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Research Article

DESIGN, SYNTHESIS AND EVALUATION OF NOVEL 2-(1-BENZYL-2-OXOINDOLIN-3-YLIDENE)-N-PHENYLHYDRAZINE CARBOXAMIDE DERIVATIVES AS ANTI CANCER AGENTS

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Abstract:

Novel 2-(1-benzyl-2-oxoindolin-6-substituted-3-ylidene)-n-phenylhydrazinecarboxamide derivatives are an important class of nitrogen containing heterocyclic's and were identified as the most active and potent classes of compounds with wide range of biological and pharmacological activities. A new series of 2-(1-benzyl-2-oxoindolin-3-ylidene)-n-phenylhydrazine carboxamide derivatives were characterized by spectral data and evaluated for Anticancer activity, Anti-Alzheimer's activity and anti-microbial activity. The compounds 7d, 7i, were found to be good inhibitors of HELA and MCF-7. Most of the compounds inhibited HELA and MCF-7 with the IC₅₀ values, ranging from 0.78 μM to 7.64 μM. Amongst them, compounds 7d, 7i with fluoro substituted indole exhibited strongest inhibitory activity against HELA and MCF-7 with IC₅₀ 1.91±0.02 μM, 0.92±0.03 μM for 7d and 1.31±0.02 μM, 0.78±0.33 μM for 7i respectively, when compared to standard Cisplatin with IC₅₀ of 0.65±0.02 μM and 0.47±0.02. The compound 7i with fluoro substituted indole containing Schiff base showed potent anti-Alzheimer's activity with IC₅₀ values 0.92±0.13, 1.01±0.12 μM against AChE and BuChE respectively when compared to Standard drug donepezil showed IC₅₀ 0.51±0.06 and 0.31±0.04 μM against AChE and BuChE respectively. 7i, 7m & 7n showing potent activity for different strains of bacteria ranging from 10mm to 14mm when compared to ciprofloxacin 13- 16mm. Thus, these Novel 2-(1-benzyl-2-oxoindolin-3-ylidene)-n-phenylhydrazine carboxamide derivatives have emerged as new cancer and AChE and BuChE inhibitors and showing anti microbial activity for further exploitation as anti-cancer and anti-Alzheimer's agents, anti bacterial agents. Docking studies of all the molecules disclosed close hydrogen bond interactions with in the binding site.

Keywords: Alzheimer's disease, anti-cancer, cholinesterase inhibitor, Anti-bacterial agents

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INTRODUCTION:**1.1 Alzheimer's Disease - History**

Alzheimer's disease (AD) is a progressive and neurodegenerative brain disorder that affects many elderly people and accounts for one-fourth of all dementia cases. According to WHO, Alzheimer's disease will be much more prevalent in the next century than AIDS, cancer, and cardiovascular disease (Prince et al. 2015).

Alois Alzheimer, a German physician, first identified AD in 1906. Alois Alzheimer first met his patient Auguste D in November 1901. He became aware during that initial talk that the 51-year-old woman exhibited symptoms unlike any he had ever seen before. Her answers to Alzheimer's questions didn't line up. She also frequently stopped in the middle of sentences as if she had lost her way of thought. She was becoming increasingly confused and tense as her memory began to desert her. Auguste passed away in April 1906, and Alzheimer received her brain for histopathological examination (Alzheimer et al. 1906). Alzheimer originally presented his research at a gathering of psychiatrists in November 1906 and suggested that he had uncovered a new illness. By German psychiatrist Emil Kraepelin, who collaborated with Dr. Alois Alzheimer, the condition

was first referred to as "Alzheimer's disease" (Moller et al. 1998). More than 46 million individuals were estimated to be affected by dementia at the time of the report. According to the Alzheimer's disease International Association publication (2015). By 2050, there will probably be 131.5 million cases of AD worldwide (World Alzheimer Report 2015), a dramatic rise from the current number due to the AD epidemic's spread. Amyloid plaques and neurofibrillary tangles are the two primary pathological conditions found in the brain of AD patients.

Cholinergic hypothesis are extracellular aggregates consisting up of β -amyloid ($A\beta$) peptides, whereas hyperphosphorylated Tau protein aggregates and forms neurofibrillary tangles inside brain cells. When hyperphosphorylated Tau protein develops the AD, it causes microtubules to become unstable, which inhibits neuronal transport and causes brain atrophy. Decreased levels of acetylcholine (ACh) causes cognition and memory problems. Medical agents that increase ACh levels have been proven to have positive impacts on the disease's cognitive, functional, and behavioral symptoms. Therefore, maintaining or regaining cholinergic function is thought to provide clinical benefits. (Scarpini et al. 2003).

