *N*-(2-allyl-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-chloroacetamide (8)

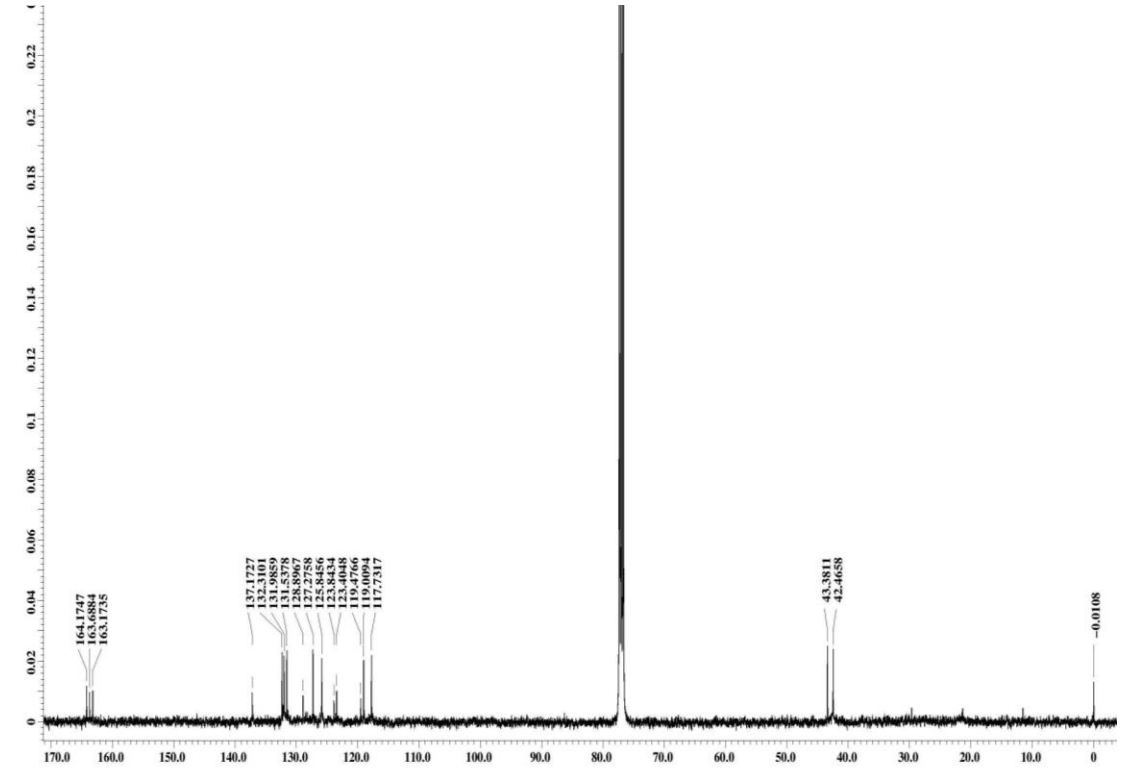


Figure 9. ^{13}C NMR spectrum of *N*-(2-allyl-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-chloroacetamide (8)

Finally, compound **8** was then refluxed with secondary amine, morpholine in presence of K_2CO_3 as base and acetonitrile as solvent for 9 h to give final derivatives **9a** in 41% yield. Column chromatography was frequently used a technique to further purify this compound in a hexane-ethyl acetate solvent systems. This compound was well characterized by ^1H and ^{13}C NMR spectrometer. ^1H NMR spectrum of compound **9a** showed one triplet at δ 2.79 ppm of four protons of mor-NCH_2, one singlet at δ 3.56 ppm of two protons of $COCH_2$, one triplet at δ 3.91 ppm of four protons of mor-OCH_2. The allylic group was confirmed by two triplets at δ 4.79 ppm and δ 4.81 ppm of N-CH_2 group, two double doublets of δ 5.21-5.23 ppm and δ 5.30-5.35 ppm of allylic CH_2 group, and a mulitplet at δ 5.95-6.05 ppm of one proton of allylic CH group. Aromatic protons of naphthalimide showed wide range of splitting pattern ranging from δ 7.81-8.71 ppm corresponding to five protons. A broad singlet at δ 10.40 ppm of one proton of the NH

