Synthesis of Naphthalimide and Imidazo[1,2-*a*]pyridine Derivatives as Anticancer Agents

A

Thesis submitted

In the partial fulfillment of the requirement for the degree of

MASTERS OF SCIENCE

IN

CHEMISTRY

Submitted By

NITYA CHAWLA

(301502025)

UNDER THE SUPERVISION

Dr. Kamaldeep Paul

(Associate Professor)

SCHOOL OF CHEMISTRY AND BIOCHEMISTRY,

THAPAR UNIVERSITY,

PATIALA-147004

2017

CERTIFICATE

This is to certify that the thesis entitled **"Synthesis of Naphthalimide and Imidazo[1,2-*a*]pyridine Derivatives as Anticancer Agents"** submitted by **Ms. Nitya Chawla** in the partial fulfillment of the requirements for the degree of **Master of Science in Chemistry** from **Thapar University, Patiala** is a bonafied piece of work carried out under the guidance and supervision of **Dr. Kamaldeep Paul**, Associate Professor, School of Chemistry and Biochemistry, Thapar University, Patiala and no part of this project has been submitted for award of any other degree in this or any other university.

Nitya

(NITYA CHAWLA)

This is to certify the above statement made by student concerned is correct and true to the best of my knowledge.

Kamaldeep Paul.

(Dr. Kamaldeep Paul)
Associate Professor (Supervisor),
School of Chemistry and Biochemistry,
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SELF DECLARATION

The work embodied in the project entitled **"Synthesis of Naphthalimide and Imidazo[1,2-*a*]pyridine Derivatives as Anticancer Agents"** has been done by me in the partial fulfillment of requirement for the award of degree of **Masters of Science in Chemistry,** submitted in the **School of Chemistry and Biochemistry, Thapar University, Patiala,** is an authentic record of my own carried out under the supervision and guidance of **Dr. Kamaldeep Paul** Associate Professor, School Of Chemistry and Biochemistry, Thapar University, Patiala. All the ideas and references have been duly acknowledged.

Date:

Place: Patiala

Nitya Chawla

This is to certify the above statement made by student concerned is correct and true to the best of my knowledge.

(Dr. Kamaldeep Paul)
Associate Professor (Supervisor),
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Nitya

Place: Patiala

Nitya Chawla

TABLE OF CONTENT

1. INTRODUCTION

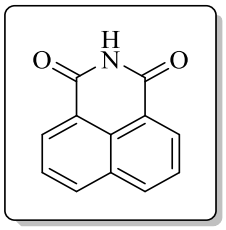
Heterocyclic chemistry is a main branch of organic chemistry which continues to be the important part of drug industry.[1] Heterocyclic compounds have been shown the deepest impression in the field of medicinal chemistry because of its excellent response towards many biochemical systems. On the basis of their biological activity on system, various heterocyclic moieties have been selected. There are many synthetic and naturally occurring heterocyclic compounds or complexes that are involved in chemical reactions inside the human body. They have the ability to interact with DNA, RNA, protein molecules or metal ions that shows excellent biochemical importance. Many heterocyclic biosynthetic and synthetic compounds have been used for therapeutic cause, such as anti-inflammatory, antifungal, muscle relaxants, anti-mycobacterial, antitumor, antidepressant and anticancer agents. There are also many other applications like anticorrosive agents, herbicides, agrochemicals, photographic developers, copolymer, fluorescent flavoring agents, fungicides etc.[2] The main motive and engineering behind the drug designing is related to the strategic incorporation of heterocyclic fragments. Selectivity and its potential through lipophilicity, aqueous solubility, bioisosteric replacements and polarity can be refined by redesigning and conditioning the mechanism of action of pharmaceutical drugs in order to achieve molecularly targeted agents. Oncology is the area where it is more noticeable due to the intrinsic limitations in the routes of chemotherapy, associated side effects and harmful to the healthy tissues. Such effects can be avoided via passively or actively into cancerous cells, selective targeting of delivery.

Cancer is a name that is given to group of related diseases in which some body cells grow uncontrollably. Now a days, cancer is known to be the second leading chief cause of the death and today it is found to be the prime health concern. Many anticancer drugs are available but they suffer from many limitations including low therapeutic window, side effects, lack of selectivity, and development of resistance against drug. DNA plays an important role in the existence and growth of the tumor.[3] Consequently, DNA is the major target to design anticancer drug. Naphthalimide and imidazo[1,2-*a*]pyridine, both have recently gained the advancement in the cancer research. Due to the planarity of the naphthalimide, it can easily intercalate with DNA and results in the disruption of the cellular process while imidazo[1,2-*a*]pyridine causes apoptosis in G_1/S phase that results in the cytotoxic activity against the cancer cells.[4,5]

2. REVIEW OF LITERATURE

2.1 Naphthalimide and its biological activities

Naphthalimide is a π deficient aromatic, flat tricyclic ring system that recently gained advancement in the cancer research because of its ability to bind with the target compound (DNA).[6] The planar structure of naphthalimide is responsible for DNA intercalation that disturb the cellular events of DNA binding by inserting itself within DNA base-pairs and thus effect the enzyme activity (TOPO II etc.).[7,8] This moiety has gained the considerable attention for its biological activities such as anticancer, anti-inflammatory, antitumor against human tumor cells and murine tumor cells,[6] antiprotozoal, antiviral, antidepressant activity, serotonin 5-HT3 and 5-HT4 receptor antagonist activity,[9] and as chemosensors[10] **(Figure 1)**. The good pharmacological activity of naphthalimide and ease of its development makes this an interesting moiety for synthesis of various therapeutic agents.



1,8-Naphthalimide

Recently, sulfonated derivatives of 1,8-naphthalimide have been identified as antiviral activity against human immunodeficiency virus, HIV-1.[11] Bromination of the 1,8-naphthalimide ring has been suggested good photo chemotherapeutic inhibition of enveloped viruses in blood and in blood products. Substitution at 5-position of the naphthalene ring confirmed the antitumor activity of the naphthalimide from the results of existing research.

A number of naphthalimide derivatives has also been shown desired anticancer activity against various cancer cell lines. Braña *et al*. synthesized the first sequence of naphthalimide for its biological activity.[6] They have synthesized the single molecule by merging different molecules of antitumor drugs such as cycloheximide containing glutarimide ring, aristocholic acid, CG-603 and tilorone. Initially, 3-nitronaphthalimide with four different side chains were synthesized.

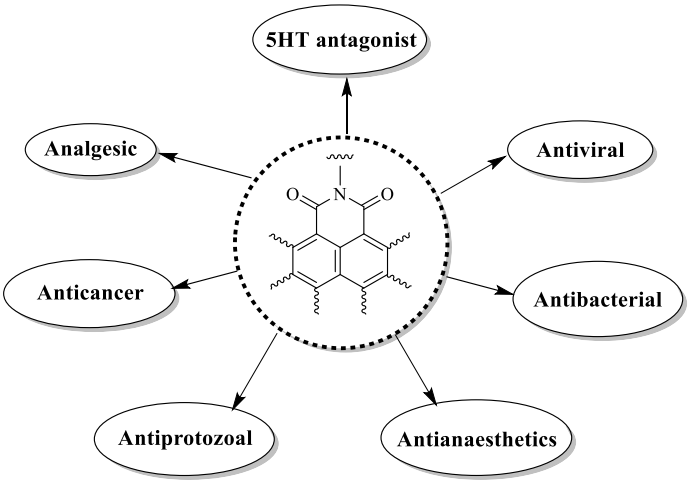
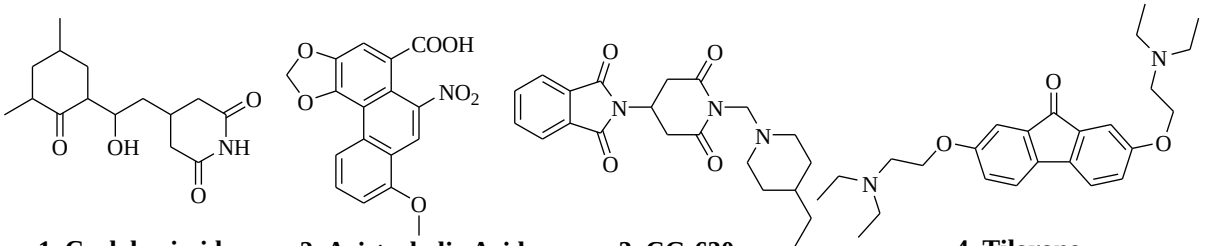
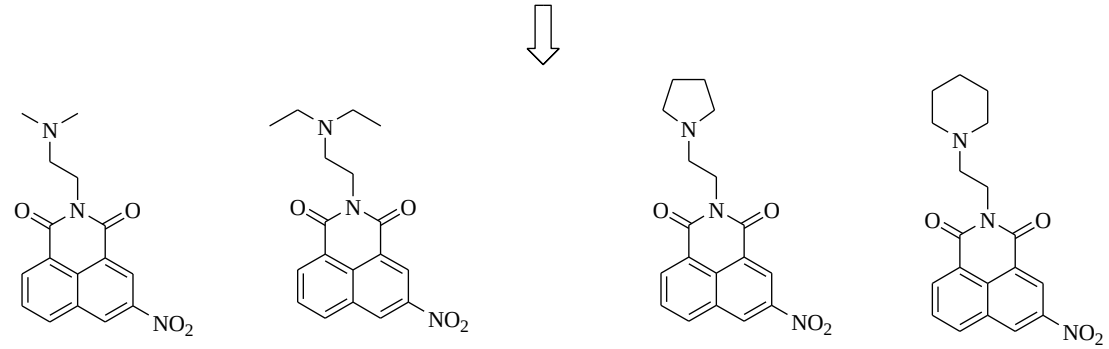


Figure 1. Biological activities of naphthalimide derivatives.