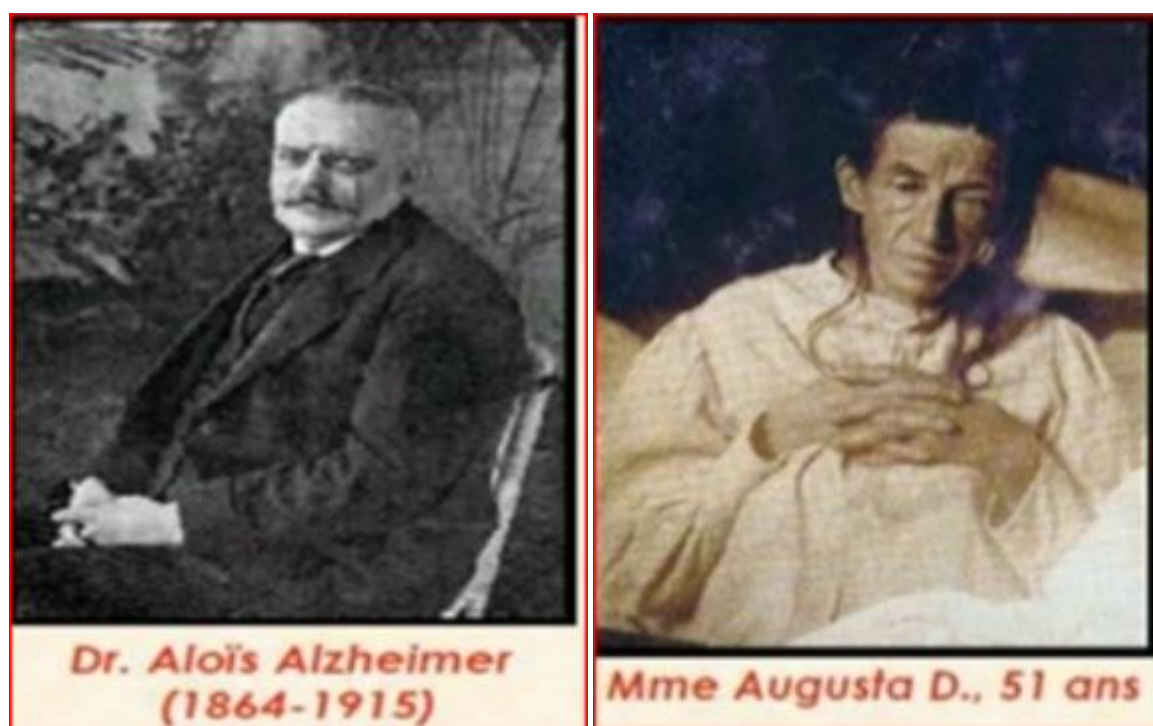


Figure 1.1: Alois Alzheimer's long term study of the female patient Auguste D

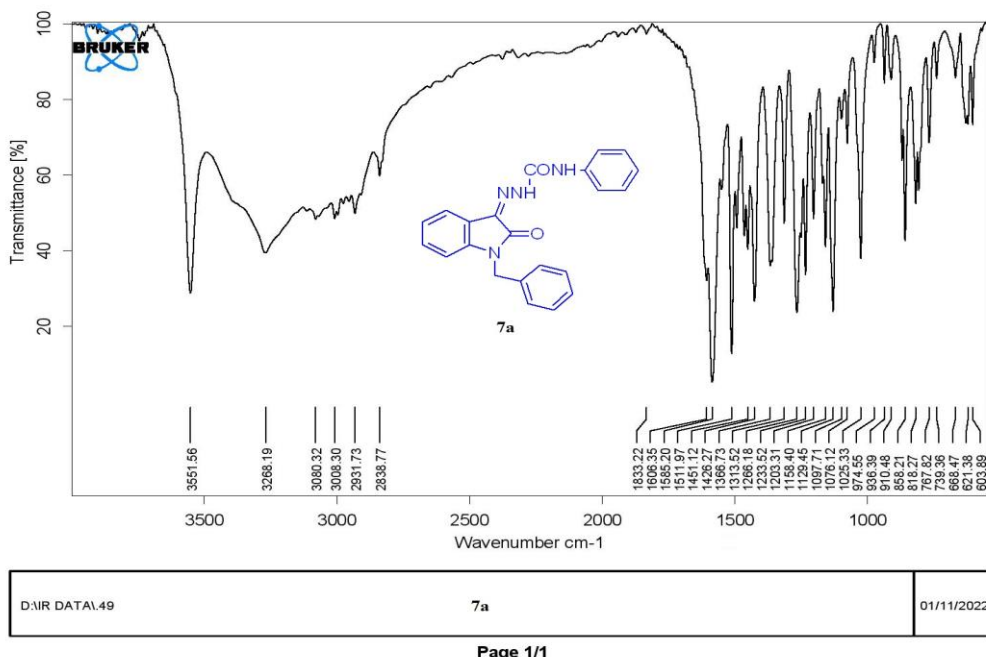
1.2. Pathophysiology of Alzheimer's disease:

1.2.1. Role of Amyloid Beta (A β) in neurodegeneration :

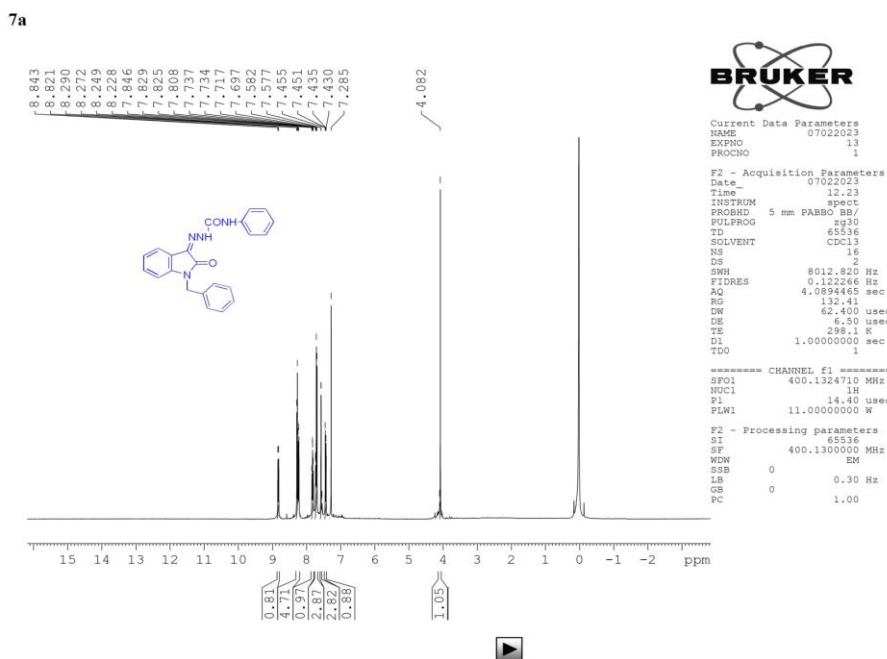
Amyloid Beta (A β), a heterogeneous combination of small peptides with 40–42 amino acids, is linked to a number of degenerative alterations in Alzheimer's disease (AD). According to the amyloid cascade hypothesis, the pathogenesis of AD is primarily caused by the aggregation of A β into amyloid oligomers and plaques. These peptides (A β) are generated through the proteolytic cleavage of the large transmembrane APP by β and γ secretases. These A β protein molecules may combine together to form soluble oligomeric bundles that can take on different forms. It is speculated that specific misfolded oligomers (sometimes referred to as "seeds") are responsible for triggering or causing other β -amyloid molecules to misfold in a series of chain reactions that result in their accumulation. The resulting amyloid deposition subsequently produces structural alterations in AD and a toxic effect on nerve cells. Tau proteins, which are also present in misfolded oligomers, are the other type of protein seen in AD. Misfolded A β has been demonstrated to trigger tau protein misfolding. The specific physiological function of A β is unknown, although animal studies have demonstrated that a lack of A β proteins does not result in a loss of any physiological function (Wildburger et al 2017). A has been linked to a number of possible activities, including activation of the kinase family of enzymes, defense against oxidative stress, reduction or control of cholesterol transport, and anti-microbial activity (mostly connected to A β 's pro-inflammatory activity). The lymphatic system is responsible for clearing β -Amyloid proteins from the mammalian brain in particular, but the rate of elimination increases significantly during sleep (Tarasoff-Conway et al 2015). The activity of γ secretases on the C-terminal end of the A peptide generates a range of isoforms (36-43 amino acid residues in length). The most prevalent isoforms are A40 and A42, which are generated by cleavage in the endoplasmic reticulum and trans-Golgi network, respectively. A40 is the more common type than A β -42, however A β -42 is fibrillogenic and thus accountable for the illness states. The increased synthesis of A β 42 has been observed during the mutations in APP responsible for the