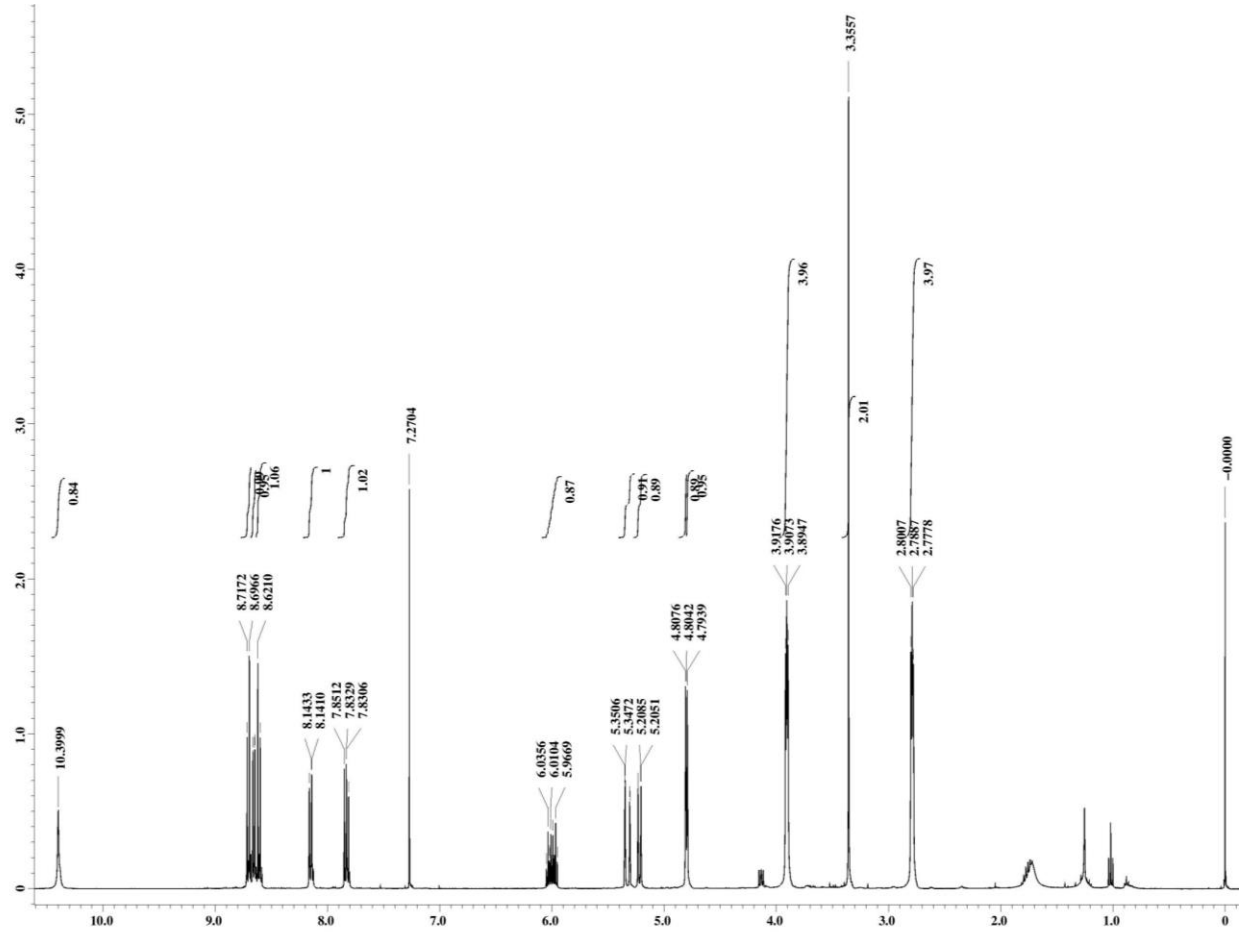


Figure 10. ^1H NMR spectrum of *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-morpholionoacetamide (9a)

was also observed. ^{13}C NMR spectrum showed distinctive peaks at δ 42.3 ppm of the N-CH_2, at δ 53.8 ppm of $COCH_2$, at δ 62.6 ppm of the N-CH_2, and at δ 67.2 ppm of the O-CH_2. The three carbonyl groups were further confirmed at δ 163.1, 163.7 and 168.3 ppm respectively. Therefore, ^{1}H and ^{13}C NMR spectra analysis confirmed the formation *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-morpholinoacetamide (**9a**) (**Figures-10**,**11**).