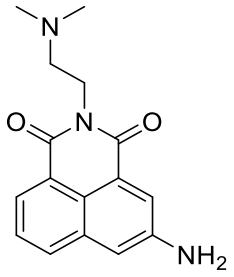
1. Cycloheximide **2. Aristocholic Acid** **3. CG-630** **4. Tilorone**



5 **6** **7** **8**

These compounds were tested against HeLa and KB cancer cell lines which showed good cytotoxic activity against them.[10] Compound **5** (mitonafide) and compound **7** have been shown significant cytotoxic activity in the range of 0.5 – 1 µM. According to the SAR studies, side chain containing basic terminal group and decrease in the basicity of the terminal nitrogen decreases the cytotoxicity of the molecule. Compound **5** was reached into clinical trials. Amonafide (**9)** from Braña group was also reached into clinical trials. Both compounds have shown significantly high cytotoxicity against HeLa cell lines with IC_{50} values of 0.47 µM and

2.8 µM, respectively and entered into the phase II of the clinical trials. But in clinical trials III, they have failed because of the toxicity of dose limiting.[12]



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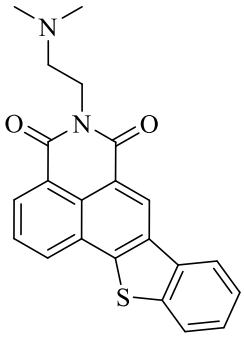


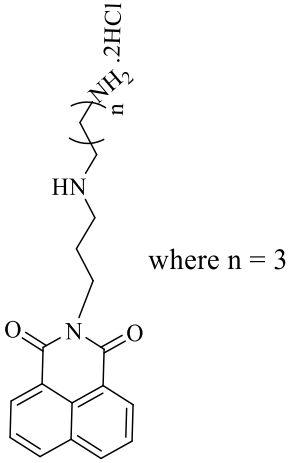
10

Hong Zhu and his coworkers synthesized 2-(2-dimethylamino)-6-thia-2-aza-benzo-[*def*]-chrysene-1,3-diones (**R16**) **10** by removing 5-NH_2 group from the ring with addition of thiol group. Compound **10** was found to be more potent than amonafide **9.** Compound **10** was tested with different cell lines including colon cancer, ovarian cancer, oral epidermoid, lung cancer and leukemia. As compared with amonafide, compound **10** was found to be more cytotoxic against liver cancer (IC_{50} = 1.92 µmol/L), ovarian cancer (IC_{50} = 5.67 µmol/L), leukemia cancer (IC_{50} = 2.08 µmol/L) and colon cancer (IC_{50} = 3.22 µmol/L) than amonafide (**9**) with IC_{50} values of 4.63, 10.10, 4.45, 6.41 µmol/L, respectively.[13]

Tian *et al*. have developed naphthalimide-diamine conjugates and studied antitumor activity against two cancer cell lines *viz*; human colon cancer cells (HCT116) and hepatoma cell line (QSG 7701) using MTT assays. On comparison with amonafide, compound **11** showed more antitumor activity towards HCT116 cells and displayed good selectivity towards QSG 7701 cell lines. However, it was observed that primary amino group at the terminal position possessing better biological activity as compared to tertiary amino group. Compound **11** has been found to be more promising anticancer agent against HCT116 and QSG-7701 cancer cell lines with IC_{50} values of 5.45 ± 1.71 µM and 19.69 ± 3.42 µM, respectively.[14]

S. Li *et al*. reported 4-pyrazolyl-1,8-naphthalimide derivatives that showed cytotoxicity against MCF-7 (human mammary cancer cells), HeLa (human cervical carcinoma cells) and A549 (human lung cancer cells) cell lines. However, as compared with amonafide, compound **12** showed better anticancer activity against MCF-7 cells. Compound **12** having 3,4,5-trimethoxy group on the phenyl ring is hindered the activity 3.3-fold more than the amonafide under the

same conditions. The IC_{50} values of compound **12** against all the three cell lines; MCF-7, HeLa and A549 were found to be 0.51, 3.09 and 5.14 µM, respectively.[15]



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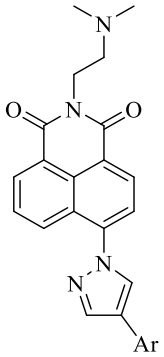
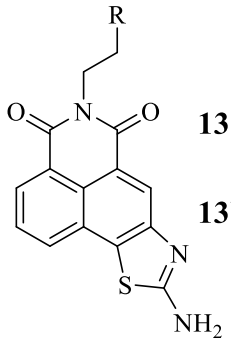


Ar = 3,4,5-$(CH_3O)_3C_6H_2$

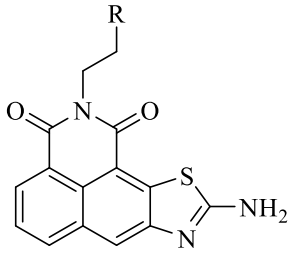
12

Qian and co-workers synthesized a series of aminothiazonaphthalimides. The compound **14a-b** was found to be highly active towards antitumor activity than its angular isomers compound **13a-b**. Compound **14a** showed high cytotoxic activity against P388 (mouse leukaemia cells) and A549 (adenocarcinomic human alveolar basal epithelial cells) cell lines. The antitumour activities of four analogues against these two cell lines were reliant highly on the side chain length. Compounds **13a** and **14a** showed better activity against antitumor than compounds **13b** and **14b** containing one more methylene group. The IC_{50} values obtained for compound **13a** against A549 and P388 cell lines were found to be respective 500 and 1027 nM and for compound **13b**, IC_{50} values were 772 and 1277 nM. The IC_{50} values were found to be 0.8 and 5 nM for compound **14a** and 21.8 and 294 nM for compound **14b** against A549 and P388 cell lines, respectively.[16]



13a, 14a : R = $N(CH_3)_2$

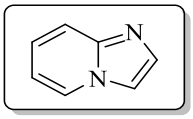
13b, 14b : R = $CH_2N(CH_3)_2$



13 **14**

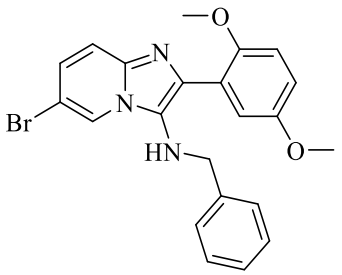
2.2 Imidazo[1,2-*a*]pyridine and its biological activities

Imidazopyridine is a nitrogen fused heterocyclic compound having pyridine and imidazole rings. There are many heterocyclic derivatives that is derived from pyridine but only imidazo [1,2-*a*]pyridine gained the importance in the field of pharmaceuticals.[17] Wide range of applications and activities have been known with this moiety such as fungicidal, cytotoxic, anti-inflammatory, antibacterial etc.[18] There are also many drugs having imidazo[1,2-*a*]pyridine moiety that are available in market such as zolpidem used in insomnia treatment,[19] Olprinone for heart failure treatment etc.[20] Imidazopyridines possess anticancer activity against CDK4 (hindered the activity of cyclin dependent kinase), caspase-3 activators,[21] inhibits the activity of Aurora-A kinase and dual KSP.[22] An excellent property of the leading moiety is its ability not to destruct the human cells that makes it magnificent anticancer agent.



Imidazo[1,2-*a*]pyridine

A number of imidazopyridines has also been shown desired anticancer activity against various cancer cell lines. N. Dahan-Farkas *et al*. synthesized different imidazo[1,2-*a*]pyridine derivatives with substitution at 6th position. The compound **15** possessed apoptosis and cytotoxicity against HT-29 and Caco-2 cell lines at very low concentrations (micromolar). Compound showed negligible cytotoxic activity against WBC cells. IC_{50} values obtained for compound **15** on the Caco-2 cell lines was 6.43 ± 1.01 µM and on HT-29 cell lines 6.57 ± 1.91 µM.[23]



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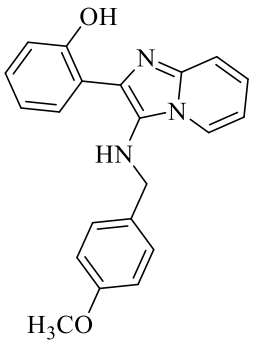
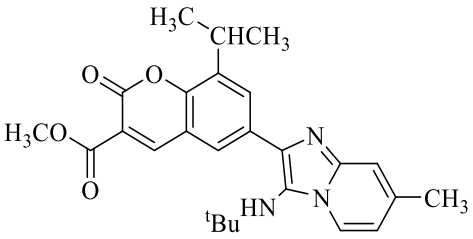


16

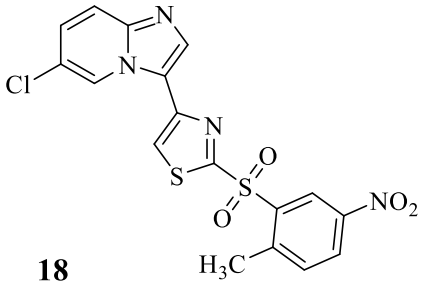
W. An *et al*. synthesized derivatives of 2-aryl-imidazo-pyridines that showed better property to seize the cells in G_2/M phases of the cell cycle and thus showed good

antiproliferative activities according to SAR studies. Compound **16** possessed highly antiproliferative activity against HeLa cell lines with IC_{50} value was found to be 0.037 ± 0.002 µM.[24]