earliest stages of Alzheimer's disease, suggesting the role of modulation of the activity of α and β and γ secretases as a possible beneficial therapy for Alzheimer's disease (Economou et al 2016). The structural sequence on the oligomeric state of β -amyloid was still scarce in 2010. Isolating pentameric disc-shaped oligomers devoid of beta structure was possible under low-temperature and low-salt conditions. After accumulation, β -amyloid plaques causes neuronal dysfunction by inhibiting mitochondrial function, increasing ROS production, and producing a toxic aldehyde known as 4-hydroxynonenal, which decreases ATPase activity, glucose transport, and, as a result, neuronal loss. The amyloid promotes glutamate-dependent depolarization of the synaptic membrane, which leads to calcium influx dependent mitochondrial dysfunction (Kudryavtseva et al. 2016). The Amyloid hypothesis proposed that extracellular Amyloid Beta (A β) deposits are cause of Alzheimer's disease. The position of the gene that regulates Amyloid Precursor Protein (APP) on chromosome 21 reinforces this hypothesis, meaning that people with Down syndrome have classic Alzheimer neuropathology because they produce too much A throughout their entire lives. Another aspect that supports the above-mentioned hypothesis is that people with trisomy 21 almost consistently develop Alzheimer's disease by the age of 40 years. Apolipoprotein E4 is also the strongest known genetic risk factor for late-onset Alzheimer's disease (Foraker et al 2016). Furthermore, transgenic mice have demonstrated that those animals that express a mutant form of the human APP gene are more likely to acquire fibrillary amyloid plaques and develop AD. Early human trials with an experimental vaccination were used to determine the extent to which it could eliminate amyloid plaque, however it had no or little effect on dementia other than to remove plaque. Researchers have rationale to suspect that non-plaque A β oligomers are the principal pathogenic type of A β . Amyloid-Derived Diffusible Ligands (ADDLs) are another name for these toxic protein oligomers. These oligomers easily bind to a neuron's cell membrane receptor and change the structure of the synapse, directing synaptic communication. A single receptor for A protein oligomers, similar to prion protein, may exist, i.e. the same proteins associated with disease and related human conditions like as Creutzfeldt-Jakob disease (Cerasoli et al 2016). (Figure 1).