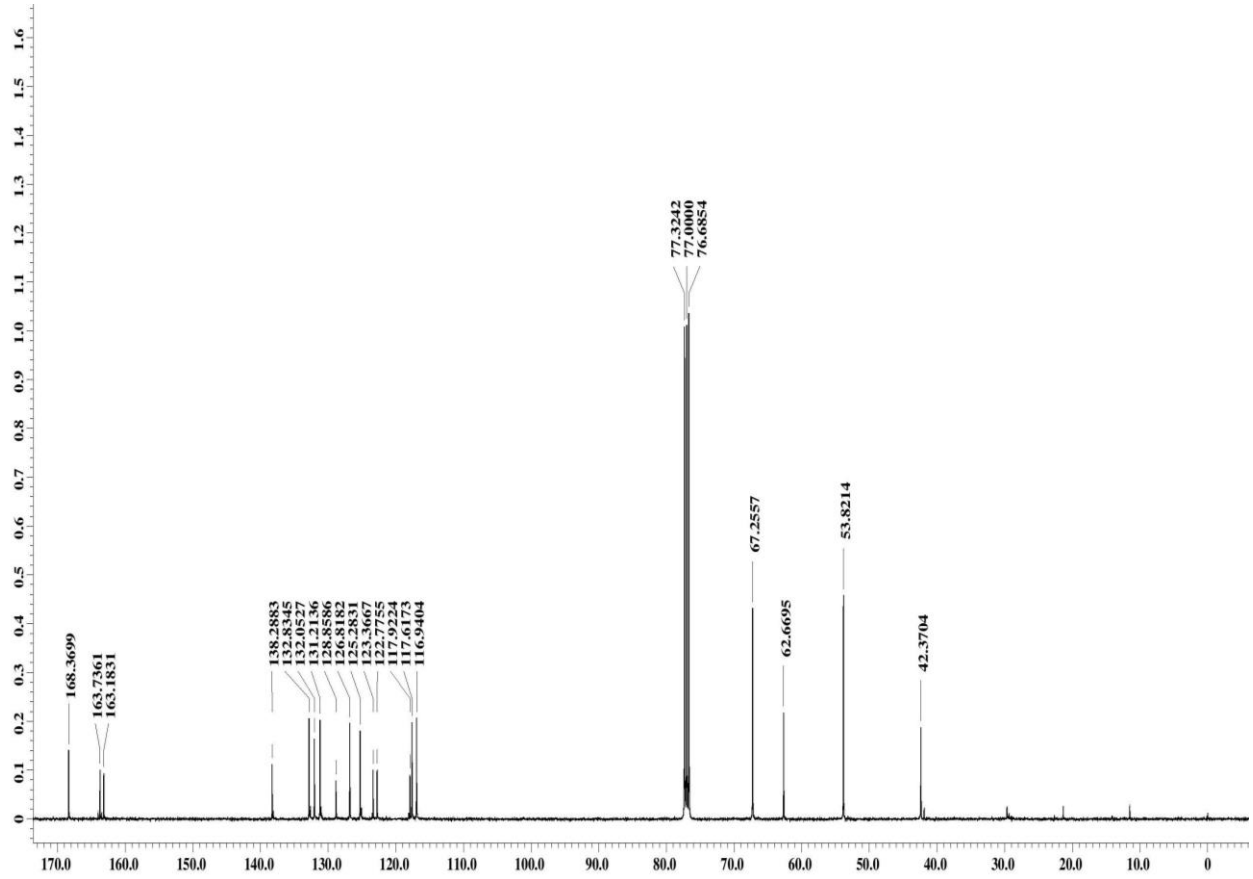


Figure 11. ^{13}C NMR spectrum of *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-morpholionoacetamide (9a)

Similarly, compound **8** was treated with pyrrolidine and piperidine under the same reaction conditions to give *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-(pyrrolidin-1-yl)acetamide (**9b**) and *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-(piperidin-1-yl)acetamide (**9c**) in 42% and 40% yields respectively. These compounds are well characterized by ^{1}H and ^{13}C NMR spectrometry.