Sashidhara and coworkers have been synthesized derivatives of 6-(imidazo[1,2-*a*]pyridin-2-yl)-2*H*-chromen-2-one and trialed on MDA-MB-231 (Breast adenocarcinoma) cancer cells. Compound **17** was found to be more potent with IC_{50} value of 14.12 ± 3.69 µM against MDA-MB-231 cell lines. In calvarial osteoblasts cells, compound **17** displayed increase in alkaline phosphate. The leading moiety **17** was found to interrupt the cell cycle at G_0/G_1 phase related to S-phase and G_2/M phase.[25]

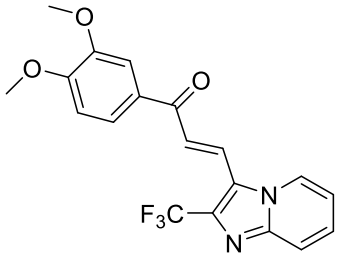


17



18

Hayakawa and coworkers developed a series of thiazole derivative of imidazo[1,2-*a*]pyridine that functioned as a strong inhibitor for p110α and showed preference over PI3 kinase. Compound **18** hindered the cell growth ability of the tumor cell both *in vivo* and *in vitro*, proposing that p110α is the main target in the treatment of cancer. The antitumor activity of **18** was analyzed on HeLa and A375 cell lines and showed greater antiproliferative activity with HeLa cell lines (IC_{50} = 0.21 µM) in contrast with A375 cell lines.[26]



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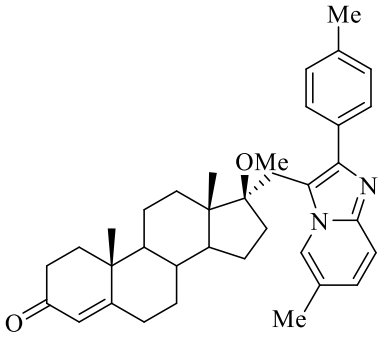
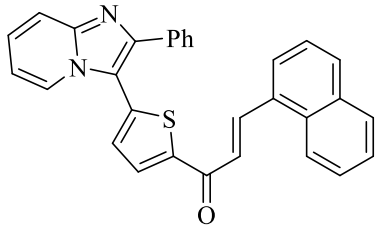


20

Kamal *et al*. synthesized a series of imidazopyridine derivatives that showed remarkable anticancer activity against many cancer cell lines with GI_{50} values in the range of 0.28 to 30.0 µM. Compound **19** showed potential of antiproliferative activity with lower value of GI_{50} (< 1

μM) against SR (IC_{50} = 0.44 μM), K-562 (IC_{50} = 0.36 μM) and CCRF-CEM (IC_{50} = 0.44 μM) in leukemia cancer, HCC-2298 (IC_{50} = 0.48 μM) and HCT-116 (IC_{50} = 0.84 μM) in colon cancer, MCF-7 (IC_{50} = 0.56 μM) in breast cancer and UACC-257 (IC_{50} = 0.62 μM) and LOXMVI (IC_{50} = 0.95 μM) in melanoma cancer cell lines.[27]

Rassokhina *et al*. developed derivatives of estrane and androstene having imidazo[1,2-*a*]pyridine moiety. Compound **20** was tested on prostate (PC-3, LNCaP-LN3 and DU 145) and human breast (MDA-MB-231, MDA-MB-453, MCF-7 and HBL-100) cancer cell lines for its cytotoxic activity. It was observed that compound **20** showed maximum activity on hormone responsive human breast cancer cell MCF-7 with IC_{50} value of 3–4 μM than estrogen receptor negative (ER α-negative) cells.[28]



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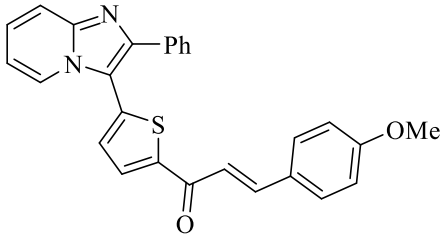
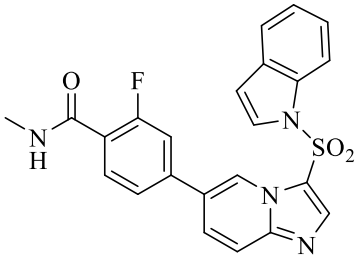


22

Vellakkaran *et. al*. has been synthesized a series of imidazopyridine derivatives by direct hetero-arylation at C-3 position of imidazole ring. Compounds **21** and **22** were trailed on four human cancer cell lines (A549, MCF7, HeLa and DU145) for its cytotoxity and it was observed that these compounds showed potential anticancer actitvity against all four cancer cell lines. IC_{50} values obtained for compound **21** against A549, MCF7, HeLa and DU145 cell lines were found to be 11.8 ± 0.21 μM, 9.8 ± 0.12 μM, 10.8 ± 0.36 μM and 11.2 ± 0.22 μM while IC_{50} values for compound **22** were found to be 11.2 ± 0.33 μM, 9.7 ± 0.32 μM, 10.4 ± 0.15 μM and 9.8 ± 0.22 μM, respectively.[29]



23

Liu and co-workers have been synthesized derivatives of imidazo[1,2-*a*]pyridine that can inhibit the activation of c-Met and were trailed on EBC-1 human cancer cell. Compound **23** showed activity by stopping the phosphorylation of c-Met that inhibit cell proliferation. Compound **23** has been found to be potent with IC_{50} value of 19.8 ± 1.6 nmol/L against EBC-1 cancer cell lines.[30]

3. RESEARCH GAPS AND OBJECTIVES

Literature survey suggests that individual moieties such as naphthalimide and imidazo[1,2-*a*]pyridine showed significant anticancer property against cancer cell lines but their hybrids with other biological active moieties are rarely known. On the other hand, substitutions of nitro derivatives of imidazopyridines are little known. So, we have synthesized hybrid derivatives of naphthalimide with benzothioazole and indole moieties. We have also synthesized phosphate and aromatic substituted nitro imidazopyridines. These compounds will also be evaluated *in vitro* for 60 human cancer cell lines.

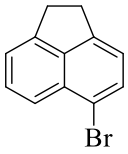
4. EXPERIMENTAL

4.1 General Chemistry

All reactions were carried out in oven-dried glasswares. Commercial grade solvents were used without further purification and were supplied by Loba, Spectrochemicals and Aldrich. Melting points were determined in open capillaries and were uncorrected. Jeol-ECS 400 MHz and 100 MHz NMR spectrometer was used for recording ^{1}H and ^{13}C NMR spectra, respectively using $CDCl_3$ as solvent. The chemical shifts were expressed in parts per million with TMS as an internal reference and *J* values are given in Hz. Reactions were monitored by thin layer chromatography (TLC) using plates coated with silica gel HF-254 and column chromatography was performed with silica gel 60-120 mesh. Hexane/ethyl acetate was the adopted solvent system.

4.2 Synthesis of naphthalimide derivatives 6a and 6b

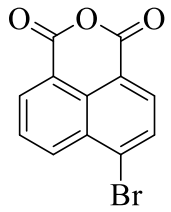
4.2.1 Synthesis of 5-bromoacenaphthene (2):-



2

Compound **2** was synthesized by suspending *N*-bromosuccinimide (1.15 g, 6.4 mmol) in dimethyl formamide (10 ml) followed by transferring into the solution of acenaphthene **(1)** (1 g, 6.4 mmol) in dimethyl formamide (10 ml). The mixture was stirred for 2 hrs at room temperature and then poured into the cold water. The solid formed was filtered and recrystallized in ethanol to give pure compound **2**. Yield = 85%; White solid; m.pt. = 54-57 ^{o}C.

4.2.2 Synthesis of 4-bromo-1,8-naphthalic anhydride (3):-

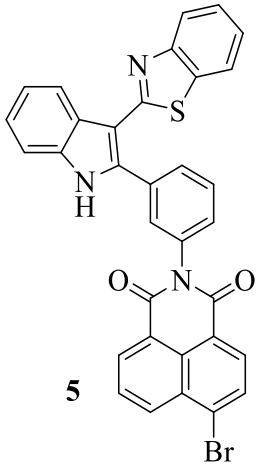


3

The compound **2** (1 g, 4.3 mmol) was dissolved in glacial acetic acid and then oxidized by adding potassium dichromate (3.8 g, 12.9 mmol). The reaction mixture was refluxed for 2.5 hrs. The solvent was removed under vacuum. The chromium salt was removed from the residue with boiling water and the product formed was recrystallized from glacial acetic acid to give pure compound.

Yield = 74%; Light pink solid; m.pt. = 217-219 °C.

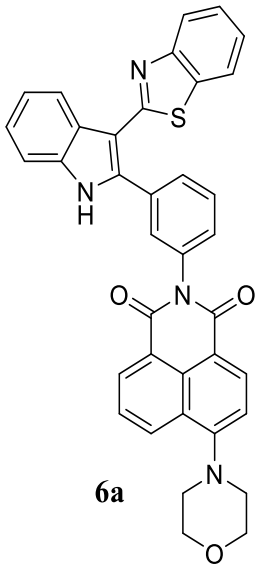
4.2.3 Synthesis of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl-6-bromo-1*H*-benzo [*de*]isoquinoline-1,3(2*H*)-dione (5):-



5

The mixture of 3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)aniline (**4)** (0.5 g, 1.4 mmol) and 4-bromo-1,8-naphthalic anhydride **(3)** (0.40 g, 1.4 mmol) was dissolved in ethanol and refluxed for 1 hr. The precipitates formed were filtered off and washed with ethanol. The product was purified by column chromatography using hexane: ethyl acetate as eluents. Yield = 62%; Brown soild; m.pt. = > 300 °C.