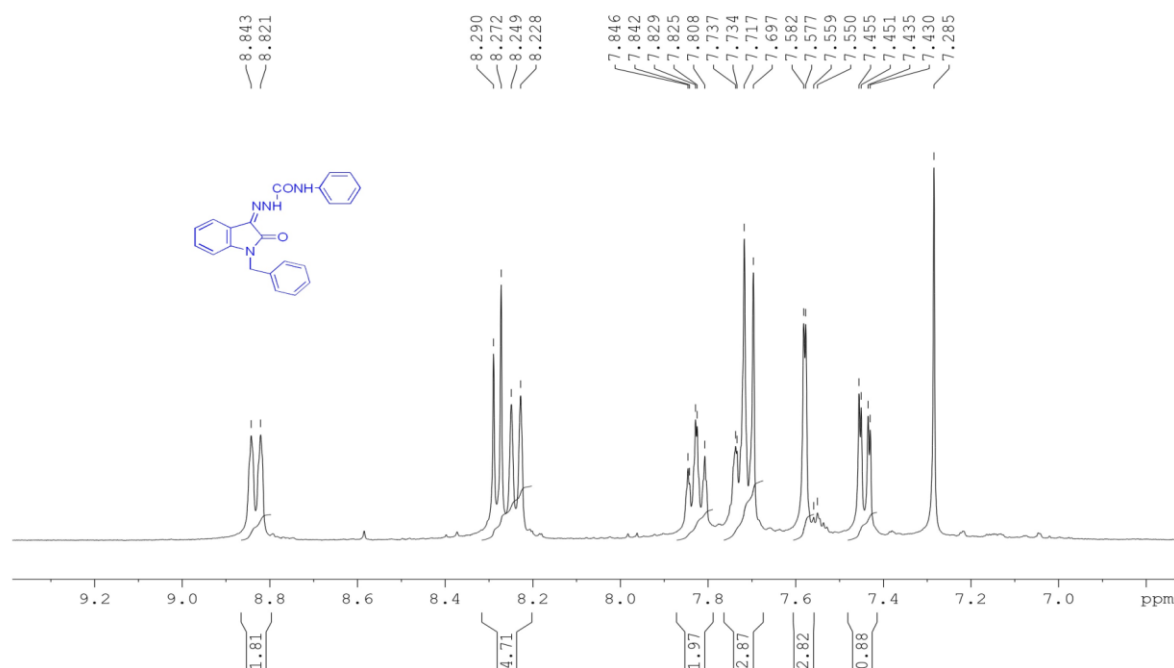
SPECTRAL DATA



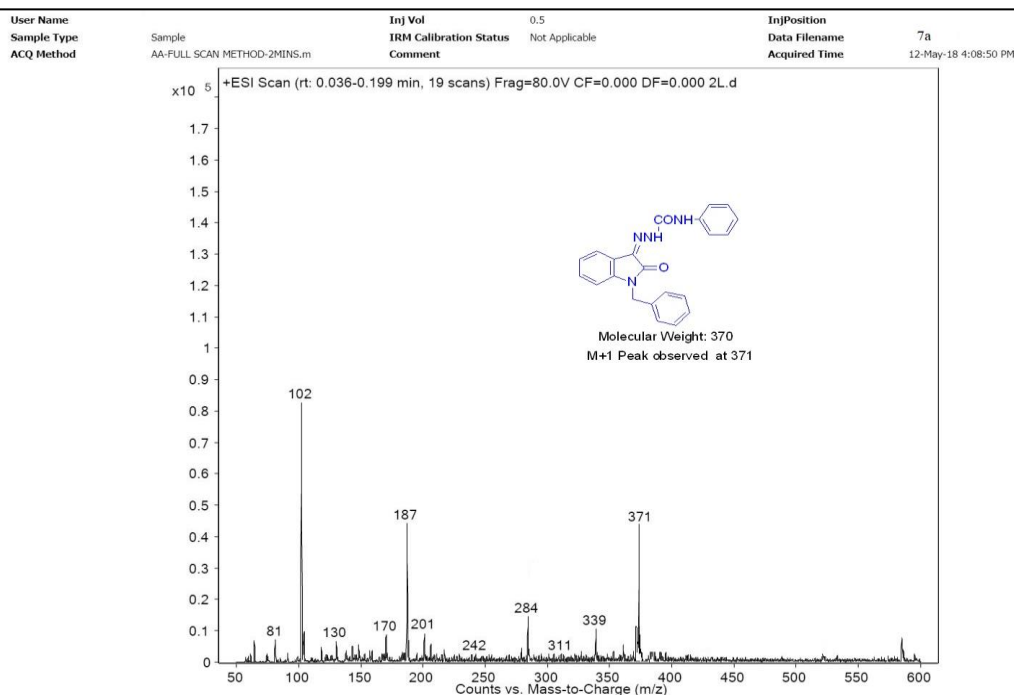
IR Spectrum of 2-(1-benzyl-2-oxoindolin-3-ylidene)-N-(3-nitrophenyl)hydrazinecarboxamide (7a)



¹H NMR Spectrum of 2-(1-benzyl-2-oxoindolin-3-ylidene)-N-(3-nitrophenyl)hydrazinecarboxamide (7a)

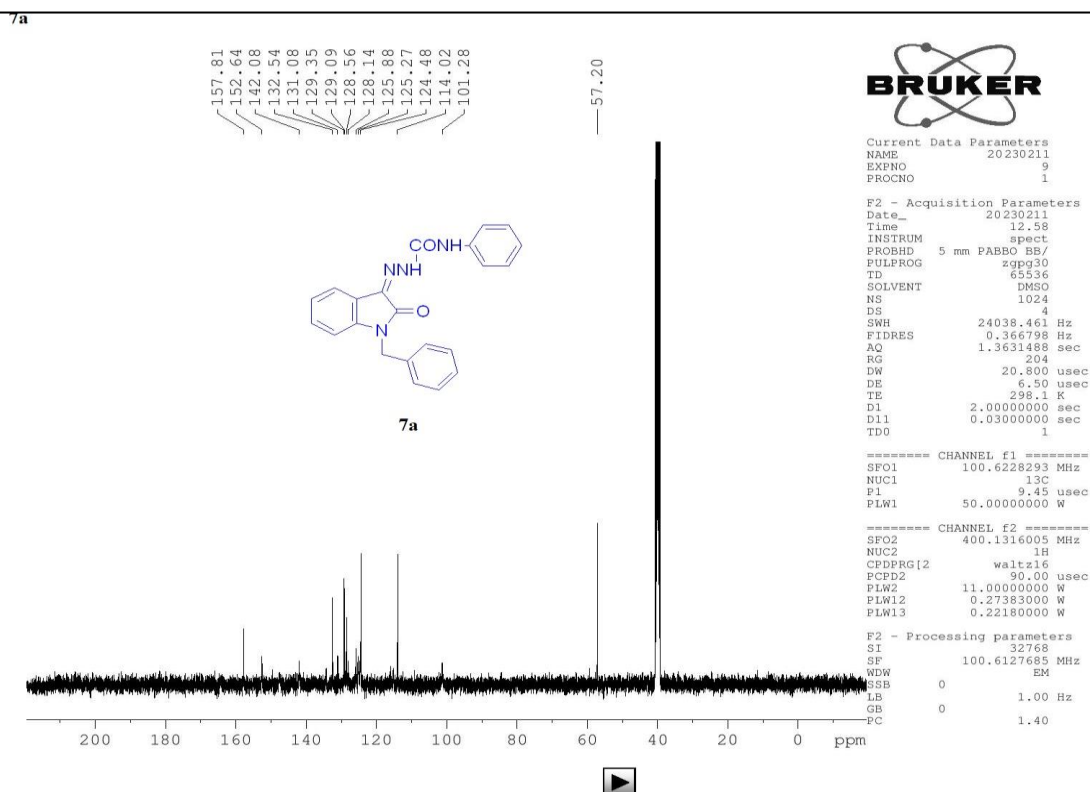


¹H NMR Spectrum of 2-(1-benzyl-2-oxoindolin-3-ylidene)-N-(3-nitrophenyl)hydrazinecarboxamide (7a)