Experimental Section

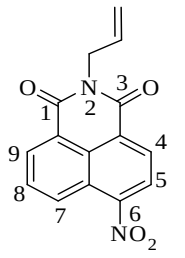
General Note :

All chemicals and solvents of commercial grade were used without further purification and were supplied by loba, spectrochemicals and Aldrich. Melting points were determined in open capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Jeol-ECS 400 MHz and 100 MHz NMR spectrometer respectively, using $CDCl_3$ and DMSO-d_6 as solvents. The chemical shifts were expressed in parts per million with TMS as internal reference and *J* values are given in Hz. Reactions were monitored by thin layer chromatography (TLC) with silica plate coated with silica gel HF-254 and column chromatography was performed with silica gel 60-120/100-200 mesh. Hexane/ethyl acetate were adopted solvent systems.

Procedure for the synthesis of 2-allyl-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4) and (5):

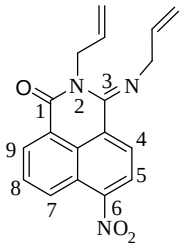
To the mixture of acenaphthene (**1**) (8 g, 51.8 mmol) and acetic acid (62 ml) was added conc. nitric acid (5.7 ml) with stirring at room temperature. After 12 h, the reaction mixture was poured into ice water. The precipitate was filtered and washed with water. The crude product was recrystallized from acetic acid and then ethanol to afford 5-nitro-1,2-dihydroacenaphthylene (**2**) (9 g, 87.21% yield, m.p. = 102-103 ^{0}C, lit. m.p.[20] = 101-102 ^{0}C). To a stirred solution of sodium dichromate (1.8 g, 7.4 mmol) and acetic acid (20 ml) was added the solution of compound **2** (2.5g, 12.5 mmol in 21 ml acetic acid). After heating at reflux for 24 h, the reaction mixture was mixed with cold water (50 ml) at 0 ^{o}C, filtered and washed with water until the filterate was neutral. The residue was dried *in vacuo* to afford the product 6-nitrobenzo[de]isochromene-1,3-dione (**3**) (2.59 g, 85% yield, m.p. = 226-228 ^{0}C, lit. m.p.[21] = 228-229 ^{0}C). Allyl amine (0.54 ml, 9.4 mmol) was quickly added to a cloudy solution of compound **3** (1.83 g, 7.5 mmol) in ethanol (40 ml) under reflux conditions. After 6 h, the reaction mixture was cooled to room temperature and extracted with chloroform. The crude product was then purified by silica gel column chromatography to give mixture of 2-allyl-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**4**) (hexane:ethylacetate :: 2:8) (1 g, 47% yield, m.p. = 185-187 ^{0}C) and 2-allyl-3-(allylimino)-7-nitro-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-1-one (**5**) (hexane:ethyl acetate :: 4:6) (600 mg, 25% yield, m.p. = 200-203 ^{0}C).

Spectral data of 2-allyl-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4): Yellow solid; %



yield: 47%; m.p.: 185-187 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.81 (t, *J* = 1.40 Hz, 1H, N-CH_2), 4.83 (t, *J* = 1.38 Hz, 1H, N-CH_2), 5.24-5.27 (dd, ^{2}J = 10.08 Hz, ^{3}J = 1.36 Hz, 1H, allyl-CH_2), 5.33-5.38 (dd, ^{2}J = 16.96 Hz, ^{3}J = 1.38 Hz, 1H, allyl-CH_2), 5.94-6.04 (m, 1H, allyl-CH), 7.98-8.02 (m, 1H, H-8), 8.42 (d, *J* = 7.80 Hz, 1H, H-4), 8.71 (d, *J* = 8.24 Hz, 1H, H-9), 8.74-8.76 (dd, ^{2}J = 7.36 Hz, ^{3}J = 0.92 Hz, 1H, H-7), 8.84-8.86 (dd, ^{2}J = 8.68 Hz, ^{3}J = 0.92 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 42.6 (N-CH_2), 118.2, 122.7, 123.5, 123.8, 126.6, 128.9, 129.2, 129.8, 129.8 131.3, 132.4, 149.4 (ArC), 162.0 (C=O), 162.8 (C=O).