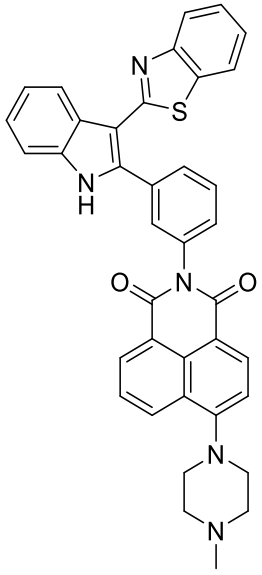
4.2.4 Synthesis of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-morpholino-1*H*-be nzo[*de*]isoquinoline-1,3(2*H*)-dione (6a):-



6a

To the compound **5** (0.5 g, 0.8 mmol) in ethanol, excess of morpholine was added with constant stirring and refluxed for 2 hrs. The product formed was monitored by TLC. Ethanol was then evaporated and the product formed was extracted with chloroform and water. Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get compound **6a**. The derivative formed was purified by column chromatography using hexane: ethyl acetate as eluents. Yield: 65%; Yellow solid; m.pt. = > 300°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.69 (s, 1H, NH), 8.63 (m, 2H, ArH), 8.58 (d, *J* = 8.24, 1H, ArH), 8.47 (d, *J* = 8.24 Hz, 1H, ArH), 8.03 (m, 1H, ArH), 7.91 (m, 1H, ArH), 7.83 (m, 3H, ArH), 7.73 (m, 1H, ArH), 7.64 (t, *J* = 7.80 Hz, 1H, ArH), 7.48 (m, 4H, ArH), 7.33 (m, 2H, ArH), 4.02 (m, 4H, mor-CH_2), 3.27 (m, 4H, mor-CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 164.4, 163.9, 159.9, 155.8, 153.2, 150.9, 139.2, 132.8, 131.5, 130.0, 129.7, 129.5, 129.2, 128.3, 127.2, 126.2, 126.0, 124.7, 122.6, 121.4, 119.2, 117.3 (ArC), 66.9 (O-CH_2), 53.3 (N-CH_2).

4.2.5 Synthesis of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-(4-methylpiperazin -1-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (6b):-

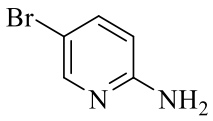


6b

The derivative **6b** was synthesized by dissolving the leading moiety **6** (0.5 g, 0.8 mmol) in ethanol. Excess of 1-methylpiperazine was added slowly and the mixture was refluxed for 2 hrs. The derivative formed was monitored by TLC. Ethanol was then evaporated and the product formed was extracted with chloroform and water. Organic layer was separated, dried with Na_2SO_4, filtered and concentrated to get compound **6b**. The crude product was purified by column chromatography using hexane: ethyl acetate as eluents. Yield = 67%; Yellow solid; m.pt. = > 300°C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.64 (s, 1H, NH), 8.62 (m, 2H, ArH), 8.57 (d, *J* = 8.24, 1H, ArH), 8.45 (d, *J* = 8.24 Hz, 1H, ArH), 8.04 (d, *J* = 8.24 Hz, 1H, ArH), 7.91 (d, *J* = 1.36 Hz, 1H, ArH), 7.82 (m, 3H, ArH), 7.72 (t, *J* = 7.32 Hz, 1H, ArH), 7.64 (t, *J* = 7.76 Hz, 1H, ArH), 7.45 (m, 4H, ArH), 7.35 (m, 2H, ArH), 3.35 (s, 4H, pip-CH_2), 2.82 (s, 4H, pip-CH_2), 2.48 (s, 3H, N-CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 164.4, 163.9, 160.0, 155.9, 153.2, 150.9, 135.1, 132.9, 131.4, 130.4, 130.1, 129.7, 129.5, 129.3, 129.2, 128.3, 127.2, 126.0, 125.7, 124.7, 122.6, 121.4, 119.2, 117.3, 115.1 (ArC), 54.9 (N-CH_2), 52.6 (N-CH_2), 45.9 (N-CH_3).

4.3 Synthesis of imidazo[1,2-*a*]pyridine derivatives 5 and 6

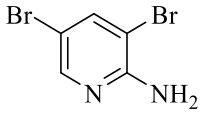
4.3.1 Synthesis of 5-bromopyridin-2-amine (2):-



2

The compound **2** was synthesized by dissolving 2-aminopyridine **(1)** (1 g, 10.6 mmol) in acetonitrile. Then, *N*-bromosuccinimide (1.89 g, 10.6 mmol) dissolved in acetonitrile was added slowly. The reaction mixture was stirred at room temperature for 2 hrs. The product formed was monitored by TLC. The solution was concentrated and the product was extracted with chloroform and water. Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get compound **2**. Yield = 88%; Brown solid; m.pt. = 135-140 ^{o}C.

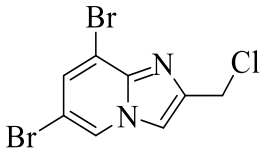
4.3.2 Synthesis of 3,5-dibromopyridin-2-amine (3):-



3

The compound **2** (0.8 g, 4.6 mmol) was again dissolved in acetonitrile and *N*-bromosuccinimide (0.82 g, 4.6 mmol) dissolved in acetonitrile was added slowly. The reaction mixture was refluxed for 2 hrs. The product formed was monitored by TLC. The solution was concentrated and the product was extracted with chloroform and water. Organic layer was separated, dried over Na_2SO_4, filtered and concentrated to get compound **3**. Yield: 82%; Brown solid; m.pt. = 103-105 ^oC.

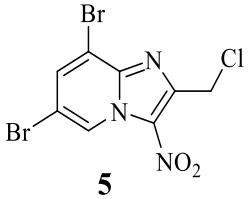
4.3.3 Synthesis of 6,8-dibromo-2-(chloromethyl)imidazo[1,2-*a*]pyridine (4):-



4

The compound **4** was synthesized by dissolving compound **3** (1 g, 3.9 mmol), in ethanol. Then, 1,3-dichloroacetone (1.25 g, 9.9 mmol) was added and the reaction mixture was refluxed for 12 hrs. The product formed was monitored by TLC. The precipitates formed was filtered off and washed with ethanol. Yield: 72%; Light brown solid; m.pt. = 160-162 ^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.21 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.55 (s, 1H, ArH), 4.76 (s, 2H, CH_2).

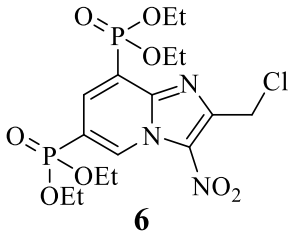
4.3.4 Synthesis of 6,8-dibromo-2-(chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine (5):-



5

The compound **4** (1 g, 3 mmol) was first dissolved in dichloromethane and then sulfuric acid (5 ml) was added dropwise at 0 ^oC. A mixture of HNO_3:H_2SO_4 (prepared in the ratio of 1**:**3), added to the above mixture drop wise and stirred at 60 ^oC for 1 hr. The product formed was monitored by TLC. This solution was then poured into the ice cold water. The solid formed was filtered off and then washed with cold water. Yield = 73%; Yellow solid; m.pt. = 175-178 ^oC.

4.3.5 Synthesis of tetraethyl(2-(chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine-6,8-diyl)bis (phosphonate) (6):-

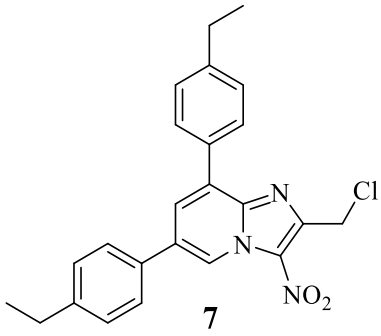


6

The compound **6** was synthesized by dissolving compound **5** (1 g, 2.7 mmol) in triethylphosphite (1.7 ml, 10.3 mmol). The reaction mixture was refluxed for 5 hrs. The product formed was monitored by TLC. The mixture was concentrated and the product was extracted with chloroform and water. Column chromatography was done to purify the compound using hexane: ethylacetate as eluents. Yield = 62%; Brown liquid, ^1H NMR ($CDCl_3$,

400 MHz): δ (ppm) 9.50 (d, *J* = 1.36 Hz, 1H, ArH), 7.93 (d, *J* = 1.84 Hz, 1H, ArH), 4.13 (m, 8H, CH_2), 3.96 (d, *J* = 16.0, 2H, CH_2), 1.30 (m, 12H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 144.8, 144.7, 141.2, 141.1, 135.7, 126.8, 112.7, 110.5 (ArC), 62.8, 62.7 (O-CH_2), 28.2 (CH_2), 16.3, 16.2 (CH_3).