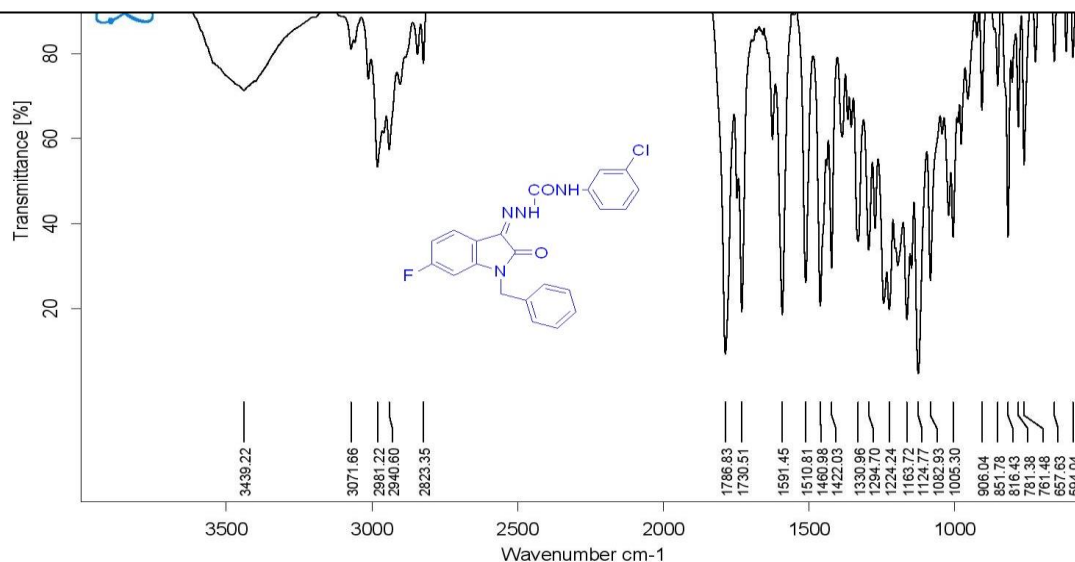


Mass Spectrum of 2-(1-benzyl-2-oxoindolin-3-ylidene)-N-(3-nitrophenyl)hydrazinecarboxamide (7a)

¹H NMR Extension Spectrum of 2-(1-benzyl-2-oxoindolin-3-ylidene)-N-(3-nitrophenyl)hydrazinecarboxamide (7a)



¹³C NMR Spectrum of 2-(1-benzyl-2-oxoindolin-3-ylidene)-N-(3-nitrophenyl)hydrazinecarboxamide (7a)