Spectral data of 2-allyl-3-(allylimino)-7-nitro-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-1-

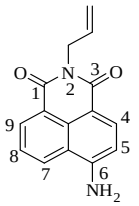


one (5): Yellow solid; yield: 25%; m.p.: 200-203 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.09 (t, *J* = 5.50 Hz, 2H, N-CH_2), 4.80 (d, *J* = 5.52 Hz, 2H, N-CH_2), 5.17-5.47 (m, 4H, allyl-CH_2), 5.96-6.09 (m, 2H, allyl-CH), 6.73 (d, *J* = 8.24 Hz, 1H, H-4), 7.63 (t, *J* = 7.78 Hz, 1H, H-8), 8.13 (d, *J* = 8.24 Hz, 1H, H-9), 8.47 (d, *J* = 8.28 Hz, 1H, H-7), 8.60 (d, *J* = 7.36 Hz, 1H, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 42.1 (N-CH_2), 46.0 (N-CH_2), 104.8, 110.5, 116.9, 117.9, 120.2, 123.0, 124.8, 125.9, 129.7, 131.2, 132.5, 132.9, 134.4, 149.1 (ArC), 163.7 (C=O), 164.3 (C=O).

Procedure for the synthesis of 2-allyl-6-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (6):

Compound **4** (1 g, 3.5 mmol) was refluxed with 1 ml of hydrazine hydrate and 0.05 g of 10% Pd/C in methanol (50 ml) for 8 h. After the completion of the reaction, the solution was filtered for with celite and filtrate was extracted with chloroform and water. The crude product was then purified with silica gel column chromatography (hexane:ethyl acetate :: 7:3) to give 2-allyl-6-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**6**) (700 mg, 65% yield, m.p. = 204-206 ^{0}C).

Spectral data of 2-allyl-6-amino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**6**): Red brown solid;

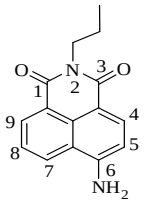


yield: 65%; m.p.: 204-206 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.79 (t, *J* = 1.38 Hz, 1H, N-CH_2), 4.81 (t, *J* = 1.38 Hz, 1H, N-CH_2), 4.97 (bs, 2H, NH_2), 5.17-5.20 (m, 1H, allyl-CH_2), 5.28-5.32 (m, 1H, allyl-CH_2), 5.95-6.05 (m, 1H, allyl-CH), 6.90 (d, 1H, *J* = 8.28 Hz, H-4), 7.65-7.69 (m, 1H, H-8), 8.11-8.13 (m, 1H, H-9), 8.44 (d, *J* = 8.24 Hz, 1H, H-7), 8.61-8.63 (dd, ^2J = 7.36 Hz, ^3J = 0.90 Hz, 1H, H-5).

Procedure for the synthesis of 6-amino-2-propyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**7**):

Compound **4** (0.5 g, 1.7 mmol) was mixed with 1 ml of hydrazine hydrate and 0.05 g of 10% Pd/C in methanol (50 ml) and stirred at room temperature in the presence of H_2 for 4 h. After the completion of reaction, the solution was filtered on celite and filterate was extracted with chloroform and water. The crude product was then purified with silica gel column chromatography using hexane:ethyl acetate as eluents to give 6-amino-2-propyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**7**) (300 mg, 78% yield, m.p. = 230-234 ^{0}C).

Spectral data of 6-amino-2-propyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**7**): Black solid;



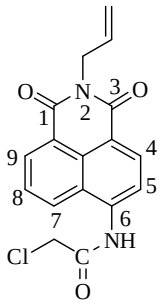
yield: 78%; m.p.: 230-234 ^{0}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 0.97 (t, *J* = 7.32 Hz, 3H, CH_3), 1.72 (m, 2H, CH_2), 4.10 (t, *J* = 7.56 Hz, 2H, N-CH_2), 6.29 (bs, 2H, NH_2), 6.86 (d, *J* = 8.24 Hz, 1H, H-4), 7.60 (t, *J* = 8.02 Hz, 1H, H-8), 8.32 (d, *J* = 8.24 Hz, 1H, H-9), 8.39 (d, *J* = 8.28 Hz, 1H, H-7), 8.54 (d, *J* = 7.32 Hz, 1H, H-5); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 10.9 (CH_3), 20.7 (CH_2), 40.7 (N-CH_2), 108.2, 109.0, 119.2, 121.8, 123.4, 127.9, 129.3, 130.5, 133.3, 150.9 (ArC), 163.3 (C=O), 164.0 (C=O).