4.3.6 Synthesis of 2-(chloromethyl)-6,8-bis(4-ethylphenyl)-3-nitroimidazo[1,2-*a*]pyridine (7):-



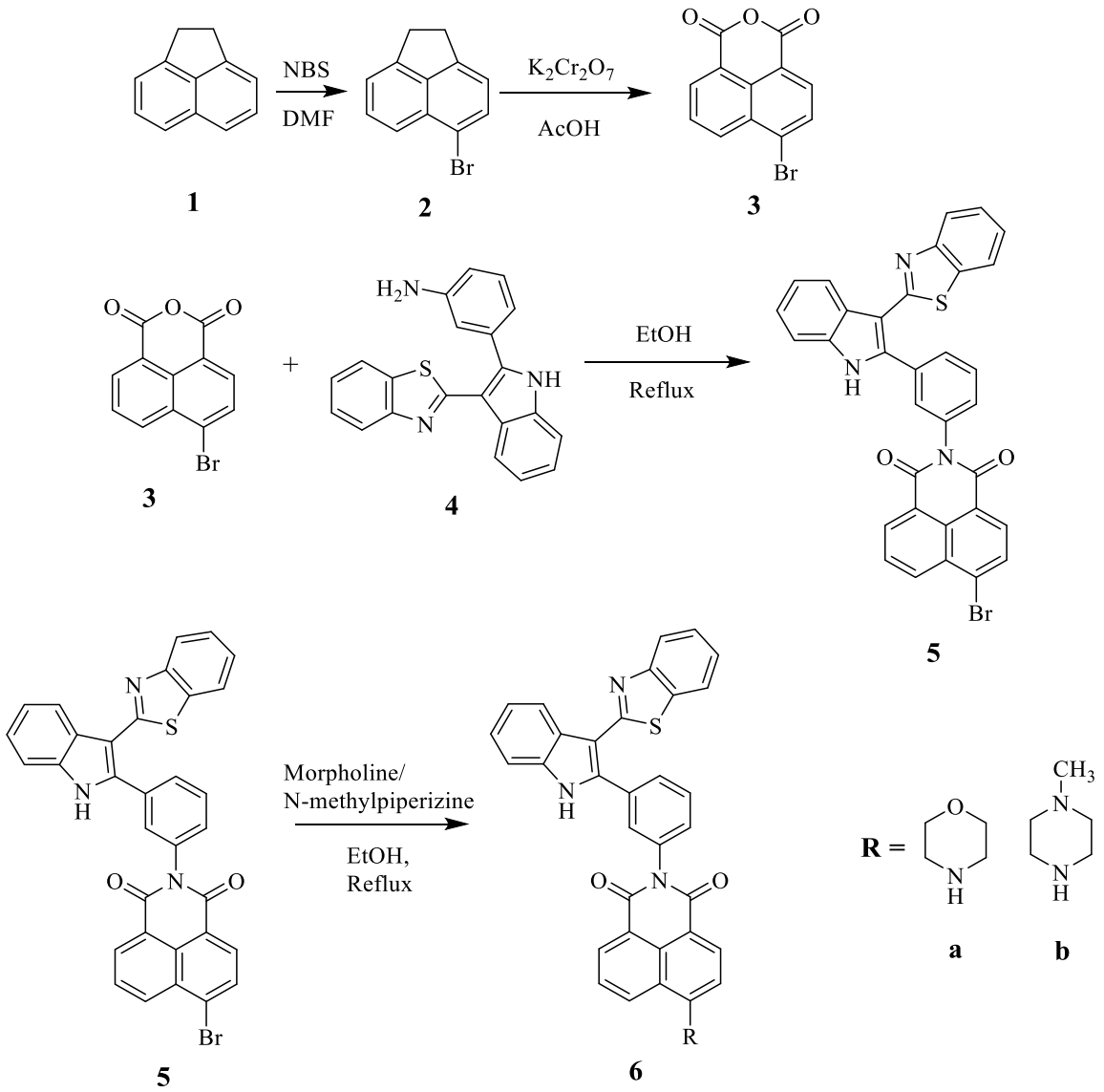
7

The compound **5** (0.8 g, 2.1 mmol) was dissolved in acetonitrile and 4-ethylphenylboronic acid (0.96 g, 6.4 mmol) was added. To this mixture K_2CO_3 (0.59 g, 4.3 mmol) was added and refluxed for 8 hrs. The product formed was monitored by TLC. The mixture was concentrated and the product was extracted with ethyl acetate and water. Column chromatography was done to purify the compound using hexane: ethylacetate as eluents. Yield = 48%; Yellow solid; m.pt. = 220-222 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 7.95 (m, 2H, ArH), 7.58 (m, 2H, ArH), 7.47 (d, *J* = 2.76 Hz, 2H, ArH), 7.40 (d, *J* = 9.16 Hz, 1H, ArH), 7.35 (m, 2H, ArH), 7.29 (d, *J* = 8.24 Hz, 1H, ArH), 4.86 (d, *J* = 20.0 Hz, 2H, CH_2), 2.73 (m, 4H, CH_2), 1.29 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 130.2, 129.7, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 127.0, 118.3 (ArC), 29.6, 28.7, 28.5 (CH_2), 15.5 (CH_3).

5. RESULTS AND DISCUSSION

5.1 Naphthalimide derivatives

Using commercially available acenaphthene as an initial substrate, naphthalimide derivatives (**6a** and **6b**) were synthesized according to the **scheme 1**. Treatment of acenaphthene **(1)** with *N*-bromosuccinimide in DMF at room temperature for 2 hrs, followed by recrystallization from ethanol, gave white solid of 5-bromoacenaphthene (**2).**



Scheme 1. Synthesis of naphthalimide derivatives **6a** and **6b**

Under refluxing conditions, oxidation of the product **2** was done with potassium dichromate in acetic acid for 2.5 hrs, gave light pink needles of 4-bromo-1,8-naphthalic anhydride **(3)**. Treatment of compound **3** with 3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)aniline **4** (obtained from the treatment of phenylhydrazine and 3-nitroacetophenone in acetic acid at room temperature followed by reaction with $POCl_3$ in DMF at 0 ^oC, followed by treatment with 2-aminothiophenol in nitrobenzene and then reduction with sodium dithionate containing excess of ammonia in THF:H_2O (2:3) in the presence of ethanol, gave brown colored solid of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl-6-bromo-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **(5)** in 62% yield. Column chromatography was used to purify this compound in a hexane-ethyl acetate solvent system. Compound **5** was further treated with excess of morpholine in the presence of ethanol as solvent for 2 hrs at reflux temperature to give derivative **6a** in 65% yield. Column chromatography was used to purify this compound in a hexane-ethyl acetate solvent system. This compound was then characterized by ^1H and ^{13}C NMR spectrometer. Aromatic protons of compound **6a** showed wide range of splitting pattern ranging from δ 8.63-7.33 ppm corresponding to seventeen protons. Two multiplets of four protons each of CH_2 were observed at δ 4.02 and δ 3.27 ppm corresponding to morpholine. ^{13}C NMR spectrum showed the signals at δ 164.4, 163.9, 159.9, 155.8, 153.2, 150.9, 139.2, 132.8, 131.5, 130.0, 129.7, 129.5, 129.2, 128.3, 127.2, 126.2, 126.0, 117.3 of aromatic carbons. Signals at δ 66.9 (O-CH_2) and δ 53.3 (N-CH_2) ppm were also observed corresponding to morpholine. So, ^1H NMR and ^{13}C NMR spectra confirmed the formation of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-morpholino-1*H*-benzo[*de*] isoquinoline-1,3(2*H*)-dione **(6a) (Figures 2** and **3)**.

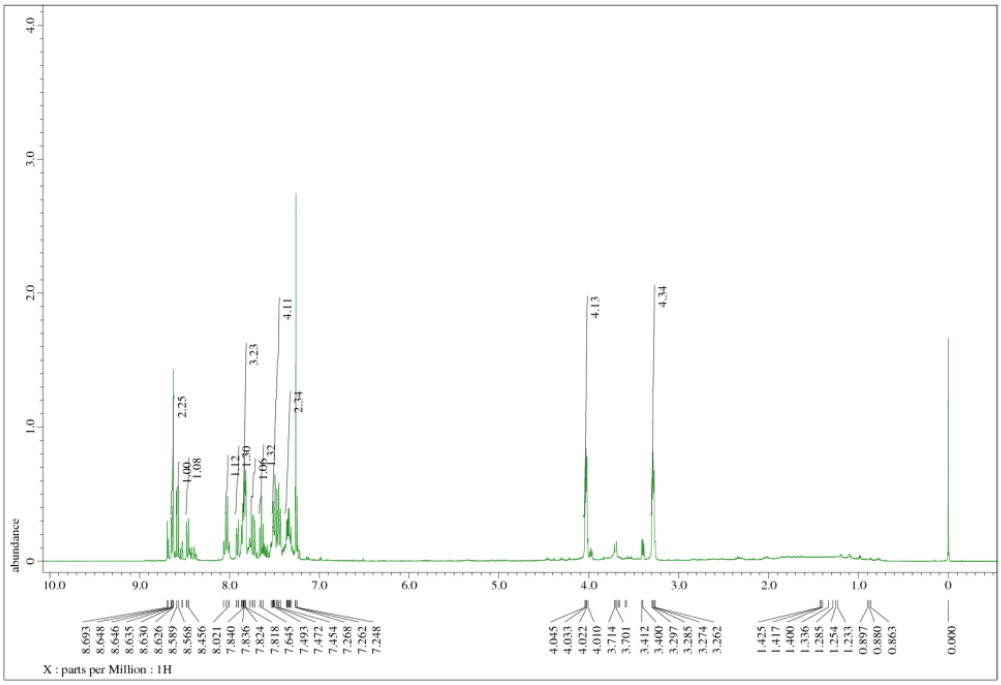


Figure 2. [1]H NMR spectrum of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-morpho lino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **(6a)**