D:\IR DATA\

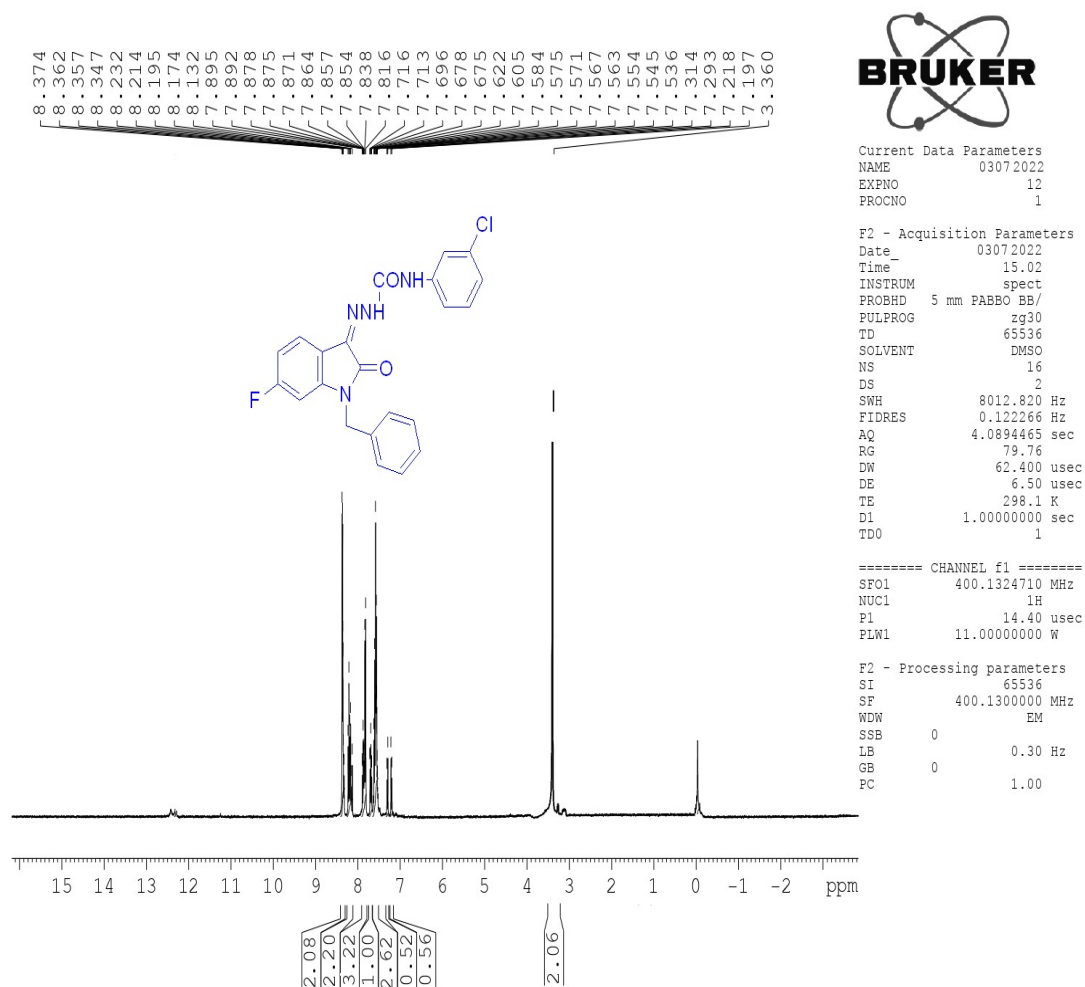
7i

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IR Spectrum of (E)-2-(1-benzyl-5-fluoro-2-oxoindolin-3-ylidene)-N-(3-chlorophenyl)-hydrazinecarboxamide (7i)