Procedure for the synthesis of *N*-(2-allyl-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-chloroacetamide (8):

Compound **6** (200 mg, 0.79 mmol) was mixed with K_2CO_3 (163 mg, 1.1 mmol) in acetonitrile (20 ml), and chloroacetyl chloride (0.093 ml, 0.36 mmol) was added drop wise with constant stirring at room temperature. The reaction was then refluxed for 2 h. The crude product was extracted with chloroform and water, concentrated to get the solid product and then purified through silica gel column chromatography in hexane:ethyl acetate eluent system (7:3) to afford *N*-(2-allyl-2,3-dihydro-1*H*-

benzo[*de*]isoquinolin-6-yl)-2-chloroacetamide (**8**) (190 mg, 62% yield, m.p. = 210-214 ^{0}C).

Spectral data of *N*-(2-allyl-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-chloroacetamide (8):

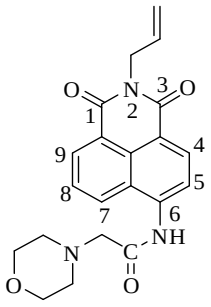


Off white solid; yield: 62%; m.p.: 210-214 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.40 (s, 2H, CO$\underline{CH_2}$), 4.81 (d, *J* = 1.88 Hz, 2H, N-CH_2), 5.22 (d, *J* = 10.08 Hz, 1H, allyl-CH_2), 5.33 (d, *J* = 16.96 Hz, 1H, allyl-CH_2), 5.95-6.05 (m, 1H, allyl-CH), 7.85 (t, *J* = 8.02 Hz, 1H, H-8), 8.21 (d, *J* = 8.24 Hz, 1H, H-4), 8.49 (d, *J* = 8.24 Hz, 1H, H-9), 8.64 (d, *J* = 8.24 Hz, 1H, H-7), 8.67 (d, *J* = 7.36 Hz, 1H, H-5), 9.17 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 42.4 (CO$\underline{CH_2}$), 43.4 (NCH_2), 117.7, 119.0, 119.4, 123.4, 123.8, 125.8, 127.2, 128.9, 131.5, 131.9, 132.3, 137.1 (ArC), 163.1 (C=O), 163.6 (C=O), 164.1 (C=O).

General procedure for the synthesis of *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-amine acetamide (9a-9c):

To the solution of compound **8** (50 mg, 0.13 mmol) in acetonitrile (20 ml), 1.5 equivalent of secondary amines viz., morpholine, pyrrolidine and piperidine and 1.5 equivalent of K_2CO_3 were added under reflux conditions for 9 h. The reaction was brought to room temperature. The crude product was then extracted with chloroform and water, purified through silica gel column chromatography in hexane-ethyl acetate eluent system to afford compounds *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-morpholinoacetamide (**9a**), *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-(pyrrolidin-1-yl)acetamide (**9b**) and *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-(piperidin-1-yl)acetamide (**9c**).

Spectral data of *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-morpholino



acetamide (9a): Off white solid; yield: 41%; m.p.: 190-194 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.79 (t, *J* = 4.58 Hz, 4H, mor-NCH_2), 3.56 (s, 2H, CO$\underline{CH_2}$), 3.91 (t, *J* = 4.58 Hz, 4H, mor-OCH_2), 4.79 (t, *J* = 1.38 Hz, 1H, N-CH_2), 4.81 (t, *J* = 1.38 Hz, 1H, N-CH_2), 5.21-5.23 (dd, ^2J = 10.08 Hz, ^3J = 1.36 Hz, 1H, allyl-CH_2), 5.30-5.35 (dd, ^2J = 16.96 Hz, ^3J = 1.36 Hz, 1H, allyl-CH_2), 5.95-6.05 (m, 1H, allyl-CH), 7.81-7.85 (m, 1H, H-8), 8.14-8.16 (m, 1H, H-4), 8.61 (d, *J* = 8.28 Hz, 1H, H-9),