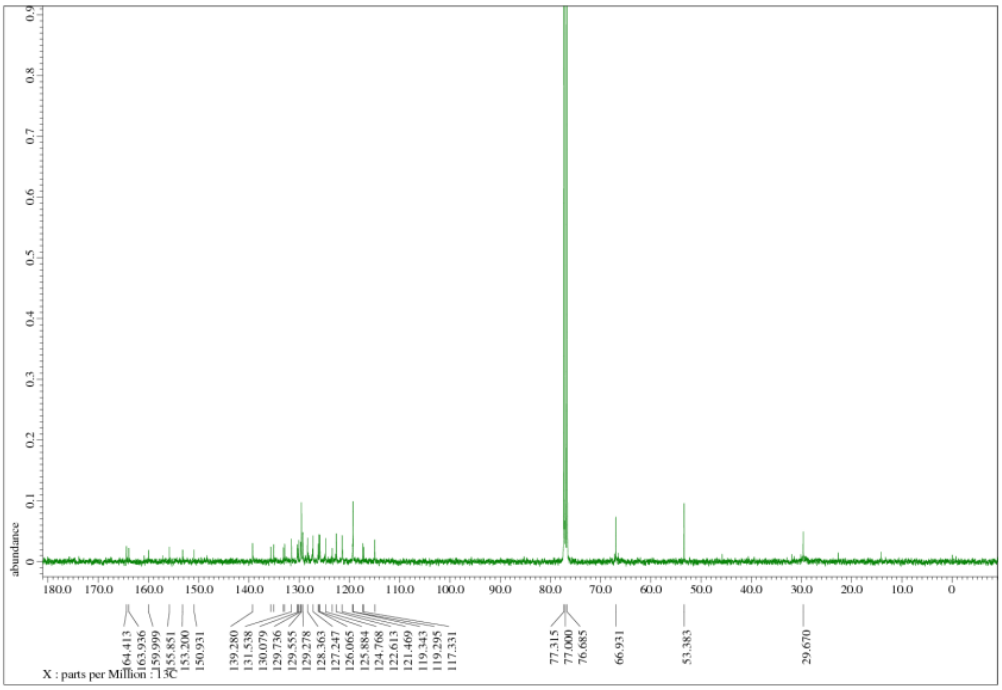


Figure 3. [13]C NMR spectrum of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-morpho lino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **(6a)**

Compound **5** was also treated with 1-methyl piperazine in the presence of ethanol at refluxing condition for 2 hrs to give final derivative **6b** in 67% yield (yellow solid). Column chromatography was used to purify this compound in hexane-ethyl acetate solvent system. This compound was then characterized by ^{1}H and ^{13}C NMR spectrometer. Aromatic protons of compound **6b** showed wide range of splitting pattern ranging from δ 8.62-7.35 ppm corresponding to seventeen protons. Two singlets of four protons each of CH_2 were observed at δ 3.35 and δ 2.82 ppm corresponding to piperazine. One singlet of three protons at δ 2.48 ppm was also observed corresponding to N-CH_3. ^{13}C NMR spectrum showed the signals at δ 164.4, 163.9, 160.0, 155.9, 153.2, 150.9, 135.1, 132.9, 131.4, 130.4, 130.1, 129.7, 129.5, 129.3, 129.2, 128.3, 127.2, 126.0, 125.7, 124.7, 122.6, 121.4, 119.2, 117.3, 115.1 of aromatic carbons. Signals at δ 54.9, 52.6, and 45.9 were also observed corresponding to *N*-methylpiperazine. So, both ^{1}H NMR and ^{13}C NMR spectra confirmed the formation of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)-*1H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **(6b) (Figures 4** and **5)**. These final compounds have been submitted to National Cancer Institute (NCI), NIH, USA for 60 human cancer cell lines studies.

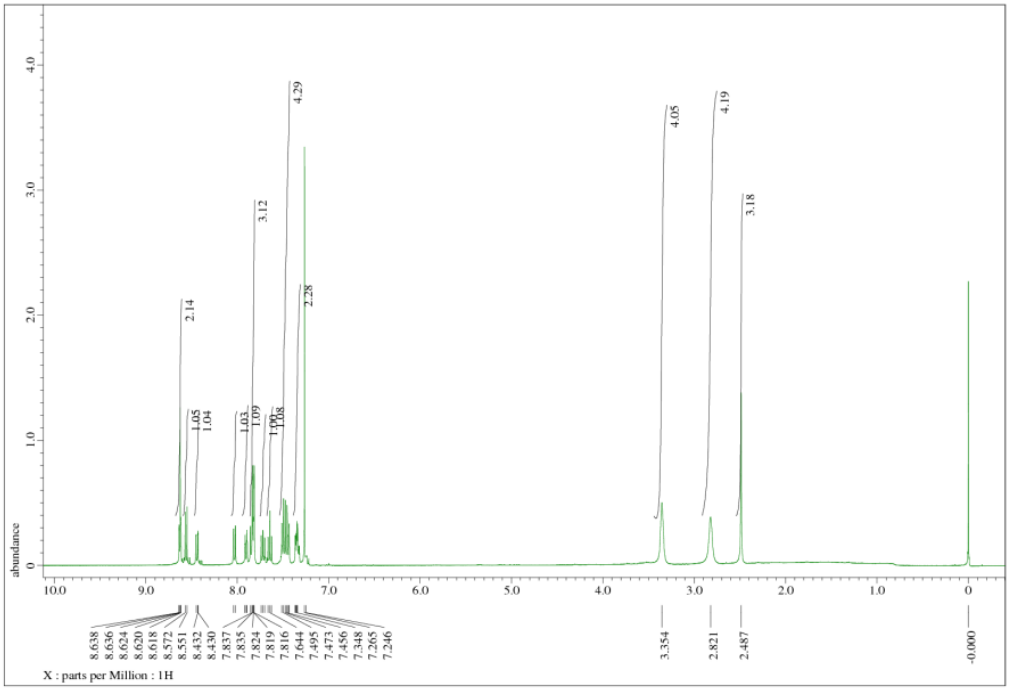


Figure 4. ^{1}H NMR spectrum of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **(6b)**

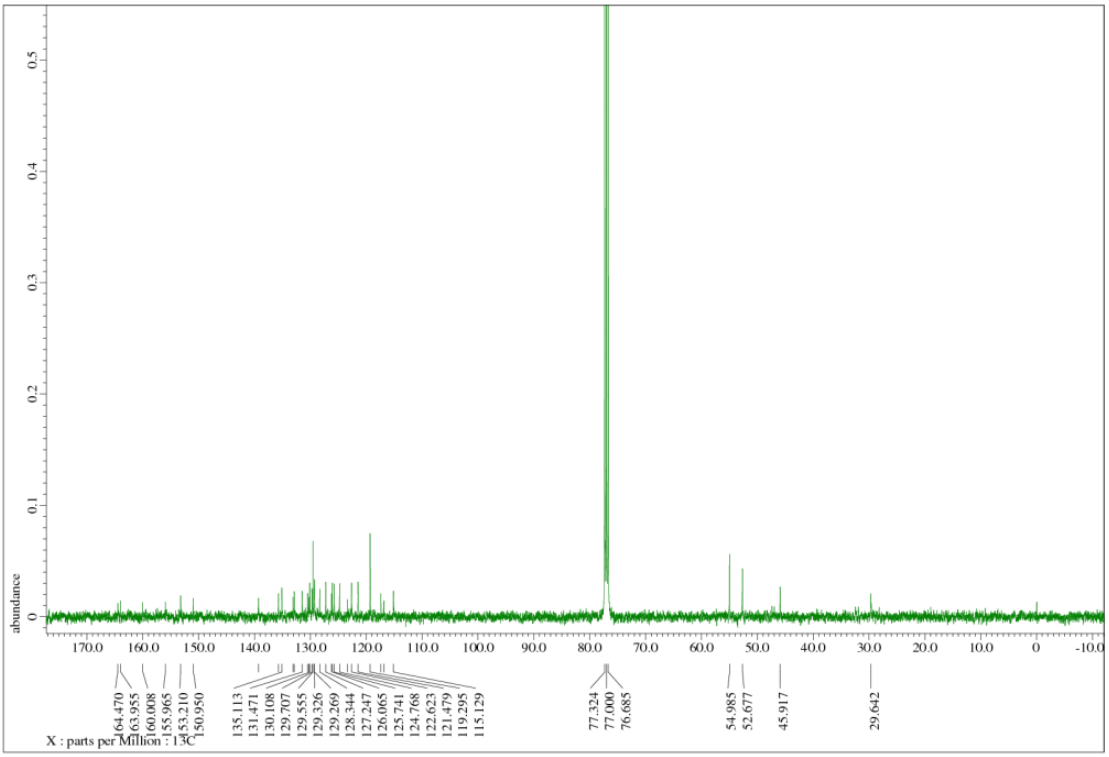
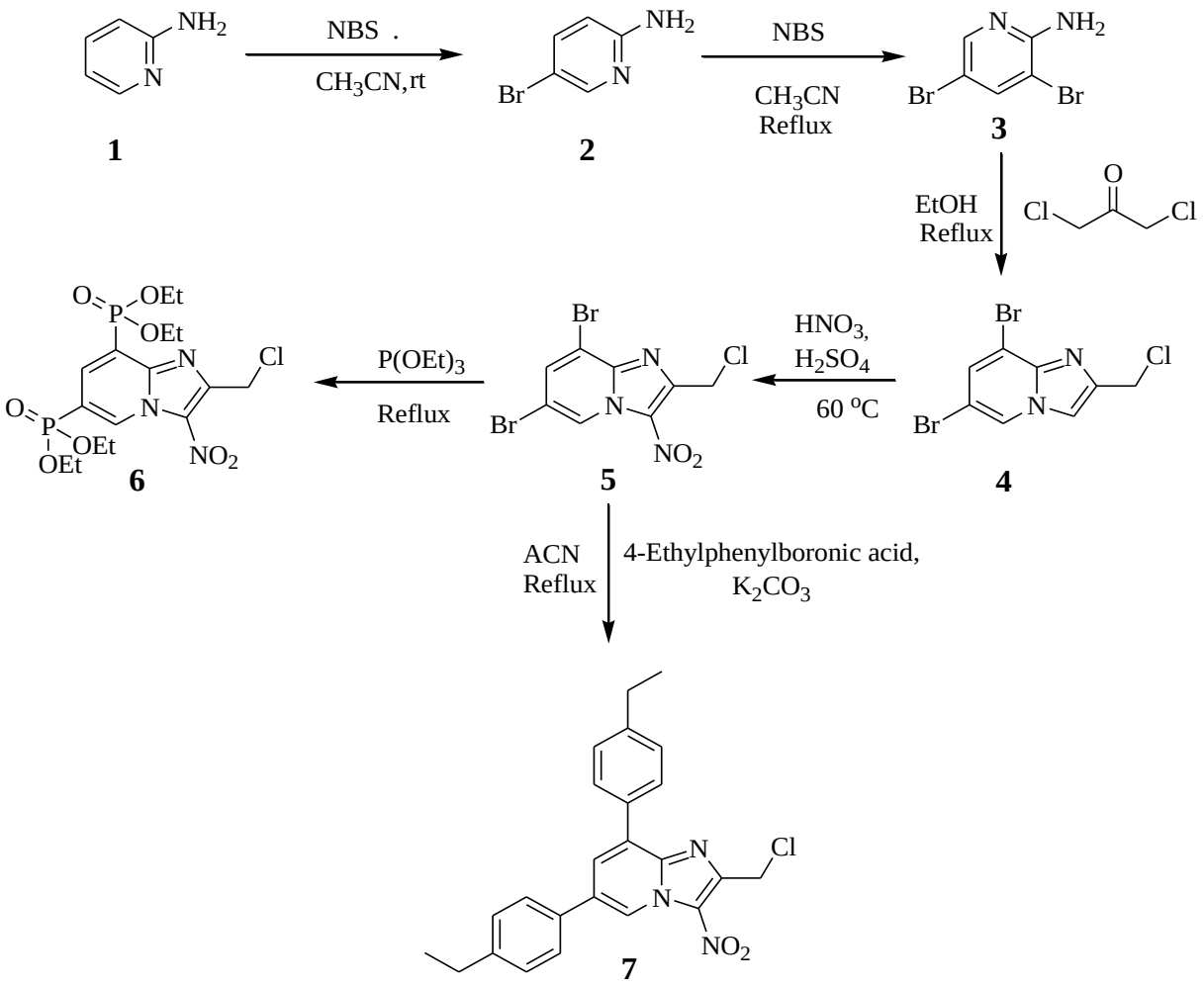