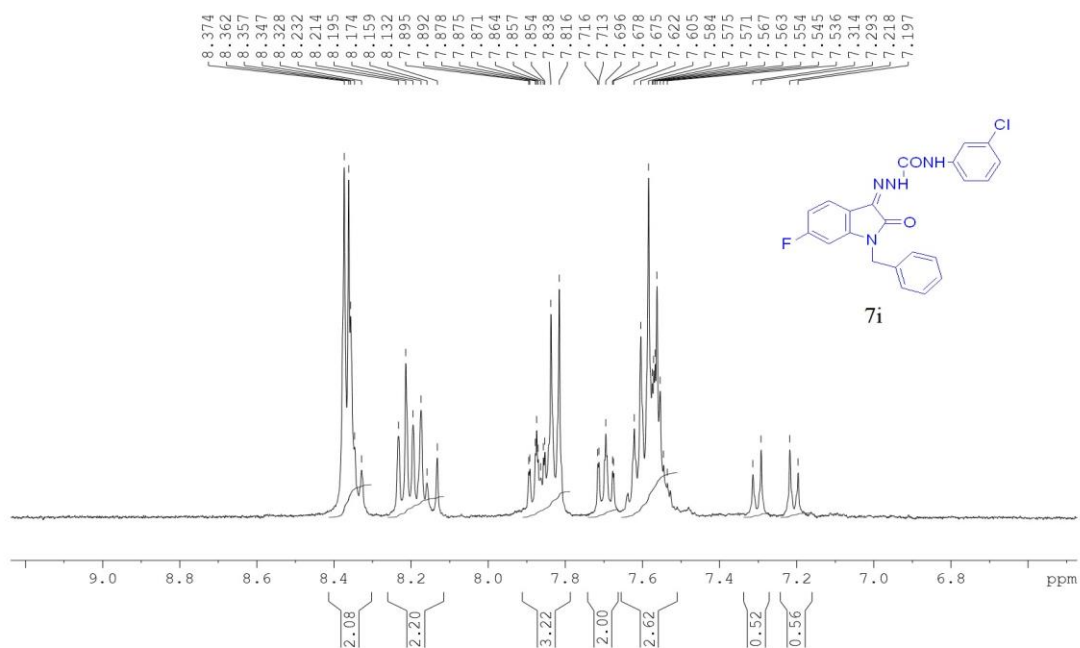
7i



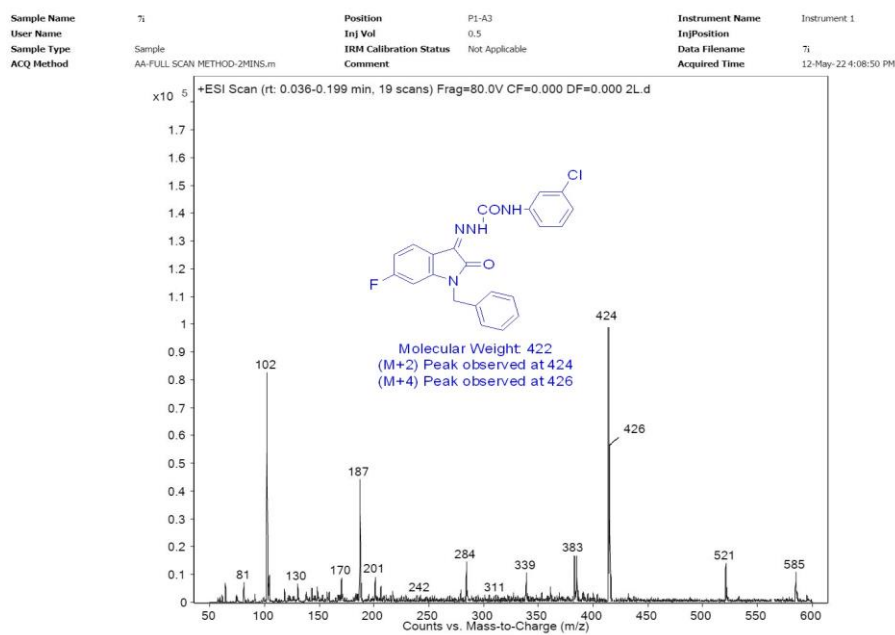
¹H NMR Spectrum of (E)-2-(1-benzyl-5-fluoro-2-oxindolin-3-ylidene)-N-(3-chlorophenyl)-hydrazine-carboxamide (7i)



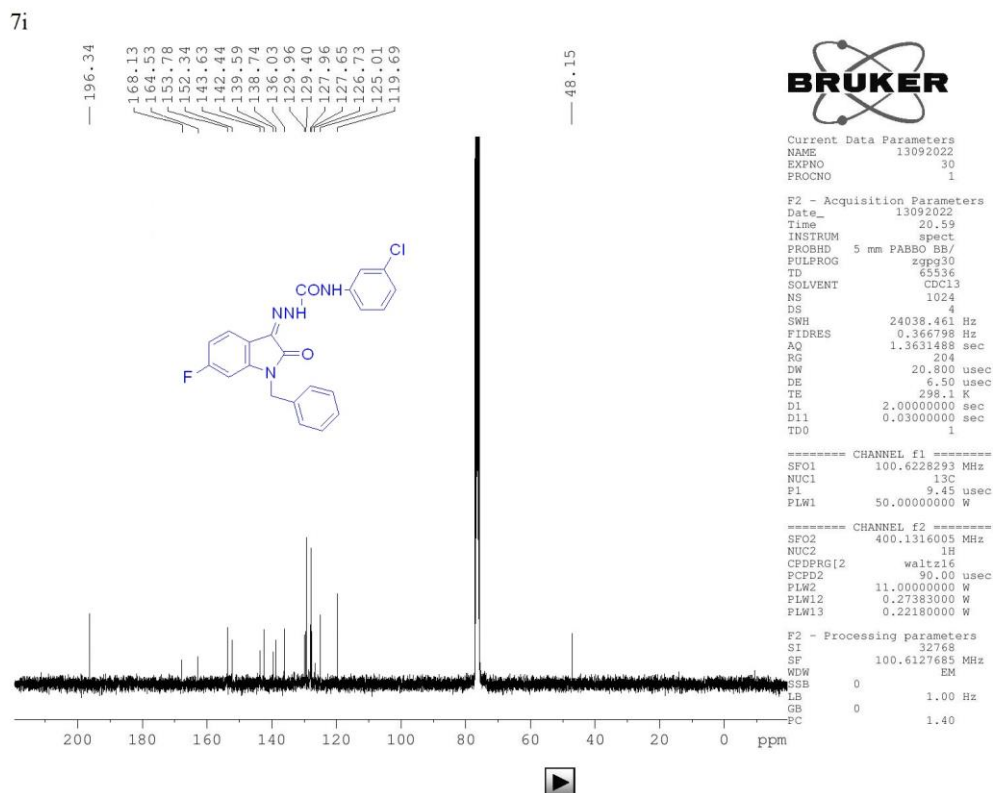
7i



¹H NMR Spectrum of (E)-2-(1-benzyl-5-fluoro-2-oxoindolin-3-ylidene)-N-(3-chlorophenyl)-hydrazine-carboxamide (7i)



Mass Spectrum of (E)-2-(1-benzyl-5-fluoro-2-oxoindolin-3-ylidene)-N-(3-chlorophenyl)-hydrazine-carboxamide (7i)



¹³C Spectrum of (E)-2-(1-benzyl-5-fluoro-2-oxindolin-3-ylidene)-N-(3-chlorophenyl)-hydrazine-carboxamide (7i)

CONCLUSION:

The present work focuses on design, synthesis, biological evaluation of novel aza indole & indole derivatives.

This work aims to design, synthesize various azaindole sulphonamide & oxindole hydrazine carboxamide derivatives compounds & to purify by column chromatography. characterize them by analytical techniques followed by biological evaluation for anticancer activity by MTT assay, Anti Alzheimer's activity by invitro, invivo and behavioural studies & developing Structural activity relation studies correlating the structure of the compound.

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