8.65-8.67 (dd, ^{2}J = 7.32 Hz, ^{3}J = 0.92 Hz, 1H, H-7), 8.71 (d, J = 8.24 Hz, 1H, H-5), 10.40 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 42.3 (N-CH_2), 53.8 (N-CH_2), 62.6 (N-CH_2), 67.2 (O-CH_2), 116.9, 117.6, 117.9, 122.7, 123.3, 125.2, 126.8, 128.8, 131.2, 132.0, 132.8, 138.2 (ArC), 163.1 (C=O), 163.7 (C=O), 168.3 (C=O).

Spectral data of *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-(pyrrolidin-1-yl)acetamide (**9b**): Light brown semisolid; yield: 42%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.01 (s, 4H, CH_2), 2.93 (s, 4H, N-CH_2), 3.58 (s, 2H, CO$\underline{CH_2}$), 4.80 (d, J = 5.52 Hz, 2H, N-CH_2), 5.21 (d, J = 10.08 Hz, 1H, allyl-CH_2), 5.32 (d, J = 17.4 Hz, 1H, allyl-CH_2), 5.95-6.05 (m, 1H, allyl-CH), 7.77 (t, J = 7.80 Hz, 1H, H-8), 8.15 (d, J = 8.48 Hz, 1H, H-4), 8.58-8.65 (m, 3H, H-5,7,9), 10.55 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 24.1 (CH_2), 29.6 (N-CH_2), 42.3 (N-CH_2), 54.6 (N-CH_2), 114.0, 117.2, 117.5, 117.8, 123.1, 125.9, 126.6, 128.8, 131.1, 132.0, 132.7, 138.6 (ArC), 163.2 (C=O), 163.8 (C=O), 168.0 (C=O).

Spectral data of *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-(piperidin-1-yl)acetamide (**9c**): Light brown semisolid; yield: 40%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.60 (t, J = 4.80 Hz, 2H, pip-CH_2), 1.78 (m, 4H, pip-CH_2), 2.71 (s, 4H, pip-NCH_2), 3.28 (s, 2H, CO$\underline{CH_2}$), 4.80 (d, J = 5.92 Hz, 2H, N-CH_2), 5.20-5.23 (dd, ^{2}J = 10.52 Hz, ^{3}J = 1.14 Hz, 1H, allyl-CH_2), 5.30-5.35 (dd, ^{2}J = 16.96 Hz, ^{3}J = 1.40 Hz, 1H, allyl-CH_2), 5.95-6.05 (m, 1H, allyl-CH), 7.79-7.83 (m, 1H, H-8), 8.17 (d, J = 8.72 Hz, 1H, H-4), 8.59 (d, J = 8.28 Hz, 1H, H-9), 8.63 (d, J = 7.32 Hz, 1H, H-7), 8.71 (d, J = 8.24 Hz, 1H, H-5), 10.68 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.4 (CH_2), 26.6 (CH_2), 42.3 (N-CH_2), 54.9 (N-CH_2), 62.9 (N-CH_2), 116.6, 117.5, 117.6, 122.7, 123.2, 125.6, 126.6, 128.8, 131.1, 132.1, 132.9, 138.7 (ArC), 163.2 (C=O), 163.8 (C=O), 169.4 (C=O).

CONCLUSION

- Monoallylated, 2-allyl-6-nitro-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione and diallylated, 2-allyl-3-(allylimino)-7-nitro-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-1-one were also synthesized.

- *N*-(2-Allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-morpholionoacetamide, *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-(pyrrolidin-1-yl)acetamide and *N*-(2-allyl-1,3-dioxo-2,3-dihydro-1*H*-benzo[*de*]isoquinolin-6-yl)-2-(piperidin-1-yl)acetamide were synthesized in good to moderate yields. These compounds were well characterized by ^{1}H and ^{13}C NMR spectrometry.

- The final compounds will further be used for its biological activity as anti-cancer agents as well as for DNA intercalation studies.

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