Figure 5. ^{13}C NMR spectrum of 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-(4-met hylpiperazin-1-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **(6b)**

5.2 Imidazo[1,2-*a*]pyridine derivatives

Using commercially available, 2-aminopyridine as an initial substrate, compounds **6** and **7** were synthesized according to the **scheme 2**. Treatment of 2-aminopyridine **(1)** with *N*-bromosuccinimide dissolved in acetonitrile, at room temperature for 2 hrs, gave brown colored solid of 5-bromopyridin-2-amine **(2)** in 88% yield. Under refluxing conditions, bromination of product **2** was again done with *N*-bromosuccinimide in acetonitrile for 2 hrs, gave brown crystals of 3,5-dibromopyridin-2-amine **(3)** in 82% yield. Treatment of 3,5-dibromopyridin-2-amine with 1,3-dichloroacetone in the presence of ethanol at refluxing temperature for 12 hrs, gave light brown coloured solid of 6,8-dibromo-2-(chloromethyl)imidazo[1,2-*a*]pyridine **(4)** in 72% yield. ^{1}H NMR spectrum of compound **4** showed three singlets of one proton each at δ 8.21, 7.68 and 7.55 ppm of aromatic protons and one singlet of two protons at δ 4.76 of CH_2. So, spectral analysis of ^{1}H NMR confirmed the formation of 6,8-dibromo-2-(chloromethyl)imidazo[1,2-*a*]pyridine **(4) (Figure 6).**



Scheme 2. Synthesis of imidazopyridine derivatives **(6** and **7)**

Treatment of compound **4** with HNO_3:H_2SO_4 (1:3) in dichloromethane at 60 ^oC for 1 hr, gave yellow coloured solid of 6,8-dibromo-2-(chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine(**5**) in 73% yield. Treatment of compound **5** with 5 equivalents of triethylphosphite at refluxing temperature for about 5 hrs, gave brown coloured liquid of tetraethyl(2-(chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine-6,8-diyl)bis(phosphonate) **(6)** in 62% yield. ^1H NMR spectrum of compound **6** showed two doublets of aromatic protons at δ 9.50 and 7.93 ppm, multiplet of four O-CH_2 at δ 4.20-4.05 ppm corresponding to eight protons, one doublet of two protons at δ 3.96 of CH_2 and multiplet of CH_3 at δ 1.32-1.28 ppm corresponding to twelve protons. ^{13}C NMR spectrum showed the signals at δ 144.8, 144.7, 141.2, 141.1, 135.7, 126.8, 112.7, 110.5 of aromatic carbons, Signals at δ 62.8 and 62.7 was observed corresponding to O-CH_2. Signal at δ 28.2 was observed for CH_2 and signals at δ 16.3 and 16.2 corresponding to CH_3. So, ^1H and ^{13}C

NMR spectral analysis confirmed the formation of tetraethyl(2-(chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine-6,8-diyl)bis(phosphonate) **(6) (Figures 7** and **8)**

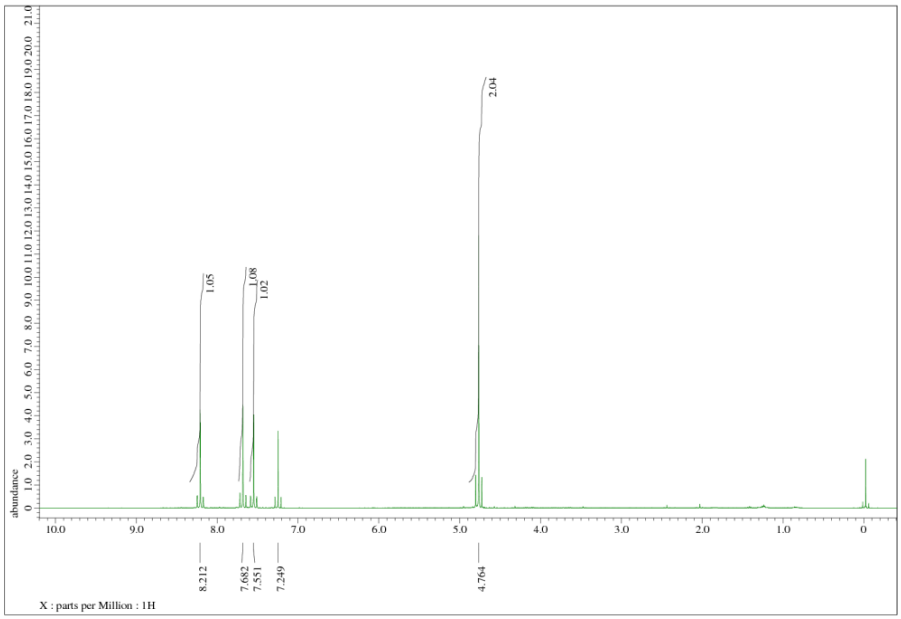


Figure 6. ^{1}H NMR spectrum of 6,8-dibromo-2-(chloromethyl)imidazo[1,2-*a*]pyridine **(4)**.

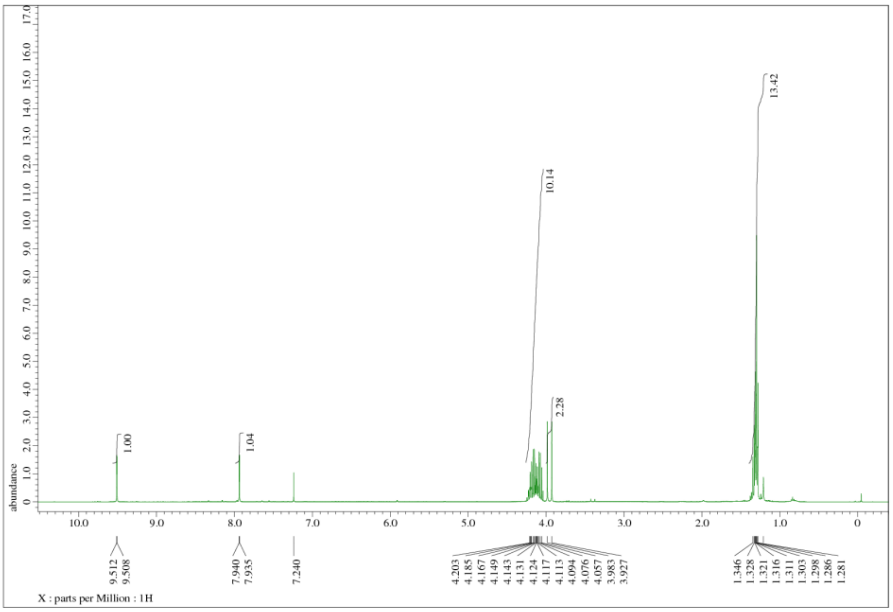


Figure 7. ^{1}H NMR spectrum of tetraethyl(2-(chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine-6,8-diyl)bis(phosphonate) **(6)**.

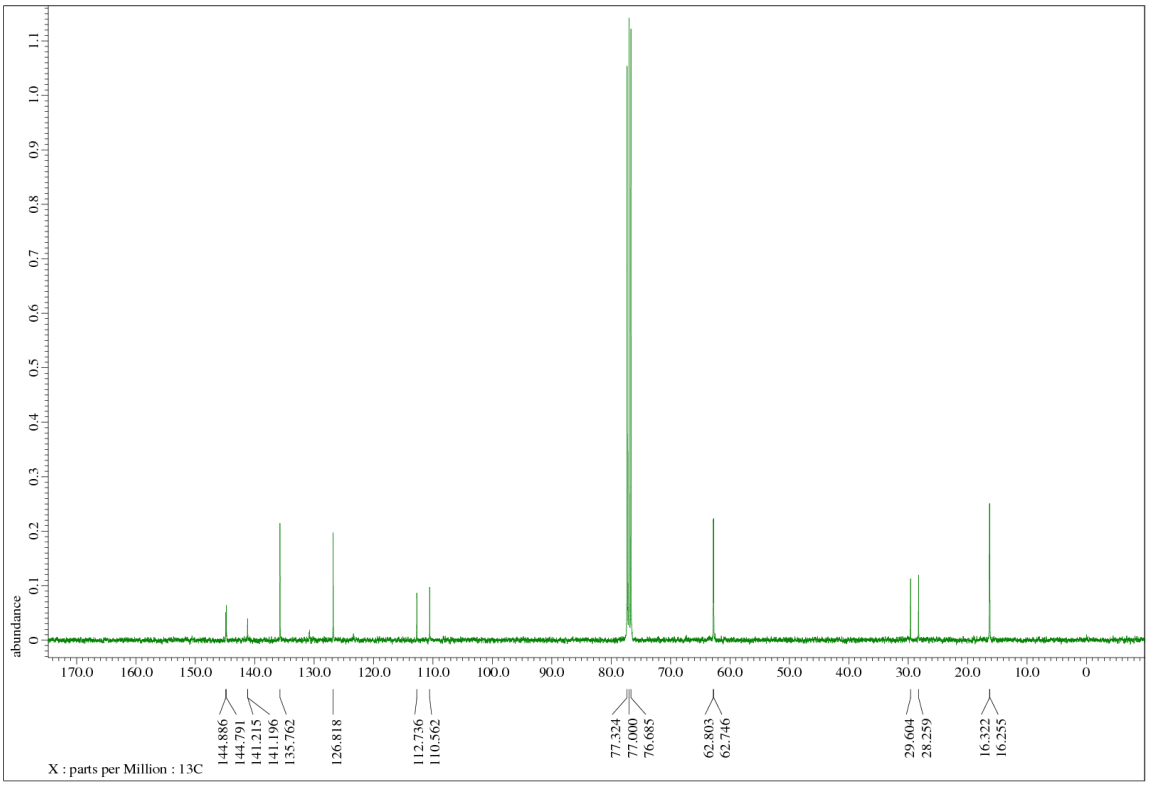


Figure 8. ^{13}C NMR spectrum of tetraethyl(2-(chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine-6,8-diyl)bis(phosphonate) **(6)**.

Treatment of compound **5** with 3.0 equivalents of 4-ethylphenylboronic acid in the presence of potassium carbonate in acetonitrile at reflux temperature for 8 hrs, gave yellow solid of 2-(chloromethyl)-6,8-bis(4-ethylphenyl)-3-nitroimidazo[1,2-*a*]pyridine **(7)** in 48% yield. Compound **7** was well characterized by ^{1}H and ^{13}C NMR spectrometry. ^{1}H NMR spectrum showed the splitting of aromatic protons over a wide range of δ 7.95-7.29 ppm corresponding to ten protons. Signal of one doublet of two protons at δ 4.86 corresponding to CH_2, one multiplet at δ 2.73 corresponding to four protons of CH_2 and one multiplet at δ 1.29 corresponding to six protons of CH_3 were observed. ^{13}C NMR spectrum showed the signals at δ 130.2, 129.7, 128.9, 128.8, 128.7, 128.6, 128.3, 128.2, 127.0, 118.3 of aromatic carbons. Three signals at δ 29.6, 28.7 and 28.3 corresponding to CH_2 and one signal at δ 15.5 due to CH_3 were observed. Thus, ^{1}H and ^{13}C NMR spectral analysis confirmed the formation of 2-(chlorome thyl)-6,8-bis(4-ethylphenyl)-3-nitroimidazo[1,2-*a*]pyridine **(7)** (**Figures 9** and **10).**

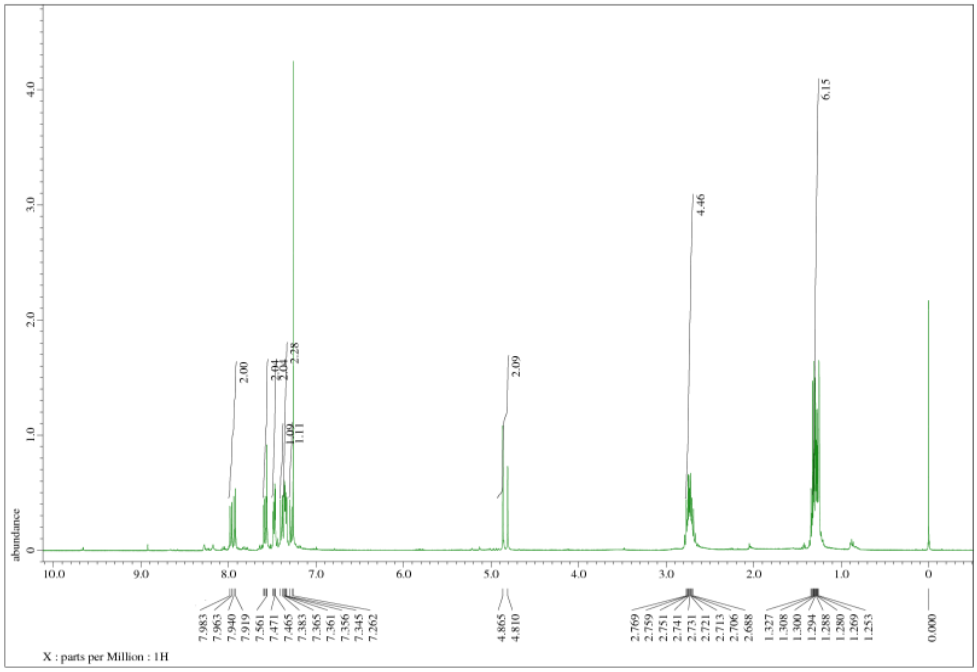


Figure 9. ^{1}H NMR spectrum of 2-(chloromethyl)-6,8-bis(4-ethylphenyl)-3-nitroimidazo[1,2-*a*]pyridine **(7)**

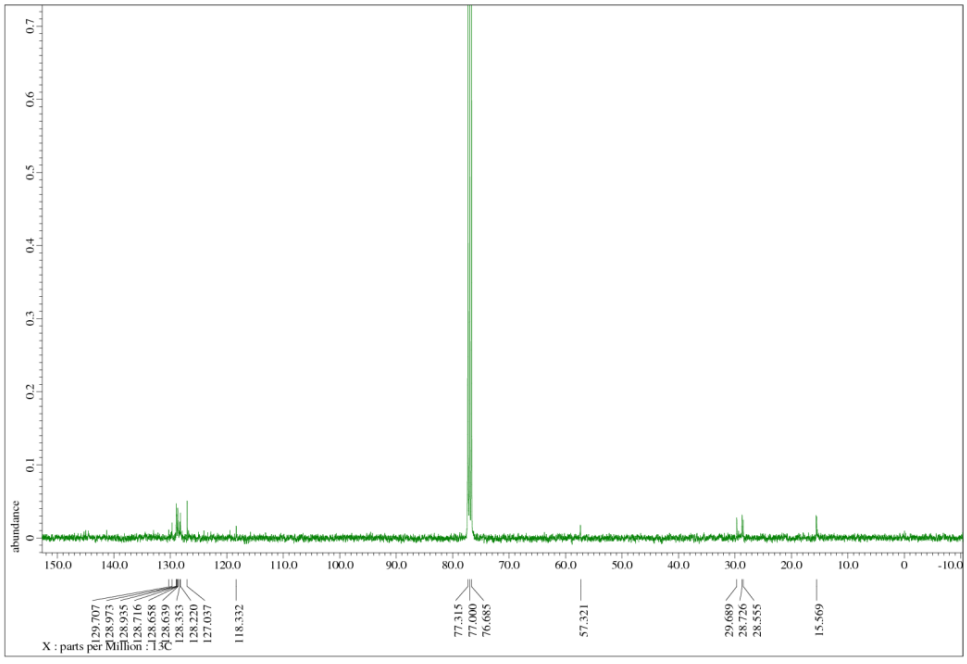


Figure 10. ^{13}C NMR spectrum of 2-(chloromethyl)-6,8-bis(4-ethylphenyl)-3-nitroimidazo[1,2-*a*]pyridine **(7)**

6. CONCLUSIONS

- Two naphthalimide derivatives 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-morpholino-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**6a**), 2-(3-(3-(benzo[*d*]thiazol-2-yl)-1*H*-indol-2-yl)phenyl)-6-(4-methylpiperazin-1-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (**6b**) were synthesized in good to moderate yields.
- Two imidazo[1,2-*a*]pyridine derivatives tetraethyl(2-(chloromethyl)-3-nitroimidazo[1,2-*a*]pyridine-6,8-diyl)bis(phosphonate) (**6**) and 2-(chloromethyl)-6,8-bis(4-ethylphenyl)-3-nitroimidazo[1,2-*a*]pyridine (**7**) were also synthesized in good yields. These compounds were well characterized by ^{1}H and ^{13}C NMR spectrometry.
- The final compounds will further be used for their biological activity as anti-cancer agents as well as for DNA intercalation.

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